Association between platelet-to-lymphocyte ratio and serum prostate specific antigen

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Abstract. There is evidence that the systemic inflammatory response may have an impact on prostate-specific antigen (PSA) levels. However, the relationship between the platelet-to-lymphocyte ratio (PLR) and PSA remains unclear. As a result, the relationship between PLR and PSA using the National Health and Nutrition Examination Survey (NHANES) database was examined. After the screening, 6,638 participants out of 52,186 in the NHANES survey conducted between 2001 to 2010 were suitable for the present study. The PLR was the independent variable in the present study, and PSA was the dependent variable. The selected subjects in the present study had an average age of 58.563±11.848 years. After controlling for covariates, the results showed that with every increase in PLR, the PSA concentration increased by 0.004 ng/ml (0.001, 0.007). This difference was statistically significant. Furthermore, a smoothing curve based on a fully adjusted model was created to investigate the possibility of a linear relationship between PLR and PSA concentration in men from USA. In men from USA, an independent and positive correlation between PLR and PSA was identified, which could potentially result in overdiagnosis of asymptomatic prostate cancer in populations with higher PLR levels.

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Abbreviations: PSA, prostate-specific antigen; PLR, platelet-to-lymphocyte ratio; NHANES, National Health and Nutrition Examination Survey; PCa, prostate cancer; SII, systemic immune inflammatory index; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; CSPCa, clinically significant PCa; CDC, Center for Disease Control; OS, overall survival

Key words: PSA, PLR, NHANES, PCa, smoothing curve fitting

Introduction

Prostate cancer (PCa) was the second-most common cause of cancer-related fatalities in humans in 2020 and the most common cancer in men (1). The most recognized biomarker for the early identification of PCa is serum prostate-specific antigen (PSA). PSA is highly specific for PCa. The widespread use of PSA testing has increased the detection rate of asymptomatic PCa, defined as highly differentiated PCa (2). Although there are more alternatives for the early diagnosis of PCa thanks to the development of new biomarkers including SelectMDx, ConfirmMDx, Pca3, MIPS, ExoDX and mpMRI, PSA testing remains the most widely used screening tool due to its favorable affordability and applicability (3). Most recently, the United States Preventive Services Task Force recently updated their guidelines, which upgraded the PSA recommendation level from a D as a screening-based level to a C as an advocate for personal screening (4,5). However, several studies have demonstrated that PSA concentrations may be influenced by additional factors that may help to cause bias in identifying PCa (6-8). Overdiagnosis or under-diagnosis affected by numerous factors, may result in inappropriate and unnecessary therapy (9). Therefore, screening PCa based on PSA concentration still has certain problems to be solved (10).

Inflammation is one of the most significant and well-known variables influencing cancer development (11). Hematological indicators that can indicate the state of the immune-inflammatory response in patients with cancer have recently received increasing attention (12,13). Systemic immune inflammatory index (SII), C-reactive protein (CRP) levels, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are some of these measures. Because NLR and PLR are readily available and inexpensive, they have been extensively examined in several malignancies (14-16). PLR is a systemic parameter based on inflammation. Previous research has explored the diagnostic function of PLR in patients with PCa; however, findings remain inconclusive. Yuksel *et al* (17) found that PLR may distinguish between benign prostatic hyperplasia and PCa, ultimately serving as a diagnostic tool for PCa. Conversely, Lee *et al* (18) determined that pre-biopsy PLR is not predictive of clinically significant PCa (CSPCa),

and thus, does not provide diagnostic value for PLR. Indeed, there may be some correlation between PLR and PSA metabolism, which may lead to detection bias in PCa diagnosis. Furthermore, to the best of the authors' knowledge, it was found that this phenomenon has never been reported before.

Consequently, a secondary data analysis was performed on the National Health and Nutrition Examination Survey (NHANES) data. After controlling for a large number of influencing factors, it was sought to clarify the relationship between PLR and PSA concentration in men without PCa in the USA.

Materials and methods

Data availability. Since 1960, the NHANES, which is designed to estimate the health and nutritional status of adults and children in the US, has been conducted by the National Center for Disease Control (CDC) and the Prevention National Center for Health Statistics. Demographic and methodological details can be found on the NHANES website (www.cdc.gov/nchs/nhanes, accessed on October 7, 2022). The National Center approved the NHANES protocols for the Health Statistics Research Ethics Review Board.

Study population. The NHANES uses a stratified, multi-stage random sampling design and is a nationally representative nutrition survey of the general USA population. Five cycles of NHANES data from 2001 to 2010 were integrated into the present study. The data used for the second analysis included PSA concentrations, socio-demographic data and laboratory data. Participants were excluded from the present study based on the following exclusion criteria: i) Participants diagnosed with PCa (n=377); ii) missing PSA (n=44,412); iii) missing PLR (n=34); iv) factors affecting PSA concentration: Diagnosed with prostatitis, stain drug user, received prostate biopsy within one week and had urinary system surgery within one month (n=284); and v) Age <40 years (n=441). After screening, 6,638 out of 52,186 participants were suitable for the present study after thorough screening (Fig. 1). It is important to note that the present study was a survey regarding the relationship between a specific clinical indicator and PSA in the general male population in USA. Patients with PCa which have significantly different PSA levels compared with the general population and patients with PCa should be excluded as a confounding factor affecting PSA (19,20). In addition, the present study complied with the Declaration of Helsinki of the World Medical Association in the design and conduct of the present study. In the present study, data analysis based on NHANES was utilized.

Statistical analysis. All statistical analyses were performed using Package R and EmpowerStats (http://www.empowerstats.com), with a complex weighted sampling design from NHANES. Participants were characterized according to the quartiles of PLR (Category 1: 2.252-96.116; Category 2: 96.116-122.198; Category 3: 122.198-156.667; Category 4: >156.667). Percentages were used for categorical variables and mean ± standard deviation for continuous variables. For comparing the differences between groups, categorical and continuous variables were analyzed by using weighted χ^2 tests and linear regression models, respectively. The link between PLR and PSA was assessed using a weighted multivariate linear regression model. An unadjusted model (Model 1) was created first, and then a minimally adjusted model (Model 2) was constructed after adjusting for age, family income, ethnicity, military status, marital status and education. Finally, fully adjusted models (Model 3) were calculated after adjusting for age, household income, ethnicity, military status, marital status, education, monocyte count, neutrophil count, platelet count, lymphocyte-to-monocyte ratio (LMR) and systemic immune inflammation index. The analysis was then stratified by age, family income, ethnicity, military status, marital status and education and tested for interactions. In the present study, a $P<0.05$ was considered to indicate a statistically significant difference.

Results

Baseline characteristics of participants. The weighted distribution of baseline characteristics is shown in Table I, including socio-demographic data and laboratory data of chosen participants selected from the NHANES (2001-2010) survey. In the present study, the average age of the chosen participants was 58.563±11.848 years. Then, different PLR were divided into four quartiles (Q1-Q4). The distribution of neutrophil and basophil count in Q1-Q4 of PLR revealed no statistical difference ($P>0.05$). Compared with the different groups in Table I, the distribution of PLR demonstrated an age difference, where aged participants had higher PLR than younger ones, had higher family income, higher platelet count, higher C-reactive protein, higher NLR, higher systemic immune inflammation index and were more likely to have a higher education level. On the other hand, participants with more elevated PLR had lower leukocyte count, lower mononuclear count, lower eosinophil count, lower red cell count, lower hemoglobin and lower LMR. In the present study, non-Hispanic whites were the main participants.

The connection between PSA concentrations and serum PLR. The results of the univariate and multivariate analyses by the weighted linear model are presented in Table II. In the non-adjusted model, PSA concentrations increased by 0.003 ng/ml (0.002, 0.004) with each increase in PLR, with a statistically significant trend indicated by a $P<0.001$. After minimal adjustment for age, household income, ethnicity, military status, marital status and education, PSA concentration increased by 0.002 ng/ml (0.001, 0.003) with each increase in PLR, with a statistically significant trend indicated by a $P<0.001$. The fully adjusted model that adjusts for age, family income, ethnicity, military status, marital status, education, mononuclear count, neutrophils count, platelet count, LMR and SII indicated that the PSA concentrations were increased by 0.004 ng/ml (0.001, 0.007) with each increase in PLR, with a statistically significant trend indicated by a $P<0.004$.

Stratified associations between PSA concentrations and PLR. As demonstrated in Table III, a stratified analysis was conducted by age, ratios of family income, ethnicity, military status, marital status and education to assess the

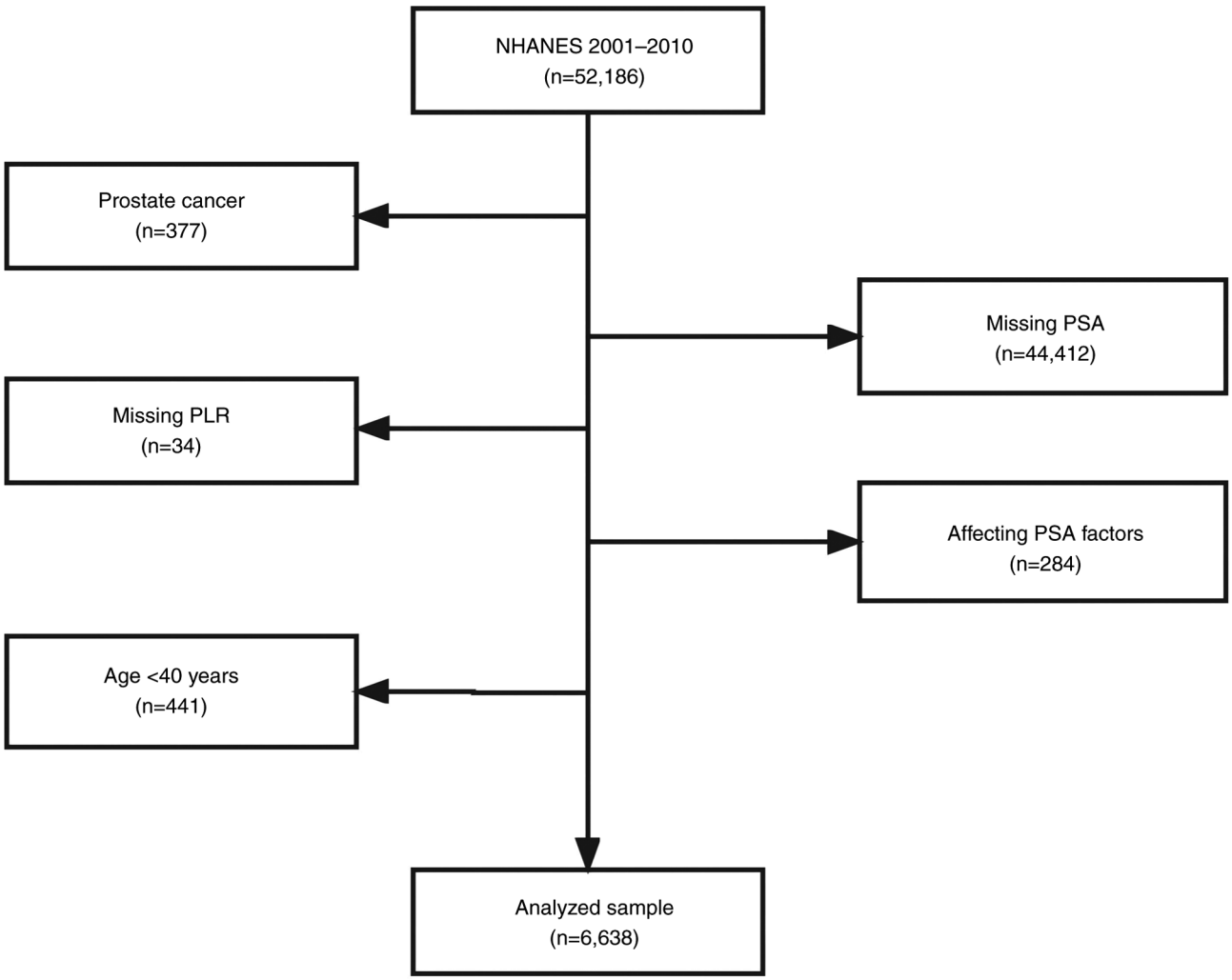

Figure 1. Flowchart in selecting the studying participants.

associations between PLR and PSA concentrations. It is likely that those aged >80 years, a low group of ratios of family income, those who had not served in the military, had married, had an education level less than 9th grade and had higher PSA concentrations, with increasing PLR displaying a significant trend (p for trend=0.0148, p for trend=0.0027, p for trend=0.0192, p for trend=0.0373 and p for trend=0.0003). However, no interactive effects were observed.

Identification of sensitivity analysis. A sensitivity analysis was conducted to confirm the accuracy and stability of the results. First, the PLR was converted as a continuous variable to the categorical variable in the quartile value, and then the P-value was calculated for the trend (Table II). Surprisingly, the result of the categorical variable was consistent with the effect of the PLR as a continuous variable. A smooth curve was constructed based on the fully adjusted model to investigate the possible linear relationship between the PLR and PSA concentrations. According to the fully adjusted model, there was a linear relationship between PLR and PSA concentration after adjusting for other covariates (Fig. 2). The results revealed that for each increase in PLR, the PSA concentrations were elevated by 0.004 ng/ml. These results indicated a positive association between PLR and PSA concentrations.

Discussion

PLR and PSA exhibited a favorable connection in the present study. To the best of the authors' knowledge, the present study is the first to examine and discover this link among men from USA without a history of cancer using the NHANES database. Although PLR and PSA have been studied previously, an association between them has not been discovered, and previous studies have suffered from small sample sizes and missing data (21). Accordingly, the connection between PLR and PSA necessitates additional research to clarify their relationship. Therefore, it is essential to further comprehend the individual variability in PSA concentrations that may emerge from PLR to prevent the bias of PSA testing during the diagnosis of prostate-related disorders. The present study population was drawn from NHANES (2001-2010), excluding 45,548 ineligible participants. The results of the present study revealed that with every increment of PLR, the PSA concentration increased by 0.004 ng/ml, which means that if the PLR increased by 100, the PSA concentration would increase by 0.4 ng/ml. Sensitivity analysis confirmed the results, which are robust.

Platelet and lymphocyte counts are routinely measured as parameters based on blood tests. PLR represents a marker of inflammation. High PLR reflects elevated platelet-dependent

Table I. Baseline characteristics of the selected participants.

Platelet-to-lymphocyte ratio quartile	Q1	Q2	Q3	Q4	P-value
N	1660	1659	1656	1663	
Total prostate specific antigen (ng/ml)	1.531±2.321	1.678±2.529	1.681±3.114	1.958±3.213	<0.001
Age, years	58.033±11.583	58.458±18.333	58.001±11.667	59.751±12.083	<0.001
Family income	2.628±1.616	2.787±1.632	2.952±1.635	2.935±1.628	<0.001
Leukocyte count (1,000 cells/μl)	8.017±3.344	7.243±1.844	6.839±1.874	6.510±3.077	<0.001
Lymphocyte count (1,000 cells/μl)	2.824±2.514	2.155±0.482	1.831±0.408	1.425±0.378	<0.001
Mononuclear count (1,000 cells/μl)	0.628±0.221	0.577±0.183	0.556±0.180	0.536±0.184	<0.001
Neutrophils count (1,000 cells/μl)	4.270±1.661	4.241±1.520	4.198±1.591	4.289±2.644	0.208
Eosinophil count (1,000 cells/μl)	0.253±0.195	0.230±0.168	0.220±0.179	0.229±0.290	<0.001
Basophils count (1,000 cells/μl)	0.112±0.063	0.109±0.038	0.107±0.034	0.120±0.221	0.259
Red cell count (million cells/μl)	4.877±0.486	4.893±0.457	4.907±0.464	4.813±0.488	<0.001
Hemoglobin (g/μl)	15.144±1.352	15.092±1.246	15.086±1.233	14.744±1.395	<0.001
Platelet count (1,000 cells/μl)	204.312±51.978	233.80±50.624	251.395±54.792	280.114±71.685	<0.001
C-reactive protein(mg/μl)	0.377±0.742	0.386±0.968	0.396±0.923	0.528±1.141	<0.001
Lymphocyte-to-monocyte ratio	4.746±2.153	4.031±1.369	3.572±1.244	2.932±1.222	<0.001
Neutrophil-to-lymphocyte ratio	1.652±0.707	2.031±0.783	2.359±0.934	3.183±1.807	<0.001
Systemic immune inflammation index	329.43±140.228	461.38±167.68	578.697±222.92	890.905±869.83	<0.001
Military status					0.008
Yes	536 (32.309%)	539 (32.489%)	566 (34.179%)	620 (37.282%)	
No	1,123 (67.691%)	1,120 (67.511%)	1,090 (65.821%)	1,043 (62.718%)	
Education					<0.001
Less than 9th grade	327 (19.723%)	287 (17.310%)	244 (14.752%)	229 (13.770%)	
9-11th grade	272 (16.405%)	242 (14.596%)	198 (11.971%)	238 (14.311%)	
High school grad	381 (22.979%)	387 (23.341%)	408 (24.667%)	364 (21.888%)	
Some college or AA degree	275 (16.586%)	370 (22.316%)	379 (22.914%)	426 (25.616%)	
College graduate or above	403 (24.306%)	372 (22.437%)	425 (25.695%)	406 (24.414%)	
Marital status					0.035
Married	1,374 (82.821%)	1,403 (84.67%)	1,437 (86.933%)	1,421 (85.448%)	
Single	183 (11.031%)	167 (10.078%)	151 (9.135%)	165 (9.922%)	
Living with a partner	102 (6.148%)	87 (5.250%)	65 (3.932%)	77 (4.630%)	
Ethnicity					<0.001
Mexican American	346 (20.843%)	312 (18.807%)	305 (18.418%)	246 (14.793%)	
Other hispanic	110 (6.627%)	136 (8.198%)	89 (5.374%)	76 (4.570%)	
Non-hispanic white	800 (48.193%)	842 (50.753%)	947 (57.186%)	975 (58.629%)	
Non-hispanic black	354 (21.325%)	298 (17.963%)	267 (16.123%)	315 (18.942%)	
Other ethnicity	50 (3.012%)	71 (4.280%)	48 (2.899%)	51 (3.067%)	

Q1-Q4, grouped by quartile according to the serum platelet-to-lymphocyte ratio. The data included PSA concentrations, sociodemographic data, laboratory data for the second analysis.

pro-tumor responses and reduced lymphocyte-mediated anti-tumor immune responses, which could potentially lead to cancer progression and a poor prognosis. Platelets have been shown to promote cancer cell growth and metastasis through direct and indirect actions (22,23). On PCa, on the one hand, platelets adhere to tumor cells with the help of fibrinogen; at the same time, they promote more fibrinogen aggregation around tumor cells by forming thrombin, thus protecting them from the cytotoxicity of natural killer cells (24); on the other hand, platelet-derived microparticles promote the invasiveness of PCa cells through upregulation of MMP-2 production (25). Currently, a considerable amount of evidence indicates that lymphocytes are the cellular basis of cancer immunosurveillance and can inhibit tumor cell proliferation and metastasis (26). Huang *et al* (27) revealed that high pre-treatment levels of circulating lymphocytes are associated with longer relapse-free survival and slightly improved overall survival (OS) in patients with oropharyngeal cancer. Sznurkowski *et al* (28) concluded that the increased number of tumor-infiltrating lymphocytes is associated with an improved prognosis in various cancers, including breast and colorectal. As a parameter combining platelet count and lymphocyte count,

Table II. Univariate and multivariate analyses by the weighted linear model.

Exposure	Non-adjusted model	Minimally adjusted model	Fully adjusted model
PLR	0.003 (0.002,0.004), <0.001	0.002 (0.001,0.003), <0.001	0.004(0.001,0.007) <0.004
PLR quartile			
Q1	Ref	Ref	Ref
Q2	0.160 (-0.025, 0.345) 0.08975	0.112 (-0.068, 0.292) 0.22344	0.133 (-0.074, 0.339) 0.20817
Q3	0.165 (-0.020, 0.350) 0.08091	0.208 (0.027, 0.389) 0.02455	0.243 (0.001,0.486) 0.04935
Q4	0.402 (0.216, 0.588) 0.00002	0.298 (0.117, 0.480) 0.00127	0.355 (0.043, 0.667) 0.02593
P for trend	<0.001	<0.001	0.028

Non-adjusted model adjusts for none. Minimally adjusted model adjusts for: Age, family income, ethnicity, military status, marital status, education. Fully adjusted model adjusts for: Age, family income, ethnicity, military status, marital status, education, mononuclear count, neutrophils count, platelet count, lymphocyte to monocyte ratio, systemic immune inflammation index. PLR, platelet-to-lymphocyte ratio.

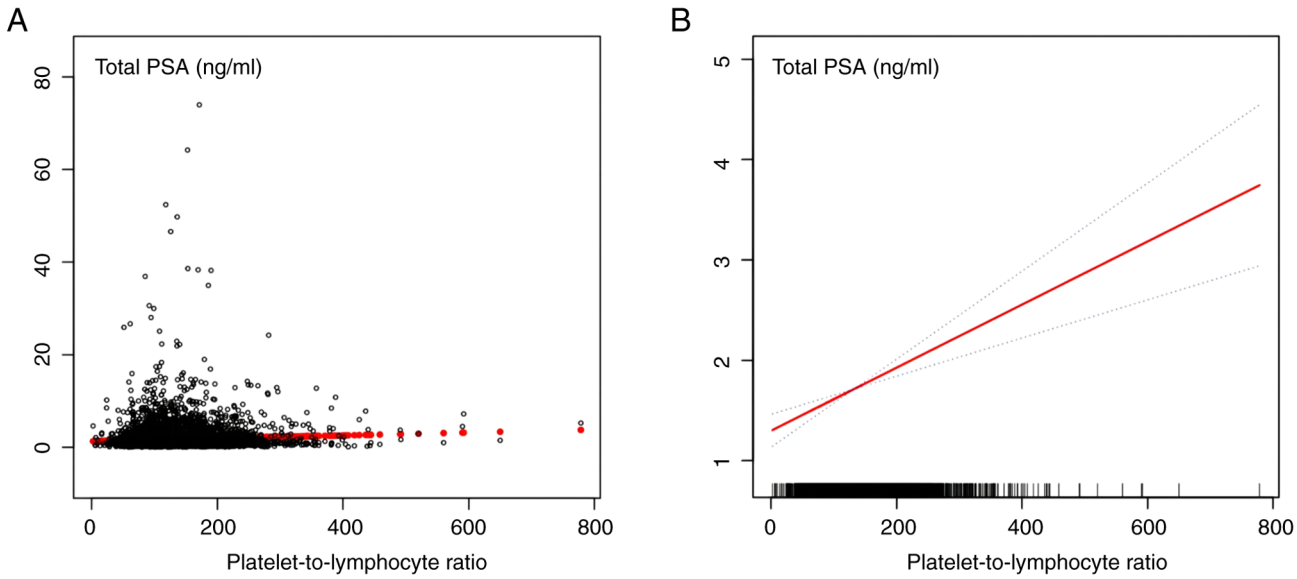

Figure 2. The relationship between platelet-to-lymphocyte ratio and serum PSA connections. (A) Each black point represents a sample. (B) Red line represents the smooth curve fit between variables. Blue lines represent the 95% of confidence interval from the fit. Age, family income, ethnicity, military status, marital status, education, mononuclear count, neutrophils count, platelet count, lymphocyte to monocyte ratio, and systemic immune inflammation index were adjusted. PSA, prostate-specific antigen.

PLR can provide relatively accurate prognostic information about cancer patients (29,30). It is widely accepted that there is a strong correlation between the development and prognosis of tumors and a systemic inflammatory response (31-33). As a commonly used marker of systemic inflammation, the prognostic value of NLR has also been powerfully demonstrated in PCa (34-36). However, the significance of PLR in PCa prognosis remains conflicting (17,18).

A previous study provided evidence that PLR is an independent prognostic factor for progression-free survival and OS in PCa patients (37). Similarly, Yuksel *et al* (17) reported that PLR has the potential to differentiate between benign prostatic hyperplasia and PCa. This can ultimately serve as a diagnostic tool for PCa. By contrast, Lee *et al* (18) concluded that pre-biopsy PLR cannot significantly predict CSPCa, rendering it inadequate for PLR diagnosis. Similar results were reported by Sun *et al* (16), revealing that there is no significant correlation between PLR and either PCa or PSA after comparing the predictive effects of several inflammatory markers on PCa. Therefore, the aforementioned study concluded that PLR has little diagnostic and prognostic value for PCa. Because most studies involved men from Asia at relatively low risk of developing PCa and the conclusions were not definitive, studies are still needed to assess the relationship between PLR and PSA levels. Therefore, it was hypothesized that PLR affects PSA concentrations and may create testing bias, which could result in inconsistent interpretations. Further cohort trials are necessary to further comprehend the function of PLR as either a protective or risk factor in the progression of PCa.

The findings of the present study, support a positive correlation between PLR and PSA. A positive correlation between PLR and PSA can lead to detection bias, which may have implications for PCa screening. Since PLR preferentially elevates PSA concentrations in men without PCa, PSA testing for PCa screening in men with high PLR can lead to the overdiagnosis of asymptomatic PCa. Therefore, if PLR can elevate

Table III. Effect size of PLR on prostate-specific antigen in the prespecified and exploratory subgroup.

PLR	N	β	95% CI low	95% CI high	P-value	p for interaction
Stratified by age						0.4961
<60	2058	0.001	-0.006	0.007	0.8635	
60-80	2072	0.002	-0.002	0.007	0.2425	
>80	2073	0.005	0.001	0.009	0.0148	
Stratified by ratio of family income						0.0646
Low group	2064	0.007	0.002	0.012	0.0027	
Median group	2071	0.003	-0.001	0.006	0.1352	
High group	2068	-0.003	-0.01	0.004	0.4659	
Stratified by ethnicity						0.846
Mexican American	1118	0.003	-0.004	0.01	0.3537	
Other hispanic	360	0.011	-0.01	0.032	0.3173	
Non-hispanic white	3365	0.002	-0.002	0.005	0.3039	
Non-hispanic black	1155	0.005	-0.002	0.012	0.1332	
Other ethnicity/ethnicity	205	0	-0.028	0.028	0.9923	
Stratified by military status						0.2802
Yes	2124	0.002	-0.002	0.005	0.3745	
No	4079	0.004	0.001	0.008	0.0192	
Stratified by marital status						0.9962
Married	5281	0.003	0	0.006	0.0373	
Single	615	0.003	-0.004	0.01	0.3613	
Living with a partner	307	0.003	-0.013	0.018	0.7538	
Stratified by education						0.0504
Less than 9th grade	997	0.012	0.005	0.018	0.0003	
9-11th grade	889	0.003	-0.005	0.011	0.4316	
High school grad	1442	0	-0.006	0.007	0.944	
Some college or AA degree	1366	0.002	-0.006	0.01	0.6173	
College graduate or above	1509	0	-0.005	0.005	0.9856	

Note 1: Above adjusts for age, family income, ethnicity, military status, marital status, education, mononuclear count, neutrophils count, platelet count, lymphocyte to monocyte ratio, systemic immune inflammation index. Note 2: In each case, the model was not adjusted for the stratification variable itself. PLR, platelet-to-lymphocyte ratio; CI, confidence interval.

the PSA produced by prostate tumors or enhance the ability of tumor-derived PSA to enter the serum, it is necessary to adjust the PSA threshold for further examine platelets as well as lymphocytes to ultimately rule out interference with PSA by PLR. For example, in a high PLR population, the actual PSA value should be used as the screening diagnostic criterion. Actual PSA=PSA measurement-PLR * 0.004. Further studies are needed to explore the mechanisms by which the PLR affects PSA concentration and its impact on PCa screening. In addition, prospective cohort studies are still needed to confirm the causal relationship and serum platelets and lymphocytes are involved in both the genesis and development of PCa, which also needs to be verified by *in vitro* and *in vivo* experiments.

Compared with prior research, the present study boasts several noteworthy findings. Firstly, it is the first large-scale cross-sectional study to find a positive association between PLR and PSA in men from USA with a non-tumor history. Secondly, the present study utilized a highly reliable, standardized, and multilayer random sample, providing a representative portrayal of the general USA population. Then, a sensitivity analysis was performed and a smoothing curve was constructed based on a fully adjusted model to investigate the possible linear relationship between PLR and PSA concentration. Nevertheless, there are certain limitations to the interpretation of the findings of the present study. Primarily, it is challenging to distinguish causality in the present study due to the inherent limitations of the NHANES database as a cross-sectional survey. Although prospective studies have demonstrated that PLR has an important predictive role in the diagnosis and prognosis of PCa (38,39), prospective cohort studies are still needed for further validation because these studies are single center with small sample sizes. To further validate the accuracy and applicability of the findings of the present study, a prospective cohort study is being designed based on a Chinese population, and the authors are working towards a multicenter study. Furthermore, participants diagnosed with PCa were excluded and those with factors impacting PSA concentrations or missing data. Consequently,

the findings of the present study cannot be generalized to the aforementioned population. Lastly, the survey is based on the NHANES database, which is limited to the individuals from USA. As a result, generalizability is geographically limited. Nonetheless, in conjunction with the existing studies in China, Italy, Austria, and other regions (16,40,41), there are favorable reasons to hypothesize that the association between PLR and PSA, or PCa, is geospatially generalizable.

In conclusion, in men from USA, there is an independent and positive association between PLR and PSA, which could potentially result in overdiagnosis of asymptomatic PCa in populations with higher PLR levels.

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Availability of data and materials

All data are available at NHANES website https://www.cdc.gov/nchs/nhanes/index.htm (accessed on October 7, 2022).

Authors' contributions

WL, HL and BH conceptualized and designed the study. BH and SH acquired and analyzed the data. MY interpreted the data. BH and SH wrote the original draft of the manuscript. WL and HL reviewed the manuscript. All authors read and approved the final version of the manuscript. BH, SH and MY confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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