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Association between platelet to lymphocyte ratio and depression and symptom severity among adults in the United States: A cross-sectional study

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ABSTRACT

Background: The pathogenesis of depression has not yet been fully understood. The association between platelet to lymphocyte ratio (PLR) and depression has been investigated in previous studies, however, the results were controversial. The objective of the study was to explore the potential relationship between PLR and depression and symptom severity.
Methods: A cross-sectional study was conducted based on the National Health and Nutrition Examination Survey (NHANES) data from 2005 to 2018. Totally 30,032 adults were analyzed, and 2480 reported depression. Depression and symptom severity were assessed with the Patient Health Questionnaire (PHQ-9). PLR was calculated as the ratio of platelets to lymphocytes. Multivariable weighted-logistic regression models and generalized additive model (GAM) were employed to evaluate the linear and nonlinear association between PLR and depression and symptom severity.
Results: There was a negative association for Q3 (odds ratio [OR]: 0.82, 95% confidence interval [CI]: 0.68 to 0.99) when comparing participants for Q1 between 10-PLR and depression after fully adjusting the covariates; however, there was no significant association between 10-PLR and symptom severity. GAM showed that 10-PLR was associated with depression and symptom severity in a nonlinear manner. The inflection points were at 12.15. Subgroup analyses showed nonlinear relationships only in specific subgroups. **Conclusions**: PLR is associated with depression among adults in the United States. U-shaped nonlinear relationships and threshold effects were observed between 10-PLR and depression and symptom severity. Additionally, inflammatory mechanisms vary in different sociodemographic subgroups.

1. Introduction

Major depressive disorder is a common [1–3], heterogeneous [4,5], recurring [6–8], and disabling disorder [9,10] with a wide range of symptoms, including impairments in mood and cognitive abilities. Multiple factors, such as biological, psychological, and

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environmental ones, are believed to cause disease [11]. The lifetime risk of depression is 15–18% worldwide, which means that nearly one in every five people will suffer from depression at some point in their lives [1]. Depression can limit psychosocial functioning [12], diminish the quality of life [13], and increase suicide risk [14].

Although the pathophysiology of depression is still not fully understood, recent mounting evidence suggests that inflammation plays a significant role in the development of depression. For example, researchers found that administering pro-inflammatory cytokines in a clinical setting could induce depressive symptoms [15]. Some clinical studies have also discovered that populations with autoimmune diseases are more likely to suffer from depression [16,17]. In addition, depressive patients frequently exhibit changes in their peripheral and/or central inflammatory states [18,19]. And the proof-of-concept concerning the use of anti-inflammatory treatments in depression was supported by the literature [20]. Thus, the role of inflammation in depression has garnered considerable attention. Some studies have investigated the association between depression and inflammatory biomarkers, such as C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-a), and interleukin-6 (IL-6) [21–23]. However, there have been no clinically reliable predictors for depression, and the relationship between depression and inflammation remains uncertain.

As a common marker of systemic inflammation, the platelet to lymphocyte ratio has been linked to depression [24,25]. Several studies have been conducted to determine the relationship between PLR and depression. For example, Puangsri et al. and Cai et al. both discovered increased PLR in the depressed group compared to the healthy control [26,27]. However, in the studies by Uçar et al. and Ozyurt et al. no significant differences were observed in PLR [28,29]. Meanwhile, another study by Kinoshita et al. demonstrated significant differences between depressed and healthy groups, exclusively in males [30]. And among the above studies, sample sizes ranged from 144 to 1015. A meta-analysis including 12 studies found that the PLR levels of depressed and healthy people were not significantly different [31]. Nevertheless, subgroup analysis showed significantly higher levels of PLR in the studies conducted in China but not in Turkey. The further limitations of prior research included statistical methods (such as handling outliers, nonlinearity, and subgroup analysis) and insufficient adjustment for potential confounding factors. Thus, further research based on large populations and specific subtypes is required.

We hypothesized underlying relationships between PLR and depression and the severity of symptoms. The first objective of the present study was to investigate the independent association between them in US adults. Secondly, we aimed to explore the nonlinear

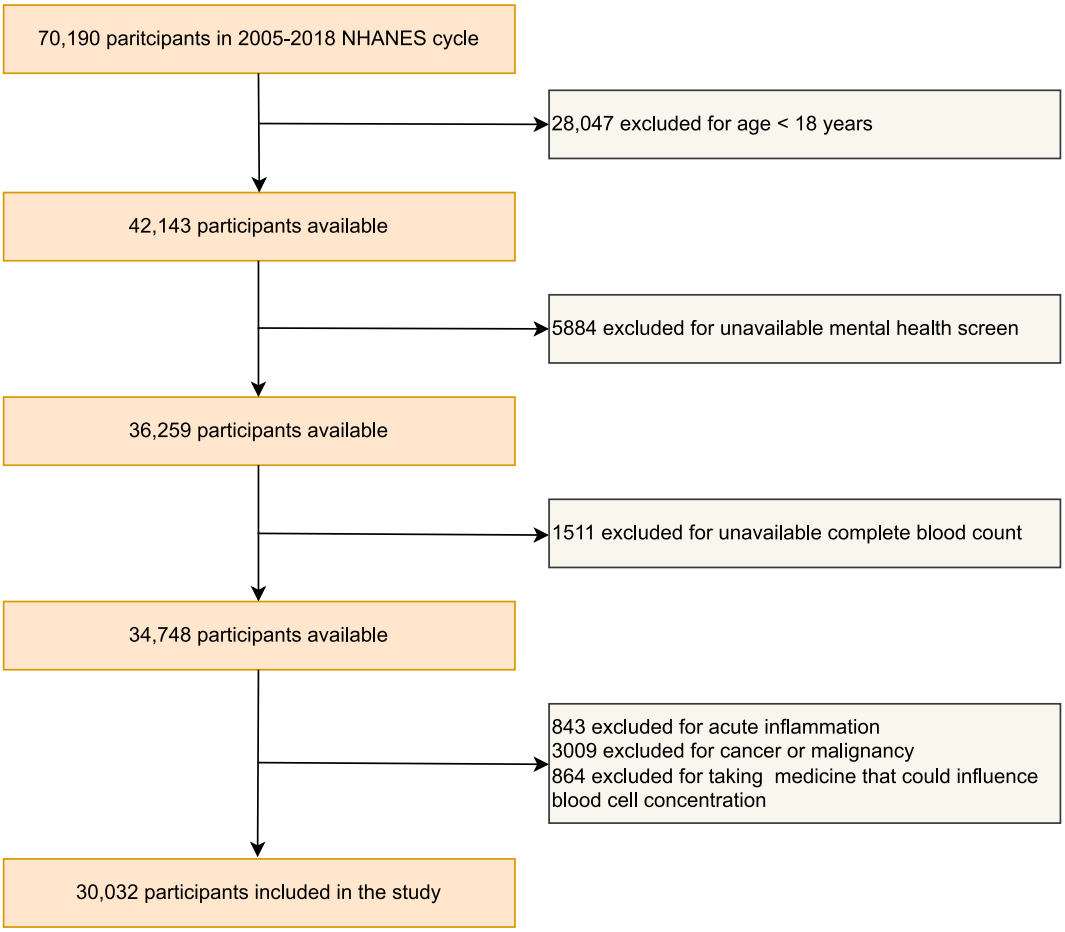

Fig. 1. Flow chart of study.

relationship and determine the effect size. Further understanding of the relationship between PLR and clinical depression can help identify the inflammatory pathway contributing to depression.

2. Methods

2.1. Participants

The National Health and Nutrition Examination Survey (NHANES) is a cross-sectional survey designed to assess the health and nutrition status of the noninstitutionalized population in the United States. It is nationally representative due to its stratified, multistage, and complex probability survey design. Sampling weights were assigned to participants to account for the different probabilities of selection and nonresponse [32]. The NHANES database is available online to users worldwide. Our analyses were based on the data collected from seven NHANES 2-year cycles (from 2005 to 2018).

The following were the inclusion criteria for the analyses: (1) the age was over 18 years. (2) the depression screener and complete blood count data were available. And the exclusion criteria included: (1) currently suffering from acute inflammation (defined as a C-reactive protein level of 10 mg/L or higher) [33]. (2) having a history of cancer or another type of malignancy. (3) taking medicine that could influence blood cell concentration (e.g., aspirin, clopidogrel, dipyridamole, and anti-infectives).

There were 70,190 participants in the 2005–2018 cycles. We excluded 28,047 individuals younger than 18 years, 5884 with missing data from the mental health assessment, 1511 with an unavailable complete blood count, 843 with acute inflammation, 3009 with cancer or malignancy, and 864 for taking medicine that could influence blood cell concentration. Finally, 30,032 adults were included in the present analysis, including 2466 with depression (Fig. 1).

All participants provided written informed consent, and the US National Center for Health Statistics Research Ethics Review Board approved the NHANES protocols (Protocol #2005–06, Protocol #2011–17, and Protocol #2018–01) (https://www.cdc.gov/nchs/nhanes/irba98.htm).

2.2. Depression and symptoms severity assessment

The outcome variable of the study was depression. The two dimensions of depression (namely, depression diagnosis and symptom severity) were assessed with the Patient Health Questionnaire (PHQ-9). PHQ-9 is a self-administered measure comprised of nine items that map directly onto the Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) criteria for major depression [34]. Each item of the questionnaire assesses the frequency of depression symptoms rated as “0" (not at all) to “3" (nearly every day) over the past two weeks. Firstly, the data of nine items without missing was extracted systematically, and the score of PHQ-9 was obtained by the sum of the nine items’ scores. The PHQ-9 score ranged from 0 to 27, with higher scores reflecting greater severity as a continuous variable [34,35]. Then the PHQ-9 score was dichotomized to distinguish major depression. When the cut-off point for PHQ-9 scores is 10 or higher, the scale is a valid screening instrument for major depression with a sensitivity of 88% and a specificity of 88% [36].

2.3. Platelet to lymphocyte ratio (PLR)

The complete blood count and the distribution of blood cells were examined for all participants with the Beckman Coulter MAXM instrument in the Mobile Examination Center. Platelet counts and lymphocyte counts were analyzed utilizing the complete blood count with a 5-part differential, and PLR was calculated using the formula of platelet count to lymphocyte count. The NHANES laboratory/medical technologists techniques manual contains a complete description of the analytical procedures (https://wwwn.cdc.gov/nchs/nhanes/).

2.4. Covariates

The following covariates were selected based on the previous research and/or plausible biological relations: age, sex, ethnicity, education, marital status, poverty income ratio, body mass index (BMI), cardiovascular disease, hypertension, diabetes, dyslipidemia, physical activity, sleep duration, alcohol use, smoking status, and antidepressant use [37,38]. The poverty income ratio was an index for the family income ratio to poverty. It was calculated by dividing the family’s income by the federal poverty guidelines. BMI was computed as weight in kilograms divided by height in meters squared. Cardiovascular disease was defined as having a history of congestive heart failure, coronary heart disease, angina pectoris, a heart attack, or a stroke. Three consecutive blood pressure readings were taken by trained personnel, and the mean blood pressure was calculated as the average of the three readings. Hypertension was defined as a history of taking antihypertensive drugs or having a blood pressure greater than 130/80 mmHg [39]. Diabetes mellitus was defined as having a history of diagnosis, taking insulin or diabetes pills, or having a hemoglobin A1c level of 6.5% or a fasting plasma glucose level of 126 mg/dL [40]. Dyslipidemia was defined as having a diagnosis history, taking lipid-lowering drugs in the past, or having a triglyceride level $\geq$150 mg/dL or a high-density lipoprotein cholesterol level $<$40 mg/dL [41]. Physical activity was classified as inactive, moderate, and vigorous based on the two following questions: “Do any moderate-intensity sports, fitness, or recreational activities that cause a small increase in breathing or heart rate, such as brisk walking, bicycling, swimming, or golf for at least 10 min continuously” and “Do any vigorous-intensity sports, fitness, or recreational activities that cause large increases in breathing or heart rate, like running or basketball for at least 10 min continuously”. Excessive alcohol use was defined as drinking five drinks per day on average in the past 12 months. Smoking status was categorized as “never smoker,” “former smoker,” or “current

smoker." A "never smoker" is an adult who has never smoked or who has smoked fewer than 100 cigarettes in their lifetime. A "former smoker" is an adult who has smoked at least 100 cigarettes in their lifetime but had quit smoking at the time of the interview. A "current smoker" is an adult who has smoked 100 cigarettes in their lifetime and who currently smokes cigarettes.

Table 1
Baseline characteristics of study participants in NHANES 2005–2018, weighted.

Characteristic	No. (%) of Participants		
	Total (n = 30,032)	Non-depression (n = 27,552)	depression (n = 2480)
Age, median(IQR), years	44.00 (30.00,57.00)	44.00 (30.00,57.00)	44.00 (31.00,55.00)
18 to ≤39	11,901 (40.16)	11,002 (40.28)	899 (38.64)
40 to ≤59	9724 (37.63)	8785 (37.33)	939 (41.51)
60 to ≤79	7060 (19.13)	6496 (19.24)	564 (17.67)
≥80	1347 (3.09)	1269 (3.16)	78 (2.18)
Sex			
Male	14,895 (49.74)	13,969 (50.73)	926 (37.14)
Female	15,137 (50.26)	13,583 (49.27)	1554 (62.86)
Race/ethnicity			
Mexican American/Other Hispanic	8157 (15.10)	7412 (14.93)	745 (17.32)
Non-Hispanic White	11,974 (66.08)	11,006 (66.48)	968 (60.95)
Non-Hispanic Black	6546 (11.26)	5972 (11.01)	574 (14.38)
Other race	3355 (7.57)	3162 (7.58)	193 (7.35)
Education			
Below high school	6840 (15.74)	6002 (14.97)	838 (25.59)
High school	6459 (23.44)	5896 (23.18)	563 (26.74)
Above high school	14,779 (60.82)	13,831 (61.85)	948 (47.67)
Marital			
Married/Living with partner	16,890 (63.32)	15,822 (64.58)	1068 (47.18)
Never married	5869 (19.58)	5321 (19.28)	548 (23.46)
Divorced/Separated/Widowed	5796 (17.10)	5040 (16.15)	756 (29.36)
Poverty income ratio			
< 1 (lowest income)	6139 (14.60)	5287 (13.51)	852 (28.67)
1 to 2	7292 (20.24)	6572 (19.51)	720 (29.55)
2 to 4	7194 (28.80)	6759 (29.23)	435 (23.24)
≥4 (highest income)	6928 (36.36)	6683 (37.75)	245 (18.54)
BMI, mean(SE),kg/m2**			
<18.5	531 (1.71)	479 (1.66)	52 (2.35)
18.5 to < 25	8626 (29.49)	8022 (29.76)	604 (26.06)
25 to 30	9746 (32.87)	9107 (33.40)	639 (26.12)
>30	10,867 (35.93)	9714 (35.18)	1153 (45.47)
Cardiovascular disease			
Yes	2151 (5.95)	1818 (5.52)	333 (11.45)
No	25,932 (94.05)	23,916 (94.48)	2016 (88.55)
Hypertension			
Yes	13,311 (42.04)	12,123 (41.66)	1188 (46.88)
No	16,239 (57.96)	14,993 (58.34)	1246 (53.12)
Diabetes			
Yes	4401 (10.97)	3889 (10.57)	512 (16.10)
No	25,631 (89.03)	23,663 (89.43)	1968 (83.90)
Dyslipidemia			
Yes	7777 (25.81)	7005 (25.41)	772 (30.91)
No	21,883 (74.19)	20,212 (74.59)	1671 (69.09)
Physical activity			
Inactive	14,462 (42.44)	12,785 (40.73)	1677 (64.30)
Moderate	7583 (27.36)	7115 (27.84)	468 (21.12)
Vigorous	7987 (30.21)	7652 (31.43)	335 (14.58)
Sleep duration, mean(SE),h	7.09 (0.01)	7.12 (0.01)	6.70 (0.06)
Excessive alcohol use			
Yes	4070 (15.64)	3451 (14.45)	619 (30.62)
No	20,667 (84.36)	19,180 (85.55)	1487 (69.38)
Smoking status			
Never	16,434 (56.56)	15,408 (57.84)	1026 (40.20)
Former	6347 (22.96)	5855 (23.15)	492 (20.57)
Current	5997 (20.48)	5115 (19.01)	882 (39.23)
Antidepressant			
Yes	2771 (11.64)	2063 (9.97)	708 (33.13)
No	27,261 (88.36)	25,489 (90.03)	1772 (66.87)
PLR	125.09 (0.49)	125.20 (0.51)	123.71 (1.17)

Abbreviation: interquartile range (IQR), standard error (SE), body mass index (BMI), platelet to lymphocyte ratio (PLR).

2.5. Statistical analysis

Following the analytic guidelines of NHANES, 14-year sample weights were applied to account for the oversampling of minorities. We first visualized the distribution of PLR using boxplots and replaced any outliers at three standard deviations and above via winsorization. Then the normality tests of PLR and PHQ-9 score were performed. PLR was divided into quartiles as a categorical variable. Continuous variables were presented as a mean ± standard error [SE] or median with interquartile range (IQR), and categorical variables were presented as frequencies and percentages. Group comparisons were performed with ANOVA analysis or the Chi-squared test. Univariable and multivariable weighted-logistic regression models were applied to evaluate the association between PLR and depression and symptom severity. The variance inflation factors (VIF) were used to evaluate the multicollinearity among all variables. If a variable changed the estimates of the PLR on depression by more than 10% or was significantly associated with depression or symptom severity in univariable analysis ($p < 0.1$), it was included in the final multivariable model as a potential confounder. Three multivariable logistic regression models were built in order to compare the coefficients of the various models and account for possible confounding factors. In the crude model, no confounder was adjusted. In model I, sociodemographic factors (age, sex, race, education level, marital status, and poverty income ratio) were adjusted. In model II, BMI, physical activity, sleep duration, smoking status, alcohol use, antidepressant use, cardiovascular disease, hypertension, diabetes, and dyslipidemia were adjusted on the basis of model I. The generalized additive model (GAM) was employed to visually confirm the nonlinear relationship between PLR and depression and the severity of symptoms. A two-piecewise linear regression mode was constructed to figure out the threshold effect if the nonlinear relationship was detected. When adjusting for the covariates, continuous variables were treated as linear by default. And GAM was performed to examine any potential nonlinear correlations in the adjusted variables. In addition, nonlinear relations between subgroups stratified by sociodemographic characteristics (age, sex, and race) were investigated to determine heterogeneity.

All the analyses were performed using the R software package (version 4.2.0, http://www.R-project.org). A 2-sided p value < 0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics of participants

Table 1 lists the weighted baseline characteristics of the participants. The median age was 44 years (IQR: 30–57), and 14,895 (49.74%) were male. 8157 (15.10%) were Mexican American or other Hispanic, 11,974 (66.08%) were non-Hispanic white, 6546 (11.26%) were non-Hispanic black, and 3355 (7.57%) were other races. 6840 (15.74%) were below high school, 6459 (23.44%) graduated from high school, and 14,779 (60.82%) were above high school. 16,890 (63.32%) were married or lived with a partner, 5869 (19.59%) were never married, and 5796 (17.10%) were divorced, separated, or widowed.

3.2. Relations between variables and depression and symptom severity

The findings of the univariable analyses showed that factors such as age, sex, race, education level, marital status, poverty income ratio, BMI, cardiovascular disease, hypertension, diabetes, dyslipidemia, physical activity, sleep duration, excessive alcohol use, smoking status, and antidepressant use were significantly associated with depression and the severity of symptoms. Additionally, the results of the variance inflation factors showed that none of these variables was multicollinear (VIF <5) (Supplementary Table S1 and Supplementary Table S2).

3.3. Association between PLR and depression and severity of symptom

The relationship between PLR and depression is shown in Table 2. In the crude model, model I and model II, there was no significant association between 10-PLR and depression or severity (all $p > 0.05$). When PLR was a categorical variable with a quartile, there was a

Table 2
Multivariable logistic regression analyses for 10-PLR and depression, Weighted.

Exposure	Crude model		Adjust model I		Adjust model II	
	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value
10-PLR(continuous)	0.99 (0.98, 1.00)	0.22	0.99 (0.98, 1.01)	0.24	0.99 (0.98, 1.01)	0.77
10-PLR(quartile/n)						
Q1 (<9.27/7506)	Reference		Reference		Reference	
Q2 (≥9.27to 11.65/7504)	0.83 (0.71, 0.96)	0.02	0.83 (0.71,0.97)	0.02	0.89 (0.74,1.07)	0.23
Q3 (≥11.65 to 14.63/7510)	0.72 (0.62, 0.84)	<0.001	0.73 (0.62,0.86)	<0.001	0.82 (0.68,0.99)	0.046
Q4 (≥14.64/7512)	0.88 (0.77, 1.00)	0.05	0.86 (0.75,0.99)	0.04	0.95 (0.80,1.13)	0.55
p for trend	0.10		0.08		0.64	

Abbreviation: platelet to lymphocyte ratio (PLR), odds ratio(OR), confidence interval (CI).
Crude model: unadjusted. Adjust model I: adjusted for age, sex, race, education level, marital status, poverty income ratio. Adjust model II: adjusted for age, sex, race, education level, marital status, poverty income ratio, BMI, physical activity, sleep duration, smoking status, alcohol use, antidepressant use, cardiovascular disease, hypertension, diabetes, dyslipidemia.

significant association for Q2 (OR: 0.83, 95% CI: 0.71 to 0.96), Q3 (OR: 0.72, 95% CI: 0.62 to 0.84), and Q4 (OR: 0.88, 95% CI: 0.77 to 1.00) compared with participants for Q1 in the crude model. In the model I, the results remained the same. After adjustment for all confounding factors, however, only a negative association for Q3 was observed (OR: 0.82, 95% CI: 0.68 to 0.99).

Table 3 presents the relationship between PLR and the severity of symptoms. In all models, no significant association was observed (all $p > 0.05$). As a categorical variable, a significant association was observed for Q2 (β: −0.24, 95% CI: −0.41 to −0.07), Q3 (β: −0.30, 95% CI: 0.44 to −0.15), and Q4 (β: −0.21, 95% CI: 0.35 to −0.08) in the crude model. In model I, similar associations were observed for Q2, Q3, and Q4 (Q1:reference vs. Q2: β, −0.23, 95%CI: −0.40 to −0.06 vs. Q3: β, −0.29, 95%CI: −0.45 to −0.13 vs. Q4: β, −0.23, 95%CI: −0.37 to −0.09). Nevertheless, no significant association was discovered in the fully adjusted model (Q1:reference vs. Q2: β, −0.14, 95%CI: −0.32 to 0.04 vs. Q3: β, −0.13, 95%CI: −0.29 to 0.05 vs. Q4: β, −0.10, 95%CI: −0.26 to 0.07).

3.4. Nonlinear relation between PLR depression and severity of symptom

GAM was used to visually assess functional relationships between PLR and depression and symptom severity. When continuous variables are treated as linear by default, the results of GAM estimation indicated that 10-PLR was associated with depression and symptom severity in a nonlinear manner after adjusting for all covariates (Fig. 2A and B). Consequently, piecewise linear regression was utilized to conduct a threshold analysis. As shown in Table 4, the inflection points were 12.15. And when GAM was performed to examine any potential nonlinear correlations in the adjusted variables, the same trends were observed (both $p < 0.05$, both edf >2) (Supplementary Fig. S1).

3.5. Subgroup analyses

The results showed no interaction between PLR and depression or symptom severity in all subgroup analyses (all p values > 0.05) (Supplementary Table S3). Subgroup analysis visually revealed nonlinear relationships among participants aged 18 to 39 ($p = 0.09$), females ($p = 0.046$), and non-Hispanic white ($p = 0.01$) groups between PLR and depression (Supplementary Fig. S2). Participants in the 18- to 39-year-old ($p = 0.009$), female ($p = 0.004$), and non-Hispanic white ($p = 0.03$) groups were found to have nonlinear relationships between PLR and the severity of depression (Supplementary Fig. S3).

4. Discussion

This cross-sectional survey study investigated the associations between PLR and depression from two perspectives: depression diagnosis and symptom severity. The results showed that 10-PLR (which ranged from 11.65 to 14.63) was associated with depression, but there was no association between 10-PLR and the severity of symptoms after adjusting for all confounding factors. Also, U-shaped nonlinear relationships and threshold effects were observed between 10-PLR and depression and symptom severity. In further subgroup analyses, nonlinearity was observed only in specific subgroups.

Platelets get involved in the first-line inflammatory response to modulate the recruitment of neutrophils, macrophages, and their effectors, as well as endothelial permeability. The lymphocyte is a specific inflammatory mediator that serves as a regulator in the adaptive immune response. The activation of platelets is stimulated through different inflammatory elements, including cytokines, epinephrine, serotonin, glutamate, dopamine, and P-selectin. Hence, PLR reflects the level of systemic inflammation. Researchers from various nations examined the relationship between PLR and depression and symptom severity in earlier studies, but came to conflicting conclusions. A few studies from Asia all found that people with depressive disorders had a higher PLR than people who were healthy [26,27,42,43]. In contrast, Okan Ekinci et al. and Halit Necmi Uçar et al. both reported no significant association [28,44]. The relationship between PLR and the severity of symptoms was investigated in the limited studies. Fatih Kayhan et al. discovered a higher PLR in patients with severe major depression and psychotic features [45], while Afsane Bahrami et al. reported that higher depression scores were associated with an increased PLR [46]. Our results supported the hypothesis that PLR is associated with depression among adults in the United States. We also determined U-shaped relationships between PLR and depression and symptom severity. The

Table 3
Multivariable logistic regression analyses for 10-PLR and depression severity, Weighted.

Exposure	Crude model		Adjust model I		Adjust model II	
	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
10-PLR(continuous)	−0.01 (−0.02, 0.001)	0.07	−0.01 (−0.02, 0.001)	0.08	−0.004 (−0.02, 0.01)	0.57
10-PLR (quartile/n)						
Q1 (<9.27/7506)	Reference		Reference		Reference	
Q2 (≥9.27to 11.65/7504)	−0.24 (-0.41, −0.07)	0.006	−0.23 (-0.40,-0.06)	0.01	−0.14 (-0.32,0.04)	0.14
Q3 (≥11.65 to 14.63/7510)	−0.30 (-0.44, −0.15)	<0.001	−0.29 (-0.45,-0.13)	<0.001	−0.12 (-0.29,0.05)	0.16
Q4 (≥14.63/7512)	−0.21 (-0.35, −0.08)	0.002	−0.23 (-0.37,-0.09)	0.002	−0.10 (-0.26,0.07)	0.24
p for trend	0.01		0.01		0.41	

Abbreviation: platelet to lymphocyte ratio (PLR), odds ratio(OR), confidence interval (CI).
Crude model: unadjusted. Adjust model I: adjusted for age, sex, race, education level, marital status, poverty income ratio. Adjust model II: adjusted for age, sex, race, education level, marital status, poverty income ratio, BMI, physical activity, sleep duration, smoking status, alcohol use, antidepressant use, cardiovascular disease, hypertension, diabetes, dyslipidemia.

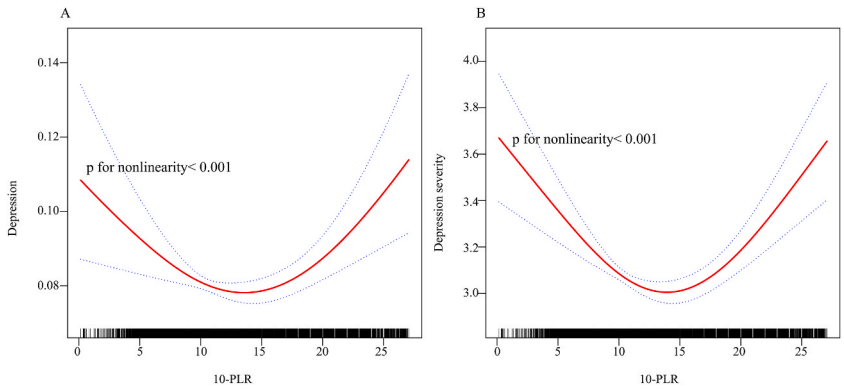

Fig. 2. The nonlinear relationship between 10-PLR and depression and depression severity by smooth curve fitting.(A) The nonlinear relation between 10-PLR and depression. (B) The nonlinear relation between 10-PLR and depression severity.

Table 4
Threshold effect analysis of 10-PLR on depression and severity of depression.

Outcome	Depression		Symptom severity	
	OR (95%CI)	p value	β (95%CI)	p value
Fitting model by two-piecewise linear regression Inflection point	12.15		12.15	
<12.15	0.96 (0.94, 0.98)	0.001	−0.06 (−0.09, −0.04)	<0.001
≥12.15	1.03 (1.01, 1.05)	<0.001	0.04 (0.02, 0.06)	<0.001
p for log likelihood ratio test	<0.001		<0.001	

Abbreviation: platelet to lymphocyte ratio (PLR), odds ratio(OR), confidence interval (CI).
Adjusted for age, sex, race, education level, marital status, poverty income ratio, BMI, physical activity, sleep duration, smoking status, alcohol use, antidepressant use, cardiovascular disease, hypertension, diabetes, dyslipidemia.

differences in sample size and methodology might explain these diverse results. In the present study, a complex, multistage probability sampling design was employed. And we excluded subjects who suffered from acute inflammation, cancer, or took medicine that could influence blood cell concentration. Moreover, we conducted comprehensive sensitivity analyses to evaluate the robustness of the association. In the future, consistent statistical methods and control variables will be required to replicate the results.

In clinical practice, a complete blood count is a convenient and low-cost routine examination. Clinicians need to pay attention to PLR. Our results suggest that one unit increase in 10-PLR is associated with a 4% reduced risk of depression when 10-PLR is < 12.15. When 10-PLR is ≥ 12.15, for each additional 10-PLR, the risk of depression increases by 3%. Similarly, one unit increase in 10-PLR is associated with a 0.06 reduction in severity score when 10-PLR is < 12.15; When 10-PLR is ≥ 12.15, for each additional 10-PLR, the severity score increases by 0.04. The results might help identify depression and evaluate the efficacy of treatment. Certainly, PLR is an alternative biomarker, and a comprehensive evaluation based on multiple inflammatory markers is recommended.

One interesting finding is the different linear patterns in various subgroups. Given the high heterogeneity of depression, we speculated that there was a complicated or even different inflammatory mechanism in different subgroups. Future research should explore the inflammatory mechanisms of different subgroups. Meanwhile, the diagnosis of depression is currently a symptom-based scientific classification. Analysis at the symptom level rather than the diagnostic level may move the process of immunopsychiatry forward.

There are some strengths in the present study. Firstly, the sample size is large enough to perform subgroup analyses. Moreover, a complex, stratified, multistage, and probability-based design is employed during the sampling. Rigorous inclusion and exclusion criteria were set to reduce the selection bias. Secondly, we handled the outliers via winsorization, adjusted for important potential confounding factors such as socioeconomic, medical, and behavioral variables, and evaluated the multicollinearity among variables to ensure the reliability of the results. Finally, in the subgroup analyses, we determined the nonlinear relationships to explore subgroup heterogeneity. Some limitations should be acknowledged. First, although the sample size and test power of this study are sufficient, we cannot infer causality from the results due to the cross-sectional nature of our analysis. Second, depression was diagnosed with a self-administered rating scale instead of a structured interview or a diagnosis by a clinician. Third, even though important confounding factors were taken into account and controlled for, it is still possible that residual or unmeasured confounding factors affected the results. Fourth, subjects suffering from hematological system diseases or other mental diseases were not considered for unavailable data. Lastly, our results were acquired based on the United States population and can't be extrapolated to other races. Additionally, it is unavailable for the population suffering from acute inflammation or having a history of cancer or malignancy. In the future, more longitudinal research based on large sample sizes will need to be replicated.

In summary, our findings suggest that PLR is associated with depression among adults in the United States. The relationship between PLR and depression, as well as depression severity, is nonlinear, and the inflection is 12.15. Additionally, inflammatory

mechanisms vary in different sociodemographic subgroups.

Author contribution statement

Moshui Shan: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Zhi Yang; Zhonghua Sun: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Yi Yang: Analyzed and interpreted the data; Wrote the paper.

Qi Cheng; Yu Pan: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

Data availability statement

Data associated with this study has been deposited at The datasets analyzed during the current study are publicly available for download from the National Center for Health Statistics at the Centers for Disease Control under the accession number https://www.cdc.gov/nchs/nhanes/index.htm.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e20127.

References

[1] G.S. Malhi, J.J. Mann, Depression, Lancet 392 (10161) (2018) 2299–2312.
[2] A.J. Ferrari, et al., Global variation in the prevalence and incidence of major depressive disorder: a systematic review of the epidemiological literature, Psychol. Med. 43 (3) (2013) 471–481.
[3] R.C. Kessler, et al., Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the national comorbidity survey replication, Arch. Gen. Psychiatr. 62 (6) (2005) 617–627.
[4] Y. Milaneschi, et al., Depression heterogeneity and its biological underpinnings: toward immunometabolic depression, Biol. Psychiatr. 88 (5) (2020) 369–380.
[5] E.I. Fried, The 52 symptoms of major depression: lack of content overlap among seven common depression scales, J. Affect. Disord. 208 (2017) 191–197.
[6] S. Beshai, et al., Relapse and recurrence prevention in depression: current research and future prospects, Clin. Psychol. Rev. 31 (8) (2011) 1349–1360.
[7] R.C. Kessler, E.J. Bromet, The epidemiology of depression across cultures, Annu. Rev. Publ. Health 34 (2013) 119–138.
[8] F. Hardeveld, et al., Prevalence and predictors of recurrence of major depressive disorder in the adult population, Acta Psychiatr. Scand. 122 (3) (2010) 184–191.
[9] G.D.a.I. Collaborators, Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019, Lancet 396 (10258) (2020) 1204–1222.
[10] G.B.D.M.D. Collaborators, Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019, Lancet Psychiatr. 9 (2) (2022) 137–150.
[11] P.A. Zunszain, N. Hepgul, C.M. Pariante, Inflammation and depression, Curr. Top Behav. Neurosci. 14 (2013) 135–151.
[12] E.I. Fried, et al., Using network analysis to examine links between individual depressive symptoms, inflammatory markers, and covariates, Psychol. Med. 50 (16) (2020) 2682–2690.
[13] B.D. Dunn, Helping depressed clients reconnect to positive emotion experience: current insights and future directions, Clin. Psychol. Psychother. 19 (4) (2012) 326–340.
[14] J.J. Mann, et al., Suicide prevention strategies: a systematic review, JAMA 294 (16) (2005) 2064–2074.
[15] L. Capuron, A.H. Miller, Cytokines and psychopathology: lessons from interferon-alpha, Biol. Psychiatr. 56 (11) (2004) 819–824.
[16] A. Feinstein, et al., The link between multiple sclerosis and depression, Nat. Rev. Neurol. 10 (9) (2014) 507–517.
[17] M.A. Stubbs, et al., Associations of symptoms of anxiety and depression with health-status, asthma control, dyspnoea, dysfunction breathing and obesity in people with severe asthma, Respir. Res. 23 (1) (2022) 341.
[18] G.E. Hodes, et al., Neuroimmune mechanisms of depression, Nat. Neurosci. 18 (10) (2015) 1386–1393.
[19] A.H. Miller, C.L. Raison, The role of inflammation in depression: from evolutionary imperative to modern treatment target, Nat. Rev. Immunol. 16 (1) (2016) 22–34.
[20] O. Kohler, et al., Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects: a systematic review and meta-analysis of randomized clinical trials, JAMA Psychiatr. 71 (12) (2014) 1381–1391.

[21] R. Haapakoski, et al., Cumulative meta-analysis of interleukins 6 and 1beta, tumour necrosis factor alpha and C-reactive protein in patients with major depressive disorder, Brain Behav. Immun. 49 (2015) 206–215.
[22] M.A. Beydoun, et al., Systemic inflammation is associated with depressive symptoms differentially by sex and race: a longitudinal study of urban adults, Mol. Psychiatr. 25 (6) (2020) 1286–1300.
[23] P. Frank, et al., Association between systemic inflammation and individual symptoms of depression: a pooled analysis of 15 population-based cohort studies, Am. J. Psychiatr. 178 (12) (2021) 1107–1118.
[24] V. Abbate, et al., The combination of inflammatory biomarkers as prognostic indicator in salivary gland malignancy, Cancers 14 (23) (2022).
[25] R. Niculescu, et al., Carotid plaque features and inflammatory biomarkers as predictors of restenosis and mortality following carotid endarterectomy, Int. J. Environ. Res. Publ. Health 19 (21) (2022).
[26] P. Puangsri, P. Ninla-Aesong, Potential usefulness of complete blood count parameters and inflammatory ratios as simple biomarkers of depression and suicide risk in drug-naive, adolescents with major depressive disorder, Psychiatr. Res. 305 (2021), 114216.
[27] L. Cai, et al., Relationship of mean platelet volume to mdd: a retrospective study, Shanghai Arch Psychiatry 29 (1) (2017) 21–29.
[28] H.N. Uçar, Ş. Eray, D. Murat, Simple peripheral markers for inflammation in adolescents with major depressive disorder, Psychiatry Clin. Psychopharmacol. 28 (3) (2018) 254–260.
[29] G. Özyurt, N.C. Binici, Increased neutrophil-lymphocyte ratios in depressive adolescents is correlated with the severity of depression, Psychiatr. Res. 268 (2018) 426–431.
[30] H. Kinoshita, et al., Higher neutrophil-lymphocyte ratio is associated with depressive symptoms in Japanese general male population, Sci. Rep. 12 (1) (2022) 9268.
[31] M. Su, X. Ouyang, Y. Song, Neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, and monocyte to lymphocyte ratio in depression: a meta-analysis, J. Affect. Disord. 308 (2022) 375–383.
[32] G. Zipf, et al., National health and nutrition examination survey: plan and operations, 1999-2010, Vital Health Stat. 1 (56) (2013) 1–37.
[33] A. Zalli, et al., Low-grade inflammation predicts persistence of depressive symptoms, Psychopharmacology (Berl) 233 (9) (2016) 1669–1678.
[34] K. Kroenke, R.L. Spitzer, J.B. Williams, The PHQ-9: validity of a brief depression severity measure, J. Gen. Intern. Med. 16 (9) (2001) 606–613.
[35] K. Kroenke, R.L. Spitzer, The PHQ-9: a New Depression Diagnostic and Severity Measure, SLACK Incorporated Thorofare, NJ, 2002, pp. 509–515.
[36] B. Levis, et al., Accuracy of Patient Health Questionnaire-9 (PHQ-9) for screening to detect major depression: individual participant data meta-analysis, BMJ 365 (2019) l1476.
[37] S.R. Horn, et al., Replication and reproducibility issues in the relationship between C-reactive protein and depression: a systematic review and focused meta-analysis, Brain Behav. Immun. 73 (2018) 85–114.
[38] M.F. O'Connor, et al., To assess, to control, to exclude: effects of biobehavioral factors on circulating inflammatory markers, Brain Behav. Immun. 23 (7) (2009) 887–897.
[39] P.K. Whelton, et al., ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American college of cardiology/American heart association task force on clinical practice guidelines, 2017, J. Am. Coll. Cardiol. 71 (19) (2018) e127–e248.
[40] A. Menke, et al., Prevalence of and trends in diabetes among adults in the United States, 1988-2012, JAMA 314 (10) (2015) 1021–1029.
[41] Dipak, F. A, Third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III) final report, Circulation 106 (25) (2002) 3143–3421.
[42] Y. Wei, et al., Characteristics of platelet-associated parameters and their predictive values in Chinese patients with affective disorders, BMC Psychiatr. 22 (1) (2022) 150.
[43] F. Meng, et al., Association of neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, and monocyte to lymphocyte ratio with depression: a cross-sectional analysis of the NHANES data, J. Affect. Disord. 315 (2022) 168–173.
[44] O. Ekinci, A. Ekinci, The connections among suicidal behavior, lipid profile and low-grade inflammation in patients with major depressive disorder: a specific relationship with the neutrophil-to-lymphocyte ratio, Nord. J. Psychiatr. 71 (8) (2017) 574–580.
[45] F. Kayhan, et al., Relationships of neutrophil-lymphocyte and platelet-lymphocyte ratios with the severity of major depression, Psychiatr. Res. 247 (2017) 332–335.
[46] A. Bahrami, et al., Depression in adolescent girls: relationship to serum vitamins a and E, immune response to heat shock protein 27 and systemic inflammation, J. Affect. Disord. 252 (2019) 68–73.