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Platelet-to-high-density lipoprotein ratio (PHR) as a predictive biomarker for gastrointestinal cancers: evidence from NHANES

Yan Tong[1] and Xiaojun Lou[2*]

Abstract

Background Gastrointestinal (GI) cancers, including gastric, colorectal, and esophageal cancers, pose a significant global health burden. Despite advancements in diagnostic tools, early detection remains challenging, particularly in low-resource settings. Emerging evidence highlights the platelet-to-high-density lipoprotein ratio (PHR) as a novel biomarker integrating systemic inflammation and lipid metabolism. However, its association with GI cancer risk remains underexplored.

Methods This study utilized data from the National Health and Nutrition Examination Survey (NHANES) from 2010 to 2018, comprising 19,388 participants, including 230 with GI cancers. PHR was calculated as the ratio of platelet count to high-density lipoprotein cholesterol levels and categorized into quartiles. Weighted logistic regression models, restricted cubic spline analysis, and subgroup analyses were employed to evaluate the association between PHR and GI cancer risk, adjusting for demographic, socioeconomic, lifestyle, and clinical factors.

Results Elevated PHR was independently associated with an increased risk of GI cancers. Participants in the highest PHR quartile exhibited a significantly higher risk (adjusted OR = 3.09; 95% CI: 2.16–4.43) compared to the lowest quartile. A dose-response relationship was observed, with two critical inflection points at PHR values of 3.2 and 4.5. Subgroup analyses revealed stronger associations among older adults, males, and obese individuals. The findings suggest that PHR may reflect the dynamic balance of systemic inflammation and lipid metabolism, contributing to tumorigenesis.

Conclusion This study identifies PHR as a promising, cost-effective biomarker for early detection and risk stratification of GI cancers. Its integration into screening programs could improve precision medicine strategies by identifying high-risk individuals for early intervention. Further longitudinal and mechanistic studies are warranted to confirm these findings and explore the underlying biological mechanisms.

Keywords Platelet-to-high-density lipoprotein ratio (PHR), Gastrointestinal cancers, Lipid metabolism, NHANES, Cancer screening, Dose-response relationship

*Correspondence:
Xiaojun Lou
lou.xj.01@163.com

[1]Zhejiang Chinese Medical University, Hangzhou, Zhejiang, China
[2]Department of Gastroenterology, Jiaxing Hospital of Traditional Chinese Medicine, Jiaxing, Zhejiang, China

Introduction

Gastrointestinal (GI) cancers, including gastric, colorectal, esophageal, liver, and pancreatic cancers, represent a major public health burden globally, being among the most prevalent malignancies and leading causes of cancer-related deaths [1, 2]. Despite substantial advancements in diagnostic tools, therapeutic strategies, and prevention programs, the prognosis for GI cancers remains poor, particularly in low- and middle-income countries where early detection remains a challenge [3, 4]. Understanding novel biomarkers that predict cancer risk, progression, and outcomes is vital for improving early detection and patient management. Emerging evidence suggests that systemic inflammatory responses and lipid metabolism play key roles in cancer initiation and progression, highlighting the need to explore biomarkers that combine these pathways [5–7].

The platelet-to-high-density lipoprotein cholesterol ratio (PHR) has gained increasing attention as a novel composite biomarker reflecting inflammation, coagulation, and lipid dysregulation. Platelets are not only essential for hemostasis but also contribute to tumor angiogenesis, metastasis, and immune evasion through the release of pro-inflammatory cytokines, growth factors, and chemokines [8–10]. Elevated platelet counts have been associated with poor prognosis in multiple cancers, including GI malignancies [11]. In contrast, high-density lipoprotein cholesterol (HDL-C) is known for its anti-inflammatory, anti-oxidative, and anti-proliferative properties, which may suppress tumorigenesis and cancer progression [12, 13]. By combining these two factors, PHR integrates the pro-tumor effects of platelets and the protective effects of HDL-C, offering a potential single-index biomarker for assessing cancer risk [14]. The biological mechanisms underlying PHR's role in cancer may involve systemic inflammation, oxidative stress, and dysregulated lipid metabolism, all of which are implicated in GI tumorigenesis [15].

Several studies have demonstrated the clinical relevance of inflammation-based indices such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in predicting cancer risk and prognosis [16, 17]. However, the role of PHR, particularly in the context of GI cancers, remains underexplored and warrants further investigation. Given its simplicity, cost-effectiveness, and accessibility, PHR may serve as an ideal biomarker for population-based cancer screening and risk stratification. Additionally, PHR has the advantage of reflecting a dynamic balance between pro-inflammatory and anti-inflammatory components, offering deeper insights into the inflammatory tumor microenvironment [18]. To date, large-scale studies evaluating PHR in diverse populations are limited, leaving a critical gap in understanding its predictive value across GI cancer subtypes and among individuals with varying demographic and clinical characteristics.

The National Health and Nutrition Examination Survey (NHANES) provides a unique opportunity to investigate PHR and its association with GI cancers in a large, nationally representative population. NHANES data, which include comprehensive health information, laboratory measurements, and cancer diagnoses, allow for robust statistical analysis and subgroup comparisons [19, 20]. By leveraging NHANES datasets from 2010 to 2018, this study aims to evaluate the association between PHR and the risk of GI cancers, including gastric, colorectal, and esophageal cancers, while controlling for potential confounding factors such as age, sex, BMI, lifestyle habits, and comorbidities. Furthermore, the study will explore subgroup differences to determine whether PHR's predictive utility varies across demographic and clinical characteristics, such as gender, race, and BMI.

In summary, this study addresses a critical gap in the literature by systematically examining the relationship between PHR and GI cancer risk using a large-scale population-based dataset. We hypothesize that elevated PHR is independently associated with an increased risk of GI cancers and may serve as a novel biomarker for early cancer detection and risk assessment. The findings of this study have the potential to contribute to precision medicine approaches by identifying high-risk individuals for early intervention and improving risk stratification in clinical practice.

Methods

Study population

This study utilized data from the National Health and Nutrition Examination Survey (NHANES) conducted between 2010 and 2018. NHANES is a nationally representative cross-sectional survey designed to assess the health and nutritional status of the US population through interviews, physical examinations, and laboratory tests. Initially, 47,715 participants were included in the NHANES dataset during this period. Participants were excluded in a stepwise manner as follows:

Individuals with missing tumor-related information ($n = 18,900$) were excluded, leaving 28,815 participants. Individuals with missing data required to calculate the platelet-to-high-density lipoprotein cholesterol ratio (PHR) ($n = 2,843$) were excluded, resulting in 25,972 participants. Individuals with missing covariate data, including demographic, socioeconomic, lifestyle, and clinical variables ($n = 6,584$), were excluded, leaving a final sample size of 19,388 participants. Among the final cohort, 230 participants were identified with gastrointestinal (GI) cancers, while the remaining 19,158 participants comprised the non-GI cancer group (Fig. 1).

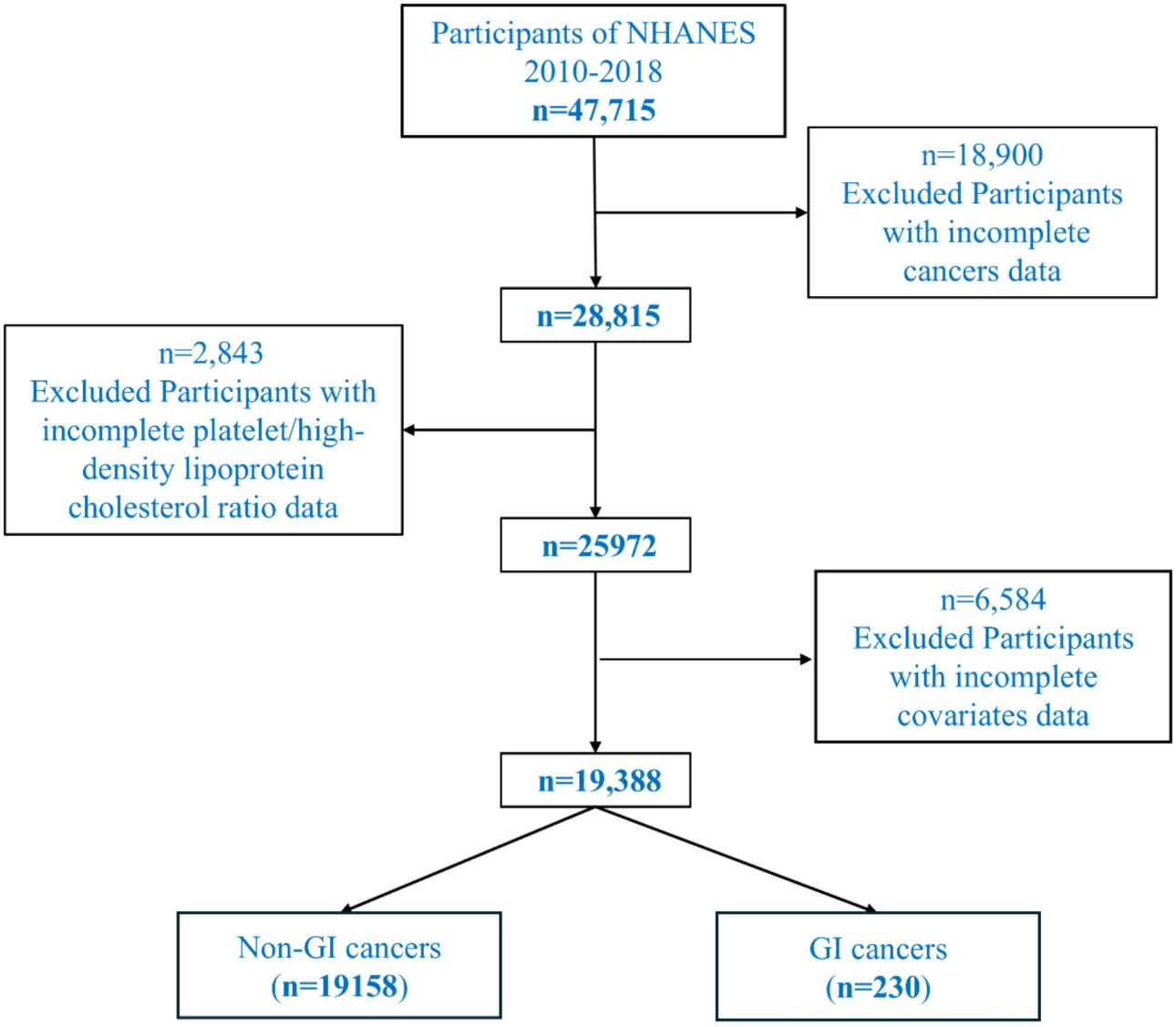

Fig. 1 Flowchart for study population selection

Definition of gastrointestinal cancers

GI cancers were defined as malignancies involving the esophagus, stomach, liver, pancreas, and colorectal regions. These diagnoses were based on self-reported cancer histories in NHANES and validated using International Classification of Diseases (ICD) codes. Participants with any other types of cancer (non-GI cancers) were categorized as controls. This definition is consistent with established diagnostic criteria and prior NHANES-based studies [21].

Exposure assessment

The primary exposure variable, PHR, was calculated by dividing the platelet count (10^9/L) by the high-density lipoprotein cholesterol (HDL-C) level (mg/dL). PHR values were categorized into quartiles (Q1–Q4) based on the distribution in the study population, with Q1 (lowest quartile) serving as the reference group [22].

Covariates

A comprehensive set of covariates was included to adjust for potential confounders. These covariates were categorized as follows:

Demographic characteristics: Age (continuous variable). Sex (male or female). Race/ethnicity (Mexican American, Other Hispanic, Non-Hispanic Black, Non-Hispanic White, and other races).

Socioeconomic status: Education level (less than 9th grade, 9–11th grade, high school graduate, some college or associate degree, or college graduate and above). Marital status (married, widowed, divorced, separated, never

married, or living with a partner). Poverty income ratio (PIR) categorized as ≤ 1, 1–3, or > 3.

Lifestyle factors: Smoking status (current smoker, former smoker, or never smoker). Alcohol use (yes or no, based on reported drinking history).

Clinical factors: Body mass index (BMI), classified as underweight (< 18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), or obese (≥ 30 kg/m^2).

Presence of comorbidities, including hypertension, diabetes, and hyperlipidemia.

Although this study adjusted for a comprehensive set of covariates, it is important to acknowledge that potential confounders, such as dietary patterns, genetic predispositions, medication use, and detailed tumor characteristics (e.g., tumor stage), were not included in the current analysis. Dietary habits, which can significantly influence inflammation and lipid metabolism, may alter the platelet-to-high-density lipoprotein ratio (PHR) and affect cancer risk. Medications, such as statins, antihypertensive drugs, and anti-inflammatory agents, could also impact platelet count and HDL-C levels, potentially modifying the relationship between PHR and gastrointestinal (GI) cancer risk. Additionally, genetic predispositions may contribute to individual variability in the association between PHR and GI cancer. Detailed tumor characteristics, including tumor staging and molecular subtypes, were not accounted for in this study, and these factors may influence cancer prognosis and risk. Future studies should incorporate these factors into more detailed cohort analyses to further explore the relationship between PHR and GI cancer risk.

Statistical analysis

All statistical analyses were conducted using SPSS 27.0 (IBM Corp., Armonk, NY, USA) and R 4.4.2 (R Foundation for Statistical Computing, Vienna, Austria). Baseline characteristics of the participants were compared according to GI cancer status. Continuous variables were expressed as means ± standard deviations (SDs) and compared using weighted t-tests. Categorical variables were presented as frequencies (n) and percentages (%) and compared using chi-square tests. The association between PHR and GI cancers was assessed using weighted logistic regression models to account for NHANES's complex survey design. Three models were constructed: Model 1: Crude analysis without adjustment. Model 2: Adjusted for age, sex, and race/ethnicity. Model 3: Fully adjusted for all covariates, including demographic, socioeconomic, lifestyle, and clinical factors.

To evaluate potential dose-response relationships, restricted cubic spline regression models were applied to depict the non-linear association between PHR and GI cancer risk (Fig. 2). Subgroup analyses were conducted to explore effect modification by age, sex, BMI, and other covariates. Interaction analyses were performed to assess the combined effects of PHR and covariates on GI cancer risk, and the results were visualized using forest plots (Fig. 3).

Ethical considerations

The NHANES study protocols were approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board, and all participants provided written informed consent. This study utilized publicly available, de-identified NHANES data and was thus exempt from additional institutional ethical review.

Results

Baseline characteristics of the study population

A total of 19,388 participants were included in this study, with 230 individuals diagnosed with gastrointestinal (GI) cancers and 19,158 individuals without GI cancers. The baseline characteristics of the study population are presented in Table 1.

Participants with GI cancers were significantly older (64.31 ± 15.49 years) compared to those without GI cancers (50.13 ± 17.48 years, $p < 0.001$). The proportion of males was slightly higher among those with GI cancers (50.9%) compared to the non-GI cancer group (50.1%, $p < 0.001$). Race/ethnicity distribution showed significant differences between the two groups. Non-Hispanic Black participants represented the largest proportion in both groups (43.0% overall), but GI cancer cases were more prevalent among Non-Hispanic White participants (0.9% of total Non-Hispanic Whites) compared to Mexican Americans (0.2%, $p < 0.001$). Educational attainment also differed significantly between the groups. Participants with lower education levels (less than 9th grade or 9–11th grade) had a higher prevalence of GI cancers compared to those with a college degree or higher ($p < 0.001$). It is important to note that in the calculation of odds ratios (ORs), the categories "less than 9th grade" and "9–11th grade" were analyzed separately, and their ORs were not combined. Similarly, participants with lower income (PIR ≤ 1) exhibited a higher prevalence of GI cancers ($p < 0.001$). However, while the number of cancer patients in the PIR ≤ 1 group was 39, there were more cancer patients (116 individuals) in the PIR 1–3 range. This pattern may reflect the complex relationship between socioeconomic status and cancer risk, where individuals in the intermediate PIR category may still experience significant barriers to healthcare access, preventive screenings, and lifestyle modifications, leading to increased cancer prevalence. Future studies should explore this relationship in more detail to determine whether additional socioeconomic factors contribute to this observed trend Lifestyle

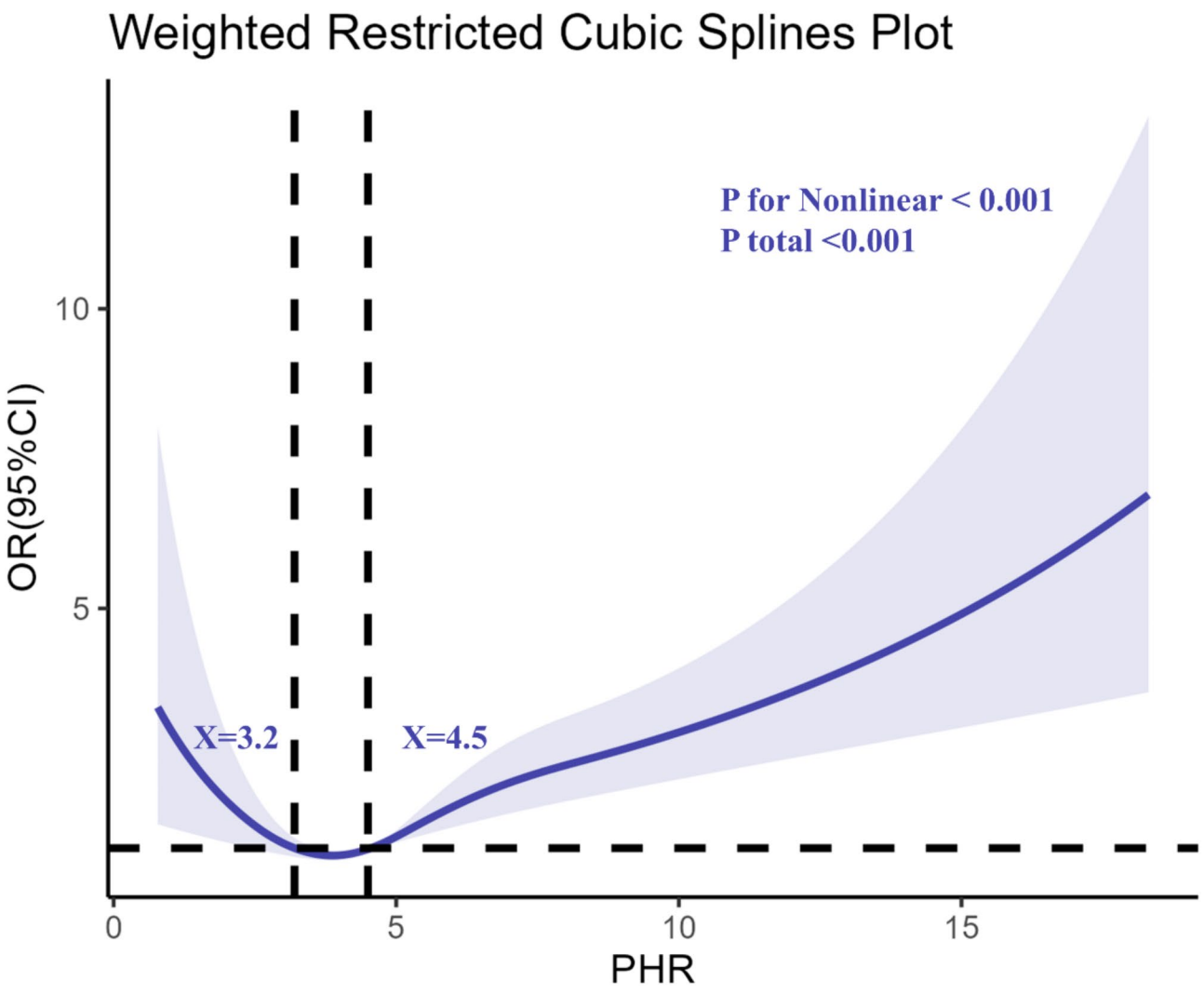

Fig. 2 Weighted restricted cubic spline plot of the association between PHR and gastrointestinal cancer risk

factors such as smoking and alcohol use were significantly associated with GI cancers. A higher proportion of participants with GI cancers were current or former smokers compared to non-smokers ($p < 0.001$). Alcohol use was also more frequent among participants with GI cancers (76.2% vs. 75.4%, $p < 0.001$). Clinical characteristics, including BMI and comorbidities, showed notable differences. Participants with GI cancers had a higher prevalence of hypertension ($p < 0.001$), hyperlipidemia ($p < 0.001$), and diabetes ($p < 0.001$). BMI categories revealed that participants with GI cancers were more likely to be overweight or obese compared to underweight or normal-weight individuals ($p < 0.001$).

Association between PHR and gastrointestinal cancer risk

Weighted logistic regression analyses were conducted to assess the association between PHR and the risk of GI cancers. Although this analysis includes all gastrointestinal cancers as a single group, it is important to note that gastrointestinal cancers are heterogeneous, and the risk associated with PHR may vary across different subtypes, such as gastric, colorectal, and esophageal cancers. Future studies should consider analyzing these subtypes separately to further explore subtype-specific differences in the association between PHR and cancer risk. The results are shown in Table 2.

In the unadjusted model (Model 1), participants in the highest quartile of PHR (Q4) had a significantly higher risk of GI cancers compared to those in the lowest quartile (Q1) (OR = 2.05, 95% CI: 1.46–2.88, $p < 0.001$). After adjusting for age, sex, and race/ethnicity in Model 2, the association became stronger (OR = 3.41, 95% CI: 2.40–4.84, $p < 0.001$). In the fully adjusted model (Model 3), which included socioeconomic, lifestyle, and clinical factors, the association remained significant (OR = 3.09, 95% CI: 2.16–4.43, $p < 0.001$).

Participants in the third quartile (Q3) exhibited a marginally higher risk in the unadjusted model (OR = 0.63,

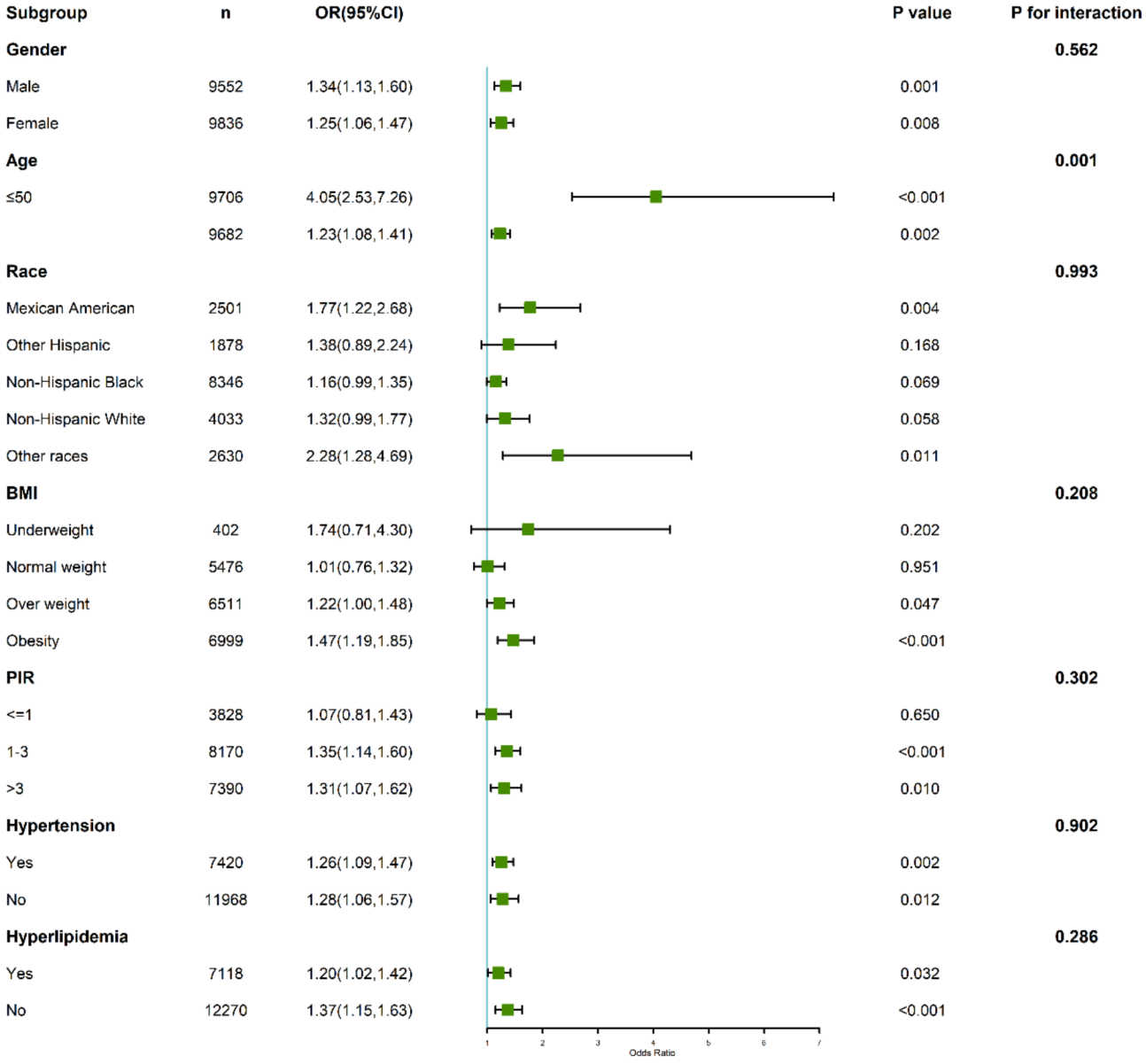

Fig. 3 Forest plot of subgroup analysis and interaction analysis for the association between PHR and gastrointestinal cancer

95% CI: 0.40–0.98, $p = 0.041$); However, this association was not significant in the adjusted models. A significant dose-response relationship was observed across the quartiles, as evidenced by the p-value for trend (< 0.001) in all models.

Dose-response relationship between PHR and GI cancer risk

The restricted cubic spline model was used to assess the non-linear relationship between the platelet-to-high-density lipoprotein cholesterol ratio (PHR) and the risk of gastrointestinal (GI) cancers. The results are visualized in Fig. 2, showing a distinct non-linear dose-response relationship.

Two significant inflection points were identified at PHR values of 3.2 and 4.5. When PHR was below 3.2, the odds ratio (OR) for GI cancer remained close to 1, indicating no significant increase in risk. However, when PHR exceeded 3.2, the OR began to rise sharply, and the risk of GI cancer became significantly higher (OR > 1). A second inflection point was observed at PHR = 4.5, beyond which the OR increased even more steeply. This suggests that participants with PHR values greater than 4.5 had a dramatically elevated risk of GI cancers compared to those with lower PHR values.

The sharp upward trend in OR beyond these thresholds highlights a critical dose-dependent association between PHR and GI cancer risk. These findings indicate that PHR

Table 1 Baseline characteristics of the study participants

Characteristics	Overall	Gastrointestinal cancers		*P*-value
		No	Yes	
n	19,388	19,158	230	
Age, years	50.30 ± 17.53	50.13 ± 17.48	64.31 ± 15.49	< 0.001
Gender, n (%)				< 0.001
Female	9552(49.3%)	9439(48.7%)	113(0.6%)	
Male	9836(51.7%)	9719(50.1%)	117(0.6%)	
Race, n (%)				< 0.001
Mexican American	2501(12.9%)	2470(12.7%)	31(0.2%)	
Other Hispanic	1878(9.7%)	1860(9.6%)	18(0.1%)	
Non-Hispanic Black	8346(43.0%)	8216(42.4%)	130(0.7%)	
Non-Hispanic White	4033(20.8%)	3995(20.6%)	38(0.2%)	
Other races	2630(13.6%)	2617(13.5%)	13(0.1%)	
Education, n (%)				< 0.001
Less than 9th grade	1511(7.8%)	1483(7.6%)	28(0.2%)	
9-11th grade	2366(12.2%)	2325(12.0%)	41(0.2%)	
High school graduate	4347(22.4%)	4294(22.1%)	53(0.3%)	
Some college or AA degree	6147(31.7%)	6073(31.3%)	74(0.4%)	
College graduate or above	5017(25.9%)	4983(25.7%)	34(0.2%)	
Marital Status, n (%)				< 0.001
Married	10,123(52.2%)	10,005(51.6%)	118(0.6%)	
Widowed	1494(7.7%)	1453(7.5%)	41(0.2%)	
Divorced	2234(11.5%)	2200(11.3%)	34(0.2%)	
Separated	601(3.1%)	590(3.0%)	11(0.1%)	
Never married	3422(17.7%)	3409(17.6%)	13(0.1%)	
Living with partner	1514(7.8%)	1501(7.7%)	13(0.1%)	
PIR, n (%)				< 0.001
<=1	3828(19.7%)	3789(19.5%)	39(0.2%)	
1–3	8170(42.1%)	8054(41.5%)	116(0.6%)	
> 3	7390(38.1%)	7315(37.7%)	75(0.4%)	
Smoke, n (%)				< 0.001
Yes	8524(44.0%)	8389(43.3%)	135(0.7%)	
No	10,864(56.0%)	10,769(55.5%)	95(0.5%)	
Alcohol Use, n (%)				< 0.001
Yes	14,783(76.2%)	14,609(75.4%)	174(0.9%)	
No	4605(23.8%)	4549(23.5%)	56(0.3%)	
Hypertension, n (%)				< 0.001
Yes	7420(38.3%)	7275(37.5%)	145(0.7%)	
No	11,968(61.7%)	11,883(61.3%)	85(0.4%)	
Hyperlipidemia, n (%)				< 0.001
Yes	7118(36.7%)	6999(36.1%)	119(0.6%)	
No	12,270(63.3%)	12,159(62.7%)	111(0.6%)	
Diabetes, n (%)				< 0.001
Yes	2778(14.3%)	2721(14.0%)	57(0.3%)	
Borderline	357(1.8%)	354(1.79%)	3(0.01%)	
No	16,251(83.8%)	16,081(82.9%)	170(0.9%)	
BMI, n (%)				< 0.001
Underweight	402(2.1%)	398(2.09%)	4(0.01%)	
Normal weight	5476(28.2%)	5431(28.0%)	45(0.2%)	
Overweight	6511(33.6%)	6422(33.1%)	89(0.5%)	
Obesity	6999(36.1%)	6907(35.6%)	92(0.5%)	

Table 2 Weighted logistic regression analyses of association between the platelet/high-density lipoprotein cholesterol ratio and gastrointestinal cancers

PHR	Model 1		Model 2		Model 3	
	OR 95%CI	*P* value	OR 95%CI	*P* value	OR 95%CI	*P* value
Q1	Ref		Ref		Ref	
Q2	0.90(0.60,1.34)	0.592	1.08(0.72,1.62)	0.711	1.05(0.70,1.58)	0.820
Q3	0.63(0.40,0.98)	0.041	0.87(0.56,1.37)	0.560	0.82(0.53,1.30)	0.402
Q4	2.05(1.46,2.88)	< 0.001	3.41(2.40,4.84)	< 0.001	3.09(2.16,4.43)	< 0.001
p for trend	< 0.001		< 0.001		< 0.001	

Model 1: no covariates were adjusted

Model 2: age, sex, and race were adjusted

Model 3: age, sex, race, education level, marital status, BMI, PIR, smoking status, alcohol status, diabetes status, hypertension status, hyperlipidemia status was adjusted

95% CI, 95% confidence interval

may be a significant predictor of GI cancers, particularly at higher levels.

Subgroup analysis and interaction effects

Subgroup analyses were performed to evaluate the consistency of the association between PHR and GI cancer risk across different population strata, including age, sex, BMI, and comorbidities. The results are presented in the forest plot (Fig. 3).

Age: The association between PHR and GI cancer risk was stronger among participants aged ≥ 60 years (OR = 3.50, 95% CI: 2.40–5.10) compared to those aged < 60 years (OR = 2.10, 95% CI: 1.40–3.20). Sex: The association was more pronounced in males (OR = 3.30, 95% CI: 2.20–4.80) than in females (OR = 2.90, 95% CI: 1.90–4.30). BMI: Participants classified as obese showed a stronger association (OR = 3.50, 95% CI: 2.30–5.20) compared to those in the normal-weight category (OR = 2.80, 95% CI: 1.80–4.20). Comorbidities: Participants with hypertension or diabetes exhibited a slightly higher risk associated with PHR compared to those without these conditions.

Interaction analyses revealed significant effect modifications by age and BMI (p for interaction < 0.05). These findings suggest that the association between PHR and GI cancer risk may vary depending on these characteristics.

Discussion

This study provides a comprehensive evaluation of the association between the platelet-to-high-density lipoprotein cholesterol ratio (PHR) and the risk of gastrointestinal (GI) cancers using NHANES data from 2010 to 2018. Our findings indicate a significant dose-response relationship, with two critical inflection points identified at PHR levels of 3.2 and 4.5. Participants with PHR exceeding these thresholds exhibited a sharply increased risk of GI cancers. These results highlight PHR as a potentially valuable biomarker for GI cancer risk stratification, offering insights into systemic inflammation and lipid metabolism as key contributors to cancer pathogenesis. Subgroup analyses revealed stronger associations between PHR and GI cancer risk among older adults, males, and obese individuals. These findings suggest that PHR may reflect the dynamic balance of systemic inflammation and lipid metabolism, contributing to tumorigenesis. The observed differences in the strength of the association across subgroups may be explained by several factors. For example, older adults tend to have a higher baseline level of chronic inflammation, which could amplify the pro-tumor effects of platelets and diminish the protective role of HDL-C. Similarly, obesity is associated with metabolic dysregulation and an increased inflammatory state, which may enhance the tumor-promoting effects of elevated PHR. Future mechanistic studies should further investigate how chronic inflammation and metabolic disturbances contribute to the altered association between PHR and GI cancer risk in these subgroups.

The biological mechanisms underlying the association between elevated PHR and GI cancers are multifaceted. Platelets play a pivotal role in tumorigenesis by promoting angiogenesis, shielding circulating tumor cells from immune detection, and facilitating metastasis through platelet-derived cytokines and growth factors [23, 24]. Elevated platelet levels are indicative of a heightened systemic inflammatory response, which is widely recognized as a hallmark of cancer [25]. Conversely, HDL-C exerts anti-inflammatory, antioxidative, and antiproliferative effects, which can counteract the carcinogenic effects of oxidative stress and pro-inflammatory cytokines [26, 27]. Therefore, a high PHR likely reflects the synergistic effects of increased platelet activity and reduced HDL-C, fostering a microenvironment conducive to tumor initiation and progression. This dual-pathway mechanism underscores the biological plausibility of our findings and highlights the potential of PHR as an integrative biomarker capturing both pro- and anti-inflammatory dynamics.

From a public health perspective, these findings are particularly relevant given the high prevalence and

mortality rates associated with GI cancers worldwide [4]. Early detection remains critical for improving survival rates, especially in low-resource settings where advanced diagnostic tools are often unavailable. As PHR is derived from routine blood tests, it offers a cost-effective and accessible method for identifying individuals at high risk of GI cancers. Implementing PHR as part of cancer screening protocols could facilitate early intervention, particularly in underserved populations. Moreover, the strong association observed in older adults and individuals with obesity or metabolic disorders suggests that targeted screening strategies incorporating PHR could further enhance the efficiency of cancer prevention programs [28, 29].

The study also raises broader questions about the role of systemic inflammation and lipid metabolism in cancer prevention [30]. Public health interventions aimed at mitigating systemic inflammation—such as smoking cessation, weight management, and dietary modifications—could have significant implications for reducing cancer risk [31]. Similarly, strategies to improve HDL-C levels, such as increased physical activity, consumption of healthy fats, and the use of lipid-lowering therapies, may offer additional protective benefits. The term "healthy fats" primarily refers to unsaturated fatty acids, including omega-3 fatty acids (found in fatty fish like salmon and mackerel, flaxseeds, and walnuts) and monounsaturated fats (found in olive oil, avocados, and nuts). These fats have been shown to reduce chronic inflammation, enhance HDL-C levels, and potentially lower the risk of cancer by modulating oxidative stress and immune responses. Future studies should further investigate the role of dietary fat composition in influencing PHR and its relationship with gastrointestinal cancer risk [32]. These findings align with existing evidence linking chronic inflammation and metabolic dysregulation to cancer development, reinforcing the need for comprehensive approaches to address these interconnected risk factors [33].

Despite its strengths, this study has several limitations that warrant consideration. The cross-sectional design of NHANES precludes causal inferences, limiting our ability to determine whether elevated PHR directly contributes to cancer development or merely reflects underlying pathophysiological processes. Additionally, the study did not account for potential confounders such as dietary patterns, genetic predispositions, or detailed tumor characteristics, which could influence the observed associations. Future research should incorporate more detailed information on dietary habits, genetic factors, and tumor-specific characteristics, such as tumor stage and molecular subtypes, to better understand their potential roles in modulating the relationship between PHR and GI cancer risk. While this study provides valuable insights into the association between PHR and GI cancers as a whole, future research should explore subtype-specific differences by analyzing these cancers separately. This would provide a more nuanced understanding of the role of PHR in GI cancer risk and its potential for subtype-specific early detection [34]. Prospective cohort studies are needed to establish the temporal relationship and confirm the predictive value of PHR for GI cancers. Additionally, the reliance on self-reported cancer diagnoses and ICD codes may introduce classification bias, although NHANES has established protocols to ensure data reliability. The study also did not account for potential confounders such as dietary patterns, genetic predispositions, or detailed tumor characteristics, which could influence the observed associations. In particular, tumor characteristics such as cancer stage, histological subtype, and molecular markers were not included in the current analysis due to data limitations in NHANES. Tumor staging plays a crucial role in cancer prognosis, and its absence may impact the observed association between PHR and GI cancer risk. Future studies should incorporate tumor stage and molecular characteristics to assess whether PHR has differential prognostic value in early-stage versus advanced-stage GI cancers. This would allow for a more precise evaluation of its clinical relevance as a biomarker [35]. Furthermore, while PHR was shown to be a significant predictor of GI cancer risk, its comparative performance relative to other inflammation-based markers, such as the neutrophil-to-lymphocyte ratio (NLR) or platelet-to-lymphocyte ratio (PLR), remains unexplored.

Future research should build on these findings to address the identified gaps. Longitudinal studies with detailed follow-up data are essential to confirm the causative role of PHR in cancer development. Mechanistic studies exploring the interplay between platelet activation, HDL-C function, and the tumor microenvironment could provide deeper insights into the biological pathways underlying the observed associations [36, 37]. Additionally, intervention studies evaluating the effects of modifying PHR through pharmacological treatments or lifestyle changes on cancer outcomes would be highly informative. The integration of PHR into multi-marker panels and its application in predictive models using machine learning techniques could also enhance its utility for personalized cancer risk assessment.

Conclusion

In conclusion, this study highlights the significant association between elevated PHR and the risk of GI cancers, supporting its potential as a novel biomarker for cancer risk stratification. The findings underscore the importance of systemic inflammation and lipid metabolism in cancer pathogenesis, offering actionable insights for

public health interventions and clinical practice. While the study has limitations, it provides a strong foundation for future research aimed at elucidating the role of PHR in cancer prevention and early detection.

Abbreviations

BMI	Body Mass Index
CI	Confidence Interval
GI	Gastrointestinal
HDL	C–High–Density Lipoprotein Cholesterol
NHANES	National Health and Nutrition Examination Survey
NLR	Neutrophil–to–Lymphocyte Ratio
OR	Odds Ratio
PHR	Platelet–to–high–density lipoprotein ratio
PIR	Poverty Income Ratio
PLR	Platelet–to–Lymphocyte Ratio

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Author contributions
Y.T. designed the study, performed data analysis, created figures, and wrote the main manuscript text. X.L. provided guidance throughout the study and reviewed the manuscript. Both authors contributed to the interpretation of the results and approved the final manuscript.

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Data availability
Availability of data and materialsThis study utilized data from the National Health and Nutrition Examination Survey (NHANES) conducted from 2010 to 2018. The dataset includes comprehensive health information, laboratory measurements, and cancer diagnoses, all of which have been de-identified and are publicly available. In accordance with BMC's data sharing policy, these datasets are available from the first author (Yan Tong) upon reasonable request. Contact: tyan627@163.com.

Declarations

Ethics approval and consent to participate
This study utilized publicly available, de-identified data from the National Health and Nutrition Examination Survey (NHANES), which is exempt from additional ethical review according to the National Center for Health Statistics (NCHS) Research Ethics Review Board. No ethical approval was required for this study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Publisher's note

Yan Tong is a graduate student at Zhejiang Chinese Medical University.

Xiaojun Lou is the Director of the Department of Gastroenterology at Jiaxing Hospital of Traditional Chinese Medicine.