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Association between the neutrophil percentage-to-albumin ratio and breast cancer risk: Evidence from the National Health and Nutrition Examination Survey 1999–2016

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Abstract

Background: Increasing evidence underscores the association between chronic inflammation and carcinogenesis. **Aim:** The aim of the study is to investigate the association between the neutrophil percentage-to-albumin ratio (NPAR) and breast cancer (BC) risk. **Methods:** This analysis utilized cross-sectional data from 16,993 participants enrolled in the National Health and Nutrition Examination Survey from 1999 to 2016. To investigate the link between NPAR and BC risk, weighted multivariate logistic regression models were applied. Nonlinear associations were explored using restricted cubic spline (RCS) models. Furthermore, a nomogram incorporating NPAR was constructed for risk stratification, and its predictive accuracy was evaluated using receiver operating characteristic curve (ROC) analysis. **Results:** After adjusting for potential confounders, elevated NPAR levels showed a significant positive association with BC (odds ratio [OR] = 1.12, 95% confidence interval [95% CI]: 1.08–1.16; $p<0.001$). Compared with the reference quartile (Q1), progressively increasing ORs associated with BC were observed across ascending NPAR quartiles: Q1: OR 1.05 (95% CI: 0.78–1.42), Q2: OR 1.35 (95% CI: 1.02–1.79), and Q3: OR 1.47 (95% CI: 1.12–1.93). Analysis using RCS indicated a linear relationship where increasing NPAR levels were associated with a higher risk of BC. The predictive model incorporating NPAR demonstrated strong accuracy for BC prediction, achieving an area under the ROC curve of 0.8068 (95% CI: 0.7904–0.8232). **Conclusion:** Our findings reveal a significant dose-dependent association between NPAR and BC risk in a nationally representative sample from the United States. Although cross-sectional designs preclude causal inference, longitudinal studies should validate these observations and explore underlying biological mechanisms. **Relevance for patients:** NPAR could potentially serve as a novel biomarker to predict BC risk in patients.

Keywords: National Health and Nutrition Examination Survey; Neutrophil percentage-to-albumin ratio; Breast cancer; Inflammatory marker

1. Introduction

Breast cancer (BC), a major threat to women's health and the leading cause of cancer-related deaths in women globally, poses substantial public health challenges due to its high incidence and mortality rates.[1,2] Its development stems from intricate interplays among genetic, hormonal, and environmental, inflammatory, and metabolic factors.[3,4] Early and accurate risk stratification combined with prognostic assessment may facilitate personalized therapeutic strategies to enhance patients' clinical outcomes.[5-7]

Among the multifactorial contributors, the dual role of chronic inflammation and metabolic dysregulation in tumorigenesis has garnered increasing attention.[8,9] The functional states of immune cells within the tumor microenvironment, particularly neutrophils, are known to exert a profound impact on disease progression,[10-12] while nutritional status and metabolic homeostasis further modulate cancer-related outcomes.[13,14] These insights have spurred the development of composite biomarkers that better reflect the inflammatory–metabolic axis underlying carcinogenesis.

The neutrophil percentage-to-albumin ratio (NPAR) has emerged as a novel composite biomarker that integrates a proxy for systemic inflammation (neutrophil percentage) with a key indicator of nutritional and metabolic status (albumin).[15,16] This combination theoretically enables NPAR to capture aspects of both pathways simultaneously,[17,18] suggesting its utility as an indicator of inflammatory–nutritional dysregulation. However, despite this potential, evidence regarding the association between NPAR and BC risk remains limited. Its potential added value over established inflammatory markers in the context of BC is especially unclear and represents a significant knowledge gap, particularly given how frequently metabolic dysregulation coexists with and fuels chronic inflammation in this disease.

Leveraging the National Health and Nutrition Examination Survey (NHANES) cross-sectional data spanning 1999–2016, we examined the association between NPAR and BC risk among women in the United States. Our primary aim was to assess whether this association exists independently of potential confounders and explore the dose–response relationship. The findings from this investigation are intended to generate novel hypotheses regarding the role of inflammatory–nutritional dysregulation in BC and provide a foundation for future prospective studies.

2. Methods

2.1. Study design and data source

Conducted by the National Center for Health Statistics, the NHANES is a nationwide initiative designed to assess the health status and nutritional behaviors of noninstitutionalized civilians in the United States.[19] Through biennial data collection cycles, NHANES gathers information to identify contemporary disease patterns and trends, thereby informing public health policies. All NHANES data are publicly accessible at https://www.cdc.gov/nchs/nhanes/index.htm.

This study collected information from 92,062 individuals over nine successive NHANES periods (1999–2016). To define the final analytical cohort, several exclusion criteria were applied. First, male participants (n = 45,336) were excluded to focus on the at-risk female population. Second, individuals aged less than 20 years (n = 20,985) were removed, aligning the cohort with the typical age range for BC risk assessment. Third, exclusion was applied to pregnant individuals (n = 1,489) to avoid potential physiological confounders. Finally, a total of 7,259 participants were excluded due to missing essential data points, namely neutrophil count values or BC status, which are fundamental for the study's primary analyses. Following rigorous screening, 16,993 participants were included in this research.[20] Figure 1 illustrates the flow chart detailing participant selection.

2.2. Measurement of NPAR

Hematological parameters (red and white blood cell counts, hemoglobin, hematocrit, and red blood cell indices) were measured using the NHANES complete blood count protocol and a Beckman Coulter DxH 900 analyzer (Beckman-Coulter, United States). This instrument utilizes automated dilution/mixing for cell counts and sizing, as well as a single-beam photometer for hemoglobin measurement. White blood cell differentials, including lymphocytes and neutrophils, were determined using the Coulter VCS system (United States).[21]

Serum albumin concentration was measured using biochemical detection methods such as the bromocresol green method. Fasting venous blood was drawn from the subjects, and after serum separation, bromocresol green reagent was added to the serum. This reagent specifically binds to albumin to form a colored complex. The absorbance was measured using a spectrophotometer, and the serum albumin concentration was calculated based on the standard curve.[22] The NPAR was calculated using Equation (1):[23]

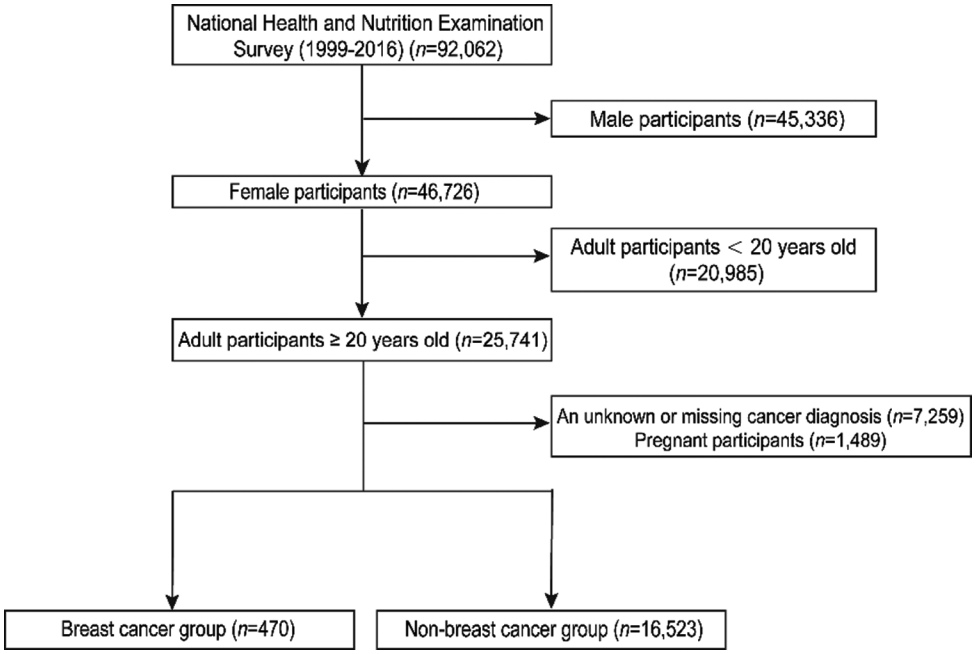

Figure 1. Comprehensive flowchart of participant recruitment. This diagram illustrates the stepwise exclusion process applied to derive the final analytic cohort for the study. Total initial female participants: 46,726. Exclusions comprised (i) participants aged <20 years (n = 20,985), (ii) those with missing/unknown cancer diagnosis (n = 7,259), and (iii) pregnant women (n = 1,489). The final analytical sample was 16,993 women, including 470 women with BC and 16,523 women without BC.
Abbreviation: BC: Breast cancer.

$$\text{Neutrophil percentage} \times 100/\text{Albumin (g/dL)} \quad (1)$$

This study classified participants into four groups according to their NPAR quartiles: <12.33, 12.33–13.92, 13.92–15.53, and ≥15.53, designating the lowest NPAR category (<12.33) as the control group.[24]

2.3. Definition of BC

BC cases were self-reported by participants in response to the question: "What kind of cancer was it?" Based on this, individuals were divided into two groups: those who reported BC and those who did not. The relevant data can be obtained from the publicly available datasets curated by the United States National Public Health Agency.[25]

2.4. Covariate selection

Drawing on prior studies and biological factors, our objective was to include a wide range of covariates known to confound BC outcomes. Key demographic characteristics collected included age, self-reported race and ethnicity, educational attainment, current marital status, history of tobacco use, and patterns of alcohol intake, as well as the family poverty–income ratio (PIR), which was collected using standardized questionnaires and face-to-face interviews. Per NHANES protocols, standardized physical exams were administered by licensed medical staff at mobile examination centers (MECs). Self-reported race/ethnicity included five categories: non-Hispanic White, Mexican American, non-Hispanic Black, other Hispanic, and other race. Education levels were grouped as less than high school (Grades <9), some high school (9–11), high school diploma/General Educational Development, some college, and college degree or higher. Marital status comprised married, divorced, widowed, separated, never married, or unmarried couples. Smoking status was defined by a lifetime consumption of ≥100 cigarettes, irrespective of current usage. Alcohol use was categorized based on a consumption of ≥12 standard alcoholic drinks during the 12 months before survey administration. Body mass index (BMI) was calculated as weight (kg)/height (m^2) and categorized according to the World Health Organization guidelines. A BMI of 25–29.9 kg/m^2 was considered overweight, and a BMI ≥30 kg/m^2 was considered obese. Laboratory tests were performed following standardized procedures to measure neutrophil counts. Given the important roles of hypertension and diabetes as factors that may affect BC, it was essential to account for their possible confounding effects. Physician-diagnosed hypertension and diabetes were defined based on positive responses to standardized NHAHES questions (e.g., "Have you ever been told by a doctor or health professional that you have hypertension, diabetes, or sugar diabetes?").[26]

2.5. Statistical analysis

Statistical significance was defined as $p<0.05$ for all analyses. Analyses were performed using R software (version 4.4.3), with the tidyverse and stats libraries employed. Continuous variables were assessed using Shapiro–Wilk normality testing. Normally distributed data are reported as mean ± standard deviation, while non-normal data are reported as median (interquartile range), and categorical variables are reported as frequency (percentage). Descriptive analyses were conducted for all variables.[27]

Normally distributed continuous variables were compared between groups using Student's *t*-test. Categorical variables were analyzed using the χ^2 test,[28] employing Fisher's exact test when expected cell counts fell below 5. Variance inflation factors (VIFs) were assessed before modeling to evaluate multicollinearity, with VIFs >5 indicating significant collinearity. We employed multivariable logistic regression to evaluate the association between NPAR and BC risk, reporting odds ratios (ORs) alongside their 95% confidence intervals (CIs). Three progressively adjusted models were constructed:

(i) Model 1: Unadjusted
(ii) Model 2: Included covariate adjustments for race/ethnicity and age
(iii) Model 3: In addition, adjusted for marital status, PIR, diabetes, smoking status, and hypertension.[29]

Group differences in survival distributions were evaluated employing the log-rank test. In addition, to flexibly model the association between NPAR and BC risk across its spectrum, we incorporated restricted cubic splines (RCS) into the logistic regression framework. Knot locations for the RCS were set at the 10th, 50th, and 90th percentiles of the NPAR distribution.[30]

Stratified analyses were conducted to examine whether the association between NPAR and BC differed across subgroups defined by age group (20–40, 40–60, ≥60 years), BMI category (<25, 25–30, >30 kg/m^2),[31] PIR level (<1, 1–3, ≥3), alcohol consumption (yes/no), smoking status (yes/no), diabetes (yes/no), and hypertension (yes/no). To investigate potential effect modification, we introduced interaction terms into the models to examine if the NPAR relationship with BC risk differed significantly across these strata.[32]

3. Results

3.1. Demographic attributes of participants

This study enrolled 16,993 female participants, a relatively large sample for similar epidemiological studies, providing a solid foundation for the stability and reliability of the analyses. Among all participants, 470 women reported a diagnosis of BC, accounting for 2.7% of the total number. This incidence proportion offers important population data support for exploring factors related to BC onset.

To more clearly describe the association between BC and various baseline characteristics, we conducted a stratified analysis of the baseline characteristics of the study population based on whether they had BC, with specific data as detailed in Table 1. Comparative analysis showed that there were significant statistical differences in multiple baseline characteristics between participants with BC and those without.

In terms of age, the average age of the BC patient group was significantly higher than that of the non-patient group. This result is consistent with findings from previous studies that age is an important risk factor for BC. This is because, as age increases, the cumulative risk of DNA damage in somatic cells increases, which may, to a certain extent, raise the likelihood of having BC.

Regarding ethnic composition, the proportion of non-Hispanic White women was significantly higher among those with BC than among other racial groups. This difference suggests that ethnic factors may play a role in BC onset, but the specific mechanisms (such as differences in genetic background and living habits) still need further research and verification.

In terms of weight-related indicators, the average BMI of women with BC was significantly lower than that of women without BC. It is worth noting that the association between BMI and BC has always been a research hotspot. Different studies may draw different conclusions due to differences in population characteristics and follow-up time. The association between lower BMI and BC observed in this study provides new population-level data for this field.

In terms of marital status, the proportion of unmarried individuals among BC patients was lower than controls. Some studies have shown that marital status may influence health outcomes through social support and lifestyle stability. Whether the observed differences are related to these mechanisms requires further exploration.

The economic status indicator showed that the PIR of women with BC was significantly higher than that of controls, indicating relatively lower economic pressure. This may be related to the fact that groups with high economic levels are more likely to access regular physical examinations and other health services, thus detecting diseases earlier. It may also involve other potential influencing factors, such as diet and environment.

Table 1. Participants' characteristics by BC status

Variables	Overall (*n*=16,993)	BC (*n*=470)	Non-BC (*n*=16,523)	*p*-value
Age				<0.001***
20–40 years	5,459 (32.12)	7 (1.49)	5,452 (33.00)	
40–60 years	5,730 (33.72)	99 (21.06)	5,631 (34.08)	
>60 years	5,804 (34.16)	364 (77.45)	5,440 (32.92)	
Race				<0.001***
Mexican American	2,918 (17.17)	42 (8.94)	2,876 (17.41)	
Non-Hispanic Black	3,357 (19.76)	71 (15.11)	3,286 (19.89)	
Non-Hispanic White	8,065 (47.46)	305 (64.89)	7,760 (46.96)	
Other races, including multi-racial	1,229 (7.23)	26 (5.53)	1,203 (7.28)	
Other Hispanic	1,424 (8.38)	26 (5.53)	1,398 (8.46)	
Education level				0.294
Less than 9th Grade	1,799 (10.59)	44 (9.36)	1,755 (10.62)	
9–11th Grade	2,436 (14.34)	63 (13.40)	2,373 (14.36)	
Some college or an Associate in Arts degree	5,271 (31.02)	136 (28.94)	5,135 (31.08)	
High school graduate/GED or equivalent	3,807 (22.40)	106 (22.55)	3,701 (22.40)	
College graduate or above	3,680 (21.66)	121 (25.74)	3,559 (21.54)	
Drinking				0.442
Yes	10,138 (59.66)	270 (57.45)	9,868 (59.72)	
No	6,855 (40.34)	200 (42.55)	6,655 (40.28)	
Hypertension				<0.001***
Yes	6,113 (35.97)	270 (57.45)	5,843 (35.36)	
No	10,880 (64.03)	200 (42.55)	10,680 (64.64)	
Diabetes				<0.001***
Yes	2,003 (11.79)	96 (20.43)	1,907 (11.54)	
No	14,990 (88.21)	374 (79.57)	14,616 (88.46)	
Smoking				0.002**
Yes	6,467 (38.06)	208 (44.26)	6,259 (37.88)	
No	10,526 (61.94)	262 (55.74)	10,264 (62.12)	
NPAR				<0.001***
1	4,242 (24.96)	88 (18.72)	4,154 (25.14)	
2	4,252 (25.02)	93 (19.79)	4,159 (25.17)	
3	4,250 (25.01)	131 (27.87)	4,119 (24.93)	
4	4,249 (25.00)	158 (33.62)	4,091 (24.76)	
BMI				0.765
<25	5,343 (31.44)	152 (32.34)	5,191 (31.42)	
25–30	4,941 (29.08)	140 (29.79)	4,801 (29.06)	
>30	6,709 (39.48)	178 (37.87)	6,531 (39.53)	
Household poverty ratio				0.003**
<1	3,588 (21.11)	71 (15.11)	3,517 (21.29)	
1–3	7,168 (42.18)	202 (42.98)	6,966 (42.16)	
>3	6,237 (36.70)	197 (41.91)	6,040 (36.56)	

(Cont'd...)

Table 1. Participants' characteristics by BC status

Variables	Overall (*n*=16,993)	BC (*n*=470)	Non-BC (*n*=16,523)	*p*-value
Marital status				<0.001***
Married	8,165 (48.05)	232 (49.36)	7,933 (48.01)	
Widowed	2,172 (12.78)	130 (27.66)	2,042 (12.36)	
Divorced	2,169 (12.76)	62 (13.19)	2,107 (12.75)	
Separated	651 (3.83)	12 (2.55)	639 (3.87)	
Never married	2,745 (16.15)	24 (5.11)	2,721 (16.47)	
Living with a partner	1,091 (6.42)	10 (2.13)	1,081 (6.54)	

Notes: Data are presented as *n* (%), unless stated otherwise. **/*** indicates $p<0.01$, and $p<0.001$, respectively.
Abbreviations: BC: Breast cancer; BMI: Body mass index; GED: General Educational Development; NPAR: Neutrophil percentage-to-albumin ratio.

In terms of behavioral habits, the smoking rate of BC patients was significantly higher than that of non-patients, while their alcohol intake was lower. As a clear carcinogenic risk factor, smoking's association with BC onset is reflected in this study. There is a dose–effect difference in the association between alcohol intake and BC. The finding that the alcohol intake was lower in the BC group in this study provides supplementary evidence for related research.

In terms of chronic disease burden, the proportion of BC patients with diabetes and hypertension was higher than controls. These two chronic diseases and BC may share common risk factors (such as unhealthy lifestyles and inflammatory reactions). The mechanism of their interaction needs in-depth research.

3.2. Correlation between the NPAR and BC risk

Before constructing the multivariable logistic model, collinearity between NPAR and the remaining covariates was assessed. All VIFs were below 5, suggesting no significant collinearity issues. Results from multivariable logistic regression models exploring NPAR's association with BC are detailed in Table 2. ORs and 95% CIs are provided for three models: an unadjusted model (Model 1), a model adjusted for race and age (Model 2), and a model additionally adjusted for hypertension, diabetes, smoking, marital status, and PIR (Model 3). After confirming the absence of problematic collinearity, we examined the link between NPAR and BC outcomes. Within the fully adjusted Model 3, elevated NPAR levels demonstrated a significant positive association with the odds of BC. Specifically, upon quartile stratification, participants in NPAR Q4 exhibited a 47% greater likelihood of BC compared to those in Q1 (adjusted OR = 1.47; 95% CI: 1.12–1.93; $p=0.006$).

3.3. Linearity assessment of the NPAR association with BC risk in patients

To characterize the dose–response relationship between NPAR and BC risk beyond simple linear assumptions, we employed RCS with three knots, placed at the 10th, 50th, and 90th percentiles of the NPAR distribution as per standard practice. This flexible modeling approach revealed a statistically significant overall association ($p<0.001$). However, the test for non-linearity yielded a non-significant result ($p=0.970$), providing strong statistical evidence against a complex curvilinear pattern and instead supporting a predominantly linear relationship across the observed range of NPAR values. This linear trend is visually confirmed in Figure 2, which demonstrates a consistent, monotonic increase in the adjusted OR for BC, even after accounting for potential confounders, including age, BMI, and smoking status, with progressively higher NPAR levels. Importantly, the entire range of estimated OR values at various NPAR points was statistically significant, as evidenced by their 95% CIs uniformly excluding the null value (OR = 1.0). The fact that the CIs exclude 1.0 indicates a robust positive association. Furthermore, the graded, increasing relationship between NPAR and BC risk observed in the RCS analysis is consistent with a potential dose–response pattern. This pattern likely reflects the continuous, underlying pathophysiological processes involving systemic inflammation (captured by the percentage of neutrophils), where neutrophil-derived pro-inflammatory cytokines may promote the formation of the tumor microenvironment and nutritional/metabolic status (reflected by albumin, a marker whose levels correlate with tissue repair capacity and metabolic homeostasis), which contribute to oncogenesis.

3.4. Subgroup analysis

Subgroup analysis included race, age categories, BMI, educational attainment, alcohol consumption patterns, smoking status, diabetes mellitus, and hypertension. The results, visually summarized in Figure 3, revealed that the positive association between elevated NPAR levels and increased BC risk was statistically more pronounced within specific subgroups. These subgroups encompassed

Table 2. Assessing the link between NPAR and BC using logistic regression

NPAR quartile	Model 1		Model 2		Model 3	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Q1	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
Q2	1.06 (0.79–1.42)	0.719	1.07 (0.79–1.44)	0.668	1.05 (0.78–1.42)	0.735
Q3	1.50 (1.14–1.97)	0.004	1.38 (1.04–1.82)	0.026	1.35 (1.02–1.79)	0.036
Q4	1.82 (1.40–2.37)	<0.001	1.49 (1.13–1.95)	0.004	1.47 (1.12–1.93)	0.006

Abbreviations: BC: Breast cancer; CI: Confidence interval; NPAR: Neutrophil percentage-to-albumin ratio; OR: Odds ratio.

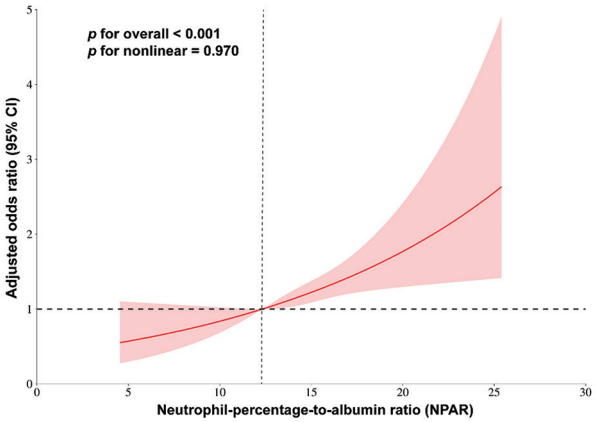

Figure 2. Restricted cubic splines curves of association between the NPAR and BC in all study participants. Solid lines: adjusted ORs (multivariate logistic regression); shaded bands: 95% CIs. Reference: NPAR=12.325 (median of 1st quartile; vertical dashed line). Horizontal line at OR=1: no association. Model adjusted for age, race/ethnicity, body mass index, education, marital status, smoking/alcohol history, household poverty rate (poverty–income ratio), hypertension, and diabetes. Junctions at the 10th (10.82%), 50th (13.92%), and 90th (17.09%) percentiles of the NPAR distribution. Non-linearity: p=0.970 (likelihood ratio test).
Abbreviations: BC: Breast cancer; CI: Confidence interval; NPAR: Neutrophil percentage-to-albumin ratio; OR: Odds ratio.

individuals identifying as belonging to racial groups classified as "Others," participants with a high school graduation or equivalent educational level, younger adults (20–40 years old), individuals classified as overweight, non-smokers, abstainers from alcohol, and individuals diagnosed with either diabetes or hypertension. Importantly, despite these observed variations in association strength across subgroups, formal statistical testing for interaction effects indicated no significant multiplicative interaction between the NPAR variable and any of the stratification variables examined.

The forest plot (Figure 3) illustrates the ORs and their 95% CIs for the association between the exposure of interest and the outcome, analyzed across different subgroups. An OR > 1 implies that the exposed group has higher odds of the outcome compared to the unexposed group, while an OR < 1 indicates lower odds. Subgroups were defined based on the following factors: (i) ethnicity, including Mexican-American, non-Hispanic, non-Hispanic Black, non-Hispanic White, and other races; (ii) education level such as below grade 9, grades 9–11, high school graduates, college graduates; (iii) alcohol consumption status (yes/no); (iv) diabetes status (yes/no); (v) hypertension status (yes/no); (vi) smoking status (yes/no); (vii) age group (20–40, 40–60, ≥60); BMI category (<25, 25–30, ≥30); PIR category (<1, 1–3, ≥3); NPAR quartiles (Q1–Q4); and marital status, such as married, widowed, divorced/separated, never married, and living with a partner.

3.5. Nomogram model for predicting BC based on participants' baseline characteristics

Using a retrospective analysis of a substantial cohort, we developed a predictive nomogram for BC risk, as illustrated in Figure 4. This tool integrates readily available baseline clinical and demographic characteristics with the NPAR score. To demonstrate its application, the nomogram was used to assess a representative case: a 69-year-old White woman with an NPAR score of 11.372. The model predicted that her odds of having BC were significantly elevated, approximately 2.86-fold higher than the reference profile. The nomogram's discriminative power, reflecting its ability to distinguish between individuals with and without BC, was rigorously quantified using receiver operating characteristic (ROC) curve analysis. This evaluation yielded an area under the curve (AUC) of 0.8068 (95% CI: 0.7904–0.8232). This high AUC signifies that the model has strong predictive capability, effectively stratifying BC risk based on the integrated assessment of clinical and inflammatory status.

4. Discussion

As a novel inflammatory–nutritional composite biomarker, NPAR integrates information from routine blood tests, reflecting the balance between pro-inflammatory neutrophils and nutrition-related albumin levels. This integration may capture aspects of systemic inflammatory and metabolic dysregulation more comprehensively than isolated markers.[33] Emerging research suggests

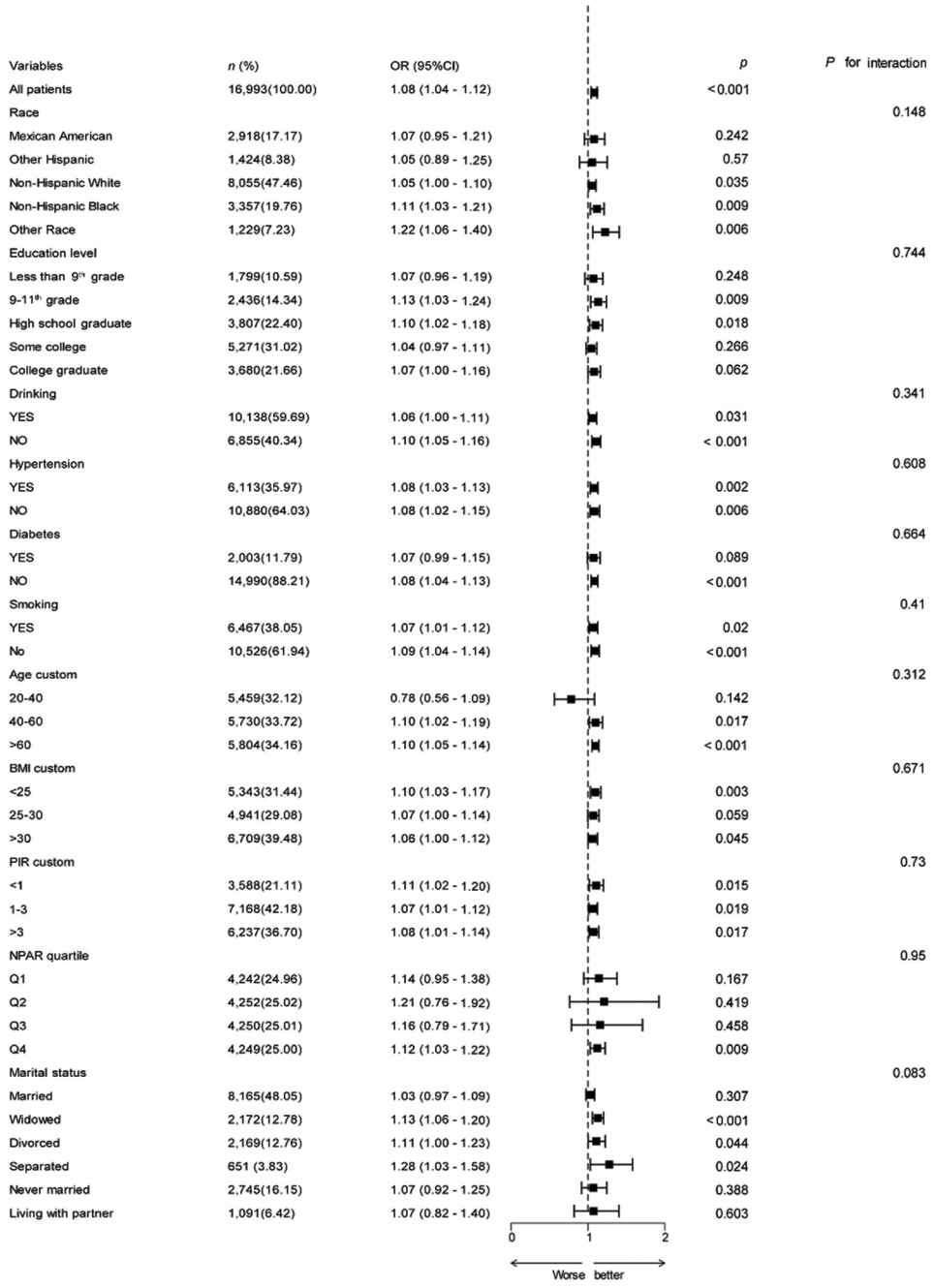

Figure 3. Subgroup analysis of the association between NPAR and BC. Each square represents the OR for a specific subgroup. The horizontal line extending from the square denotes the 95% CI.

Abbreviations: BC: Breast cancer; CI: Confidence interval; NPAR: Neutrophil percentage-to-albumin ratio; OR: Odds ratio.

that composite biomarkers, such as NPAR, may offer advantages over traditional inflammatory indices, like the neutrophil-to-lymphocyte ratio or the systemic immune-inflammation index, by integrating multifaceted pathological processes—specifically, the simultaneous pro-inflammatory component (neutrophil percentage) and nutritional–metabolic component (albumin) status.[34] Although direct comparative studies in BC are currently lacking, NPAR's promising diagnostic and prognostic utility is evidenced across a spectrum of chronic conditions. It achieved an AUC of 0.810 (95% CI: 0.794–0.825) in discriminating individuals with and without non-alcoholic fatty liver disease[35] and demonstrated strong discriminatory power for diabetic retinopathy risk stratification, as well as

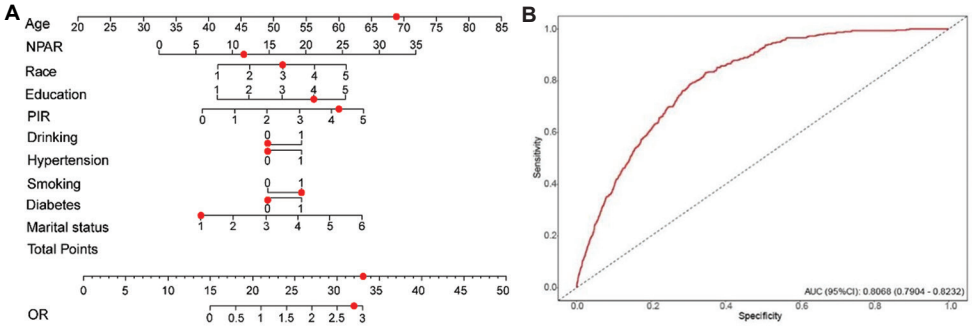

Figure 4. Development and evaluation of the BC risk prediction nomogram. (A) Nomogram for predicting the odds ratio (OR) of BC risk, integrating baseline clinical and demographic characteristics and the NPAR score. Red markers indicate reference values or illustrative examples, depending on the context. (B) Receiver operating characteristic (ROC) curve depicting the discriminative ability of the predictive model for BC risk. The red solid line represents the ROC curve of the model, illustrating the trade-off between sensitivity and specificity across different prediction thresholds. The dashed diagonal line serves as a reference for a random classifier, for which the area under the curve (AUC) would be 0.5 (no discriminative power).
Abbreviations: BC: Breast cancer; CI: Confidence interval; NPAR: Neutrophil percentage-to-albumin ratio; PIR: Poverty–income ratio.

for predicting mortality after hip fracture surgery in older adults.[36] It also showed favorable sensitivity/specificity in assessing severity in anti-N-methyl-D-aspartate receptor encephalitis.[37] This consistent performance across diverse disease contexts underscores NPAR's potential as a sensitive indicator of systemic inflammatory–metabolic–immune dysregulation. However, its applications in oncology, particularly in BC, remain nascent. The mechanistic underpinnings of NPAR in cancer pathogenesis and its clinical translatability necessitate systematic investigation, especially through direct comparisons with established indices within the same cohorts.

Using a large, nationally representative multi-stage stratified sample from NHANES, this study identified a significant positive association between higher NPAR levels and increased risk of BC among women in the United States. RCS analyses revealed a monotonically increasing trend in BC risk with rising NPAR levels (p<0.001), indicating a graded relationship consistent with a potential dose–response pattern, although the cross-sectional design precludes causal inference. This association remained robust across subgroups stratified by age and BMI, supporting the generalizability of the finding.

The observed association may be interpreted in the context of BC pathophysiology. Chronic inflammation is implicated in tumor initiation and progression; neutrophils, in particular, are known to facilitate invasion and metastasis through mechanisms including epithelial–mesenchymal transition and the formation of pre-metastatic niches.[38] Concurrently, low albumin levels may reflect not only malnutrition but also ongoing systemic inflammation, potentially contributing to immunosuppression within the tumor microenvironment.[39] Furthermore, breast tumors, often driven by estrogen signaling, may exhibit enhanced neutrophil recruitment through estrogen-mediated upregulation of chemokines such as chemokine (C-X-C motif) ligand 8.[40] This hormone–inflammation interplay might be particularly relevant in estrogen receptor-positive subtypes, suggesting a plausible biological context for the association observed in this study. Nevertheless, the exact mechanisms linking NPAR to BC remain speculative and warrant further investigation.

The clinical appeal of NPAR is underpinned by its low cost and high accessibility, as it is derived from routine blood parameters obtained through standard venipuncture. Its estimated cost is a fraction of that of mammography. While mammography remains the gold standard for BC detection, its limitations—including reduced sensitivity in dense breasts and higher associated costs—highlight the need for complementary screening tools. We propose a stratified screening strategy in which NPAR could serve as an initial pre-screening tool to identify individuals at higher risk (e.g., NPAR ≥ 2.5), who could then be prioritized for mammographic examination. Modeling studies based on similar approaches suggest that this strategy could reduce unnecessary mammograms by 30–40% and improve early-stage cancer detection rates.[41,42] In addition, the ease of serial measurement makes NPAR a candidate for ongoing risk monitoring in high-risk populations, potentially bridging the intervals between routine imaging. Consequently, our findings suggest that NPAR, as a low-cost and accessible measure, could be a candidate for further investigation in BC risk assessment. If its value is validated in prospective studies, it could be implemented in resource-limited settings, helping to address healthcare access disparities among low-income women.

This study has several strengths, including the use of a nationally representative sample with complex survey weighting, which enhances the generalizability

of the findings. Extensive adjustment for confounders strengthens the validity of the observed associations. Limitations include the lack of temporal sequencing inherent in cross-sectional designs, the absence of detailed cancer characteristics (e.g., stage, molecular subtype), and insufficient data on other inflammatory markers, which would be necessary for direct comparison with NPAR. Future research should prioritize prospective validation of NPAR in independent cohorts, ideally with repeated measurements and accompanied by molecular subtyping. Mechanistic studies exploring the role of neutrophils and albumin in the breast tumor microenvironment—particularly in relation to hormone receptor status—would help clarify the biological relevance of NPAR. Finally, comparative analyses with other inflammatory indices are needed to determine whether NPAR offers substantive advantages in clinical prediction.

5. Conclusion

In conclusion, this study explored, for the first time, the association between NPAR and BC risk, highlighting a potential synergistic link between inflammation and nutritional status in the context of BC. As a convenient and cost-effective composite indicator, NPAR, combined with the high predictive performance of the nomogram model, offers novel insights for early screening and risk stratification of BC. Future studies should further validate its clinical applicability and explore its value in personalized prevention strategies. These findings not only enrich the etiological understanding of BC but also provide a scientific foundation for future public health interventions.

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Conflict of interest

The authors declare that they have no competing interests.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

The data used in this study are publicly available from the National Health and Nutrition Examination Survey (NHANES) database, which is maintained by the U.S. Centers for Disease Control and Prevention (CDC). The dataset is de-identified and approved for unrestricted public access by the CDC/National Center for Health Statistics Institutional Review Board. Researchers can access the data through the official NHANES portal: https://www.cdc.gov/nchs/nhanes/index.htm.

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