

Article

Association between peripheral neutrophil percentage and depressive symptoms among adults with a history of cancer: a population-based NHANES study

Yanbo Liu^{1,2,*,#}, Yuhui Li^{3,#}, Jinmin Chen¹, Yongxia Cai¹, Lukai Lv⁴

¹ Department of Emergency, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang Province, China.

² Department of Emergency, Zhejiang University Sir Run Run Shaw Alaer Hospital, Alaer, Xinjiang, China.

³ Department of Ultrasonography Lab, Women's Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang Province, China.

⁴ Department of Emergency, Wuyi County People's Hospital, Jinhua, Zhejiang Province, China.

*Corresponding author: Yanbo Liu, yanboliu9544@163.com

#These authors equally contributed to this work.

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Abstract: Depressive symptoms represent a prevalent and burdensome comorbidity among adults with a history of cancer, yet the relationship between routinely available inflammatory markers and depression in this population remains insufficiently characterized, particularly regarding potential nonlinear patterns. This cross-sectional study analyzed data from 4,175 adults with a history of cancer in the National Health and Nutrition Examination Survey (NHANES) to examine the association between neutrophil percentage and clinically significant depressive symptoms, defined as a Patient Health Questionnaire-9 (PHQ-9) score ≥ 10 , using multivariable logistic regression, restricted cubic spline (RCS) regression, and piecewise threshold analyses with sequential covariate adjustment. When neutrophil percentage was categorized into quartiles, participants in the third quartile (Q3) exhibited significantly higher odds of depressive symptoms compared with the lowest quartile (adjusted OR = 1.91, 95% CI: 1.11–3.29). RCS regression revealed a significant nonlinear association, with inflection points identified at 50.15% and 64.42%. Within this intermediate range, each 1% increment in neutrophil percentage was associated with a 16.4% increase in depression odds (OR = 1.164, 95% CI: 1.090–1.242, $P < 0.001$), whereas no significant associations were observed outside this interval. These findings indicate that in adults with a history of cancer, the segmented neutrophil percentage is non-linearly associated with depressive symptoms, and the higher odds of clinically significant depressive symptoms is confined to a specific intermediate range. The identified inflection point should be regarded as an exploratory, study-derived threshold for stratification, and further prospective validation is required.

Keywords: depression; cancer; neutrophil percentage; NHANES; cross-sectional study

1. Introduction

Depressive symptoms constitute a significant component of the psychosocial burden experienced by individuals affected by cancer[1]. Importantly, current clinical guidelines from the European Society for Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO) recognize anxiety and depression as core concerns in cancer care, underscoring the imperative for systematic screening and evidence-based intervention[2,3]. Nevertheless, the manifestation of depressive symptoms in this population cannot be fully elucidated by psychosocial stress or sociodemographic factors alone, which has spurred growing interest in delineating the biological underpinnings that may account for interindividual variability in symptom severity[4].

Cancer is frequently accompanied by substantial perturbations in both innate and adaptive immunity[5]. Among circulating immune cells, neutrophils are one of the most abundant subsets and play critical roles in host defense, tissue remodeling, tumor-associated inflammation, and inflammatory responses to anticancer therapies[6–8]. Previous studies have examined the links between various inflammatory markers and depressive symptoms, with mounting evidence from general population-based studies indicating that novel composite indices, such as the neutrophil-to-albumin ratio (NPAR), are positively associated with higher odds of depressive symptoms[9,10]. However, the specific relationship between peripheral neutrophil percentage and depressive symptoms in adults with a history of cancer remains unclear[11–13]. Of additional concern is the possibility that immune–psychological interactions may not be adequately captured by conventional linear frameworks, thereby motivating explicit evaluation of nonlinear relationships rather than a sole reliance on linear terms or quantile-based categorization.

To address these gaps, the present study leveraged data from the National Health and Nutrition Examination Survey (NHANES) to examine the association between neutrophil percentage and depressive symptoms among adults with a history of cancer, with a particular focus on detecting potential nonlinear patterns. This investigation aimed to advance the current understanding of the relationship between cancer-related depression and inflammatory profiles, and to offer preliminary evidence supporting the utility of routine hematological parameters as accessible indicators for identifying adults with a history of cancer at elevated odds of depressive symptoms.

2. Materials and methods

2.1. Study design and data source

This cross-sectional investigation utilized data from the NHANES, an ongoing program conducted by the National Center for Health Statistics (NCHS) designed to evaluate the health and nutritional status of the noninstitutionalized civilian population in the United States. NHANES employs a complex, stratified, multistage probability sampling design. The present analysis restricted inclusion to survey cycles in which information on cancer history, differential white blood cell (WBC) counts, the nine-item Patient Health Questionnaire (PHQ-9), and the requisite covariates were concurrently available.

2.2. Study population

This analysis included adults with a self-reported history of cancer, complete data on differential WBC counts, PHQ-9 scores, and covariates of interest. The final analytic sample comprised 4,175 participants from NHANES cycles 2005–2023.

2.3. Study variables

2.3.1. Exposure and outcome definitions

Primary exposure: Neutrophil percentage, derived from standardized complete blood counts with differential (CBC-D) using Beckman Coulter methodology.

Primary outcome: Depressive symptoms were evaluated using the PHQ-9 in NHANES cycles with compatible data. Each of the nine items assesses the frequency of a given depressive symptom over the preceding two-week period. Clinically significant depressive symptoms were defined as a PHQ-9 total score of ≥ 10 , a threshold that has been validated for detecting clinically meaningful depression in adults with a history of cancer.

2.3.2 Covariate assessment

Comprehensive covariates were selected across three domains: (1) demographic characteristics, including age, sex, race, educational level, poverty status, and marital status; (2) comorbid conditions, comprising diabetes (identified by self-report or $\text{HbA1c} \geq 6.5\%$), hypertension (blood pressure $\geq 140/90$ mmHg or use of antihypertensive medication), chronic kidney disease (estimated glomerular filtration rate < 60 mL/min/1.73 m²), and hyperlipidemia (low-density lipoprotein cholesterol ≥ 130 mg/dL or lipid-lowering medication use); and (3) lifestyle factors, encompassing smoking status and alcohol consumption.

2.4. Statistical approach

All primary analyses were conducted accounting for the complex sampling design of NHANES, with appropriate application of examination or subsample weights, strata, and primary sampling units. For analyses pooling multiple survey cycles, sampling weights were recalculated in accordance with NHANES analytic guidelines and the specific cycles included in the present study.

Descriptive analyses were performed to characterize the study population. Continuous variables were summarized as weighted means with standard deviations, whereas categorical variables were presented as unweighted percentages with weighted percentages.

Multivariable logistic regression models were employed to evaluate the association between neutrophil percentage and depression. The exposure was entered into the models both as a continuous variable and as a categorical variable, using three sequential adjustment strategies: Model 1 was unadjusted; Model 2 adjusted for demographic factors including age, sex, and race/ethnicity; and Model 3 further adjusted, on the basis of Model 2, for marital status, educational level, poverty status, smoking status, alcohol consumption, hypertension, diabetes mellitus, hyperlipidemia, and chronic kidney disease.

To explore potential nonlinear relationships, restricted cubic spline (RCS) regression was performed with three to five knots. The likelihood ratio test was applied to compare the fit of linear versus nonlinear models, and when a significant nonlinear association was detected, threshold effect analysis was subsequently conducted. Based on the inflection points derived from the RCS models, participants were stratified into subgroups to compute subgroup-specific adjusted odds ratios (aORs).

All statistical analyses were performed using R software version 4.3.1 (R Foundation for Statistical Computing) with the ‘survey’ package to account for the complex sampling design.

3. Results

3.1. Baseline characteristics

The present study included 4,175 participants (mean age 63.17 ± 13.95 years; 57% female), who were stratified into quartiles (Q1–Q4) based on neutrophil percentage (**Figure 1**, **Table 1**). Participants in the highest quartile (Q4) were significantly older, more likely to be Non-Hispanic White, and less likely to be Non-Hispanic Black compared with those in the lowest quartile (Q1) (all $P < 0.001$). Notably, comorbidity burden rose progressively across higher neutrophil quartiles. The prevalence of chronic kidney disease (Q4: 34% vs. Q1: 20%, $P < 0.001$) and hypertension (Q4: 65% vs. Q1: 54%, $P < 0.001$) was substantially elevated in Q4

relative to Q1, whereas the increasing trend for diabetes mellitus did not attain statistical significance (Q4: 26% vs. Q1: 20%, $P = 0.063$). Current smoking was more frequent in Q4 than in Q1 (18% vs. 14%), though this difference was not statistically significant ($P = 0.3$). Sex distribution varied significantly across quartiles ($P < 0.001$), with a greater representation of males in Q4 (51%) than in Q1 (37%). In contrast, educational attainment, marital status, and hyperlipidemia exhibited no significant differences across quartiles (all $P > 0.05$), whereas poverty status demonstrated a modest yet statistically significant difference ($P = 0.004$).

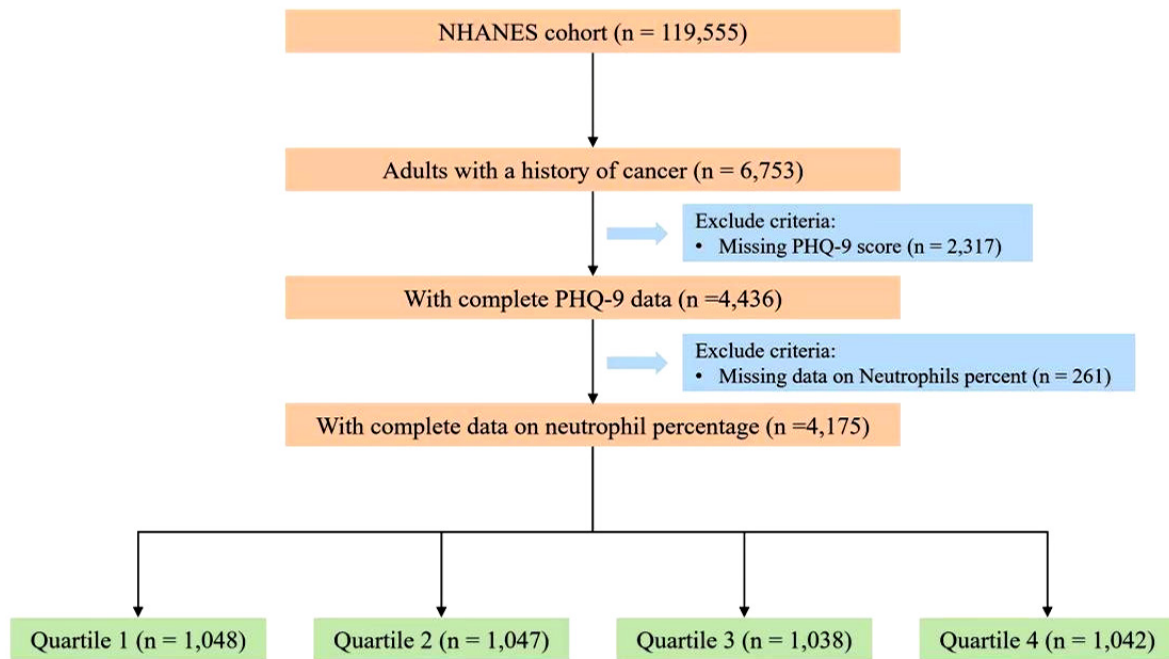


Figure 1. Flowchart of participant selection and quartile stratification.

Table 1. Baseline characteristics of adults with a history of cancer by neutrophil percentage quartiles

Characteristic	Overall N = 4,175	Q1 N = 1,048	Q2 N = 1,047	Q3 N = 1,038	Q4 N = 1,042	P^2
Age, years	63.17 (13.95)	61.30 (14.07)	62.03 (13.83)	63.40 (14.34)	66.07 (13.05)	< 0.001
Sex						< 0.001
Female	2,241 (57%)	632 (63%)	583 (60%)	550 (57%)	476 (49%)	
Male	1,934 (43%)	416 (37%)	464 (40%)	488 (43%)	566 (51%)	
Race						< 0.001
Mexican American	145 (3%)	33 (3%)	41 (3%)	40 (3%)	31 (2%)	
Non-Hispanic Asian	99 (2%)	27 (2%)	34 (2%)	14 (1%)	24 (1%)	
Non-Hispanic Black	360 (5%)	153 (9%)	81 (4%)	71 (4%)	55 (3%)	
Non-Hispanic White	1,934 (84%)	401 (78%)	475 (84%)	512 (87%)	546 (89%)	
Other Hispanic	185 (3%)	47 (3%)	63 (4%)	46 (3%)	29 (2%)	

Continuation Table:

Characteristic	Overall N = 4,175	Q1 N = 1,048	Q2 N = 1,047	Q3 N = 1,038	Q4 N = 1,042	<i>P</i> ²
Other Race – Including Multi-Racial	124 (4%)	34 (5%)	30 (3%)	36 (3%)	24 (3%)	
Education level						0.600
College graduate or above	1,258 (35%)	319 (37%)	326 (37%)	312 (34%)	301 (33%)	
High school equivalent	903 (22%)	216 (21%)	218 (21%)	239 (24%)	230 (23%)	
Less than high school	732 (11%)	182 (11%)	177 (9%)	176 (11%)	197 (12%)	
Some college	1,281 (32%)	331 (31%)	326 (32%)	311 (31%)	313 (33%)	
Marital status						0.400
Previously married	1,393 (29%)	335 (27%)	348 (30%)	349 (30%)	361 (31%)	
Living with partner	87 (2%)	29 (3%)	29 (3%)	16 (2%)	13 (1%)	
Married	2,386 (62%)	597 (62%)	602 (62%)	600 (62%)	587 (61%)	
Never married	306 (6%)	87 (7%)	67 (5%)	73 (6%)	79 (7%)	
Poverty-to-income ratio	3.33 (1.56)	3.36 (1.57)	3.48 (1.58)	3.29 (1.55)	3.17 (1.53)	0.004
Alcohol consumption						0.049
Former	1,065 (21%)	249 (18%)	253 (20%)	274 (22%)	289 (26%)	
Heavy	416 (11%)	98 (11%)	112 (11%)	104 (12%)	102 (10%)	
Mild	1,712 (44%)	425 (42%)	427 (45%)	425 (43%)	435 (44%)	
Moderate	507 (15%)	152 (18%)	131 (15%)	118 (14%)	106 (11%)	
Never	462 (9%)	120 (10%)	122 (9%)	114 (9%)	106 (9%)	
Smoking status						0.300
Former	1,317 (37%)	312 (35%)	326 (36%)	315 (38%)	364 (39%)	
Never	1,585 (48%)	450 (51%)	397 (49%)	394 (48%)	344 (43%)	
Now	528 (15%)	125 (14%)	133 (15%)	124 (14%)	146 (18%)	
Diabetes mellitus						0.063
Yes	1,137 (23%)	252 (20%)	273 (22%)	315 (26%)	297 (26%)	
No	3,028 (77%)	796 (80%)	774 (78%)	721 (74%)	737 (74%)	
Chronic kidney disease						< 0.001
No	2,216 (73%)	628 (80%)	569 (75%)	532 (71%)	487 (66%)	
Yes	1,120 (27%)	236 (20%)	268 (25%)	283 (29%)	333 (34%)	
Hypertension						< 0.001
No	1,533 (42%)	410 (46%)	411 (46%)	389 (41%)	323 (35%)	
Yes	2,642 (58%)	638 (54%)	636 (54%)	649 (59%)	719 (65%)	

Continuation Table:

Characteristic	Overall	Q1	Q2	Q3	Q4	<i>P</i> ²
	N = 4,175	N = 1,048	N = 1,047	N = 1,038	N = 1,042	
Hyperlipidemia						0.600
No	1,002 (22%)	226 (21%)	250 (22%)	259 (24%)	267 (23%)	
Yes	3,146 (78%)	814 (79%)	791 (78%)	772 (76%)	769 (77%)	

Abbreviations: SD, standard deviation; NHANES, National Health and Nutrition Examination Survey.

Note: ¹ Weighted N represents the estimated population size; data are presented as weighted mean (SD) for continuous variables and unweighted n (weighted %) for categorical variables. ² *P* were derived from design based Kruskal Wallis tests for continuous variables and Rao Scott chi square tests for categorical variables, accounting for the complex survey design of NHANES.

3.2. Association of neutrophil percentage with depression

Multivariable logistic regression analyses were conducted to examine the association between neutrophil percentage and odds of depressive symptoms, with results summarized in **Table 2**. When the exposure was modeled as a continuous variable (per 1% increment), no statistically significant relationship emerged across any of the three sequential models (Model 1: OR = 1.00, 95% CI: 0.99–1.01, *P* = 0.95; Model 2: OR = 1.01, 95% CI: 1.00–1.03, *P* = 0.11; Model 3: OR = 1.00, 95% CI: 0.98–1.03, *P* = 0.75).

Table 2. Multivariate logistic regression analysis of the association between neutrophil percentage and depression risk in adults with a history of cancer

Variables	Model 1		Model 2		Model 3	
	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>
Neutrophil percentage (per 1% increment)	1.00 (0.99, 1.01)	0.95	1.01 (1.00, 1.03)	0.11	1.00 (0.98, 1.03)	0.75
Neutrophil percentage quartiles						
Q1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q2	1.35 (0.94, 1.96)	0.11	1.41 (0.86, 2.29)	0.17	1.19 (0.65, 2.17)	0.57
Q3	1.46 (1.03, 2.08)	0.03	1.93 (1.24, 3.00)	0.004	1.91 (1.11, 3.29)	0.02
Q4	1.10 (0.77, 1.58)	0.60	1.65 (1.03, 2.63)	0.04	1.15 (0.61, 2.18)	0.65

Abbreviations: OR, odds ratio; CI, confidence interval; NHANES, National Health and Nutrition Examination Survey. Model 1: Unadjusted.

Model 2: Adjusted for age, sex, and race.

Model 3: Adjusted for age, sex, race, marital status, educational level, poverty status, smoking status, alcohol consumption, hypertension, diabetes mellitus, hyperlipidemia, and chronic kidney disease.

Note: Neutrophil percentage was modeled both as a continuous variable (per 1% increment) and as quartiles (Q1–Q4), with Q1 as the reference. All models accounted for the complex survey design of NHANES using appropriate sampling weights. Data are presented as odds ratios with 95% confidence intervals.

When neutrophil percentage was categorized into quartiles (with Q1 serving as the reference), participants in Q3 demonstrated consistently elevated odds of depressive symptoms relative to those in Q1 across all models, with the association remaining robust after comprehensive adjustment (Model 3: aOR = 1.91, 95% CI: 1.11–3.29, $P = 0.02$). For Q4, a significant positive association was observed in the age-, sex-, and race-adjusted model (Model 2: OR = 1.65, 95% CI: 1.03–2.63, $P = 0.04$); however, this effect was substantially attenuated upon further adjustment for all remaining covariates and no longer reached statistical significance in the fully adjusted model (Model 3: aOR = 1.15, 95% CI: 0.61–2.18, $P = 0.65$). Notably, the association between the highest quartile and odds of depressive symptoms appeared to be largely explained by demographic and clinical confounders. No significant associations were identified for Q2 in any of the three models (all $P > 0.05$).

3.3. Nonlinear relationship between neutrophil percentage and odds of depressive symptoms

To further characterize the dose–response relationship beyond the categorical framework, RCS regression was performed within the fully adjusted model (Model 3). The likelihood ratio test revealed a significant departure from linearity (P for nonlinearity < 0.001), indicating a complex, nonlinear association between neutrophil percentage and the odds of depressive symptoms. Visual inspection of the spline curve demonstrated a distinct pattern: the odds of depressive symptoms remained relatively stable at both the lower and upper tails of the neutrophil percentage distribution, yet exhibited a pronounced upward slope within a specific mid-range. Notably, the curve identified two salient inflection points, located at approximately 50.15% and 64.42%, which served as critical junctures demarcating three distinct phases of the exposure–response relationship (**Figure 2**).

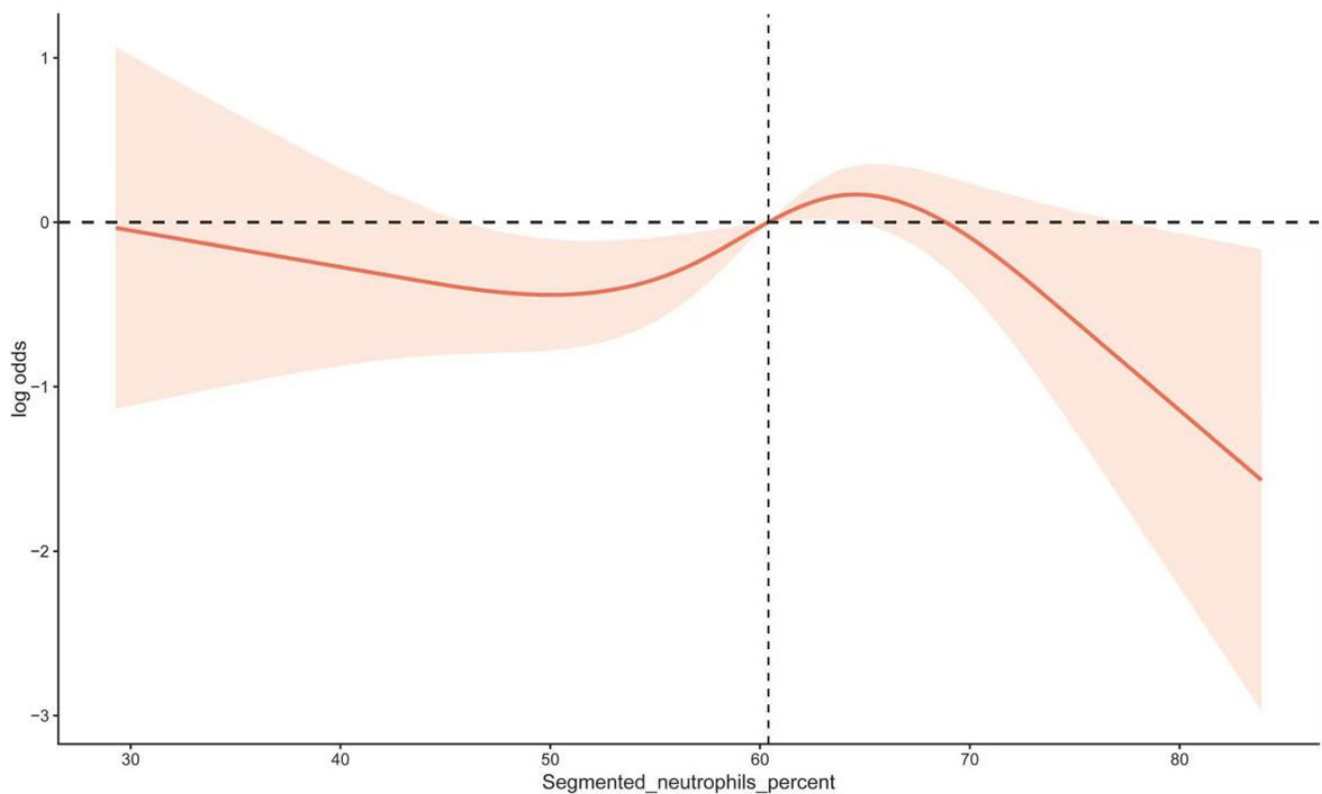


Figure 2. Nonlinear association between neutrophil percentage and odds of depressive symptoms.

3.4. Threshold effect analysis at the inflection point

To quantitatively evaluate the association across distinct segments of the exposure spectrum, we conducted a piecewise multivariable logistic regression analysis stratified by the two inflection points derived from the RCS curve (i.e., 50.15% and 64.42%). Accordingly, the study population was partitioned into three intervals: < 50.15%, 50.15%–64.42%, and > 64.42%. Within the intermediate interval (50.15%–64.42%), after comprehensive adjustment for all covariates in Model 3, each 1% increment in neutrophil percentage was significantly associated with a 16.4% elevation in the odds of depressive symptoms (OR = 1.164, 95% CI: 1.090–1.242, $P < 0.001$) (**Table 3**). In contrast, no statistically significant associations were observed in either the lower interval (< 50.15%) or the upper interval (> 64.42%) within the same fully adjusted model (OR = 1.059, 95% CI: 0.964–1.162, $P = 0.215$; and OR = 0.951, 95% CI: 0.884–1.023, $P = 0.173$, respectively). The further exploration results suggest that the positive association between neutrophil percentage and depressive symptoms is not uniform across the entire distribution, but rather manifests selectively within a defined mid-range threshold.

Table 3. Piecewise logistic regression analysis of neutrophil percentage and depression risk stratified by inflection points in adults with a history of cancer

Interval	OR	95% CI	<i>P</i>
< 50.15%	1.059	(0.964, 1.162)	0.215
50.15%–64.42%	1.164	(1.090, 1.242)	< 0.001
> 64.42%	0.951	(0.884, 1.023)	0.173

Abbreviations: OR, odds ratio; CI, confidence interval; RCS, restricted cubic spline; PHQ-9, Patient Health Questionnaire-9.

Note: All estimates were derived from the fully adjusted model (Model 3), adjusting for age, sex, race, marital status, educational level, poverty status, smoking status, alcohol consumption, hypertension, diabetes mellitus, hyperlipidemia, and chronic kidney disease. The three intervals were defined based on the two inflection points (50.15% and 64.42%) identified from the RCS regression. The outcome was clinically significant depressive symptoms, defined as a PHQ-9 score ≥ 10 . The OR represents the change in the odds of depression per 1% increment in neutrophil percentage within each respective interval.

4. Discussion

In this cross-sectional analysis of 4,175 adults with a history of cancer, we observed a nonlinear association between neutrophil percentage and depressive symptoms, with a significantly elevated odds ratio confined to the 50.15%–64.42% range. Importantly, this finding represents a research-derived pattern requiring prospective validation rather than a clinical cutoff or a basis for immediate clinical intervention.

Previous investigations in oncology have generally supported an association between peripheral inflammation and depressive symptoms. A systematic review and meta-analysis by McFarland et al. included 73 cancer studies, of which 54 (5,017 patients) were quantitatively synthesized, demonstrating significant associations of interleukin-6 (IL-6), tumor necrosis factor (TNF), and C-reactive protein (CRP) with depressive symptoms; the neutrophil-to-lymphocyte ratio (NLR) showed a concordant association, though with fewer contributing studies[14]. Evidence from

lung cancer populations also supports neutrophil involvement: one study of 109 lung cancer patients found that NLR was positively correlated with depressive symptoms, independent of age, sex, and marital status[15]; another study of 186 treatment-naïve stage IV non-small cell lung cancer patients reported that PHQ-9 scores were positively correlated with NLR and platelet-to-lymphocyte ratio, and moderate-to-severe depression was associated with worse systemic inflammation[16]. These findings are broadly consistent with our observation that a moderately elevated neutrophil percentage is associated with higher odds of clinically significant depressive symptoms, supporting the notion that peripheral immune profiles may be related to depressive symptomatology in cancer patients.

Notably, our study revealed a significant nonlinear association, with the effect predominantly concentrated within 50.15%–64.42%, whereas no significant associations were observed outside this range. This pattern suggests the presence of a potential "effect window" that may not be captured by conventional linear approaches. Mechanistically, it has been postulated that activated neutrophils, when moderately elevated, may contribute to neuroinflammation and neurotransmitter dysregulation through the release of myeloperoxidase, neutrophil extracellular traps (NETs), and pro-inflammatory cytokines, though direct evidence linking these pathways to depressive outcomes in cancer patients remains limited[17–20]. Preclinical sepsis models have validated that peripheral NETs elevate circulating TNF- α , IL-1 β and IL-6, disrupt blood-brain barrier integrity, induce microglial overactivation, and ultimately drive depression-like behavioral phenotypes; inhibition of NET formation largely reverses such emotional disturbances[21]. In tumor-bearing hosts, tumor-derived sphingosine-1-phosphate further amplifies neutrophil NETosis, which in turn mediates neuronal damage and exacerbates cancer-related depressive behaviors in murine breast cancer models[20]. One speculative explanation for the reduced odds at very high neutrophil percentages is that endogenous counter-regulatory mechanisms may be activated via vagal anti-inflammatory reflexes to constrain excessive systemic inflammation and neurotoxicity[22]. However, direct mechanistic evidence linking extreme neutrophilia to compensatory immune regulation is lacking, and this hypothesis needs experimental testing in future tumor-bearing animal models and prospective clinical cohorts.

Most prior epidemiological studies have modeled neutrophils as continuous linear variables or dichotomized them by clinical reference values, which may have obscured more complex dose–response patterns[14–16]. Consistent with our analytical framework, multiple recent NHANES-based cross-sectional studies applied identical restricted cubic spline and piecewise threshold regression strategies to delineate segmented nonlinear relationships between peripheral leukocyte-derived inflammatory ratios and depressive symptoms, consistently identifying distinct risk inflection points that linear models failed to capture[23]. Standard linear approaches assume uniform effect magnitude across the full biomarker distribution, which cannot reflect context-dependent immune effects modulated by tumor burden, anticancer treatment, and chronic comorbidities in cancer survivor populations[11]. By employing restricted cubic spline regression with piecewise threshold analysis, the present study provides a more nuanced characterization of this relationship and highlights the potential value of examining nonlinear associations in future psycho-oncology research focused on routine hematological biomarkers.

From a psycho-oncology perspective, the observed association may also have practical implications for the routine care of adults with a history of cancer.

Psychological distress and depressive symptoms remain common but are frequently underrecognized in survivorship settings, particularly when clinical follow-up is predominantly focused on disease recurrence and treatment-related complications. Although neutrophil percentage should not be interpreted as a stand-alone diagnostic marker for depression, routinely available hematological parameters may provide complementary information that could help identify individuals who warrant closer psychological assessment, especially when considered alongside established distress-screening tools and clinical risk factors. Neutrophil percentage is an inexpensive and routinely available laboratory parameter, and elevated values may alert clinicians to a broader inflammatory and psychosocial risk profile in adults with a history of cancer[16,24]. The threshold identified in this study may inform risk stratification in future research; however, it should not be construed as a diagnostic cutoff or as a standalone indicator for clinical intervention[25,26]. Patients with elevated neutrophil percentages, especially those with concurrent fatigue, pain, sleep disturbance, systemic inflammation, or treatment-related toxicity, may warrant further evaluation in prospective studies using validated screening tools and established referral pathways[27,28]. Future prospective studies are needed to determine whether neutrophil-related biomarkers incrementally improve the prediction of odds of depressive symptoms beyond well-established clinical, demographic, cancer-specific, and psychosocial factors[29–31].

In practice, patients with persistent inflammatory alterations and concurrent psychosocial vulnerability could be prioritized for standardized screening using validated instruments, followed by stepped supportive care when clinically indicated. Such care may include psychoeducation, counseling, psychiatric evaluation, symptom management, and referral to psychosocial or behavioral interventions. Integrating these assessments within multidisciplinary survivorship programs involving oncology, primary care, psycho-oncology, nursing, and rehabilitation services may facilitate earlier recognition of depressive symptoms and more coordinated management of both physical and psychological sequelae of cancer.

Several limitations of this study should be acknowledged. First, the NHANES is a cross-sectional survey, in which exposure and outcome were assessed concurrently; therefore, temporal precedence cannot be established, and causal inferences are not warranted[9]. Second, depressive symptoms were identified using the PHQ-9, rather than through clinical diagnostic interviews by psychiatrists, which may introduce outcome misclassification bias. Third, the single measurement of neutrophil percentage may be influenced by recent infections, medication use, acute stress, or ongoing anticancer treatments, and thus may not fully capture an individual's long-term inflammatory burden. Fourth, the adults with a history of cancer in NHANES is inherently heterogeneous, but key clinical information, such as tumor stage, disease activity, treatment regimens, recurrence or metastasis, and time since diagnosis, is not fully available, which may leave residual confounding. Fifth, a considerable proportion of participants with cancer history were excluded due to missing data on PHQ-9 scores or neutrophil percentage, which may introduce selection bias that cannot be entirely ruled out. Finally, the inflection points identified in this study were derived from the same analytical sample and may be data-dependent; their generalizability requires validation in independent cancer cohorts and prospective longitudinal studies.

5. Conclusion

In summary, the present study suggests that segmented neutrophil percentage

may be nonlinearly associated with depressive outcomes in adults with a history of cancer, with the association confined to a specific intermediate range rather than following a simple linear dose-response relationship. Higher odds of depressive symptoms were primarily observed within a moderately elevated range, suggesting that peripheral immune-inflammatory status may be associated with depressive symptoms among adults with a history of cancer, although the observed association may also be influenced by disease status, treatment-related factors, and other unmeasured clinical characteristics. Future prospective longitudinal studies are warranted to validate this association and to evaluate its potential utility in stratifying the odds of depressive symptoms for research-based risk assessment, incorporating information on cancer type, disease stage, and treatment regimens.

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Conflict of interest: The authors declare no conflict of interest.

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