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Research Article

Association Between Neutrophil Percentage-to-Albumin Ratio and Risk of Endometriosis in US Population: Results from the National Health and Nutrition Examination Survey (1999–2006)

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Abstract

Aim: To explore the relationship between NPAR and endometriosis in women over 20 years old.

Material and methods: We screened the data from National Health and Nutrition Examination Survey (NHANES) 1999–2006. A total of 4595 eligible women were included in this study. To estimate the independent association of NPAR with the risk of endometriosis, we used weighted multivariate logistic regression models and cubic spline analyses.

Results: Among women over the age of 20 in the NHANES 1999–2006 database, NPAR values were significantly and positively associated with endometriosis. And patients in the highest quartile of NPAR values (Q4) had a prevalence of endometriosis that was approximately 2.19 times that of patients in the lowest quartile (Q1) (95% CI: 1.52-3.14, P <0.001). After multivariable adjustment, higher NPAR values were found to be associated with a higher prevalence of endometriosis (OR: 2.24, 95% CI: 1.55–3.23, P for trend = 0.001). Spline regression showed a non-linear correlation (P-non-linear ≤ 0.001) between NPAR and the incidence of endometriosis, which was N-shaped with a node value of 11.162 (P-overall ≤ 0.001).

Conclusion: Our findings suggest that there is an association between NPAR and endometriosis, and lower NPAR values may be associated with a lower risk of endometriosis, which provides new ideas for the serological diagnosis of endometriosis

INTRODUCTION

The distinctive feature of endometriosis is the proliferation of endometrial glands and stroma at abnormal locations. Its distribution range breaks through the inherent boundaries between the endometrium and stroma of the uterine cavity, and is found outside the uterine. Ectopic lesions form in other parts of the uterus [1]. It is one of the most common gynecological diseases, with the main symptoms being severe dysmenorrhea, deep dyspareunia and chronic pelvic pain, as well as bowel symptoms (such as abdominal pain, bloating, nausea, constipation, vomiting, painful defecation and diarrhea) and bladder symptoms (such as hematuria and dysuria) [2-4].

Endometrial cell attachment outside the uterus is central to the development, persistence, and progression of the disease. This process involves changes in multiple pathways, including changes in local and systemic chemokines activation in immune function, as well as changes in apoptosis, invasion ability, and angiogenesis. These changes are triggered by pro-inflammatory, angiogenic, and angiostatic chemokines [5].

Neutrophils are crucial in the human innate immune system, and counting neutrophils is a simple and economical way to identify inflammation [6,7]. Albumin is a highly soluble and negatively charged stable protein with the highest content in plasma. It plays a key role in buffering, antioxidation, immunomodulation, detoxification and transport [8,9]. On this basis, Neutrophil percentage-to-albumin ratio (NPAR) is a new serological indicator that is associated with neutrophils and albumin, and is closely linked to systemic inflammation and stress levels, opening up a new path for in-depth exploration of pathophysiology

[10]. It has been identified as a predictor of outcome in patients with a variety of conditions, including malignancy, acute kidney injury, septic shock, and cardiogenic shock [11-13]. Up to now, there are few detailed records and explanations on the relationship between NPAR and endometriosis in the existing academic materials, and the relevant literature is in a relatively scarce state. Exploring the association between NPAR levels and endometriosis correlation may contribute to the early diagnosis and treatment of endometriosis.

Based on this premise, this study used the 1999-2006 National Health and Nutrition Examination Survey (NHANES) dataset to conduct a cross-sectional analysis with the aim of exploring the potential association between NPAR and endometriosis.

MATERIALS AND METHODS

Data source and population

NHANES is a large, cross-sectional, population-based study conducted by the National Center for Health Statistics (NCHS) at the Centers for Disease Control and Prevention (CDC). NHANES aims to accurately assess exposure levels to environmental chemicals and provide a comprehensive monitoring of the health and nutritional status of the American population. Therefore, a complex stage sampling scheme was used to recruit a sample that was representative of the civilian and noninstitutionalized population of the United States. The implementation of NHANES is divided into two stages: family interview and health examination. Data are collected through interviews, physical examinations and laboratory tests.

We conducted a cross-sectional study using data on female participants from four NHANES data cycles: 1999-2000, 2001-2002, 2003-2004, and 2005-2006 (n = 21,210). During the home interviews, participants were asked questions on a range of topics including demographics, family characteristics, medical conditions, and physical activity. In addition, we also used the same multi-faceted questionnaire to survey a subsample of participants during their visits to the Mobile Examination Centre (MEC) (such as Alcohol Use, Reproductive Health, Diabetes). The MEC exam also included blood samples from the patients, as well as body measurements assessed by NHANES examiners. Because the reproductive health questionnaire only collected information on endometriosis in patients aged 20 years and above, we excluded data from patients younger than 20 years (n=10509). At the same time, 6106 cases with missing data on independent variables, dependent variables, and covariates were excluded. Finally, 4595 female participants were included in the study. The study flow chart is shown in Figure 1.

Definition of endometriosis and NPAR

During four cycles of NHANES (1999-2000, 2001-2002, 2003-2004, and 2005-2006), participants who were marked as female by NHANES field home interviewers were questioned during reproductive health examinations at MECs. NHANES only collects information on the diagnosis of endometriosis in women aged 20 to 54 years. Participants were asked, “Have your doctor told you that you have endometriosis?” If the participant answered “yes,” they were considered to have endometriosis. Using this information, we created a binary variable for history of endometriosis diagnosis (“no” or “yes”).

The data required to calculate NPAR are all provided by Laboratory Data in NHANES database. Hematological parameters were determined based on the complete blood count data of NHANES using the Beckman Coulter DxH900 fully automatic hematology analyzer (Beckman Coulter, California, USA), which assessed total leukocytes, neutrophils, hemoglobin, and erythrocytes. The analyzer system processes the sample using methods such as automated dilution and mixing systems and measures the blood cells and their components using a single-beam photometer. The method used to measure the albumin concentration on the LX20 is a bichromatic digital endpoint method. Using the above information, we calculated the NPAR value to form a continuous variable.

The calculation formula for NPAR in whole blood is as follows

Neutrophil percentage (total white blood cell count) (%) × 100/Albumin(g/dL)

Covariates

Based on previous studies and clinical experience, the following covariates were included in the analysis: Age (years), Race (Mexican American, Non-Hispanic Black, Non-Hispanic White, Other),Poverty income ratio (PIR), Education level (Less than high school, High school graduate/GED, Some college or AA degree, College graduate or above), Married or live with partner (Yes or No), Body mass index (BMI), diabetes (Yes or No), Alcohol intake (Yes or No), Smoking status (Current smoker, Former smoker and Never smoker), Pregnant history (≥ one birth or nulliparity) and use of female hormones (Yes or No).

BMI is determined by dividing weight in kilograms by height in meters squared (kg/m^2) Participants were classified as underweight (<18.5 kg/m^2), normal-weight (18.5 kg/m^2 – 24.9 kg/m^2), overweight (25.0 kg/m^2–29.9

kg/m^2), and obesity (≥30 kg/m^2) based on BMI [14]. The diabetes assessment criteria used are: the patient has been informed of diabetes by the doctor, is currently taking hypoglycemic drugs or insulin, has glycated hemoglobin A1c exceeding 6.5%, and has fasting blood glucose equal to or greater than 7.0 mmol/L. Poverty levels are assessed based on the Poverty Income Ratio (PIR) and are categorized as follows: low-income (PIR<1.5), medium-income (1.5≤PIR<3.0), and high-income (PIR≥3.0).

STATISTICAL ANALYSES

All analyses were performed according to the NHANES analysis guidelines. In order to make our results available to estimate the overall situation of the American population over the eight- year cycle and adjust for the clustered sampling design, we first conducted a weighted analysis of the data. Categorical variables were compared using the κ^2 test, and continuous variables were compared using the t test or the Wilcoxon rank-sum test according to the results of the normality test. The participants were divided into 4 groups (Q1, Q2, Q3, and Q4) according to the quartiles of NPAR, with the Q1 group serving as the reference group. Univariate and multivariate logistic regression models were used to calculate odds ratios (OR) and 95% confidence intervals (CI) to evaluate the relationship between NPAR and endometriosis. Initially, a relatively simple model (Model 1) was used, which only considered NPAR as the only factor. Then, two adjusted and optimized models were used. Among them, Model 2 fully considered factors such as age, race, education level, marital status and PIR, and made corresponding adjustments accordingly. In Model 3, all relevant variables were further adjusted. In addition, we estimated the linear trends among NPAR quartiles by including the median of each quartile as a continuous variable in the regression models. Finally, we used the Restricted cubic spline (RCS) models model based on the logistic regression model to observe the association between NPAR and the risk of endometriosis. All statistical analyzes were performed using R software (version 4.4.1). All *P* values were two-sided, and *P*<0.05 was considered statistically significant.

RESULTS

Participant characteristics

General characteristics of the study population: We included a total of 4595 female participants in the study (Figure 1). The baseline characteristics between endometriosis and non-endometriosis groups are presented in Table 1.

Among them, 313 (6.8%) had endometriosis, while

Table 1: Descriptions of study individuals' characteristics

Level	Total	Non-endometriosis	Endometriosis	P
Total	4595	4282	313	
Age(years)(%)				<0.001
20-30	1654 (36.0)	1606 (29.7)	48 (10.9)	
31-40	1287 (28.0)	1173 (28.2)	114 (36.0)	
>40	1654 (36.0)	1503 (42.1)	151 (53.1)	
PIR(%)				0.029
<1.5	1544 (33.6)	1473 (25.7)	71 (19.7)	
1.5≤ <3	1130 (24.6)	1063 (24.0)	67 (20.7)	
≥3	1921 (41.8)	1746 (50.3)	175 (59.6)	
Education level(%)				0.014
Less than high school	1053 (22.9)	1015 (15.0)	38 (10.0)	
High school graduate/GED	1001 (21.8)	920 (22.1)	81 (30.3)	
Some college or AA degree	1503 (32.7)	1392 (35.5)	111 (33.5)	
College graduate or above	1038 (22.6)	955 (27.4)	83 (26.2)	
Married/live with partner(%)				0.377
Yes	2974 (64.7)	2765 (65.6)	209 (68.8)	
No	1621 (35.3)	1517 (34.4)	104 (31.2)	
Race/ethnicity(%)				<0.001
Mexican American	1066 (23.2)	1039 (8.6)	27 (2.6)	
Non-Hispanic Black	927 (20.2)	879 (12.0)	48 (7.1)	
Non-Hispanic White	2190 (47.7)	1971 (68.4)	219 (84.6)	
Other	412 (9.0)	393 (11.0)	19 (5.8)	
Female hormones (%)				<0.001
Yes	562 (12.2)	447 (13.7)	115 (40.9)	
No	4033 (87.8)	3835 (86.3)	198 (59.1)	
Pregnant history (%)				0.029
Yes	3871 (84.2)	3601 (79.8)	270 (86.3)	
No	724 (15.8)	681 (20.2)	43 (13.7)	
Level	Total	Non-endometriosis	Endometriosis	P
BMI(kg/m^2)(%)				0.965
underweight	109 (2.4)	102 (3.0)	7 (2.7)	
normal-weight	1502 (32.7)	1398 (37.8)	104 (37.0)	
overweight	1279 (27.8)	1195 (25.4)	84 (25.5)	
obesity	1705 (37.1)	1587 (33.7)	118 (34.9)	
Smoking (%)				0.009
Current smoker	1011 (22.0)	924 (24.4)	87 (32.3)	
Former smoker	747 (16.3)	692 (17.4)	55 (18.0)	
Never smoker	2837 (61.7)	2666 (58.1)	171 (49.7)	
DM history(%)				0.181
Yes	292 (6.4)	278 (5.6)	14 (3.6)	
No	4303 (93.6)	4004 (94.4)	299 (96.4)	
Alcohol intake(%)				0.036
Yes	2835 (61.7)	2624(67.9)	211(70.7)	
No	1760 (38.3)	1658(32.1)	102(29.3)	
NPAR, (mean±SD)				0.002
	15.0±3.5	14.98±2.74	15.33±2.09	
NPAR_q4 (%)				0.01
Q1	1074 (23.4)	1026 (25.9)	48 (15.9)	
Q2	1010 (22.0)	940 (25.0)	70 (24.9)	
Q3	1015 (22.1)	936 (24.6)	79 (29.3)	
Q4	1496 (32.6)	1380 (24.6)	116 (29.9)	

4,282 (93.2%) did not have endometriosis. Compared with women who did not suffer from endometriosis, women with this condition tended to show the following characteristics: older age and relatively better financial status. However, their education level was at a low level, and in terms of racial composition, Non-Hispanic White accounted for a significantly higher proportion. They used hormones more frequently, and the proportion of pregnant experience had increased significantly. At the same time, smoking and drinking behaviors were more common in this group. It is worth noting that women with endometriosis had higher NPAR values (15.33 vs 14.98), and the difference was statistically significant (P = 0.002).

Associations between endometriosis and study variables: Table 2 shows the results of univariate and multivariate logistic regression. In univariate linear regression analysis, we found that age, education level, race, female hormone use, alcohol intake, and NPAR value were significantly associated with the prevalence of endometriosis. Further multivariate analysis, after adjusting for confounders, revealed that NPAR values were positively associated with the incidence of endometriosis. Specifically, patients in the highest quartile of NPAR values (Q4) had a prevalence of endometriosis that was approximately 2.19 times that of patients in the lowest quartile (Q1) (95% CI: 1.52-3.14, P <0.001).

Table 3 shows the trend of OR and correlation between NPAR and endometriosis incidence in logistic regression model. In all models, the prevalence of endometriosis increased with increasing NPAR quartiles compared to those in the lowest NPAR quartile (Model3, OR:2.24, 95% CI:1.55-3.23, P for trend = 0.001).

RCS model of the relationship between NPAR and prevalence of endometriosis were shown in Figure 2. The

Table 2: Results of univariate and multivariate logistic regression

Variables	Level	OR (univariable)	OR (multivariable)	OR (final)
Age(years)	20-30	Ref	Ref	
	31-40	3.25 (2.30-4.59, p<.001)	2.85 (2.00-4.06, p<.001)	2.91 (2.05-4.14, p<.001)
	>40	3.36 (2.41-4.69, p<.001)	1.97 (1.36-2.86, p<.001)	2.04 (1.42-2.94, p<.001)
Poverty income ratio	<1.5	Ref	Ref	
	1.5≤ <3	1.31 (0.93-1.84, p=.125)	1.11 (0.78-1.59, p=.563)	
	≥3	2.08 (1.56-2.76, p<.001)	1.33 (0.95-1.86, p=.096)	
Education level	Less than high school	Ref	Ref	
	High school graduate/GED	2.35 (1.58-3.49, p<.001)	1.54 (1.01-2.35, p=.045)	
	Some college or AA degree	2.13 (1.46-3.11, p<.001)	1.35 (0.89-2.05, p=.153)	
	College graduate or above	2.32 (1.57-3.44, p<.001)	1.22 (0.77-1.94, p=.395)	
Married/live with partner	No	Ref		
	Yes	1.10 (0.86-1.41, p=.432)		
Race/ethnicity	Mexican American	Ref	Ref	
	Non-Hispanic Black	2.10 (1.30-3.40, p=.002)	1.90 (1.16-3.13, p=.011)	2.10 (1.29-3.42, p=.003)
	Non-Hispanic White	4.28 (2.85-6.42, p<.001)	2.90 (1.87-4.50, p<.001)	3.49 (2.31-5.28, p<.001)
	Other	1.86 (1.02-3.38, p=.042)	1.64 (0.89-3.04, p=.114)	1.81 (0.99-3.32, p=.054)
Female hormones	No	Ref	Ref	
	Yes	4.98 (3.88-6.40, p<.001)	4.14 (3.11-5.52, p<.001)	4.21 (3.16-5.60, p<.001)
Pregnant history	No	Ref		
	Yes	1.19 (0.85-1.66, p=.310)		
BMI	normal-weight	Ref		
	underweight	0.92 (0.42-2.04, p=.842)		
Variables	Level	OR (univariable)	OR (multivariable)	OR (final)
	obesity	1.00 (0.76-1.31, p=.997)		
	overweight	0.94 (0.70-1.27, p=.709)		
Smoking	Never smoker	Ref	Ref	
	Current smoker	1.47 (1.12-1.92, p=.005)	1.18 (0.87-1.60, p=.300)	
	Former smoker	1.24 (0.90-1.70, p=.182)	0.93 (0.66-1.30, p=.657)	
DM history	No	Ref		
	Yes	0.67 (0.39-1.17, p=.160)		
Alcohol intake	No	Ref	Ref	
	Yes	1.31 (1.02-1.67, p=.032)	1.03 (0.79-1.36, p=.818)	
NPAR_q4	Q1	Ref	Ref	
	Q2	1.59 (1.09-2.32, p=.016)	1.55 (1.04-2.29, p=.030)	1.56 (1.05-2.30, p=.027)
	Q3	1.80 (1.25-2.61, p=.002)	1.89 (1.29-2.78, p=.001)	1.90 (1.29-2.79, p=.001)
	Q4	1.80 (1.27-2.54, p<.001)	2.20 (1.53-3.17, p<.001)	2.19 (1.52-3.14, p<.001)

Table 3: Association between NPAR quartiles and endometriosis

			Model 1	Model 2	Model 3
	Non-endometriosis(N=4282)	Endometriosis(N=313)	Odds ratio (95% confidence interval)	Odds ratio (95% confidence interval)	Odds ratio (95% confidence interval)
NPAR_q4					
Q1	1026 (24%)	48 (15.3%)	Ref	Ref	Ref
Q2	940 (22%)	70 (22.4%)	1.59 (1.09-2.32)	1.49 (1.02-2.18)	1.53 (1.03-2.25)
Q3	936 (21.9%)	79 (25.2%)	1.80 (1.25-2.61)	1.71 (1.18-2.48)	1.89 (1.29-2.78)
Q4	1380 (32.2%)	116 (37.1%)	1.80 (1.27-2.54)	1.96 (1.38-2.78)	2.24 (1.55-3.23)
P for trend			0.005	0.009	0.001

results showed a non-linear correlation (*P*-non-linear ≤ 0.001) between NPAR and the incidence of endometriosis, which was N-shaped with a node value of 11.162 (*P*-overall ≤ 0.001).

DISCUSSION

Endometriosis is one of the most common gynecologic diseases in women of reproductive age [15,16]. Currently, laparoscopic surgery remains the mainstay of endometriosis diagnosis [17].

However, laparoscopic surgery not only requires general anesthesia for the patient, but also carries the risk of surgical complications [18,19]. In addition, the popularity of laparoscopic surgery varies geographically around the world, depending on the level of development, economic income, and other factors [19]. As a consequence of this, the estimated time interval between insurgence of the disease and definitive diagnosis is very long and consists of 8–12 years [20], making it one of the most underdiagnosed and undertreated diseases [21-24]. Given this background, it is clear that the development of accurate and reliable blood tests for the non-invasive diagnosis of endometriosis has important value and significance that cannot be ignored in clinical practice.

In endometriosis, inflammation is the central pathophysiologic mechanism of endometriosis, playing a role in pain, lesion implantation, fibrosis, and angiogenesis [25]. Immune dysregulation with inflammatory cytokines damages the ovaries and pelvic tissue, leading to the disruption of uterine function [26]. In the pathology of endometriosis, ectopic endometrial tissue can directly induce an inflammatory response, which in turn leads to a pathologically increased level of pro- inflammatory cytokines in the peritoneal fluid [27].

As a cost-effective and easily available new inflammatory marker, NPAR has been shown to be associated with a variety of diseases. It has been used as a predictor based on systemic inflammation in patients with palliative pancreatic cancer [28], acute kidney injury [29], and septic shock. It is also associated with mortality in patients with atrial fibrillation [30], and cirrhosis [31].

NPAR consists of the ratio of neutrophil percentage to albumin. On the one hand, neutrophil percentage is used to assess the presence of inflammation. Elevated neutrophils are one of the most important factors contributing to poor prognosis and outcome because they play a critical role in the inflammatory response triggered by trauma to the body [32,33]. It has been shown that patients with endometriosis have increased neutrophil infiltration in the corpuscular circulation and peritoneal fluid compared to women without disease [34-37]. In addition, neutrophils in the systemic circulation of endometriosis patients have a unique transcriptomic profile compared to neutrophils in the healthy population [35]. On the other hand, albumin is a medium-sized house- keeping protein, which has a variety of functions including osmoregulation, antioxidant and anti- inflammatory properties, and accounts for more than half of the total composition of human serum.

As a negative acute phase reactant, albumin is negatively correlated with oxidative stress and inflammation. It has antioxidant and anti-inflammatory effects, and its concentration is influenced by inflammation [38]. Based on this, endometriosis as a chronic inflammatory disease, it is reasonable to hypothesize that the ratio of neutrophil percentage to albumin is significantly associated with the risk of endometriosis. Moreover, it is easier to obtain, cheaper and more widely used than other indicators. For patients who wish to be treated conservatively or have reproductive needs, NPAR measurement can be a good auxiliary diagnostic method.

Our cross-sectional study was designed to investigate the association between NPAR and the risk of endometriosis in women of reproductive age. After adjusting for other covariates, we found that NPAR was positively associated with the risk of endometriosis. That is, the higher the NPAR value, the higher the risk of endometriosis (*P* for trend = 0.001). Specifically, we used multivariable adjusted spline regression analysis to explore whether there was a linear association between the two after adjusting for age, education level, race, and other confounding factors. The results showed an N-curve relationship between NPAR levels and risk of endometriosis with a node value

of 11.162. When the NPAR value was less than 11.162, OR < 1, indicating that NPAR was a protective factor for endometriosis, and the smaller the value, the lower the risk of disease. The OR > 1 when NPAR > 11.162 indicates that NPAR is an exposure factor for endometriosis. However, at this time the curve showed a tendency to increase and then decrease, and its significance may not be as clear as when NPAR < 11.162. Therefore, NPAR may be more suitable as an exclusion criterion. Meaning that when ultrasound or other imaging examinations cannot clearly determine whether a lesion exists, a lower NPAR value can help exclude the diagnosis of EMS or help differentiate it from other diseases.

The possible mechanisms for the inverse relationship between NPAR and endometriosis are as follows. On the one hand, the ectopic endometrium causes heterogeneous chronic inflammation, activating neutrophil chemoattractant and thus increasing the percentage of neutrophils in the blood. On the other hand, reduced serum albumin levels may reflect a chronic inflammatory state or poor nutritional status of the patient's body. This is because people with endometriosis may have insufficient protein intake due to pain and other symptoms that interfere with eating, or due to chronic inflammation that depletes the body's albumin reserves. Lower albumin levels may also be associated with severe conditions such as pelvic adhesions in patients with endometriosis, as severe pelvic adhesions are often accompanied by a more intense inflammatory response and tissue damage, which can further disturb the body's protein metabolic balance. In general, the inflammatory progression of endometriosis leads to opposite changes in neutrophils and albumin, so the increased ratio of the two reflects the abnormal state of patients with endometriosis.

This study has many advantages. This study initially included nationally representative NHANES data so that a broad sample of U.S. adults from a variety of age groups could be included. However, after applying specific exclusion criteria to this analysis, the final study population may no longer fully reflect the national population. Therefore, we weighted the data from the four cycles to make the results of this study more representative of the characteristics of all U.S. adults.

Our statistical model extensively analyzed the correlation between NPAR and elevated levels of endometriosis. In addition, we created RCS curves to represent the link between these two variables, allowing us to examine correlations from multiple perspectives and enhancing the robustness of our findings.

Of course, this study still has some limitations. First, the study was a cross-sectional one and establishing a causal relationship between NPAR and endometriosis was difficult. Secondly, there was a lack of previous similar studies to provide evidence for this study, but this reflects the innovative nature of this study. In addition, much of the data in our study (e.g., smoking and drinking habits) were based on self-reporting and thus could be biased.

CONCLUSION

In conclusion, we found a positive correlation between NPAR and the risk of developing endometriosis. As NPAR increased, the risk of endometriosis continued to rise. This relationship was particularly evident at NPAR less than 11.162. Our study provides a new idea for the noninvasive diagnosis of endometriosis and provides a serologic basis for its early diagnosis and differential diagnosis. In the future we need more balanced and representative cohort studies to refine our findings.

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