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Original Article

The Association between Red Blood Cell Distribution Width to Albumin Ratio and Gallstones: A Cross-Sectional Study with Propensity Score Matching

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Abstract:

Background: The ratio of red blood cell distribution width to albumin (RAR) is an emerging and cost-effective composite inflammatory indicator that can reflect the systemic inflammatory status of the body. However, the potential relationship between RAR and gallstones has not been systematically evaluated.

Methods: This study is based on data from the National Health and Nutrition Examination Survey (NHANES) in the United States, conducted from 2017 to 2020, involving 7,679 adults. Use propensity score matching (PSM) to control for selection bias and construct a multivariate logistic regression model to evaluate the association between RAR and gallstones. A restrictive cubic spline (RCS) is employed to investigate potential nonlinear relationships, while subgroup analysis is used to assess interactions and heterogeneity.

Results: The elevated level of RAR is significantly positively correlated with the risk of gallstones (OR=1.358, 95% CI: 1.194-1.545), and this correlation remains robust after PSM (OR=1.357, 95% CI: 1.156-1.593). RCS analysis suggests a linear relationship between RAR and the incidence of gallstones. The subgroup analysis results showed that this association remained consistent in most populations, and alcohol consumption and physical activity had significant moderating effects on this association (p for interaction < 0.05).

Conclusions: RAR is significantly positively correlated with the risk of gallstones, suggesting that it can be used as a convenient and easily accessible potential inflammatory biomarker to assist in early risk identification and population screening of gallstones. This discovery provides a new research perspective and intervention basis for the stratified management and precise prevention and treatment of gallstones.

Keywords: Red blood cell distribution width to albumin ratio, gallstone, Propensity score matching, cross-sectional study.

1. Introduction

Gallstones refer to stone lesions that occur in the biliary system (including the gallbladder and bile ducts), and are a common digestive system disease. According to statistics, about 6% of people worldwide suffer from gallstones, and unhealthy lifestyles and metabolic abnormalities have been driving this proportion up year by year in recent years [1, 2]. In clinical practice, 20% of patients with gallstones will experience a series of processes from asymptomatic to symptomatic, from mild digestive discomfort to acute biliary colic, which can lead to biliary obstruction in severe cases [3]. Meanwhile, about 1-2% of patients with gallstones may experience complications such as acute cholecystitis, acute cholangitis, and biliary pancreatitis. If not intervened promptly, it may directly endanger the patient's life[4]. In addition, gallstones will increase the risk of exposure to other diseases, such as diabetes, cerebrovascular diseases, and

cancer [5-7]. This indicates that gallstones have become an increasingly prominent public health event, but their formation is a complex, multifactorial process, and the exact mechanism has not yet been fully elucidated.

More and more evidence suggests that an inflammatory response may be a key factor in the formation and development of gallstones. Research has found that inflammation promotes the formation of gallstones by regulating bile concentration and bile cholesterol secretion to increase bile salt concentration [8]. At the same time, cholesterol crystals can promote the secretion of gallbladder mucin by activating inflammasomes. Gallbladder mucin is considered a key mediator of cholesterol crystal aggregation, which accelerates the formation of gallstones [9]. Further research has confirmed that inhibiting the inflammatory pathway in gallbladder epithelial cells can reduce the stone burden in experimental animals[10]. Clinical data show that patients with gallstones have enhanced immune and inflammatory responses, and multiple inflammatory pathways are activated. Multiple inflammatory markers, such as IL-6, IL-10, and C-reactive protein, are positively correlated with the risk of gallstones [11-13]. Given the important role of inflammation in the development of gallstones, it is of great significance to search for effective inflammatory markers for the risk assessment of gallstones.

The RAR is an economically accessible new inflammatory indicator, which integrates two classic hematological parameters, red blood cell distribution width (RDW) and serum albumin. RDW is a common hematological parameter used to quantitatively evaluate the size heterogeneity of circulating red blood cells. Elevated RDW usually indicates severe dysregulation of red blood cell homeostasis, including impaired red blood cell production and abnormal survival, which may be associated with various potential metabolic abnormalities such as oxidative stress, inflammatory response, poor nutritional status, red blood cell fragmentation, and changes in erythropoietin function [14, 15]. Serum albumin is a commonly used indicator for evaluating the nutritional and immune status of the body and disease prognosis, and a decrease in its level is positively correlated with systemic inflammation and high nutritional risk [16, 17]. Meanwhile, albumin can reduce inflammatory response by antioxidant stress, binding and transporting inflammatory mediators [18]. RAR integrates these two classic parameters closely related to inflammation to form a new composite index that can more comprehensively reflect the inflammatory status of the body. Existing research has shown that RAR is significantly associated with the inflammatory processes of various diseases such as urinary incontinence and arthritis, and has become a potential prognostic indicator for evaluating mortality rates in various diseases [19-21]. However, the relationship between RAR and gallstones has not been fully studied. Based on the above background, this study conducted a cross-sectional analysis of the potential association between RAR and gallstones using NHANES data from 2017 to 2020.

1. Materials and methods

2.1 Study population

This study used data from the NHANES in the United States and selected samples from 2017 to 2020 as the research subjects (n=15,560). We first excluded individuals under the age of 20 (n=6,328), and then excluded participants with missing RAR data (n=1,354) and uncertain gallstones status (n=19), as well as participants with missing covariates (n=180). Therefore, the final sample size included in the analysis was 7,679 participants. The specific screening process is shown in Figure 1.

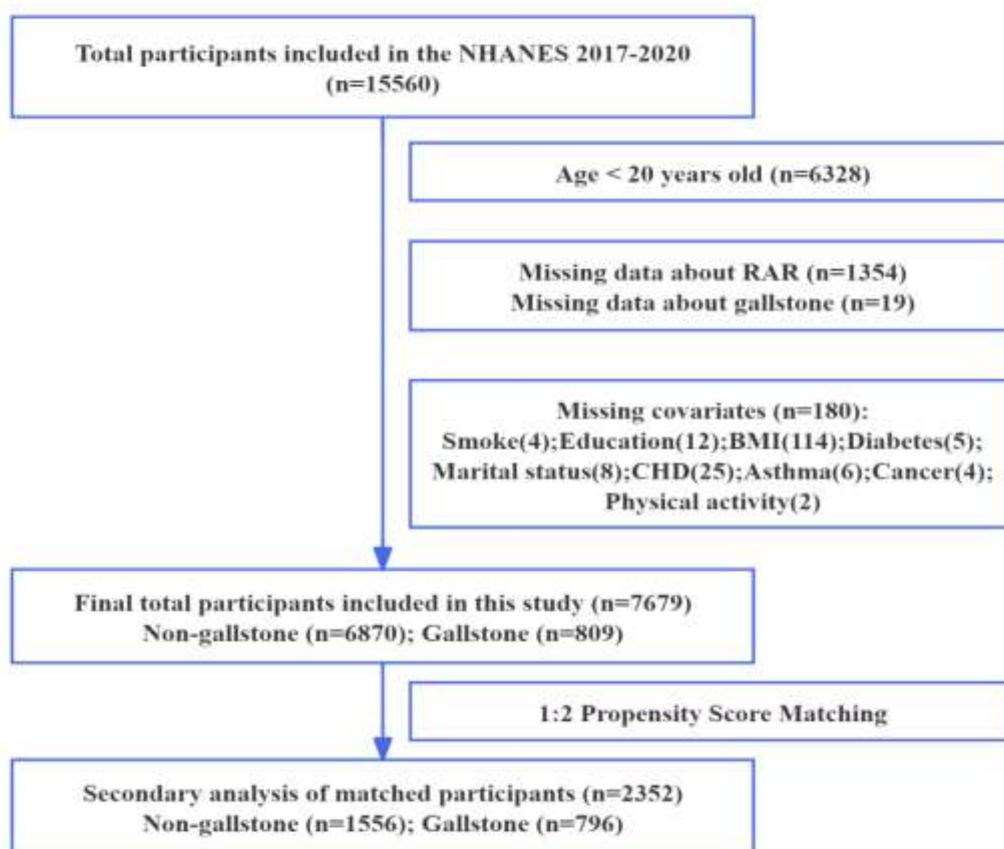

Figure 1. Flowchart of participant selection

2.2 Evaluation of RAR

RAR is the exposure variable in this study [19], calculated using the following formula:

$$\text{RAR} = \text{Red blood cell distribution width (RDW, \%)} / \text{serum albumin (g/dL)}.$$

RDW through Kurt ® The DxH 800 analyzer is obtained from peripheral blood samples and follows standardized NHANES laboratory procedures conducted at a mobile testing center. Serum albumin was measured using the bromocresol violet method, and the absorbance of the albumin bromocresol violet complex was recorded at 600 nm by spectrophotometry.

2.3 Evaluation of Gallstones

Our study focused on NHANES data from 2017 to March 2020, and participants who answered yes to the questionnaire question “Have doctors ever said you have gallstones?” were considered to have gallstones [22].

2.4 Covariance

Based on previous research, we selected several key potential covariates [23, 24], including gender, age, race (Mexican American, other race, non Hispanic white, African black) BMI ($\leq$25kg/m^2, >25kg/m^2) 、 Education, marital status, family poverty income ratio (PIR), physical activity, smoking, drinking, hypertension, diabetes, asthma, coronary heart disease and cancer. The answer to the question 'Has the doctor told you that you have hypertension?' in the questionnaire is' Yes', and participants with blood pressure readings ≥ 130/80 mmHg are classified as having hypertension. The answer "Yes" to the question "Did the doctor tell you that you have diabetes?" in the questionnaire is classified as diabetes. The classification of alcohol consumption depends on whether participants have consumed any type of alcohol in the past year. The classification of smoking status is based on the question 'Have you smoked at least 100 cigarettes in your lifetime?', and answering 'yes' is classified as a smoker. The classification of physical activity is based on the question "Does the subject engage in any moderate intensity

exercise, fitness, or leisure activity during a typical week, such as brisk walking, cycling, swimming, or volleyball, for at least 10 minutes, resulting in a slight increase in breathing or heart rate?" Answering "Yes" is classified as having physical activity.

To maximize sample size retention and reduce potential bias, this study used the missing indicator method for analysis. Specifically, we will treat missing values as a separate category of variables and include them in subsequent regression models and propensity score matching analyses to ensure the stability of model estimates and reduce information loss caused by sample exclusion. This method is widely used in dealing with the problem of missing real-world data. The missing variables include PIR (n=1,022) and alcohol consumption (n=423).

2.5 Statistical Analysis

All statistical analyses were conducted in R software (version 4.2.2) and EmpowerStats software (version 4.1). Continuous variables are expressed as mean ± standard deviation (SD), while categorical variables are expressed as frequency (%). The comparison of differences between groups is conducted using a t-test or a chi-square test. To control confounding factors and reduce selection bias, a 1:2 ratio PSM method was used to match the gallstones group with the non-gallstones group. PSM is constructed based on all covariates, and the matching algorithm selects the nearest neighbor method. The caliper width is set to 0.02. Three multivariate logistic regression models were constructed in the population before and after PSM matching to estimate the Odds Ratio (OR) and its 95% confidence interval (95% CI) between RAR and gallstones risk. Model 1: No covariates were adjusted (crude model); Model 2: Adjust for basic demographic variables (gender, age, race, BMI, education level, marital status, poverty to income ratio); Model 3: further adjust lifestyle and associated disease variables (physical activity, alcohol consumption, smoking, diabetes, hypertension, asthma, coronary heart disease, cancer). To evaluate the dose-response relationship between RAR and gallstones, the RCS function was fitted in Model 3 to test its nonlinear trend. In addition, subgroup analysis was conducted, and interaction P-values were calculated to explore the stability and heterogeneity of the relationship between RAR and gallstones in different populations. All statistical tests are two-sided tests, and $P<0.05$ is considered statistically significant.

2. Results

2.1 Baseline Characteristics of Selected Participants

This study included a total of 7,679 participants, of whom 809 were reported to have gallstones. Before PSM matching, the gallstones group had a higher average age, BMI, female proportion, heavier burden of chronic diseases, and significantly higher RAR levels than the non-gallstones group (3.631 ± 0.569 vs. 3.445 ± 0.533). After using PSM matching, a total of 1,556 non-gallstone participants and 796 gallstone patients were matched. After matching, the two groups achieved good balance on most covariates, and the differences between groups were not significant ($P>0.05$). The PSM method effectively controlled for confounding bias.

Table 1. Baseline characteristics of participants

	Pre-PSM			**Post-PSM**		
Characteristic	Non-gallstone N= 6870	Gallstone N=809	p value	Non-gallstone N=1556	Gallstone N=796	p value
Sex			<0.001			0.522
female	3393 (49.389%)	578 (71.446%)		1,124(72.237%)	565(70.980%)	
male	3477 (50.611%)	231 (28.554%)		432(27.763%)	231(29.020%)	
Age(years)	49.90 ± (17.38)	58.03 ± (15.75)	<0.001	57.410 ± (16.18)	57.780 ± (15.73)	0.755

BMI(kg/ m^2)			<0.001			0.644
>25	5003 (72.824%)	702 (86.774%)		1336 (85.86%)	689 (86.56%)	
≤25	1867 (27.176%)	107(13.226%)		220 (14.14%)	107 (13.44%)	
RAR	3.445 ± (0.533)	3.631 ± (0.569)	<0.001	3.536 ± (0.55)	3.629 ± (0.57)	<0.001
Race			<0.001			0.812
Non-Hispanic White	926 (12.059%)	818 (11.907%)		204 (13.111%)	107 (13.442%)	
Other Race	2090 (27.217%)	1891(27.525%)		414 (26.607%)	197 (24.749%)	
Non-Hispanic Black	2712 (35.317%)	2365 (34.425%)		645 (41.452%)	337 (42.337%)	
Mexican American	1951 (25.407%)	1796 (26.143%)		293 (18.830%)	155 (19.472%)	
Education			0.560			0.960
under high school	1272 (18.515%)	146 (18.047%)		284 (18.252%)	143 (17.965%)	
High school	1632 (23.755%)	206 (25.464%)		398 (25.578%)	201 (25.251%)	
above high school	3966 (57.729%)	457 (56.489%)		874 (56.170%)	452 (56.784%)	
Marital status			<0.001			0.641
Married/ Living with Partner	4009 (58.355%)	485 (59.951%)		955 (61.375%)	478 (60.050%)	
Widowed /Divorced /Separated	1482 (21.572%)	226 (27.936%)		431 (27.699%)	221 (27.764%)	
Never married	1379 (20.073%)	98 (12.114%)		170 (10.925%)	97 (12.186%)	
PIR			0.100			0.773
<1.3	1667 (24.265%)	189 (23.362%)		366 (23.522%)	186 (23.367%)	
1.3~3.5	2306 (33.566%)	305 (37.701%)		605 (38.882%)	298 (37.437%)	
≥3.5	1972 (28.705%)	218 (26.947%)		390 (25.064%)	215 (27.010%)	

Missing value	925 (13.464%)	97 (11.990%)		195 (12.532%)	97 (12.186%)	
Smoke			<0.001			0.667
yes	4037 (58.763%)	437 (54.017%)		859 (55.206%)	432 (54.271%)	
no	2833 (41.237%)	372 (45.983%)		697 (44.794%)	364 (45.729%)	
Drink			0.675			0.803
yes	5920 (86.172%)	692 (85.538%)		1321(84.897%)	681(85.553%)	
no	577 (8.399%)	67 (8.282%)		126 (8.098%)	65(8.166%)	
Missing value	373 (5.429%)	50 (6.180%)		109 (7.005%)	50(6.281%)	
Physical activity			<0.001			0.673
yes	2886 (42.009%)	285 (35.229%)		563 (36.183%)	281(35.302%)	
no	3984 (57.991%)	524 (64.771%)		993(63.817%)	515 (64.698%)	
Diabetes			<0.001			0.192
yes	1039 (15.124%)	222 (27.441%)		378 (24.293%)	213 (26.759%)	
no	5831 (84.876%)	587 (72.559%)		1178 (75.707%)	583 (73.241%)	
Hypertension			<0.001			0.111
yes	2983 (43.421%)	488 (60.321%)		879 (56.491%)	477 (59.925%)	
no	3887(56.579%)	321(39.679%)		677 (43.509%)	319 (40.075%)	
Asthma			0.100			0.609
yes	1042 (15.167%)	166 (20.519%)		299 (19.216%)	160 (20.101%)	
no	5828 (84.833%)	643 (79.481%)		1257 (80.784%)	636 (79.899%)	
CHD			<0.001			0.299
yes	270 (3.930%)	72 (8.900%)		105 (6.748%)	63 (7.915%)	
no	6600 (96.070%)	737 (91.100%)		1488 (93.252%)	728 (92.085%)	
Cancer			<0.001			0.119
yes	649 (9.447%)	142 (17.553%)		224 (14.396%)	134 (16.834%)	
no	6221 (90.553%)	667 (82.447%)		1355 (85.604%)	661 (83.166%)	

3.2 Association between RAR and Gallstones

As shown in Table 2, there is a significant positive correlation between RAR and gallstones in the three stepwise adjusted regression models for confounding factors. In Model 3, for every unit

increase in RAR, the risk of gallstones increased by 35.8% (OR=1.358; 95% CI: 1.194-1.545, P<0.001). Using the lowest quartile of RAR (Q1) as the reference group, subjects in the highest quartile of RAR (Q4) had a significantly increased risk of gallstones by 74.4% (OR=1.744, 95% CI: 1.360-2.236, P<0.001).

In the matched samples, the positive correlation between RAR and gallstones remains significant and stable. In the fully adjusted model, for every unit increase in RAR, the risk of gallstones increased by 35.7% (OR=1.357, 95% CI: 1.156-1.593, P<0.001). Quartile analysis also showed that the Q4 group had the highest risk (OR=1.794, 95% CI: 1.382-2.328, P<0.001), supporting a dose-dependent relationship between RAR and gallstones.

Table 2. The relationship between RAR and gallstone pre and post PSM.

	Model 1 OR(95%CI) p-value	Model 2 OR(95%CI) p-value	Model 3 OR(95%CI) p-value
Pre-PSM			
RAR	1.685 (1.504, 1.888) <0.001	1.455 (1.278, 1.657) <0.001	1.358 (1.194, 1.545) <0.001
RAR quartile			
Q1 2.44-3.12	Ref.	Ref.	Ref.
Q2 3.12-3.36	1.638 (1.282, 2.094) <0.001	1.245 (0.967, 1.604) 0.090	1.236 (0.960, 1.592) 0.101
Q3 3.36-3.68	2.039 (1.608, 2.585) <0.001	1.363 (1.063, 1.750) <0.015	1.303 (1.012, 1.679) 0.041
Q4 3.68-8.81	2.951 (2.351, 3.703) <0.001	1.919(1.502, 2.452) <0.001	1.744 (1.360, 2.236) <0.001
P for trend	<0.001	<0.001	<0.001
Post- PSM			
RAR	1.336 (1.149, 1.552) <0.001	1.373 (1.172, 1.609) <0.001	1.357 (1.156, 1.593) <0.001
RAR quartile			
Q1 2.44-3.20		Ref.	Ref.
Q2 3.20-3.44	1.118 (0.870, 1.436) 0.384	1.133 (0.879, 1.460) 0.336	1.122 (0.869, 1.448) 0.377
Q3 3.44-3.80	1.219 (0.954, 1.559) 0.114	1.259 (0.976, 1.622) 0.076	1.245 (0.964, 1.606) 0.0928
Q4 3.80-7.42	1.714 (1.345, 2.183) <0.001	1.822 (1.409, 2.356) <0.001	1.794 (1.382, 2.328) <0.001
P for trend	<0.001	<0.001	<0.001

Model1: no-adjusted model, adjust for none. Model2: adjusted for sex, age, race, BMI, education, marital status, PIR. Model3: adjusted for all covariates.

The RCS plot reveals the dose-response relationship between RAR and the risk of gallstones (Figure 2). Both in the original population (Figure 2A) and the post PSM population (Figure 2B), RAR showed a stable linear positive correlation with the incidence of gallstones (p-non-linear>0.05).

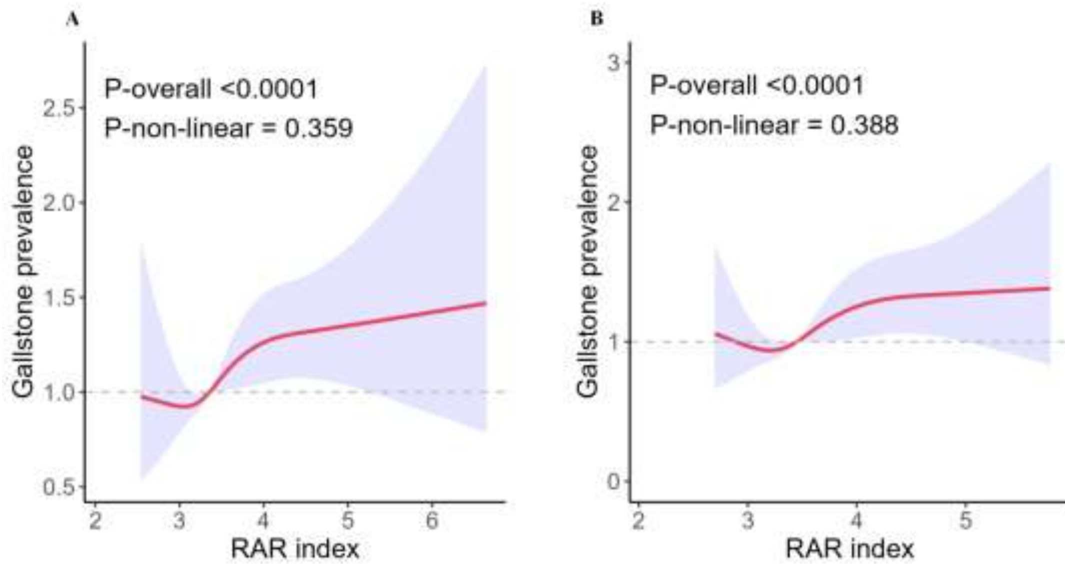

Figure 2. Dose response analysis of RAR and the prevalence of gallstone before and after PSM through RCS. A: RCS before PSM under the Model 3. B: RCS after PSM under the Model 3.

3.3 Subgroup analysis

The results showed that in terms of gender, age, and BMI, in the subgroups of smoking, hypertension, diabetes, and cancer, the positive association between RAR and gallstones was stable, and there was no significant interaction (all P for interaction > 0.05), indicating that the association had strong consistency and robustness. It is worth noting that there is a significant interaction between drinking status and physical activity level with RAR (P for interaction < 0.05) (Figure 3A, 3B). Specifically, the association between RAR and the risk of gallstones is more significant in non physically active or alcohol consuming populations, suggesting that lifestyle factors may play a regulatory role in the relationship between RAR and gallstones.

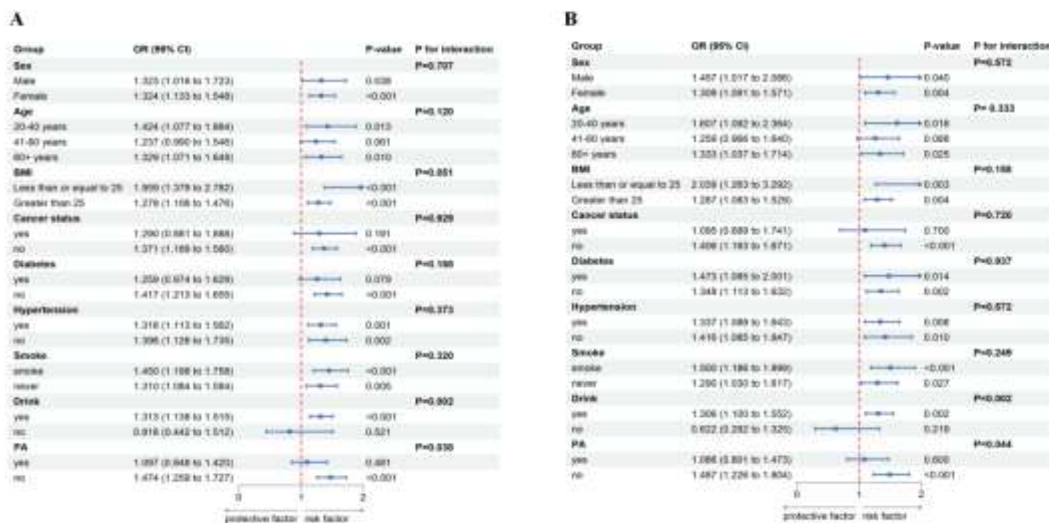

Figure 3. Relationship between RAR and gallstones before and after PSM. Notes: A stands for before PSM. B stands for after PSM.

3. Discussion

Our cross-sectional study utilized NHANES data from 2017 to 2020 and systematically evaluated that RAR is significantly positively correlated with the risk of gallstones, and this positive

correlation is stable in most subgroups. These results indicate that RAR has the potential to serve as a valuable biomarker in the risk assessment of gallstones.

This study found that an increase in RAR is associated with an increased risk of gallstones. An increase in RAR usually indicates an increase in RDW or a decrease in albumin levels. In clinical practice, an increase in RDW is often caused by ineffective red blood cell production, including iron deficiency, vitamin and folate deficiency, increased red blood cell destruction, and blood transfusion [25]. Among them, iron deficiency and vitamin D deficiency can lead to gallbladder stasis, thereby promoting the formation of gallstones [26, 27]. Meanwhile, elevated RDW is also a commonly used diagnostic indicator for iron deficiency anemia. Iron can regulate liver enzyme activity that affects cholesterol and bile salt levels, maintaining bile flow and component homeostasis. Iron deficiency leads to impaired gallbladder motility, thereby increasing the risk of gallstone formation [28, 29]. Albumin is a reliable indicator of oxidative stress, as it is in a redox state at cysteine-34 and has been proven to be a biomarker for assessing systemic oxidative load. Low levels of albumin often indicate excessive oxidative stress [30]. Oxidative stress leads to a large accumulation of reactive oxygen species, which directly interact with lipids and cholesterol in bile to form oxidized cholesterol derivatives. These oxidative compounds have lower solubility in bile and are more likely to precipitate, promoting the nucleation and growth of cholesterol crystals, leading to the formation of gallstones [31]. In addition, albumin can bind and transport free cholesterol, avoiding its accumulation in bile. Abnormal albumin metabolism exacerbates the supersaturation of cholesterol in bile, promoting the formation of gallstones [32].

The subgroup analysis results indicate that there is a significant interaction between alcohol consumption and physical activity in the association between RAR and the risk of gallstones. Existing research has shown that alcohol promotes the production of reactive oxygen species by activating cytochrome P450 enzyme activity, thereby exacerbating oxidative stress [33, 34]. Elevated levels of RAR often indicate abnormal albumin metabolism, making cholesterol more easily oxidized and promoting the formation of cholesterol crystals[35]. Alcohol induced oxidative stress further exacerbates this process, ultimately amplifying the association between RAR and gallstones. Regular exercise can promote bile clearance by enhancing gallbladder peristalsis, prevent biliary stasis, and reduce the risk of gallstones [36]. In addition, regular physical exercise can improve insulin sensitivity, reduce abdominal obesity, and effectively regulate blood lipid levels, reducing the risk of gallstone formation [37]. Lack of physical activity weakens these protective mechanisms; therefore, in groups that do not engage in physical activity, inflammation and metabolic abnormalities reflected by RAR are more likely to promote the formation of gallstones, making their association more prominent().

However, our research has some limitations. Firstly, this study is a cross-sectional design and cannot clarify the causal time sequence between RAR and gallstones. In the future, prospective cohort or intervention studies are still needed to verify the causal direction. Secondly, asymptomatic gallstones are common in the population, and the diagnosis of gallstones in studies relies on self-report, which is susceptible to recall bias and may lead to disease classification bias, diluting the true correlation strength. Finally, although this study included multidimensional confounding factors, there may still be unmeasured residual confounding factors (such as genetic susceptibility, occupational exposure), drug interventions (such as bile acid regulating drugs), and interference with the accuracy of the association.

4. Conclusion

This study suggests a significant positive correlation between RAR and the risk of gallstones, and RAR may serve as a useful tool for identifying gallstones. This discovery helps to accurately identify asymptomatic patients with gallstones in the early stages of the disease, thereby improving clinical management strategies and providing biomarker-based evidence for stratified management and precise prevention and treatment of gallstones.

Declarations

Ethics approval and consent to participate

Not applicable.

Funding:

Not applicable.

Availability of data and materials

Data available on request from the authors.

Authors' Contributions

JY and XJY contributed to the study design. DY conducted the literature search. JY、XJY ang DY acquired the data. JY performed data analysis. XJY and DY drafted. JY was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

Competing Interests

The authors declare that they have no potential conflicts of interest.

Acknowledgments

Not applicable.

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