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Association between neutrophil to lymphocyte ratio and psoriasis: A cross-sectional study of National Health and Nutrition Examination Survey 2011–2014

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Abstract

Objectives: To investigate the association between the neutrophil to lymphocyte ratio (NLR) and psoriasis using a nationally representative sample of the US population.

Design: Cross-sectional study.

Setting: National Health and Nutrition Examination Survey 2011–2014.

Participants: A subsample of 8387 subjects aged 18 years and older were screened for inclusion, of whom 238 had a diagnosis of psoriasis.

Primary and secondary outcome measures: Psoriasis and the degree of psoriasis were defined according to participants' self-report. Weighted logistic regression models, subgroup analysis, and restricted cubic spline (RCS) were built to estimate the potential relationship of NLR with psoriasis.

Results: In the fully adjusted models, the fourth quartile of NLR was significantly and positively associated with the presence of psoriasis using the first quartile as reference (OR 2.22, 95%CI 1.27–3.87, P=0.01). Elevated NLR displayed an increase in risk of developing more severe psoriasis for the highest quartile (vs the lowest quartile) with OR of 2.43 (95%CI 1.10–5.36, P=0.003). The association between NLR and psoriasis differed across pre-specified subgroups by age, sex, race, income, and education. A nonlinear correlation of NLR with psoriasis was observed using univariable and multivariable RCS (all P for non-linearity <0.05).

Conclusions: Increasing NLR was independently associated with higher risk of psoriasis as well as higher severity of psoriatic lesions, and the link between NLR and the presence of psoriasis was complex and nonlinear. The potential role and value in the clinical diagnosis and prognostic assessment of NLR in psoriasis calls for further longitudinal studies.

Keywords: psoriasis; NHANES; public health.

Strengths and limitations of this study

1. This study included the use of a nationally representative sample and adopted strict methods of statistical adjustment to minimize potential confounding.
2. We have explored and identified for the first time the nonlinear relationship between NLR and psoriasis.
3. Any causal inferences cannot be made as this was a cross-sectional observational study.
4. The observed outcomes may be subject to recall bias because the definition of psoriasis and comorbidities relied on self-reports from the respondents.
5. Unknown and unmeasured confounders may have impacted our estimates.

Introduction

Psoriasis is a chronic and disfiguring skin disease affecting multiple systems and organs throughout the body that imposes tremendous physical and psychological burdens.[1] Approximately 3% of the population and an estimated 7.5 million adults in the United States have received a diagnosis of psoriasis.[2] It afflicts men and women at all ages in all countries.[3] People living with psoriasis are at a higher risk of developing other severe systemic diseases than is the general population, most commonly cardiovascular diseases and metabolic syndrome. In addition, those with greater psoriasis severity are more susceptible to gastrointestinal discomfort and mood disorders.[4] Psoriasis is an incurable disease with substantial impairment on patients' quality of life, and a large number of people suffer unnecessarily from psoriasis due to poor or delayed diagnosis, inadequate therapy, inappropriate care, and social stigma.[3] Therefore, the pressing need for raised awareness regarding psoriasis should be recognized.

Over the last 2 decades, the systemic inflammatory response induced by T lymphocytes has been considered to be predominant in the etiopathogenesis of psoriasis.[5] The neutrophil to lymphocyte ratio (NLR) is an inexpensive and validated marker of systemic inflammation, which can be readily accessible from existing datasets of routine laboratory tests.[6] The NLR was at first devised to offer a convenient and efficient measure to assess the intensity of systemic inflammation in critically ill patients following stressful events,[7] but later proved to exhibit prognostic value for clinical outcomes in various diseases.[8–11] In recent years, this index has gained much attention owing to its wide availability and ease of access.[12,13] Published study provided evidence that increasing NLR is a risk factor of mortality related to heart disease, chronic lower respiratory disease and kidney disease.[14] A higher NLR has been suggested as a predictor of adverse survival in subjects with cancer.[15] Moreover, there is a rapidly evolving body of literature pointing to the presence of abnormal NLR levels in some psychiatric disorders.[16–18]

Since inflammation serves a pivotal part in the causative mechanisms of psoriasis, several researchers have sought to shed light on the involvement of NLR in psoriasis. Emerging evidence exits that NLR and psoriasis were associated closely.[19–22] However, previous studies were primarily limited by the relatively small enrollment of participants, and results on the relationship between NLR and psoriasis severity remained inconclusive.[23,24] Hence, we processed data from the National Health and Nutrition Examination Survey (NHANES) from 2011 through 2014 to carry out a large-scale study based on the US civilian population. Our purposes were to unravel the potential association of NLR levels with psoriasis, and to clarify whether NLR could be a valuable parameter indicating the inflammatory conditions and the extent of disease in psoriasis patients.

Methods

Study design and participants

NHANES is a biennial cross-sectional survey with the aim of tracking and evaluating the health and dietary nutrition status of community-dwelling US population. The survey employs a complex, multi-stage cluster sampling method to ensure that it is representative of the nation as a whole. In this study, data from two NHANES cycles (2011–2012 and 2013–2014) were extracted for investigation, as these two cycles offer the most updated information on psoriasis. Our analyses were performed in conjunction with appropriate sampling weights to obtain unbiased estimates from the complicated NHANES sampling design. We included adult participants and excluded subjects who had missing or implausible data on self-reported psoriasis, neutrophil count, lymphocyte count and those with missing covariates. As a result, a total of 8387 individuals were ultimately included in the pool of eligible people. The flowchart of participant inclusion and exclusion is depicted in Figure 1. NHANES was approved by the National Center for Health Statistics Institutional Review Board, and participants provided written informed consent.

Diagnosis of psoriasis and measurement of NLR

The outcome was a diagnosis of psoriasis based on a self-reported history of being told by a physician that they had psoriasis. To evaluate the severity levels of skin involvement, respondents were then asked to accomplish a set of questionnaires, containing questions on the extent of psoriasis plaques on the body gauged by palms. Participants were required to characterize their psoriasis into a category, including (i) little or no psoriasis, (ii) only a few patches, (iii) scattered patches and (iv) extensive psoriasis. For the sake of avoiding an increase in sampling error, we merged (ii), (iii), and (iv), which had smaller frequencies. These survey questionnaires were administered using the Computer-Assisted Personal Interviewing (CAPI) system by highly trained personnel.

Our predictor variables of prime interest were NLR levels, calculated as dividing the neutrophil count by the lymphocyte count, which can be derived from laboratory data. Blood specimen collection was undertaken at the Mobile Examination Centers (MECs). The Beckman Coulter methodology was applied to figure out complete blood count parameters.

Assessment of covariates

On the basis of published literature, we considered sociodemographic,[25] lifestyle,[26] and comorbid factors[27,28] that may affect both psoriasis and NLR as potential confounders, including age, sex, race, poverty income ratio (PIR), education, body mass index (BMI), smoking, alcohol intake, a history of hypertension, diabetes, and cardiovascular disease (CVD). We utilized the same terminology as NHANES to describe racial categories. The PIR was measured by dividing the household's or individual's income by a specific poverty guideline. we classified the PIR into 3 levels: low income (≤1.3), medium income (>1.3 to 3.5), and high income (>3.5). Education attainment was grouped as high school or less, some college or an AA degree, and college graduate or above. Smokers were separated into the following categories: never smokers (those who have either never smoked or have smoked less than 100 cigarettes

during their lifetime), former smokers (smoked at least 100 cigarettes but had quit currently), and current smokers. We defined alcohol drinker as someone who had consumed at least 12 drinks in any given year. Comorbid conditions were ascertained by respondent self-reports.

Statistical analysis

We used the STROBE cross-sectional checklist when writing our report.[29] We first compared the baseline characteristics among individuals with and without psoriasis, using Student's t-test for normally distributed quantitative variables, nonparametric Kruskal-Wallis test for skewed quantitative variables, and chi-square test for qualitative variables. Descriptive statistics were presented as mean (SD) or median (interquartile range) for continuous variables and the number (percentage) of participants for categorical variables. Binary and multinomial logistic regression models were then fitted to estimate the relation of NLR with psoriasis and psoriasis lesion severity, respectively. Three different multivariate models were developed. Model 1 was a basic unadjusted model. In model 2, adjustments were made for age, sex, ethnicity, PIR, and educational attainment. Model 3 included all variables in model 2 plus confounding medical comorbidities. Linear trend tests were done by treating the median concentration of each NLR quartile as a continuous variable. We entered NLR into logistic regression analysis as a continuous variable and as a quartile categorical variable to explore the strength of risk association with psoriasis. Stratified analyses were conducted using multivariate logistic regression according to age (18–39, 40–59, 60–79, and ≥80 years), sex, race, PIR and education at baseline, incorporating a two-way interaction term between NLR and subgroup status. Then, we employed restricted cubic splines (RCS) with 4 knots to model a nonlinear relationship between NLR and the presence of psoriasis. All analyses were done using the software package R (version 4.1.3). $P<0.05$ (two–sided) were considered statistically significant.

Results

Of 11977 participants aged over 18 years from NHANES 2011-2014 cycles, those with missing relevant data (n=3590) were excluded from analyses, leaving 238 adults with psoriasis and 8149 adults without psoriasis for inclusion. 4254 were female (50.7%), and 4133 were male (49.3%), with an average age of 48.7 years.

Table 1 illustrated the demographic, lifestyle and clinical features of included subjects stratified by the presence and absence of psoriasis. In comparison to the group without psoriasis, individuals with psoriasis were older (51.3 vs 47.2, $P<0.001$) and more likely to be non-Hispanic whites (79.7% vs 68.4%, $P=0.001$), but less likely to be current smokers (10.9% vs 20.0%, $P<0.001$). The prevalence of hypertension (42.2% vs 32.7%, $P=0.032$), diabetes (16.7% vs 10.0%, $P=0.006$), and CVD (12.1% vs 8.2%, $P=0.024$) at baseline were higher among participants with psoriasis than those without psoriasis. In addition, higher levels of NLR were observed in patients who had psoriasis (2.4 vs 2.0, $P<0.001$). The group of psoriasis and non-psoriasis did not differ significantly with regard to sex, income, educational attainment, BMI, and alcohol use.

The results of binary logistic regression were summarized in Table 2. In univariate models, NLR as a continuous variable was associated with 19% increased risk of psoriasis (OR 1.19, 95%CI 1.11–1.28, P<0.001), and the OR for quartile 4 was significantly higher than the OR for quartile 1 (Q4 vs Q1: OR 2.62, 95%CI 1.58–4.32, P_{trend}<0.001). The association between NLR and psoriasis persisted even after adjusting for sociodemographic and lifestyle variables (OR 1.16, 95%CI 1.08–1.24, P<0.001). In the fully adjusted models, those with highest quartile of NLR had more than two times greater odds of having psoriasis than those with the lowest quartile (Q4 vs Q1: OR 2.22, 95%CI 1.27–3.87, P=0.01).

Findings from the multinomial logistic regression were detailed in Table 3. A pronounced correlation was found between NLR and the degree of psoriasis, except for a slight difference that did not attain statistical significance between NLR and those with little or no psoriasis after adjusting for all variables, regardless of NLR being used as a continuous (OR 1.08, 95%CI 1.00–1.17, P=0.06) or quartile variable (Q4 vs Q1: OR 2.04, 95%CI 1.00–4.17, P=0.052). In all models, the ORs of psoriasis severity augmented as the quartile of NLR upgraded. Compared to participants with NLR≤1.47 (Q1), those with NLR>2.63 (Q4) had a significant increase in the odds of "Few patches to extensive psoriasis" (Q4 vs Q1: OR 2.43, 95%CI 1.10–5.36, P=0.003). Elevated NLR value was associated with higher risk of developing more severe psoriasis.

Stratified analyses were undertaken by dividing the participants into pre-specified subgroups of sociodemographic position at baseline, to assess the consistency of the relationship between the main predictors and outcome (supplemental table S1). Increased NLR was a risk factor for the presence of psoriasis in participants aged 40 to 59 (OR 1.28, 95%CI 1.05–1.56, P=0.019), and those aged 60 to 79 (OR 1.24, 95%CI 1.09–1.41, P=0.004). For each unit increase of NLR, the adjusted OR for psoriasis risk was 1.22 in female (P=0.016), 1.13 in male (P=0.03), 1.17 in non-Hispanic white (P=0.006), 2.50 in other race (P=0.023), and 1.21 in participants with medium PIR (P=0.021). As for the subgroup stratified by education level, the association of NLR with psoriasis was non-significant only in the "Some College or AA degree" stratification (OR 0.96, 95%CI 0.77–1.20, P=0.693). Moreover, there was no evidence of interaction effects between multiple stratification factors and NLR (all P for interaction >0.1). As displayed in Figure 2, The results of RCS analysis confirmed that NLR was related with psoriasis in a non-linear manner (all P for non-linearity <0.05).

Discussion

In this observational study, we analyzed standardized data from a large cohort of participants in a US population sample. Our study identified that the level of NLR was raised in psoriasis patients and positively correlated with the severity of involvement. Taking into account that imbalance in the baseline characteristics of participants may modify the association between NLR and psoriasis, adjustments were made for potential confounders in regression analysis; nevertheless, we still detected a significant association of NLR with psoriasis, indicating that this association cannot be solely attributed to risk factors and that NLR could independently predict either the presence

of psoriasis or the severity of psoriatic skin lesions. Furthermore, we also found evidence that NLR was correlated with psoriasis in a sophisticated nonlinear fashion.

Neutrophils and T lymphocytes play a critical role in the development and progression of psoriasis. Massive infiltration of neutrophils within dermis and epidermis is one of the classic histological features of psoriasis.[30] As the first line of defense against immune attack, neutrophils are actively recruited to the affected skin and responsible for propagating inflammation.[31] Respiratory burst, degranulation and the neutrophil extracellular traps formation are the main offensive mechanisms of neutrophils, which contribute to the immunopathogenesis of psoriasis.[32] T lymphocytes that produce high levels of IL-17 driven by IL-23 has been corroborated as the pathogenic culprits in psoriasis.[5] IL-17 mediates effects on keratinocytes, which facilitates recruitment of more IL-17-producing lymphocytes and neutrophils into inflamed psoriatic lesions, setting up a self-amplifying feedback loop to maintain and exacerbate the inflammatory events in psoriasis.[5,33] NLR originating from the ratio of neutrophils to lymphocytes in peripheral blood may have the ability to mirror the balance between innate and adaptive immune response.[28] Aberrant NLR values are representative of inflammatory conditions in the body, but as of now there is no universally acceptable NLR cutoff value that defines its range of normalcy.[34] The circulating levels of neutrophils and lymphocytes vary from person to person, and fluctuate over the course of an individual's disease. Besides, patients' medication usage has an impact on peripheral leukocyte levels. Thus, it remains a challenge to make sure that NLR become a reasonable and individually standardized predictor of health outcomes.

Recently, a number of investigators have looked into the diagnostic and prognostic value of NLR in psoriasis. In an observational study comprising of 60 psoriasis patients along with 50 healthy controls, elevated NLR values were found in patient group when compared to controls, which is in line with our results.[35] Prior studies have shown that greater NLR values were associated with higher scores on Psoriasis Area and Severity Index (PASI).[36,37] Similar findings were mirrored in another study that reported a significant elevation of NLR in patients with PASI scores of 10 or more compared to patients with PASI scores of less than 10.[20] Nevertheless, several studies failed to find significant association between NLR and the clinical severity of psoriasis.[38,39] Moreover, NLR was proposed to be a robust predictor for the emergence of psoriatic arthritis in patients who had psoriasis.[20,40,41] It has been reported that NLR was capable of predicting all-cause mortality and cardiovascular risk,[42] and the index might be a novel biomarker to assess the risk of subclinical atherosclerosis in patients with psoriasis.[22,43] NLR was believed to possess the potential of predicting treatment response, because a remarkable reduction of NLR was observed in psoriasis patients who received effective treatment.[44,45] As mentioned above, NLR levels were raised in psoriasis patients and declined after treatment, whereas initial works investigating the relation of NLR with psoriasis severity produced inconsistent results. These studies were limited by sample size and bias, and the association between NLR and psoriasis may be influenced by sociodemographic characteristics,[25] personal health habits,[46,47] and individual medical history.[48,49] Given that too high or too low levels of NLR might

signal a pathological state, there is a strong likelihood of a nonlinear relationship between NLR and psoriasis, that has not yet been explored and identified in the earlier researches.

Our study has some strengths and clinical implications. Foremost, we used a nationally representative sample from NHANES, which offered sufficient statistical power to draw a conclusion and made our findings likely generalizable to the entire US population. The NHANES database contains comprehensive information on sociodemographic status, lifestyle exposures, physical measurements, and medical history, which enabled us to control for numerous confounding factors. Additionally, NLR is a readily available index and it may assist clinicians in identifying patients at high risk of severe psoriasis. Despite the large sample size and adjustments for potential confounders in our study, several limitations should be noted. First, as this was a cross-sectional observational study, inferences regarding whether this association is or is not causal cannot be drawn. Additional prospective studies are thus needed to ascertain if such a longitudinal relationship exists. Furthermore, because the definition of psoriasis and comorbidities (e.g., hypertension, diabetes, and CVD) relied on self-reports from the respondents instead of diagnoses made by two or more experienced dermatologists, the observed outcomes may be subject to recall bias. Second, although we controlled for multiple potential confounders, unknown and unmeasured confounders may have impacted our estimates. For instance, immunomodulatory drugs have been linked to both psoriasis and NLR,[50,51] their usage may influence the correlation between the two. However, information on the use of immunomodulatory drugs is not available in the current NHANES data set. Future rigorously designed and sufficiently powered studies with greater use of immunomodulatory drugs may offer valuable insights into the complex interplay between psoriasis and NLR.

Conclusion

In summary, our study elucidated that NLR was independently associated with psoriasis and that the association was nonlinear rather than simply linear. We also found evidence in favor of a clear link between NLR levels and psoriasis severity. NLR, which reflects a heightened state of systemic inflammation, might become an objective indicator in conveying warning alerts for patients at risk of severe psoriasis, and be accounted as a monitoring tool in management of psoriasis. However, further research is warranted to elaborate the detailed mechanism of NLR in psoriasis.

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Author Contributions

JH designed the research, conducted statistical analysis, and wrote the manuscripts. ML

and NL directed the study and revised the manuscripts. All authors contributed to the article and approved the submitted version.

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Competing interests None declared.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Ethics approval

NHANES was approved by the National Center for Health Statistics Institutional Review Board, and participants provided written informed consent.

Data availability statement

Data are available in a public, open access repository. Open access data are available on the NHANES website. (www.cdc.gov/nchs/nhanes/).

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Figure legends

Figure 1. Flow diagram of participants screened from National Health and Nutrition Examination Survey (NHANES) 2011 to 2014.
Covariates included age, sex, race, income, education, body mass index, smoking, alcohol use, history of hypertension, diabetes and cardiovascular disease.

Figure 2. Nonlinear association between NLR and psoriasis by restricted cubic spline regression.
Fitted regression line was shown as red solid line; black dashed lines indicated where the OR equals 1; 95%CI is represented by shaded region.

Table 1 Baseline characteristics of participants with and without psoriasis.

Characteristic	Without psoriasis (n=8149)	With psoriasis (n=238)	P value
Age, mean (SD), y	47.2 (17.0)	51.3 (15.4)	<0.001
Sex			0.408
Female	4128 (51.0)	126 (53.8)	
Male	4021 (49.0)	112 (46.2)	
Race			0.001
Mexican American	904 (7.9)	15 (4.1)	
Other Hispanic	759 (5.8)	24 (5.1)	
Non-Hispanic White	3467 (68.4)	136 (79.7)	
Non-Hispanic Black	1842 (10.7)	28 (4.8)	
Non-Hispanic Asian	931 (4.6)	26 (4.0)	
Other Race	246 (2.6)	9 (2.3)	
Poverty income ratio			0.81
Low	2793 (23.9)	84 (22.7)	
Medium	2800 (34.5)	76 (33.8)	
High	2556 (41.6)	78 (43.5)	
Education			0.405
High school or less	3444 (35.4)	91 (30.4)	
Some college or AA degree	2559 (32.8)	79 (33.4)	
College graduate or above	2146 (31.8)	68 (36.2)	
BMI			0.071
Underweight (<18.5)	133 (1.4)	0 (0.0)	
Normal (18.5 to <25)	2382 (28.8)	52 (20.8)	
Overweight (25 to <30)	2618 (33.2)	89 (41.6)	
Obese (30 or greater)	3016 (36.6)	97 (37.6)	
Smoking status			<0.001

Never smoker	4594 (56.2)	121 (49.4)	
Former smoker	1888 (23.9)	82 (39.7)	
Current smoker	1667 (20.0)	35 (10.9)	
Alcohol drinker			0.899
No	2157 (20.6)	65 (20.3)	
Yes	5992 (79.4)	173 (79.7)	
Hypertension			0.032
No	5207 (67.3)	129 (57.8)	
Yes	2942 (32.7)	109 (42.2)	
Diabetes			0.006
No	7090 (90.0)	190 (83.3)	
Yes	1059 (10.0)	48 (16.7)	
History of CVD			0.024
No	7352 (91.8)	197 (87.9)	
Yes	797 (8.2)	41 (12.1)	
NLR	2.0 (1.5, 2.6)	2.4 (1.8, 3.2)	<0.001

Median (SD) or median (interquartile range) for continuous; n (%) for categorical.
Abbreviation: BMI, body mass index; CVD, cardiovascular disease; NLR, neutrophil to lymphocyte ratio.

Table 2 Association between neutrophil to lymphocyte ratio (NLR) and the presence of psoriasis.

Variable	Model 1		Model 2		Model 3	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
NLR (continuous)	1.19 (1.11, 1.28)	<0.001	1.16 (1.08, 1.24)	<0.001	1.15 (1.05, 1.25)	0.006
NLR (quartile)						
Q1 (≤1.47)	Reference		Reference		Reference	
Q2 (1.47–1.96)	1.14 (0.67, 1.94)	0.613	1.05 (0.61, 1.82)	0.849	1.05 (0.59, 1.89)	0.848
Q3 (1.96–2.63)	1.48 (0.93, 2.36)	0.095	1.34 (0.83, 2.18)	0.218	1.31 (0.77, 2.24)	0.282
Q4 (>2.63)	2.62 (1.58, 4.32)	<0.001	2.25 (1.35, 3.76)	0.004	2.22 (1.27, 3.87)	0.01
P for trend	<0.001		0.001		0.004	

Model 1: no covariates were adjusted. Model 2: adjusted for age, sex, race, income, education. Model 3: adjusted for age, sex, race, income, education, body mass index, smoking status, alcohol use, history of hypertension, diabetes and cardiovascular disease.

Table 3 Association between neutrophil to lymphocyte ratio (NLR) and the degree of psoriasis.

Model	Psoriasis severity	Continuous OR (95% CI)	P value	OR (95%CI) Q1	Q2	Q3	Q4	P value
Model 1	Little or no psoriasis	1.13 (1.06, 1.21)	<0.001	Reference	1.30 (0.59, 2.85)	1.81 (0.97, 3.35)	2.41 (1.30, 4.48)	0.01
	Few patches to extensive psoriasis	1.22 (1.11, 1.34)	<0.001	Reference	0.95 (0.37, 2.44)	1.09 (0.47, 2.55)	2.86 (1.34, 6.07)	<0.001
Model 2	Little or no psoriasis	1.10 (1.03, 1.18)	0.008	Reference	1.18 (0.52, 2.72)	1.62 (0.85, 3.09)	2.07 (1.08, 3.96)	0.034
	Few patches to extensive psoriasis	1.20 (1.10, 1.31)	<0.001	Reference	0.89 (0.35, 2.29)	1.00 (0.41, 2.44)	2.49 (1.17, 5.29)	0.003
Model 3	Little or no psoriasis	1.08 (1.00, 1.17)	0.06	Reference	1.21 (0.49, 2.96)	1.61 (0.80, 3.22)	2.04 (1.00, 4.17)	0.052
	Few patches to extensive psoriasis	1.19 (1.07, 1.33)	0.004	Reference	0.88 (0.33, 2.34)	0.95 (0.36, 2.54)	2.43 (1.10, 5.36)	0.003

In multinomial logistic regression models, association between NLR and psoriasis severity was tested with patients never diagnosed with psoriasis as the reference group. Q1, NLR≤1.47; Q2, NLR 1.47–1.96; Q3, NLR 1.96–2.63; Q4, NLR>2.63.

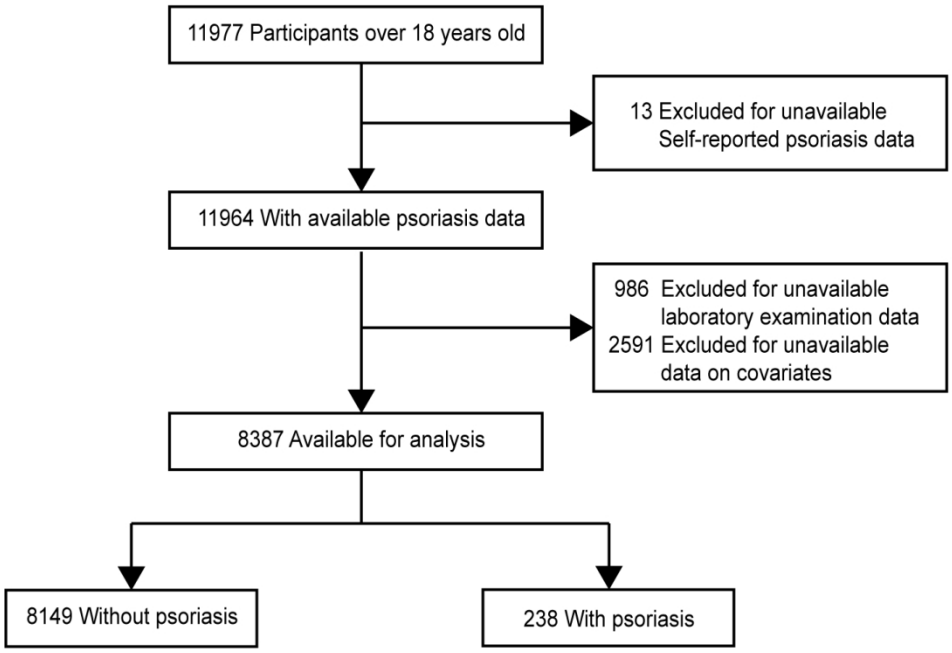

Figure 1. Flow diagram of participants screened from National Health and Nutrition Examination Survey (NHANES) 2011 to 2014. Covariates included age, sex, race, income, education, body mass index, smoking, alcohol use, history of hypertension, diabetes and cardiovascular disease.

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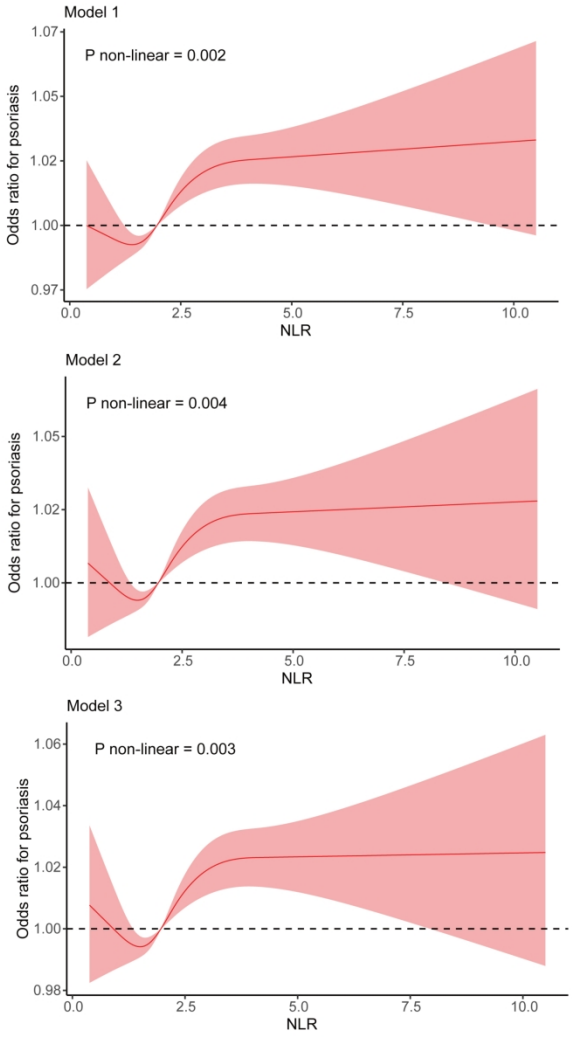

Figure 2. Nonlinear association between NLR and psoriasis by restricted cubic spline regression. Fitted regression line was shown as red solid line; black dashed lines indicated where the OR equals 1; 95%CI is represented by shaded region.

210x297mm (300 x 300 DPI)

Table S1 Subgroup analysis for the association between neutrophil to lymphocyte ratio (NLR) as a continuous variable and the presence of psoriasis.

Subgroup	OR (95%CI)	P value	P for interaction
Age, y			0.118
18-39	1.01 (0.74, 1.37)	0.972	
40-59	1.28 (1.05, 1.56)	0.019	
60-79	1.24 (1.09, 1.41)	0.004	
≥80	0.99 (0.82, 1.19)	0.921	
Sex			0.301
Female	1.22 (1.05, 1.43)	0.016	
Male	1.13 (1.01, 1.25)	0.03	
Race			0.984
Mexican American	1.04 (0.86, 1.25)	0.613	
Other Hispanic	1.17 (0.83, 1.64)	0.331	
Non-Hispanic White	1.17 (1.05, 1.30)	0.006	
Non-Hispanic Black	1.16 (0.96, 1.39)	0.114	
Non-Hispanic Asian	1.14 (0.74, 1.76)	0.522	
Other Race	2.50 (1.17, 5.34)	0.023	
Poverty income ratio			0.63
Low	1.09 (0.88, 1.35)	0.397	
Medium	1.21 (1.03, 1.41)	0.021	
High	1.14 (0.93, 1.39)	0.185	
Education			0.181
High school or less	1.18 (1.07, 1.31)	0.004	
Some college or AA degree	0.96 (0.77, 1.20)	0.693	
College graduate or above	1.26 (1.05, 1.52)	0.019	

Each stratification was adjusted for all covariates except the stratification factor itself.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-5
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	4,5
		(*e*) Describe any sensitivity analyses	5
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	4
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5
		(b) Indicate number of participants with missing data for each variable of interest	4,5
Outcome data	15*	Report numbers of outcome events or summary measures	5
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6
		(*b*) Report category boundaries when continuous variables were categorized	6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6
Discussion			
Key results	18	Summarise key results with reference to study objectives	6-7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7-8
Generalisability	21	Discuss the generalisability (external validity) of the study results	8
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Association between the neutrophil-to-lymphocyte ratio and psoriasis: A cross-sectional study of the National Health and Nutrition Examination Survey 2011–2014

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Association between the neutrophil-to-lymphocyte ratio and psoriasis: A cross-sectional study of the National Health and Nutrition Examination Survey 2011–2014

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Abstract

Objectives: To investigate the association between the neutrophil-to-lymphocyte ratio (NLR) and psoriasis.

Design: Cross-sectional study.

Setting: National Health and Nutrition Examination Survey 2011–2014.

Participants: A subsample of 8387 individuals aged 18 years and older were screened for inclusion, of whom 238 reported a diagnosis of psoriasis.

Primary and secondary outcome measures: Psoriasis and the severity of psoriasis were defined according to participants' self-reports. Weighted logistic regression, subgroup, and restricted cubic spline (RCS) analyses were conducted to estimate the potential relationship of the NLR with psoriasis.

Results: In the fully adjusted models, the fourth quartile of the NLR was significantly and positively associated with the presence of psoriasis using the first quartile as a reference (OR 2.22, 95% CI 1.27–3.87, P=0.01). Elevated NLR was associated with an increased odds of having more severe psoriasis for the highest quartile (vs. the lowest quartile), with an OR of 2.43 (95% CI 1.10–5.36, P=0.003). The association between the NLR and psoriasis differed across prespecified subgroups by age, sex, race, income, and education. A nonlinear correlation of the NLR with psoriasis was observed using univariable and multivariable RCS (all P for nonlinearity <0.05).

Conclusions: The NLR was nonlinearly and positively correlated with the presence of psoriasis, and our findings suggest a significant association between the NLR and the severity of psoriasis. The potential role and value in the clinical diagnosis and prognostic assessment of the NLR in psoriasis calls for further longitudinal studies.

Keywords: psoriasis; NHANES; public health.

Strengths and limitations of this study

1. This study included the use of a nationally representative sample and adopted strict methods of statistical adjustment to minimize potential confounding.
2. We have explored and identified for the first time the nonlinear relationship between the NLR and psoriasis.
3. Causal inferences cannot be made, as this was a cross-sectional observational study.
4. The observed outcomes may be subject to recall bias because the diagnosis and severity of psoriasis were based on respondents' self-reports.
5. Unknown and unmeasured confounders may have impacted our estimates.

Introduction

Psoriasis is a chronic and disfiguring skin disease affecting multiple systems and organs throughout the body that imposes tremendous physical and psychological burdens (1). Approximately 3% of the population and an estimated 7.5 million adults in the United States have received a diagnosis of psoriasis (2). It afflicts men and women at all ages in all countries (3). People living with psoriasis are at a higher risk of developing other severe systemic diseases than the general population, most commonly cardiovascular diseases and metabolic syndrome. Numerous studies have suggested associations between psoriasis and other comorbidities, such as gastrointestinal disease, kidney disease, malignancy, and mood disorders (4). Psoriasis is an incurable disease that substantially impairs patients' quality of life, and a large number of people suffer unnecessarily from psoriasis due to poor or delayed diagnosis, inadequate therapy, inappropriate care, and social stigma (3). Therefore, the pressing need for increased awareness regarding psoriasis should be recognized.

Over the last 2 decades, the systemic inflammatory response induced by T lymphocytes has been considered to be predominant in the etiopathogenesis of psoriasis (5). The neutrophil-to-lymphocyte ratio (NLR) is an inexpensive and validated marker of systemic inflammation that can be readily calculated from existing datasets of routine laboratory tests (6). The NLR was first devised to offer a convenient and efficient measure to assess the intensity of systemic inflammation in critically ill patients following stressful events (7) but later proved to exhibit prognostic value for clinical outcomes in various diseases (8-11). In recent years, this index has gained much attention owing to its wide availability and ease of access (12, 13). A published study has reported that an increasing NLR is a risk factor for mortality related to heart disease, chronic lower respiratory disease and kidney disease (14). An increased NLR has been suggested as a predictor of poor survival in individuals with cancer (15). Moreover, there is a rapidly evolving body of literature indicating the presence of abnormal NLR in some psychiatric disorders (16-18).

Since inflammation plays a pivotal role in the causative mechanisms of psoriasis, several researchers have sought to shed light on the involvement of the NLR in psoriasis. Emerging evidence indicates that the NLR and psoriasis are closely associated (19-22). However, previous studies were primarily limited by the relatively small enrolment of participants, and results on the relationship between the NLR and psoriasis severity remain inconclusive (23, 24). Hence, we processed data from the National Health and Nutrition Examination Survey (NHANES) from 2011 through 2014 to carry out a large-scale study based on the US civilian population. Our purposes were to unravel the potential association of the NLR with psoriasis, and to clarify whether the NLR could be a valuable parameter indicating the extent of inflammation and disease in psoriasis patients.

Methods

Study design and participants

The NHANES is a biennial cross-sectional survey with the aim of tracking and evaluating the health and dietary nutrition status of community-dwelling US populations (25). The survey employs a complex, multistage cluster sampling method to ensure that it is representative of the nation as a whole (26). In this study, data from two NHANES cycles (2011–2012 and 2013–2014) were extracted for investigation, as these two cycles offer the most updated information on psoriasis (27). Our analyses were performed in conjunction with appropriate sampling weights to obtain unbiased estimates from the complicated NHANES sampling design (26). We included adult participants and excluded individuals who had missing or implausible data on self-reported psoriasis, neutrophil count, or lymphocyte count and those with missing covariates. As a result, a total of 8387 individuals were ultimately included in the pool of eligible people. The flowchart of participant inclusion and exclusion is depicted in Figure 1. NHANES was approved by the National Center for Health Statistics Institutional Review Board, and participants provided written informed consent.

Diagnosis of psoriasis and measurement of the NLR

The outcome was a diagnosis of psoriasis based on a self-reported history of being told by a physician that they had psoriasis. To evaluate the severity levels of skin involvement, respondents were then asked to complete a set of questionnaires containing questions on the extent of psoriasis plaques on the body gauged by the number of palm-sized patches. Participants were needed to characterize their psoriasis into a category, including (i) little or no psoriasis, (ii) only a few patches, (iii) scattered patches and (iv) extensive psoriasis. For the sake of avoiding an increase in sampling error, we merged (ii), (iii), and (iv), which had smaller frequencies.

Our predictor variable of prime interest was the NLR, calculated by dividing the neutrophil count by the lymphocyte count, which can be derived from laboratory data. Blood specimen collection was undertaken at mobile examination centers (MECs). The Beckman Coulter methodology was applied to determine complete blood count parameters (28).

Assessment of covariates

On the basis of published literature, we considered sociodemographic (29), lifestyle (30), and comorbid factors (31, 32) that may affect both psoriasis and NLR as potential confounders, including age, sex, race, poverty income ratio (PIR), education, body mass index (BMI), smoking, alcohol consumption, and a history of hypertension, diabetes, and cardiovascular disease (CVD). We utilized the same terminology as NHANES to describe racial categories. The PIR was measured by dividing the household's or individual's income by a specific poverty guideline. We classified the PIR into 3 levels: low income (≤1.3), medium income (>1.3 to 3.5), and high income (>3.5). Educational attainment was grouped as high school or less, some college or an AA degree, and college graduate or above. Smokers were separated into the following categories: never smokers (those who have either never smoked or have smoked less than 100 cigarettes during their lifetime), former smokers (smoked at least 100 cigarettes but had quit currently), and current smokers. We defined alcohol drinkers as

those who had consumed at least 12 drinks in any given year. Comorbid conditions were ascertained by respondent self-reports.

Statistical analysis

We used the STROBE cross-sectional checklist when writing our report (33). We first compared the baseline characteristics among individuals with and without psoriasis, using Student's t test for normally distributed quantitative variables, the nonparametric Kruskal–Wallis test for skewed quantitative variables, and the chi-square test for qualitative variables. Descriptive statistics are presented as the mean (SD) or median (interquartile range) for continuous variables and the number (percentage) of participants for categorical variables. Binary and multinomial logistic regression models were then fitted to estimate the relation of the NLR with psoriasis and psoriasis lesion severity, respectively. Three different multivariate models were developed. Model 1 was a basic unadjusted model. In Model 2, adjustments were made for age, sex, ethnicity, PIR, and educational attainment. Model 3 included all variables in Model 2 plus BMI, smoking, alcohol consumption status and medical comorbidities (hypertension, diabetes, and CVD). Linear trend tests were performed by treating the median concentration of each NLR quartile as a continuous variable. We entered the NLR into logistic regression analysis as a continuous variable and as a quartile categorical variable to explore the strength of risk association with psoriasis. Stratified analyses were conducted using multivariate logistic regression according to age (18–39, 40–59, 60–79, and ≥80 years), sex, race, PIR and education at baseline, incorporating a two-way interaction term between the NLR and subgroup status. We then used restricted cubic spline (RCS) regressions with four knots to detect the possible nonlinear relationship of the NLR with psoriasis. All analyses were performed using R software (version 4.1.3). $P<0.05$ (two–sided) was considered indicative of statistical significance.

Results

Of 11977 participants aged over 18 years from the 2011-2014 NHANES cycles, those with missing relevant data (n=3590) were excluded from the analyses, leaving 238 adults with psoriasis and 8149 adults without psoriasis for inclusion. A total of 4254 were female (50.7%), and 4133 were male (49.3%), with an average age of 48.7 years.

Table 1 illustrates the demographic, lifestyle and clinical features of the included subjects stratified by the presence and absence of psoriasis. In comparison to the group without psoriasis, individuals with psoriasis were older (51.3 vs. 47.2, $P<0.001$) and more likely to be non-Hispanic whites (79.7% vs. 68.4%, $P=0.001$) but less likely to be current smokers (10.9% vs. 20.0%, $P<0.001$). The prevalence of hypertension (42.2% vs. 32.7%, $P=0.032$), diabetes (16.7% vs. 10.0%, $P=0.006$), and CVD (12.1% vs. 8.2%, $P=0.024$) at baseline was higher among participants with psoriasis than among those without psoriasis. In addition, higher NLR levels were observed in patients who had psoriasis (2.4 vs. 2.0, $P<0.001$). The psoriasis and nonpsoriasis groups did not differ

significantly with regard to sex, income, educational attainment, BMI, or alcohol consumption.

The results of binary logistic regression are summarized in Table 2. In univariate models, NLR as a continuous variable was associated with a 19% increased risk of psoriasis (OR 1.19, 95% CI 1.11–1.28, P<0.001), and the OR for quartile 4 was significantly higher than the OR for quartile 1 (Q4 vs. Q1: OR 2.62, 95% CI 1.58–4.32, P_{trend}<0.001). The association between the NLR and psoriasis persisted even after adjusting for sociodemographic variables (OR 1.16, 95% CI 1.08–1.24, P<0.001). In the fully adjusted models, those with the highest quartile of the NLR had more than two times greater odds of having psoriasis than those with the lowest quartile (Q4 vs. Q1: OR 2.22, 95% CI 1.27–3.87, P=0.01).

Findings from the multinomial logistic regression are detailed in Table 3. A pronounced correlation was found between the NLR and the severity of psoriasis, except for a slight nonsignificant relationship between the NLR and those with little or no psoriasis after adjusting for all variables, regardless of whether the NLR was used as a continuous (OR 1.08, 95% CI 1.00–1.17, P=0.06) or quartile variable (Q4 vs. Q1: OR 2.04, 95% CI 1.00–4.17, P=0.052). In all models, the ORs of psoriasis severity increased as the quartile of the NLR increased. Compared to participants with an NLR≤1.47 (Q1), those with an NLR>2.63 (Q4) had a significant increase in the odds of "few patches to extensive psoriasis" (Q4 vs. Q1: OR 2.43, 95% CI 1.10–5.36, P=0.003). High NLR values were associated with having more severe psoriasis.

Stratified analyses were undertaken by dividing the participants into prespecified subgroups of sociodemographic position at baseline to assess the consistency of the relationship between the main predictors and outcome (Supplemental Table S1). An increased NLR was a risk factor for the presence of psoriasis in participants aged 40 to 59 (OR 1.28, 95% CI 1.05–1.56, P=0.019) and 60 to 79 (OR 1.24, 95% CI 1.09–1.41, P=0.004) years. For each unit increase in the NLR, the adjusted OR for psoriasis risk was 1.22 in females (P=0.016), 1.13 in males (P=0.03), 1.17 in non-Hispanic white individuals (P=0.006), 2.50 in other races (P=0.023), and 1.21 in participants with a medium PIR (P=0.021). For the subgroup stratified by education level, the association of the NLR with psoriasis was nonsignificant only in the "Some College or AA degree" stratification (OR 0.96, 95% CI 0.77–1.20, P=0.693). Moreover, there was no evidence of interaction effects between multiple stratification factors and the NLR (all P for interaction >0.1).

To flexibly model and visualize the relationship between the NLR and psoriasis, restricted cubic splines were used (Figure 2). We observed a strong nonlinear association between the NLR and psoriasis. In Model 1, the OR of psoriasis decreased continuously before the NLR reached 1.40, after which it started to increase and became relatively stable when the NLR reached 2.97 or higher (P for nonlinearity=0.002). Similar results were observed in the multivariable-adjusted models. The curve plots of Model 2 and Model 3 showed that the OR values decreased within a lower range of NLR, reached the lowest point at an NLR of 1.50, and then started to increase. The RCS curves of Model 2 and Model 3 reached a plateau after the NLR reached 3.08 and 3.13, respectively (Model 2: p for nonlinearity=0.004; Model 3: p for nonlinearity=0.003).

In the partially adjusted model (i.e., Model 2), the OR value for psoriasis was 1 when the NLR was 0.84 and 2.01, while in the fully adjusted model (i.e., Model 3), the OR value for psoriasis was 1 when the NLR was 0.89 and 2.01.

Discussion

In this observational study, we analysed standardized data from a large cohort of participants in a US population sample. Our study identified that the NLR was increased in psoriasis patients and positively correlated with the disease severity. Taking into account that an imbalance in the baseline characteristics of participants may modify the association between the NLR and psoriasis, adjustments were made for potential confounders in regression analysis; nevertheless, we still detected a significant association of the NLR with psoriasis, indicating that this association cannot be solely attributed to risk factors and that the NLR could independently predict either the presence of psoriasis or the severity of psoriatic skin lesions. In the multivariable-adjusted RCS analysis, the NLR showed a strong nonlinear association with psoriasis risk, with the lowest risk at an NLR of 1.50. We also found that an NLR ranging between 0.89 and 2.01 was associated with a lower risk of psoriasis after accounting for all covariates, which meant that an NLR within an appropriate range might be a protective factor against psoriasis.

Neutrophils and T lymphocytes play critical roles in the development and progression of psoriasis. Massive infiltration of neutrophils within the dermis and epidermis is one of the classic histological features of psoriasis (34). As the first line of defence against immune attack, neutrophils are actively recruited to the affected skin and are responsible for propagating inflammation (35). Respiratory burst, degranulation and neutrophil extracellular trap formation are the main anti-inflammatory mechanisms of neutrophils that contribute to the immunopathogenesis of psoriasis (36). T lymphocytes that produce high levels of IL-17 driven by IL-23 have been corroborated as pathogenic culprits in psoriasis (5). IL-17 mediates effects on keratinocytes, which facilitates the recruitment of more IL-17-producing lymphocytes and neutrophils into inflamed psoriatic lesions, establishing a self-amplifying feedback loop to maintain and exacerbate inflammatory events in psoriasis (5, 37). The NLR, originating from the ratio of neutrophils to lymphocytes in peripheral blood, may have the ability to mirror the balance between innate and adaptive immune responses (32). Aberrant NLR values are representative of inflammatory conditions in the body, but as of now, there is no universally acceptable NLR cut-off value that defines its range of normalcy (38). The circulating levels of neutrophils and lymphocytes vary from person to person and fluctuate over the course of an individual's disease. In addition, patients' medication usage has an impact on peripheral leukocyte levels. Thus, it remains a challenge to ensure that the NLR becomes a reasonable and individually standardized predictor of health outcomes.

Recently, a number of investigators have examined the diagnostic and prognostic value of the NLR in psoriasis. In an observational study comprising 60 psoriasis patients along with 50 healthy controls, increased NLR values were found in the patient

group when compared to controls, which is in line with our results (39). Prior studies have shown that greater NLR values were associated with higher scores on the Psoriasis Area and Severity Index (PASI) (40, 41). Similar findings were mirrored in another study that reported a significant increase in the NLR in patients with PASI scores of 10 or more compared to patients with PASI scores of less than 10 (20). Nevertheless, several studies failed to find a significant association between the NLR and the clinical severity of psoriasis (23, 42). Moreover, the NLR was proposed to be a robust predictor for the emergence of psoriatic arthritis in patients who had psoriasis (20, 43, 44). It has been reported that the NLR is capable of predicting all-cause mortality and cardiovascular risk (45), and this index might be a novel biomarker to assess the risk of subclinical atherosclerosis in patients with psoriasis (22, 46). The NLR is believed to have the potential to predict treatment response because a remarkable reduction in the NLR was observed in psoriasis patients who underwent effective treatment (47, 48). As mentioned above, the NLR was increased in psoriasis patients, but it declined after treatment, whereas initial works investigating the relationship of the NLR with psoriasis severity produced inconsistent results. These studies were limited by sample size and bias, and the association between the NLR and psoriasis may be influenced by sociodemographic characteristics (29), personal health habits (49, 50), and individual medical history (51, 52). Given that a too high or too low NLR might signal a pathological state, there is a strong likelihood of a nonlinear relationship between the NLR and psoriasis that has not yet been explored and identified in earlier studies.

Our study has some strengths and clinical implications. Foremost, we used a nationally representative sample from NHANES, which offered sufficient statistical power to draw a conclusion and made our findings likely generalizable to the entire US population. The NHANES database contains comprehensive information on sociodemographic status, lifestyle exposures, physical measurements, and medical history, which enabled us to control for numerous confounding factors. Additionally, the NLR is a readily available index that may assist clinicians in identifying patients at high risk of severe psoriasis.

However, there were several limitations to this study that should be noted. First, as this was a cross-sectional observational study, inferences regarding whether this association is causal cannot be drawn. The true causality and possible mechanisms underlying the relationship between the NLR and psoriasis should be further examined. Second, because the definition of psoriasis and comorbidities (e.g., hypertension, diabetes, and CVD) relied on self-reports from the respondents instead of diagnoses made by two or more experienced dermatologists, the observed outcomes may be subject to recall bias. Additionally, the extent of psoriatic skin involvement was assessed by questionnaires instead of structured diagnostic scales, such as the Psoriasis Area Severity Index, which might affect the validity of the findings. NHANES categorizes psoriasis as (i) little or no psoriasis, (ii) only a few patches, (iii) scattered patches and (iv) extensive psoriasis, which cannot represent the severity of psoriasis in clinical practice. Finally, although we controlled for multiple potential confounders, unknown and unmeasured confounders may have impacted our estimates. For instance, the use of immunomodulatory drugs may influence the correlation between the NLR

and psoriasis (53, 54). However, NHANES did not collect any information on the use of immunomodulatory medication. Future rigorously designed and sufficiently powered studies with greater use of immunomodulatory drugs may offer valuable insights into the complex interplay between psoriasis and the NLR.

Conclusion

In summary, our study elucidated that the NLR was independently associated with psoriasis and that the association was nonlinear rather than simply linear. We also found evidence in favour of a clear link between the NLR and psoriasis severity. However, further research is warranted to elaborate the detailed mechanism of the NLR in psoriasis.

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Author Contributions

JH designed the research, conducted statistical analysis, and wrote the manuscripts. ML and NL directed the study and revised the manuscripts. All authors contributed to the article and approved the submitted version.

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Competing interests None declared.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Ethics approval

NHANES was approved by the National Center for Health Statistics Institutional Review Board, and participants provided written informed consent.

Data availability statement

Data are available in a public, open access repository. Open access data are available on the NHANES website (www.cdc.gov/nchs/nhanes/).

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Figure legends

Figure 1. Flow diagram of participants screened from the National Health and Nutrition Examination Survey (NHANES) 2011 to 2014.
Covariates included age, sex, race, income, education, body mass index, smoking, alcohol consumption, history of hypertension, diabetes and cardiovascular disease.

Figure 2. Nonlinear association between the NLR and psoriasis by restricted cubic spline regression.
The fitted regression line is shown as a red solid line; black dashed lines indicate where the OR equals 1; 95% CI is represented by a shaded region.

Table 1 Baseline characteristics of participants with and without psoriasis.

Characteristic	Without psoriasis (n=8149)	With psoriasis (n=238)	P value
Age, mean (SD), y	47.2 (17.0)	51.3 (15.4)	<0.001
Sex			0.408
Female	4128 (51.0)	126 (53.8)	
Male	4021 (49.0)	112 (46.2)	
Race			0.001
Mexican American	904 (7.9)	15 (4.1)	
Other Hispanic	759 (5.8)	24 (5.1)	
Non-Hispanic White	3467 (68.4)	136 (79.7)	
Non-Hispanic Black	1842 (10.7)	28 (4.8)	
Non-Hispanic Asian	931 (4.6)	26 (4.0)	
Other Race	246 (2.6)	9 (2.3)	
Poverty income ratio			0.81
Low	2793 (23.9)	84 (22.7)	
Medium	2800 (34.5)	76 (33.8)	
High	2556 (41.6)	78 (43.5)	
Education			0.405
High school or less	3444 (35.4)	91 (30.4)	
Some college or AA degree	2559 (32.8)	79 (33.4)	
College graduate or above	2146 (31.8)	68 (36.2)	
BMI			0.071
Underweight (<18.5)	133 (1.4)	0 (0.0)	
Normal (18.5 to <25)	2382 (28.8)	52 (20.8)	
Overweight (25 to <30)	2618 (33.2)	89 (41.6)	
Obese (30 or greater)	3016 (36.6)	97 (37.6)	
Smoking status			<0.001
Never smoker	4594 (56.2)	121 (49.4)	
Former smoker	1888 (23.9)	82 (39.7)	
Current smoker	1667 (20.0)	35 (10.9)	
Alcohol drinker			0.899
No	2157 (20.6)	65 (20.3)	
Yes	5992 (79.4)	173 (79.7)	
Hypertension			0.032
No	5207 (67.3)	129 (57.8)	
Yes	2942 (32.7)	109 (42.2)	
Diabetes			0.006
No	7090 (90.0)	190 (83.3)	
Yes	1059 (10.0)	48 (16.7)	
History of CVD			0.024
No	7352 (91.8)	197 (87.9)	
Yes	797 (8.2)	41 (12.1)	
NLR	2.0 (1.5, 2.6)	2.4 (1.8, 3.2)	<0.001

Median (SD) or median (interquartile range) for continuous; n (%) for categorical.
Abbreviations: BMI, body mass index; CVD, cardiovascular disease; NLR, neutrophil-to-lymphocyte ratio.

Table 2 Association between the neutrophil-to-lymphocyte ratio (NLR) and the presence of psoriasis.

Variable	Model 1		Model 2		Model 3	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
NLR (continuous)	1.19 (1.11, 1.28)	<0.001	1.16 (1.08, 1.24)	<0.001	1.15 (1.05, 1.25)	0.006
NLR (quartile)						
Q1 (≤1.47)	Reference		Reference		Reference	
Q2 (1.47–1.96)	1.14 (0.67, 1.94)	0.613	1.05 (0.61, 1.82)	0.849	1.05 (0.59, 1.89)	0.848
Q3 (1.96–2.63)	1.48 (0.93, 2.36)	0.095	1.34 (0.83, 2.18)	0.218	1.31 (0.77, 2.24)	0.282
Q4 (>2.63)	2.62 (1.58, 4.32)	<0.001	2.25 (1.35, 3.76)	0.004	2.22 (1.27, 3.87)	0.01
P for trend	<0.001		0.001		0.004	

Model 1: no covariates were adjusted. Model 2: adjusted for age, sex, race, income, and education. Model 3: adjusted for age, sex, race, income, education, body mass index, smoking status, alcohol consumption, history of hypertension, diabetes and cardiovascular disease.

Table 3 Association between the neutrophil-to-lymphocyte ratio (NLR) and the severity of psoriasis.

Model	Psoriasis severity	Continuous OR (95% CI)	P value	OR (95%CI) Q1	Q2	Q3	Q4	P value
Model 1	Little or no psoriasis	1.13 (1.06, 1.21)	<0.001	Reference	1.30 (0.59, 2.85)	1.81 (0.97, 3.35)	2.41 (1.30, 4.48)	0.01
	Few patches to extensive psoriasis	1.22 (1.11, 1.34)	<0.001	Reference	0.95 (0.37, 2.44)	1.09 (0.47, 2.55)	2.86 (1.34, 6.07)	<0.001
Model 2	Little or no psoriasis	1.10 (1.03, 1.18)	0.008	Reference	1.18 (0.52, 2.72)	1.62 (0.85, 3.09)	2.07 (1.08, 3.96)	0.034
	Few patches to extensive psoriasis	1.20 (1.10, 1.31)	<0.001	Reference	0.89 (0.35, 2.29)	1.00 (0.41, 2.44)	2.49 (1.17, 5.29)	0.003
Model 3	Little or no psoriasis	1.08 (1.00, 1.17)	0.06	Reference	1.21 (0.49, 2.96)	1.61 (0.80, 3.22)	2.04 (1.00, 4.17)	0.052
	Few patches to extensive psoriasis	1.19 (1.07, 1.33)	0.004	Reference	0.88 (0.33, 2.34)	0.95 (0.36, 2.54)	2.43 (1.10, 5.36)	0.003

In multinomial logistic regression models, the association between the NLR and psoriasis severity was tested with patients never diagnosed with psoriasis as the reference group. Q1, NLR≤1.47; Q2, NLR 1.47–1.96; Q3, NLR 1.96–2.63; Q4, NLR>2.63.

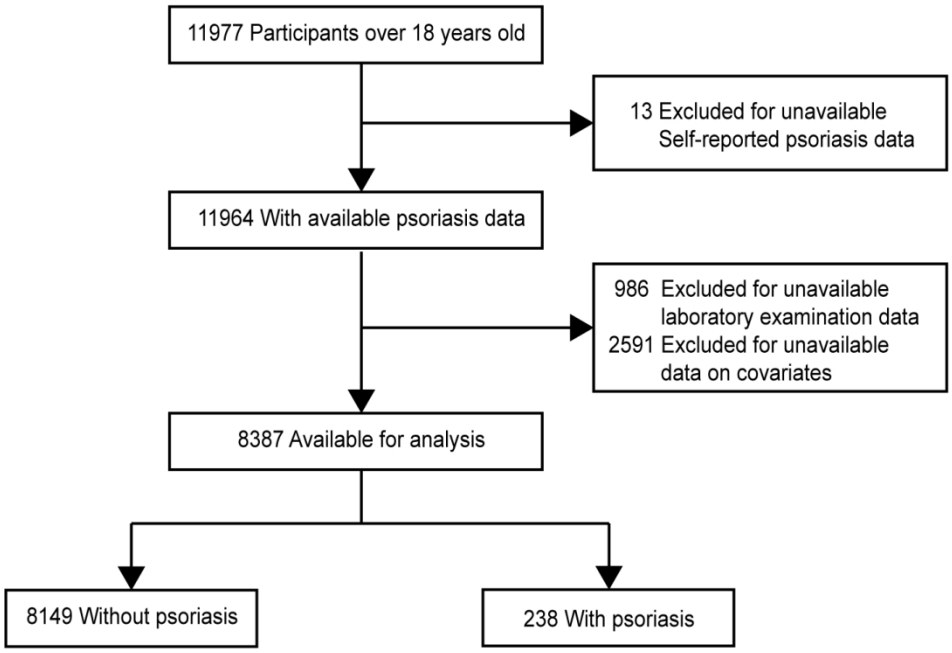

Figure 1. Flow diagram of participants screened from National Health and Nutrition Examination Survey (NHANES) 2011 to 2014. Covariates included age, sex, race, income, education, body mass index, smoking, alcohol use, history of hypertension, diabetes and cardiovascular disease.

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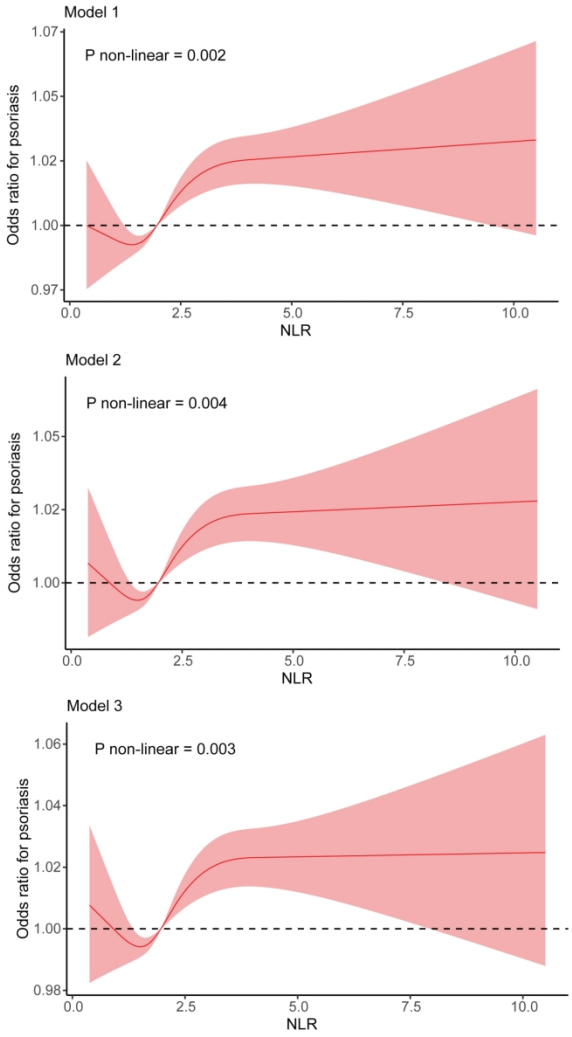

Figure 2. Nonlinear association between NLR and psoriasis by restricted cubic spline regression. Fitted regression line was shown as red solid line; black dashed lines indicated where the OR equals 1; 95%CI is represented by shaded region.

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Table S1 Subgroup analysis for the association between the neutrophil-to-lymphocyte ratio (NLR) as a continuous variable and the presence of psoriasis.

Subgroup	OR (95%CI)	P value	P for interaction
Age, y			0.118
18-39	1.01 (0.74, 1.37)	0.972	
40-59	1.28 (1.05, 1.56)	0.019	
60-79	1.24 (1.09, 1.41)	0.004	
≥80	0.99 (0.82, 1.19)	0.921	
Sex			0.301
Female	1.22 (1.05, 1.43)	0.016	
Male	1.13 (1.01, 1.25)	0.03	
Race			0.984
Mexican American	1.04 (0.86, 1.25)	0.613	
Other Hispanic	1.17 (0.83, 1.64)	0.331	
Non-Hispanic White	1.17 (1.05, 1.30)	0.006	
Non-Hispanic Black	1.16 (0.96, 1.39)	0.114	
Non-Hispanic Asian	1.14 (0.74, 1.76)	0.522	
Other Race	2.50 (1.17, 5.34)	0.023	
Poverty income ratio			0.63
Low	1.09 (0.88, 1.35)	0.397	
Medium	1.21 (1.03, 1.41)	0.021	
High	1.14 (0.93, 1.39)	0.185	
Education			0.181
High school or less	1.18 (1.07, 1.31)	0.004	
Some college or AA degree	0.96 (0.77, 1.20)	0.693	
College graduate or above	1.26 (1.05, 1.52)	0.019	

Each stratification was adjusted for all covariates except the stratification factor itself.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-5
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	4,5
		(*e*) Describe any sensitivity analyses	5
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	4
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5-6
		(b) Indicate number of participants with missing data for each variable of interest	5
Outcome data	15*	Report numbers of outcome events or summary measures	5
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6
		(*b*) Report category boundaries when continuous variables were categorized	6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6
Discussion			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8-9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7-8
Generalisability	21	Discuss the generalisability (external validity) of the study results	8
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.