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Association between platelet-to-high-density lipoprotein cholesterol ratio and gallstone prevalence in the American adult population: a cross-sectional study analysis

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Abstract

Objective The platelet-to-high-density lipoprotein cholesterol ratio(PHR), a novel marker of inflammatory response and metabolic dysregulation, has been linked to various chronic conditions.This study aimed to evaluate the association between PHR and the prevalence of gallstones.

Methods This cross-sectional study analyzed data collected from the United States National Health and Nutrition Examination Survey(NHANES)between 2017 and 2023. Multivariate logistic regression, generalized additive models, and subgroup analyses were employed to assess the relationship between PHR and gallstone prevalence.

Results A total of 13,163 participants were included, of whom 1,441(10.95%) self-reported a history of gallstones. After adjusting for potential confounders, a positive association was observed between the natural log-transformed PHR(LN[PHR])and gallstone prevalence(OR = 1.27, 95%CI: 1.09–1.49). This positive correlation became more pronounced with increasing PHR levels(P-trend = 0.01). Smooth curve fitting analysis indicated a linear relationship between PHR and gallstone prevalence. Subgroup analyses revealed that the association was strongest in participants aged 20–39 years, women, and individuals of other racial/ethnic groups.

Conclusion Elevated PHR levels are significantly associated with a higher risk of gallstones. While our observational data suggest plausibility for PHR-gallstone, these findings should be interpreted as hypothesis-generating rather than definitive clinical evidence. Future mechanistic studies should elucidate whether this association reflects causal pathways or epiphenomenal relationships.

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Introduction

Gallstones are among the most prevalent digestive disorders worldwide, representing a significant risk factor for gallbladder cancer [1, 2]. In the United States alone, gallstones impose a substantial healthcare burden, affecting over 10%of the population [3]. While most individuals with gallstones remain asymptomatic, approximately 10–25% may develop symptoms such as biliary pain or acute cholecystitis, with 1–2% experiencing severe complications [4, 5]. Given the potential for serious outcomes, identifying effective clinical indicators for the early detection and intervention of gallstone risk factors is critical for reducing the global public health burden associated with this condition.

Recent epidemiological studies have identified a variety of factors influencing the development of gallstones, including age, gender, pregnancy, obesity, sedentary lifestyle, diet, and inflammatory responses [6, 7]. Among these, inflammation has garnered significant attention. Research suggests that pro-inflammatory markers such as IL-6, IL-8, TNF-α, and CRP are associated with an increased risk of gallstones, while anti-inflammatory markers like IL-4 appear to reduce the risk [8, 9]. During inflammatory processes, changes in neutrophil and lymphocyte counts, platelet(PLT)levels, and acute-phase proteins are commonly observed [10].

Platelets play a central role in inflammation by aggregating and releasing cytokines, which can amplify inflammatory responses [11]. Studies have demonstrated an association between elevated platelet count and the presence of gallstones in adults [12]. Furthermore, gallstone formation is often accompanied by dyslipidemia [13, 14]. High-density lipoprotein cholesterol(HDL-C), known for its anti-inflammatory and antioxidant properties, facilitates dietary cholesterol efflux through reverse cholesterol transport. A recent Mendelian randomization study revealed an inverse linear relationship between HDL-C levels and gallstone risk [15, 16]. These findings suggest that the combined assessment of platelet count and HDL-C levels may provide insights into gallstone risk.

The PHR, a marker of inflammatory and metabolic abnormalities, has been strongly linked to the severity of metabolic sysfunction-associated steatotic liver disease(MASLD)and metabolic syndrome(MetS) [17, 18]. However, its association with gallstones has not yet been explored.We hypothesize that PHR may be a novel predictor of gallstone development. To test this, we analyzed the relationship between PHR and gallstones using data from a nationally representative survey, while adjusting for established risk factors. This study represents the first investigation into the independent association between PHR and gallstone risk.

Methods

Data Sources and participants

The NHANES is a cross-sectional survey that has been updated and released every two years since 1999. For this study, we utilized data from participants in the NHANES surveys conducted between 2017 and 2023, covering three consecutive cycles.Given that data on gallstones were only collected from participants aged 20 years or older, we applied specific inclusion and exclusion criteria to define the study population.A detailed flowchart outlining the inclusion and exclusion process is presented in Fig. 1. Through a systematic exclusion process, individuals aged < 20 years ($n = 10{,}645$), those with missing data on gallstone status ($n = 30$), PHR index ($n = 3{,}602$), education level ($n = 13$), asthma history ($n = 11$), hypertension status ($n = 15$), diabetes status ($n = 4$), and cancer history ($n = 10$) were excluded. The final analytical cohort comprised 13,163 participants, including 1,441 individuals with gallstones and 11,722 without gallstones.

The PHR was designated as the primary exposure variable. PHR, calculated as the ratio of platelet count (PC) to HDL-C, was natural log-transformed (Ln-PHR) due to its non-normal distribution. The primary outcome variable was the presence of gallstones. The accuracy of self-reported gallstone status has been validated in previous studies [1]. Participants were classified as having gallstones if they answered "yes" to the question regarding a history of gallstone diagnosis. Gallstone occurrence, therefore, was the primary outcome variable.

Potential covariates that could confound the association between the PHR index and gallstone prevalence were incorporated into a multivariable-adjusted model. Based on relevant references combined with clinical experience, we included some relevant confounders for adjustment [5, 8, 9]. The covariates considered in this study included demographic factors (age, gender, ethnicity, WWI index [5]), socioeconomic indicators (education level and poverty income ratio [PIR]), lifestyle behaviors (alcohol consumption, physical activity, and smoking status), clinical variables (cholesterol levels, hypertension, diabetes, asthma, and cancer), and inflammatory markers (C-reactive protein [CRP]). Previous studies have reported associations between CRP and gallstone prevalence [8, 9], warranting its inclusion as an adjustment variable. These adjustments aimed to minimize potential confounding and better isolate the relationship between the PHR index and gallstones.

Statistical analysis

All statistical analyses adhered to CDC guidelines and accounted for the complex, multistage, stratified sampling design of the NHANES survey, using appropriate sampling weights as recommended. Detailed guidance on NHANES weight analyses is available on the official

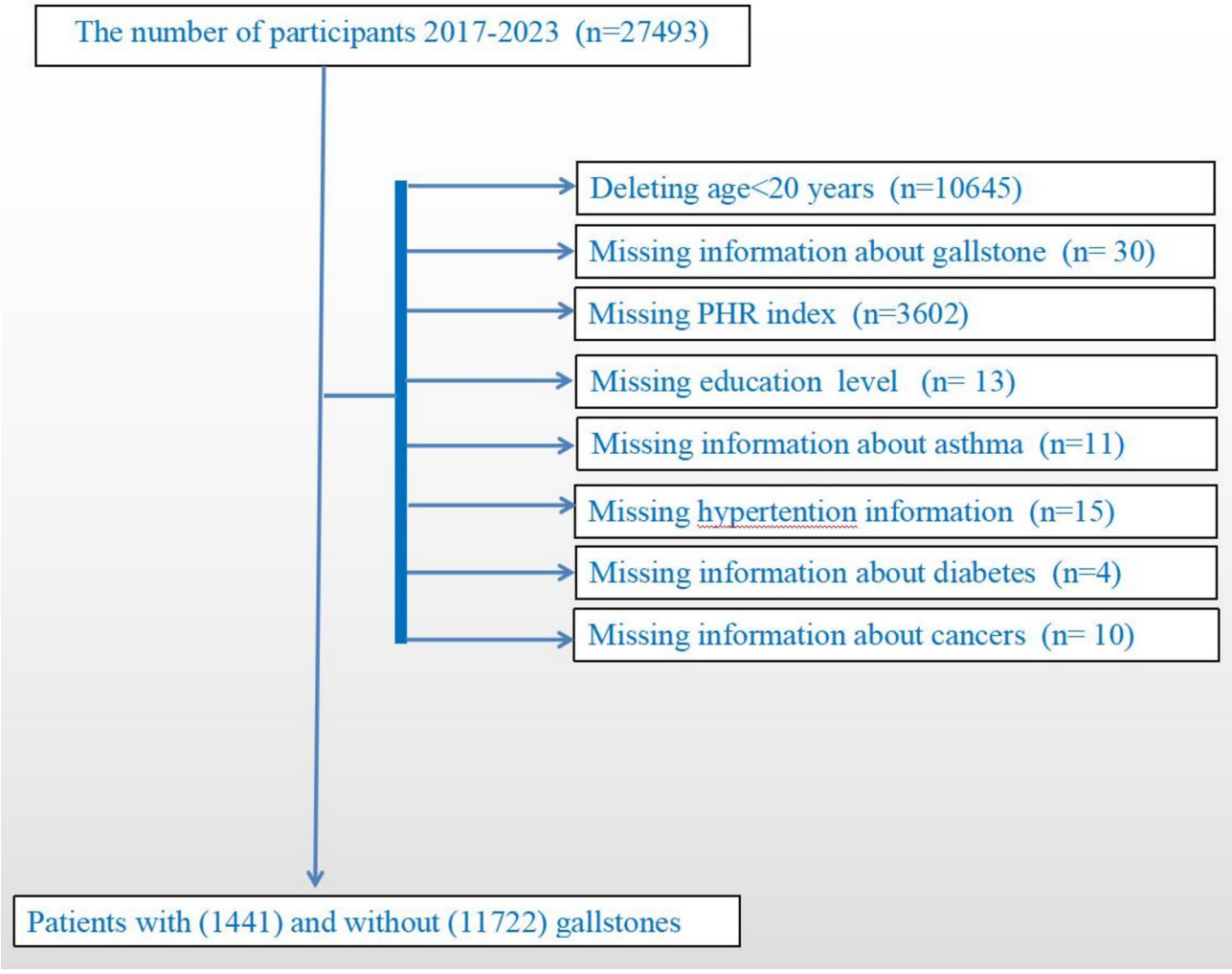

Fig. 1 The participants selecting flow chart

website. Sampling weights were incorporated into the analysis using the survey design package in R software.

Continuous variables were analyzed using survey-weighted linear regression, while categorical variables were evaluated with survey-weighted chi-square tests to compare group differences. Continuous variables were expressed as weighted means with 95% confidence intervals (CIs), while categorical variables were presented as weighted proportions with 95% CIs.

In compliance with the STROBE guidelines, three multivariable logistic regression models were developed to investigate the relationship between PHR and gallstones.

- Model 1: No covariates were adjusted.
- Model 2: Adjusted for sex, age, race, education level, and history of comorbidities such as hypertension, diabetes, asthma, and cancer.
- Model 3: Adjusted for all variables included in the study.

For sensitivity analyses, the PHR index was categorized into tertiles, and its robustness was evaluated by analyzing the association using tertiles. Linear trend testing was performed by treating the tertiles of PHR as an ordinal variable. Additionally, generalized additive models (GAMs) and smooth curve fitting were applied to detect potential non-linear relationships between PHR and gallstones. If a non-linear correlation was observed, a two-segment linear regression model (segmented regression) was employed to calculate the threshold effect and fit relationships within each segment.

A significance threshold of $p < 0.05$ was used for all analyses. Statistical analyses were conducted using EmpowerStats software (www.empowerstats.com; X & Y Solutions, Inc., Boston, MA, USA) and R software (version 4.2.0; http://www.R-project.org, The R Foundation).

Results

Baseline characteristics

Figure 1 illustrates the detailed population screening criteria, resulting in a total of 13,163 participants being included in the final analysis, of which 1,441 (10.95%) had a self-reported history of gallstones. The demographic and baseline characteristics of the included participants are summarized in Table 1. Participants were categorized

Table 1 Baselines characteristics of participants

Characteristic	Non-stone formers	Stone formers	*P*-value
	N **= 11,722**	***N*** **= 1441**	
Age(years)	48.19 (47.46,48.92)	57.67 (56.46,58.89)	< 0.0001
CRP(mg/L)	3.65 (3.42,3.88)	5.28 (4.66,5.91)	< 0.0001
TC(mg/L)	188.62 (187.03,190.22)	185.85 (182.97,188.72)	0.0672
PHR Index	193.86 (190.71,197.01)	203.10 (195.65,210.55)	0.023
Gender(%)			< 0.0001
Male	50.78 (49.61,51.95)	26.75 (24.03,29.65)	
Female	49.22 (48.05,50.39)	73.25 (70.35,75.97)	
Race(%)			0.0004
Mexican American	7.74 (5.77,10.31)	7.35 (4.81,11.07)	
Other Hispanic	8.53 (6.65,10.87)	8.17 (5.80,11.39)	
Non-Hispanic White	61.75 (57.07,66.22)	68.13 (62.09,73.63)	
Non-Hispanic Black	10.95 (8.78,13.57)	7.04 (5.19,9.47)	
Other Race	11.04 (9.37,12.95)	9.32 (7.33,11.77)	
Education Level(%)			0.0044
Less than high school	10.23 (9.19,11.38)	11.61 (9.83,13.65)	
High school	25.50 (23.19,27.96)	29.43 (25.87,33.25)	
More than high school	64.27 (61.52,66.92)	58.97 (55.17,62.66)	
Alcohol(%)			< 0.0001
Yes	12.41 (11.34,13.58)	22.58 (18.78,26.90)	
No	72.44 (70.85,73.98)	61.46 (57.94,64.87)	
Unclear	15.14 (13.53,16.92)	15.96 (13.33,18.99)	
High Blood Pressure(%)			< 0.0001
Yes	30.35 (28.74,32.01)	49.65 (46.31,53.01)	
No	69.65 (67.99,71.26)	50.35 (46.99,53.69)	
Diabetes(%)			< 0.0001
Yes	10.58 (9.70,11.52)	21.31 (18.54,24.37)	
No	89.42 (88.48,90.30)	78.69 (75.63,81.46)	
Asthma(%)			< 0.0001
Yes	15.86 (14.82,16.94)	22.53 (19.48,25.90)	
No	84.14 (83.06,85.18)	77.47 (74.10,80.52)	
Cancers(%)			< 0.0001
Yes	10.57 (9.75,11.44)	19.54 (16.99,22.36)	
No	89.43 (88.56,90.25)	80.46 (77.64,83.01)	
Smoked(%)			0.0009
Yes	40.04 (37.91,42.21)	45.38 (41.31,49.51)	
No	59.96 (57.70,62.00)	54.62 (50.44,58.63)	
WWI Index(%)			< 0.0001
Lower	55.70 (53.72,57.66)	30.71 (26.69,35.04)	
Higher	40.40 (38.39,42.45)	63.65 (59.52,67.59)	
Unclear	3.90 (3.18,4.77)	5.65 (4.13,7.68)	
PIR(%)			0.0003
<1.3	15.86 (14.13,17.75)	18.21 (14.95,21.99)	
≥ 1.3<3.5	31.23 (29.09,33.44)	37.72 (32.96,42.73)	
≥ 3.5	40.62 (37.68,43.63)	32.52 (28.36,36.98)	
Unclear	12.30 (10.99,13.73)	11.55 (9.56,13.88)	

Data of continuous variables are shown as survey-weighted mean(95%CI),*P* value was calculated by survey-weighted linear regression.Data of categorical variables are shown as survey-weighted percentage(95%CI),*P* value was calculated by survey-weighted Chi-square test

into two groups based on the presence or absence of gallstones. Significant differences in baseline characteristics were observed between the two groups. The gallstone group exhibited older age, higher PHR index levels, and a greater prevalence of comorbidities such as hypertension, asthma, cancer, and diabetes. Additionally, participants in the gallstone group demonstrated higher rates of alcohol consumption and smoking and included a significantly higher proportion of women compared to the non-stone group ($p < 0.05$).

Higher PHR index was associated with a higher prevalence of gallstones

Logistic regression analysis, based on the fully adjusted model (Model 3), revealed a positive correlation between the Ln (PHR index) and the prevalence of gallstones (OR = 1.27, 95% CI: 1.09–1.49), indicating that a unit increase in Ln (PHR) was associated with a 27% increased risk of gallstone development. To further explore this relationship, the PHR index was converted from a continuous variable into categorical tertiles. Compared to the lowest tertile (Low), participants in the highest tertile (High) exhibited a significantly increased risk of gallstones (OR = 1.24, 95% CI: 1.07–1.44)(Table 2). A trend analysis confirmed that the association between the PHR index and gallstone prevalence became progressively stronger with increasing PHR index levels (P for trend < 0.01). Additionally, a generalized additive model (GAM) and smooth curve fitting were employed to further evaluate this association, which demonstrated a nearing linear positive correlation between the PHR index and gallstone prevalence (Fig. 2). Threshold effect analysis showed that the association between PHR and gallstone prevalence remained linear (OR = 1.27, 95% CI: 1.09, 1.49, P for log-likelihood ratio = 0.058)(Table 3).

Table 2 Logistic regression analysis between PHR index with gallstone prevalence

Characteristic	Model 1 OR(95%CI)	Model 2 OR(95%CI)	Model 3 OR(95%CI)
PHR Index	1.18 (1.02, 1.36)	1.46 (1.26, 1.71)	1.27 (1.09, 1.49)
Categories			
Lower			
Middle	1.02 (0.89, 1.17)	1.12 (0.97, 1.29)	1.07 (0.93, 1.23)
Higher	1.15 (1.01, 1.31)	1.39 (1.21, 1.61)	1.24 (1.07, 1.44)
P for trend	< 0.01	< 0.01	< 0.01

Model 1 was adjusted for no covariates;

Model 2 was adjusted for race, gender, age, education, diabetes,,blood pressure, asthma and cancers;

Model3 was adjusted for covariates in Model 2 + PIR, smoked, alcohol use, serum cholesterol, CRP, WWI index were adjusted

Subgroup analysis

Subgroup analysis was conducted to assess the robustness of the association between the PHR index and the prevalence of gallstones(Table 4). The results indicated significant heterogeneity in the strength of the association across different subgroups:

- Male group: OR = 1.06, 95% CI: 0.80–1.41;
- Female group: OR = 1.39, 95% CI: 1.15–1.67;
- Age < 40 years: OR = 2.31, 95% CI: 1.52–3.50;
- Age 40–59 years: OR = 1.28, 95% CI: 0.97–1.69;
- Age ≥ 60 years: OR = 0.95, 95% CI: 0.77–1.17;
- Mexican-American group: OR = 0.90, 95% CI: 0.53–1.52;
- Hispanic White group: OR = 1.14, 95% CI: 0.70–1.84;
- Non-Hispanic White group: OR = 1.23, 95% CI: 0.98–1.54;
- Black group: OR = 1.31, 95% CI: 0.89–1.92;
- Other ethnic groups: OR = 1.90, 95% CI: 1.22–2.96;
- BMI < 25 kg/m^2: OR = 1.23, 95% CI: 0.82–1.87;
- BMI 25–29.9 kg/m^2: OR = 1.01, 95% CI: 0.74-1.39;
- BMI ≥ 30 kg/m^2: OR = 1.07, 95% CI: 0.86-1.34.

These results demonstrate that the association between the PHR index and gallstone prevalence was most pronounced in females, younger individuals (< 40 years), and participants from the "Other" ethnic group. However, the correlation was weaker or not significant in older age groups (≥ 60 years) and certain ethnic groups, such as Mexican-Americans and Hispanic Whites.

Discussion

In this nationally representative cross-sectional study using data from the NHANES database, we explored the relationship between the PHR and gallstone prevalence. To our knowledge, this is the first epidemiological study to report such an association. After adjusting for sociodemographic factors, laboratory results, personal medical history, lifestyle factors, dietary patterns, and comorbid conditions, our findings indicate that higher PHR levels are significantly associated with an increased prevalence of gallstones in the United States. Specifically, we observed that each unit increase in the PHR index was associated with a 20% higher risk of developing gallstones. To further illustrate this relationship, we employed generalized additive models (GAM) and smooth curve fitting, which confirmed a linear positive correlation between the PHR index and the incidence of gallstones. These results suggest that obesity management, as reflected by the PHR index, may play an important role in reducing the risk of gallstone development.

By screening populations with appropriate PHR index, the prevention of gallstones can be effectively improved. To this end, we conducted subgroup analyses, which

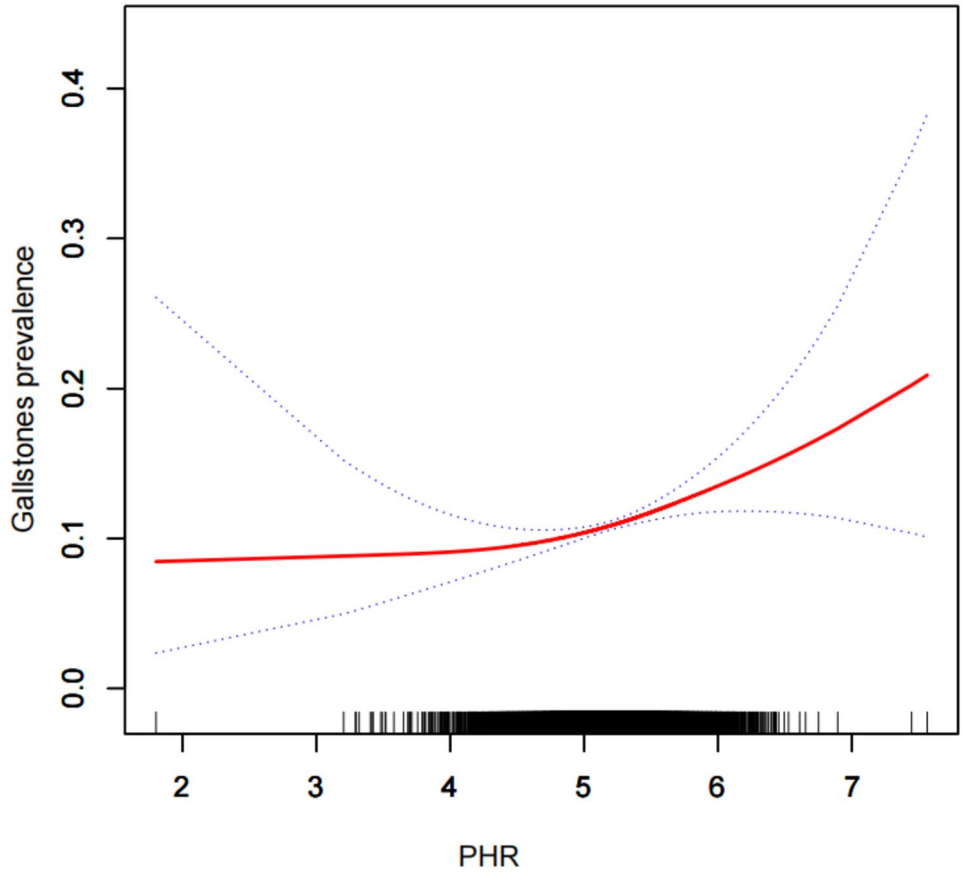

Fig. 2 Density dose-response relationship between PHR index with gallstone prevalence.The area between the upper and lower dashed lines is represented as 95% CI. Each point shows the magnitude of the PHR index and is connected to form a continuous line. Adjusted for all covariates except effect modifier

Table 3 Threshold effect analysis of PHR index on gallstone prevalence

	Adjusted OR (95% CI)
Gallstone Prevalence	
Total	1.27 (1.09, 1.49)
Fitting by two-piecewise Cox proportional risk model	
Inflection point	4.58
TyG index < 8.939	0.61 (0.30, 1.26)
TyG index ≥ 8.939	1.37 (1.15, 1.63)
P for Log-likelihood ratio	0.058

revealed that the PHR index had the most significant impact on gallstone prevalence in individuals under 40 years of age within the age-stratified groups. The controversy regarding age as a risk factor for cholelithiasis persists: an Italian study [19]identified increasing age as a risk factor for gallstone development, and a Taiwanese study [20] also confirmed the association between age and gallbladder diseases as well as fatty liver diseases. However, some studies suggest that metabolic syndrome and obesity have a more pronounced effect on gallstones in younger populations [21], and Wang et al. [22] and Yan et al. [23], based on NHANES studies, have reached conclusions consistent with ours. In terms of gender differences, multiple studies [24, 25] indicate that female patients have a higher risk of gallstone development, a viewpoint supported by our findings. Additionally, our data show that other ethnic groups have the highest prevalence of cholelithiasis, which may be related to dietary and lifestyle differences among races. Gong et al., in another NHANES study, also found that an elevated TyG index in other U.S. populations is a risk factor for increased gallstone prevalence [26]. Although the studied populations are not identical, this finding, to some extent, lends credibility to our results.

Previous studies have explored the relationship between the PHR and MetS, finding that PHR is associated with all five components of MetS: abdominal obesity, hypertriglyceridemia, low HDL-C levels, hyperglycemia, and hypertension [27]. Additionally, PHR levels have been shown to increase with the severity of MetS [17]. Given the established connection between MetS and gallstones [28, 29], it is noteworthy that the risk of gallstones rises with the number of metabolic syndrome components, as demonstrated by recent studies [30]. Moreover,

Table 4 Subgroup analysis between PHR index with gallstone prevalence

Characteristic	Model 1 OR(95%CI)	Model 2 OR(95%CI)	Model 3 OR(95%CI)
Stratified by gender			
Male	0.93 (0.71, 1.21)	1.18 (0.89, 1.56)	1.06 (0.80, 1.41)
Female	1.39 (1.18, 1.65)	1.59 (1.33, 1.91)	1.39 (1.15, 1.67)
Stratified by race			
Mexican American	0.60 (0.38, 0.95)	0.97 (0.58, 1.61)	0.90 (0.53, 1.52)
Other Hispanic	0.87 (0.56, 1.35)	1.23 (0.77, 1.97)	1.14 (0.70, 1.84)
Non-Hispanic White	1.16 (0.94, 1.42)	1.41 (1.13, 1.75)	1.23 (0.98, 1.54)
Non-Hispanic Black	1.68 (1.18, 2.38)	1.66 (1.15, 2.39)	1.31 (0.89, 1.92)
Other Race	1.56 (1.03, 2.34)	2.00 (1.30, 3.09)	1.90 (1.22, 2.96)
Stratified by age(years)			
20–39	3.03 (2.06, 4.46)	2.84 (1.91, 4.24)	2.31 (1.52, 3.50)
40–59	1.56 (1.20, 2.04)	1.47 (1.12, 1.92)	1.28 (0.97, 1.69)
60–85	1.12 (0.92, 1.36)	1.05 (0.85, 1.29)	0.95 (0.77, 1.17)
Stratified by BMI			
BMI < 25 kg/m^2	1.15 (0.77, 1.72)	1.27 (0.85, 1.90)	1.23 (0.82, 1.87)
BMI 25–29.9 kg/m^2	0.70 (0.53, 0.94)	0.99 (0.73, 1.34)	1.01 (0.74, 1.39)
BMI ≥ 30 kg/m^2	0.89 (0.73, 1.09)	1.17 (0.94, 1.45)	1.07 (0.86, 1.34)

Model 1 = no covariates were adjusted

Model 2 = Model 1 + race, gender, age, education, diabetes,,blood pressure, asthma and cancers were adjusted

Mode3 = adjusted for all covariates except effect modifier

several studies have confirmed a significant association between obesity and gallstone disease, indicating that obesity increases the risk of gallstones by approximately twofold [31, 32]. Dyslipidemia, particularly the relationship between HDL-C and gallstones, has also been well-documented. Research by Wang [33], Banim [34], and Zhang [35] demonstrated that higher HDL-C levels are negatively associated with the risk of gallstones. In contrast, elevated triglycerides have been positively associated with gallstone susceptibility [34–36]. Given that both MetS and gallstones share common pathophysiological features such as inflammation and insulin resistance, it is plausible to suggest that PHR may serve as an important biomarker linking metabolic disturbances to gallstone formation.

The relationship between the PHR and gallstones involves complex pathophysiological mechanisms that are not fully understood. As a composite measure of PLT and HDL-C, PHR may reflect underlying states of both inflammatory and metabolic abnormalities [37]. Inflammation is recognized as a key factor in the formation of gallstones. During the inflammatory response, platelets interact with neutrophils and lymphocytes, which in turn enhances monocyte adhesion, motility, and the release of various inflammatory mediators [38].

A study conducted in the United States identified higher levels of interleukins (IL-6, IL-10, IL-12(p70), IL-13) as being associated with an increased risk of gallstones [8]. It was proposed that inflammation may alter the metabolism of proteins and lipids, leading to changes in cholesterol and bile acid metabolism. These alterations could increase the levels of bile salts, which in turn promote the formation of gallstones [39]. Therefore, inflammation may partially explain the association between PHR and the prevalence of gallstones, suggesting that elevated PHR levels could indicate a heightened inflammatory state that facilitates the development of gallstones.

The PHR is an index that reflects the interaction between PLT and HDL-C. PHR levels can increase due to either elevated platelet levels or reduced HDL levels. Gallstones, which can include cholesterol stones, have been closely linked to metabolic changes involving cholesterol and bile acids. Research has shown that lower HDL-C levels impair the effective transport of cholesterol from peripheral tissues to the liver, potentially contributing to cholesterol deposition in the gallbladder and the formation of cholesterol stones [40]. HDL-C plays a critical role in promoting the synthesis of bile acids [41] and in increasing the solubility of cholesterol in bile, which helps reduce cholesterol saturation levels [42]. Additionally, HDL suppresses endothelial inflammation and reduces the expression of key cell adhesion molecules, which modulate the inflammatory state and can inhibit stone formation [43].

On the other hand, platelets are active participants in systemic inflammation. When activated, platelets contribute to vascular inflammation, endothelial injury, atherosclerosis, and thrombosis [44–46]. Platelet factor 4 (PF4, also known as CXCL4), the most abundant protein secreted by activated platelets, is deposited on the endothelium. Studies have shown that patients with chronic inflammation have higher circulating levels of PF4 [47–49]. PF4 has been shown to contribute to inflammation by promoting leukocyte recruitment and the production of neutrophil extracellular traps (NETs) [50]. Given these roles of both HDL and platelets in metabolic and inflammatory processes, PHR is strongly associated with gallstone formation. However, it remains unclear whether PHR is a direct pathogenic risk factor for gallstones or merely a marker of underlying metabolic and inflammatory disturbances that contribute to gallstone

development. Further studies are needed to elucidate whether PHR plays a causal role in the pathogenesis of gallstones or if it simply reflects the presence of other risk factors.

Our study has several strengths. First, we utilized data from the NHANES, which adheres to a well-designed study protocol and accounts for sampling weights, ensuring that the results are highly representative of the general U.S. population. Additionally, the large sample size of our study enabled us to perform subgroup analyses, further supporting the robustness of our findings. However, there are some limitations in our study.

- Cross-sectional design: Given the cross-sectional nature of the study, we were unable to establish a causal relationship between the PHR and the prevalence of gallstones. Longitudinal studies are needed to clarify this association.
- Potential confounding: Although we adjusted for various potential confounders, there may still be unmeasured or unknown variables that could have influenced the results. These confounding factors could limit the ability to fully account for all the contributing factors to gallstone prevalence.
- Gallstone data collection: The data on gallstone prevalence was self-reported via a questionnaire, which could introduce recall bias. Additionally, asymptomatic gallstones, which are not diagnosed in some individuals, may have been overlooked, potentially affecting the accuracy of our findings.
- While PHR monitoring shows statistical association, its clinical utility for risk stratification requires validation in prospective studies with clinical endpoints.Clinical implementation cannot be recommended without trials demonstrating improved patient outcomes.

Despite these limitations, our study provides valuable insights into the association between PHR and gallstones, and future studies should aim to address these limitations to better understand the causal mechanisms underlying this relationship.

Summary

The higher the PHR index, the higher the likelihood of gallstones, and we hypothesized that the PHR index as a proxy could somewhat suggest the risk of gallstones, but of course, the causal relationship between the PHR index and gallstone prevalence is still unclear and needs to be clarified by further prospective cohort studies.

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Author contributions
YL and CY contributed to conception and design of the study. YL organized the database. YL, CY, XF, and SL participated in acquisition of data. XF and JZ performed the statistical analysis. YL wrote the first draft of the manuscript. CY contributed to manuscript revision. All authors contributed to the article and approved the submitted version.

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Data Availability
Publicly available datasets were analyzed in this study. This data can be found here: NHANES (https://wwwn.cdc.gov/nchs/nhanes/Default.aspx).

Declarations

Ethics approval and consent to participate
The studies involving human participants were reviewed and approved by National Center for Health Statistics (NCHS) 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.

Conflict of interest
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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