

Association Between Systemic Immune-Inflammation Index and CA125 in Older Women: Insights from a Cross-Sectional NHANES Study

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Introduction: The Systemic Immune-Inflammation Index (SII) is a novel biomarker that has been implicated in the pathogenesis of various neoplastic and non-neoplastic diseases. This study aimed to evaluate the association between SII and the conventional tumor marker CA125 (Carbohydrate antigen 125) in a population of postmenopausal women.

Methods: This cross-sectional study utilized data from the National Health and Nutrition Examination Survey (NHANES), focusing on postmenopausal women with available data on SII and CA125. The SII was calculated using the formula: platelet count $\times$ neutrophil count/lymphocyte count. To evaluate the relationship between the SII and cancer antigen 125 (CA125), we conducted multivariate regression analyses. The linear association between these variables was further explored by fitting a smoothed curve to examine nuances in their relationship. Additionally, subgroup analyses were performed based on age, age at menarche and menopause, and hormone replacement therapy status to assess the heterogeneity of the relationship between SII and CA125 between different demographic groups.

Results: A total of 741 postmenopausal women with a mean age of 72.0 (± 8.24) years were included in this analysis. The results demonstrated a significant positive correlation between SII and CA125 levels ($\beta = 0.01$; 95% CI, 0.00–0.02, $p = 0.0128$). Subgroup analyses and interaction tests revealed that variables such as age, age at menarche and menopause, and hormone replacement therapy did not significantly modify this association ($p > 0.05$).

Conclusion: This study demonstrated a positive correlation between SII and CA125 in older female patients in the United States.

Keywords: elderly women, SII, CA125, NHANES, cross-sectional study

Introduction

Carbohydrate antigen 125 [CA125, also known as cancer antigen 125 carcinoma antigen 125, or mucin 16 (MUC16)] is a complex glycoprotein encoded by the human MUC16 gene.¹ As early as 1981, this marker was recognized by the 125th antibody produced by an ovarian cancer cell line, containing approximately 22,000 amino acids, making it the largest membrane-associated mucin.² CA125 is mainly synthesized by mesothelial cells in the pericardium, pleura, or peritoneum.³ Although its biological role is unknown, it may be involved in a variety of pathways, including cell-mediated immune responses.⁴ CA125 has been extensively studied as a circulating biomarker for monitoring ovarian cancer.¹ In addition, elevated CA125 levels can be seen in other malignant tumors, such as pancreatic cancer,⁵ lung cancer,⁶ rectal cancer,⁷ and gastric cancer.⁸ Increased CA125 expression in the tumor microenvironment enhances gemcitabine/cisplatin resistance in bladder cancer.⁹ Moreover, CA125 also plays a role in many benign diseases. It has been shown that CA125 can be used as a biomarker for heart failure,² while CA125 has been associated with dysmenorrhea in adenomyosis.¹⁰

The Systemic Immune-Inflammation Index (SII) is a comprehensive and novel inflammatory biomarker that reflects both local immune responses and systemic inflammation.^{11,12} In past studies, SII has been used to predict and evaluate tumor development as well as prognosis. Previous studies have shown that elevated SII is positively associated with the risk of prostate cancer¹³ and also predicts the prognosis of patients after radical resection for colorectal and hepatocellular carcinoma.^{14,15} There is evidence that SII independently predicts prognosis and survival in patients with cervical and bladder cancer undergoing radical resection.^{16,17} As well, SII is strongly associated with diseases such as bone mineral density,¹⁸ hepatic lipofibrosis,¹⁹ hyperlipidemia,²⁰ and hypertension.²¹ SII affects the prognosis of many neoplastic and non-neoplastic diseases, and there are no studies on the correlation between SII and CA125, an important tumor marker.

The guidelines published by the American College of Obstetrics and Gynecology (ACOG) no longer recommend the use of a specific CA125 threshold for premenopausal women, as CA125 in women is strongly influenced by the levels of other hormones that stimulate it.^{22,23} To exclude the effect of hormone levels, we included older women aged >60 years for analysis. Therefore, the present study was designed to explore the relationship between SII and CA125 using a sample of elderly women over the age of 60 who participated in the 2001–2002 National Health and Nutrition Examination Study (NHANES).

Methods

Survey Description

We obtained study data from the NHANES public database, which is led by the National Center for Health Statistics (NCHS), as a way to manage and assess the health and nutritional status of the US population. All NHANES data are publicly available at <https://www.cdc.gov/nchs/nhanes/>. To explore possible associations between SII and CA125 in older women over 60 years of age, we based our analyses on the NHANES database from 2001 to 2002, as this was the only survey cycle that included data on the variable CA125. First, a total of 11,039 participants were recruited, after excluding participants younger than 60 years ($n = 1,603$), missing data on CA125 ($n = 8,648$), SII ($n = 41$), and other relevant data anomalies and missing data ($n = 6$). Ultimately, 741 participants were included in our analysis (Figure 1). The NCHS Research Ethics Review Board approved human subjects for NHANES, and written informed consent was obtained from each participant.

Definition of Exposure and Outcome Variables

Serum samples from female participants aged ≥ 20 years were assayed for CA125 at the Genital Tract Biology Laboratory (Brigham and Women's Hospital, Boston, MA) according to standardized operating procedures for preanalytical, analytical, and postanalytical procedures. Measurements were performed using the Meso Scale Discovery electrochemiluminescence immunoassay platform. A coefficient of variation (CV) < 25% was set as the threshold for acceptance of data, and CA125 measurements are reported in U/mL. Changes in CA125 levels were considered an outcome variable in our analysis.

Blood samples were obtained from NHANES participants at a standardized, mobile screening center. Lymphocytes, neutrophils, and platelets were measured by a complete blood count using an automated hematology analysis device (Coulter® DxH 800 analyzer) and expressed as $\times 10^3$ cells/mL. As reported in previous studies, we obtained SII by calculating platelet count $\times$ neutrophil count/lymphocyte count. In our analysis, SII was designed as the exposure variable.

Exposure Variables

Potential covariates that might confound the association between SII and CA125 levels were summarized in multivariate correction models. The selection of covariates was based primarily on previous studies and factors that may be biologically associated with CA125. These factors included demographics (age, race, education, marital status), drinking, body mass index (BMI, kg/m^2), waist circumference (cm), reproductive history (age at menarche, age at last menstruation, number of births, number of pregnancies, fertility, use of contraceptives, use of hormones), history of gynecologic surgery (hysterectomy, oophorectomy, tubal ligation), previous history of cancer, and CRP (C-reactive protein).

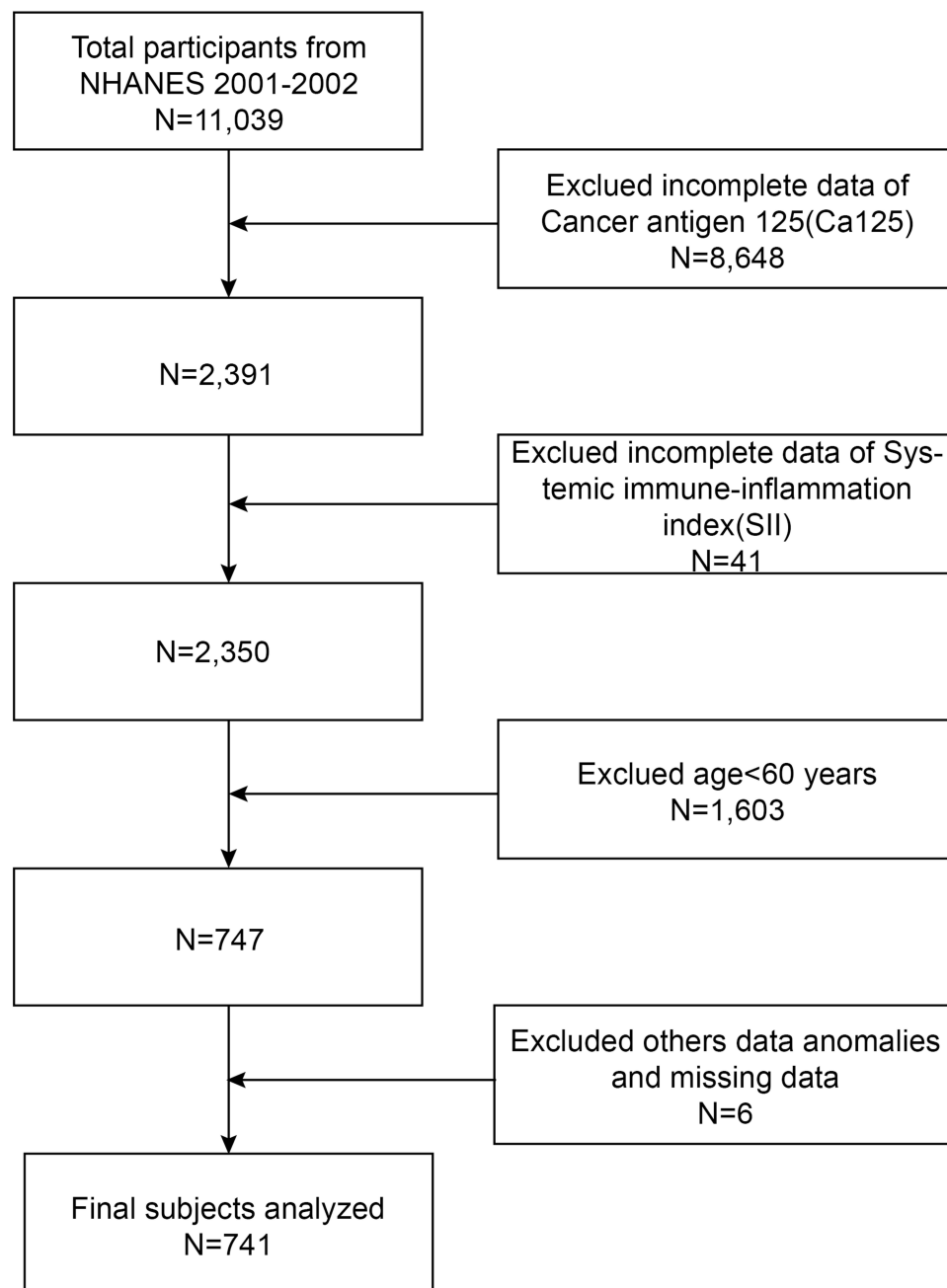


Figure 1 Flow chart of the inclusion and exclusion of study participants.

Demographic data were collected at the time of the interview. BMI and waist circumference data were obtained from physical measurements taken from survey participants at the time of the screening visit. BMI was categorized as BMI <18.5, BMI <25, $25 \leq \text{BMI} < 30$, and BMI ≥ 30 kg/m², corresponding to low weight, normal weight, overweight, and obese populations of the participants, respectively. The Reproductive Health Questionnaire (RHQ) interviewed participants through a complex and detailed set of questions using a skip-answer mode of administration and was edited through rigorous review to ensure data accuracy. Based on previous studies, age at first menstruation was categorized as “ ≤ 12 years” or “ > 12 years”. Age at first menstruation was categorized as “ < 46 years”, “46–49 years”, “50–52 years”, and “ > 52 years”. The number of births and pregnancies were counted based on self-reporting and were categorized as “yes” and “no” by asking “ever breastfeeding, use of contraceptives, and use of hormonal medications”. Similarly, a history of hysterectomy, oophorectomy, salpingo-oophorectomy, or tumors are defined in this form as “ever” or “none”. Alcohol

consumption was categorized as “no alcohol” and “at least one drink per day” based on average daily alcohol consumption in the 12 months before the interview. Serum CRP levels (mg/dL) are determined by latex-enhanced turbidimetry, and the Beckman Coulter® MAXM instrument performs a complete blood count on the blood specimen, obtaining the corresponding platelet, neutrophil, and lymphocyte counts. All detailed measurement procedures for the above variables are publicly available at www.cdc.gov/nchs/nhanes/.

Statistical Analysis

All statistical analyses were done according to guidelines set by the Centers for Disease Control and Prevention (CDC). The analyses used the correct NHANES sampling weights and a complex multistage clustered survey design. Continuous variables are expressed as means and standard deviations, and categorical variables are expressed as percentages. Differences between SII (quartiles) groups were assessed using weighted Student’s t-tests (for continuous variables) or weighted chi-square tests (for categorical variables). Weighted linear regression models were used to calculate the differences between each group. Subgroup analyses were performed using stratified multiple regression analysis. In Model 1, covariates were not adjusted. Model 2 was adjusted for age and race. Model 3 was adjusted for age, race, education level, marital status, body mass index (kg/m²), circumference, drinking, age at menarche, last menstrual period, CRP, number of pregnancies, history, ligation, contraceptive use, hormone use, and previous history of cancer. Smoothed curve fitting (penalized spline method) and weighted generalized additive model (GAM) regression were used to further assess the nonlinear relationship between SII and CA125 levels. Subgroup analyses stratified by race, BMI, age at first and last menstruation, and hormone use were also performed by stratified multivariate regression analysis. p < 0.05 was considered statistically significant. Empower software (www.empowerstats.com; X&Y Solutions, Inc., Boston, MA, USA) and R version 3.4.0 (<http://www.Rproject.org>, R Foundation) were used.

Results

Baseline Characteristics of Subjects

A total of 741 elderly women with a mean age of 72.0 years (±8.24) were included in this study (Table 1). They were categorized into four quartiles based on the weighted characteristics of individual SII (Q1: 75–367.82; Q2:

Table 1 Baseline Characteristics of Subjects

Systemic Immune-Inflammation Index	Q1 (75–367.82)	Q2 (367.923–516.35)	Q3 (516.92–744.35)	Q4 (745.31–2605.36)	P-value
	N=185	N=185	N=185	N=186	
Age (year)	71.03 ± 8.35	70.76 ± 7.81	71.98 ± 7.90	74.39 ± 8.44	<0.001
CRP (mg/dL)	0.43 ± 0.59	0.51 ± 0.62	0.52 ± 0.60	0.79 ± 1.10	<0.001
Waist Circumference (cm)	96.38 ± 13.80	98.51 ± 13.98	97.27 ± 14.36	95.69 ± 12.94	0.352
Number of pregnancies	4.87 ± 3.00	4.72 ± 2.84	4.33 ± 2.75	4.24 ± 2.74	0.128
Fertility	4.11 ± 2.61	4.19 ± 2.60	3.67 ± 2.29	3.57 ± 2.21	0.104
CA125 (U/mL)	13.78 ± 41.75	12.38 ± 8.94	14.08 ± 12.17	17.65 ± 25.76	<0.001
Race, %					<0.001
Mexican American	15.68%	18.38%	17.84%	14.52%	0.036
Other Hispanic	3.78%	5.41%	2.70%	1.61%	
Non-Hispanic White	44.32%	57.84%	70.27%	76.34%	
Non-Hispanic Black	31.35%	16.76%	8.65%	6.45%	
Other Races	4.86%	1.62%	0.54%	1.08%	
Education level, %					0.036
Less than junior high school	27.57%	22.70%	16.22%	15.05%	
Middle to high school	15.68%	18.38%	19.46%	12.90%	
High school graduate/GED or equivalent	25.95%	26.49%	23.78%	34.41%	

(Continued)

Table I (Continued).

Systemic Immune-Inflammation Index	Q1 (75–367.82)	Q2 (367.923–516.35)	Q3 (516.92–744.35)	Q4 (745.31–2605.36)	P-value
	N=185	N=185	N=185	N=186	
Some College or AA degree	22.70%	21.08%	24.86%	23.66%	0.549
College Graduate or above	8.11%	11.35%	15.68%	13.98%	
Marital Status, %					
Married	94.59%	96.76%	94.05%	96.24%	0.504
Never married	5.41%	3.24%	5.95%	3.76%	
Age at menarche(year), %					
≤12	40.83%	39.41%	44.19%	36.14%	0.026
>12	59.17%	60.59%	55.81%	63.86%	
Last menstrual period, %					
<46	53.90%	44.44%	37.89%	40.76%	0.047
46–49	12.34%	20.37%	13.04%	15.92%	
50–52	18.18%	20.99%	27.95%	29.94%	
>52	15.58%	14.20%	21.12%	13.38%	0.428
Breastfeeding history, %					
Yes	62.18%	52.29%	64.02%	51.92%	
No	37.82%	47.71%	35.98%	48.08%	0.416
Hysterectomy, %					
Yes	53.18%	51.15%	45.81%	46.29%	
No	46.82%	48.85%	54.19%	53.71%	0.942
Ovariectomy, %					
Yes	87.76%	93.18%	97.06%	94.00%	
No	12.24%	6.82%	2.94%	6.00%	0.566
Tubal ligation, %					
Yes	18.50%	17.54%	20.11%	18.60%	
No	81.50%	82.46%	79.89%	81.40%	0.649
Contraceptive use, %					
Yes	34.68%	33.91%	32.78%	28.16%	
No	65.32%	66.09%	67.22%	71.84%	0.456
Drinking, %					
Yes	38.38%	44.32%	43.78%	42.47%	
No	61.62%	55.68%	56.22%	57.53%	0.202
Hormone use, %					
Yes	46.24%	45.09%	51.69%	43.68%	
No	53.76%	54.91%	48.31%	56.32%	0.333
Previous history of cancer, %					
Yes	12.97%	17.30%	19.46%	20.97%	
No	87.03%	82.70%	80.54%	79.03%	
Body mass index (kg/m²), %					
Low weight	3.55%	1.70%	1.16%	3.12%	
Normal weight	27.81%	22.73%	1.21%	35.00%	
Overweight	34.91%	37.50%	34.10%	33.12%	
Obesity	33.73%	38.07%	33.53%	28.75%	

Notes: Mean ± SD for continuous variables; the P value was calculated by the weighted linear regression model(%) for categorical variables: the P value was calculated by the weighted chi-square test. BMI was categorized as <18.5, 18.5–24.9, 25–29.9, and ≥30 kg/m², which corresponded to low weight, normal weight, overweight, and obese populations, respectively.

Abbreviations: CRP, c-reactive protein; CA125, cancer antigen 125.

367.923–516.35; Q3: 516.92–744.35; Q4: 745.31–2605.36). Participants' serum CA125 (mean ± standard deviation) was 14.464 ± 25.684 and increased with increasing quartiles of SII (Q1:13.78 ± 41.75; Q2:12.38 ± 8.94; Q3:14.08 ± 12.17; Q4:17.65 ± 25.76, p<0.001), and the higher quartiles of SII Subjects in the higher SII quartiles tended to exhibit higher

levels of CA125. There were large differences in baseline characteristics between SII quartiles, with those with elevated SII tending to be older non-Hispanic whites, as well as being associated with high levels of CRP and CA125, older age at the last menstrual period, and a lower number of births.

SII is Positively Correlated with CA125 Levels

The results showed that higher levels of SII were positively correlated with a rising CA125. In the fully adjusted model, the positive correlation between SII and CA125 was significant, demonstrating that each unit increase in SII was associated with a 0.01 U/mL rise in the value of CA125 ($\beta = 0.01$; 95%CI 0.00,0.02; $p = 0.0128$). SII was analyzed by converting it from a continuous variable to a categorical variable (quartiles). The results showed that SII as a continuous variable was consistent with the categorical variable results (Table 2). Subjects in the highest SII quartile (Q4) had a statistically significant increase in CA125 levels of 4.48 U/mL compared to the lowest SII quartile (Q1) ($\beta = 4.48$; 95% CI: 0.90, 8.06, $p = 0.0145$).

Subgroup Analysis

Subgroup analyses were also performed in this study to evaluate the stability of the association between SII and CA125 levels. Interactions between age, BMI, age at first and last menstruation, and hormone replacement therapy were tested. In the association between SII and CA125, the difference between different levels of obesity was statistically significant ($p = 0.0002$). The correlation between SII and CA125 was higher when BMI was at a low weight, and this correlation stabilized with increasing obesity in the MBI stratum. However, the interaction test for the remaining indicators was not statistically significant ($p > 0.05$). Our results suggest that the positive correlation between SII and CA125 was similar across age, age at first and last menstruation, and hormone replacement therapy status (Figure 2).

Linear Relationship Between SII and CA125

To investigate the possible linear relationship between SII and CA125, we constructed a smoothing curve based on the fully adjusted model (Figure 3). SII and CA125 levels were linearly related, with increasing levels of CA125 as SII increased. The results showed a linear positive correlation between SII and CA125.

Discussion

This study is the first to investigate the association between SII and CA125 in older American women, according to the NHANES database. In the cross-sectional study of 741 subjects included, we observed an increased likelihood of patients with higher SII exhibiting elevated CA125. Subgroup analyses and interaction tests indicated that this association was similar across population settings. The findings suggest that higher SII levels in older female patients may be associated with elevated CA125.

Table 2 Relationship Between SII and CA 125

	Crude Model (Model1) β (95% CI), p-value	Minimally Adjusted Model (Model2) β (95% CI), p-value	Fully Adjusted Model (Model3) β (95% CI), p-value
Continuous	0.01 (0.00, 0.01), 0.0262	0.01 (0.00, 0.01), 0.0299	0.01 (0.00, 0.01), 0.0003
Categories			
Q1	Reference	Reference	Reference
Q2	-1.40 (-6.63, 3.83), 0.5997	-1.68 (-6.87, 3.50), 0.5247	0.54 (-2.90, 3.97), 0.7595
Q3	0.30 (-4.93, 5.53), 0.9113	-0.21 (-5.39, 4.97), 0.9370	2.86 (-0.58, 6.29), 0.1034
Q4	3.87 (-1.36, 9.09), 0.1471	3.74 (-1.44, 8.92), 0.1574	4.48 (0.90, 8.06) 0.0145
P for trend	0.0786	0.0826	0.0064

Notes: SII was converted from a continuous variable to a categorical variable. Model 1: covariates were not adjusted. Model 2: was adjusted for age and race. Model 3: was adjusted for age, race, education level, marital Status, body mass index (kg/m2), waist circumference, drinking, age at menarche, last menstrual period, CRP, number of pregnancies, fertility, CA125, breastfeeding history, hysterectomy, ovariectomy, tubal ligation, contraceptive use, hormone use and previous history of cancer.

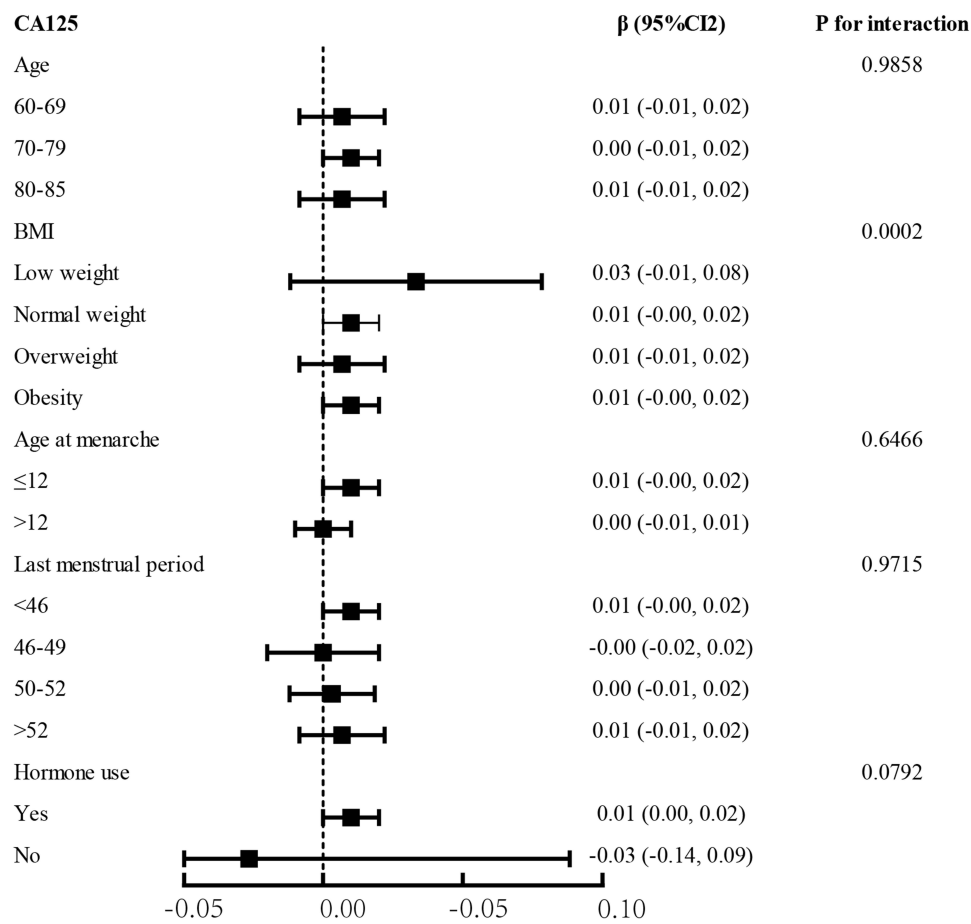


Figure 2 Subgroup analysis of the relationship between SII and CA125.

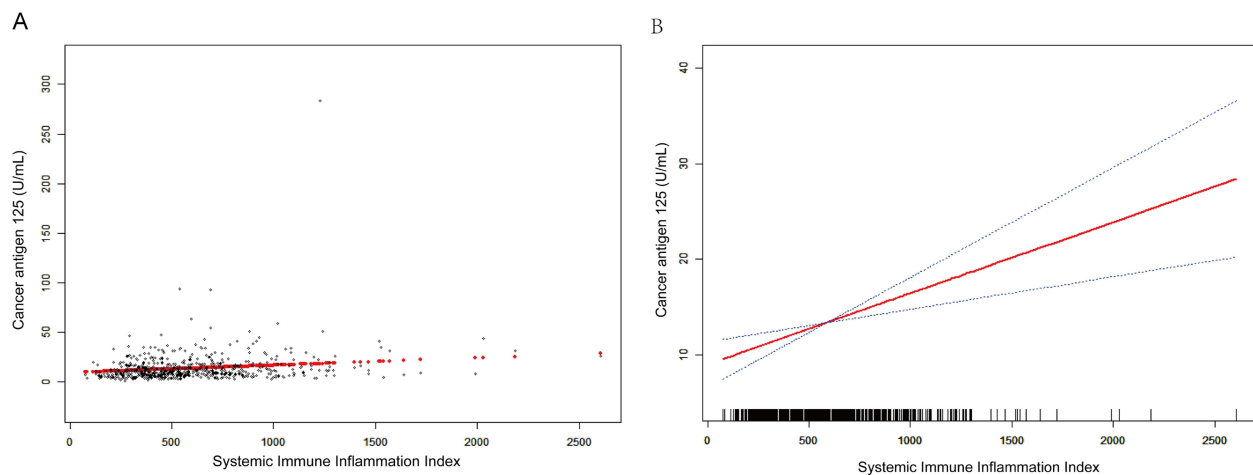


Figure 3 Relationship between SII and CA125. (A) Scatter diagram. (B) Fitting a smoothed graph.

SII was determined based on counts of three types of circulating immune cells: neutrophils, lymphocytes, and platelets. SII levels reflect the inflammatory state and can be used as an easily detectable biomarker of systemic inflammatory activity.²⁴ SII is influenced by a number of physiological factors, with age, gender and pregnancy status being particularly significant. With age, the body gradually exhibits a chronic, low-grade inflammatory response, a phenomenon known as “inflammatory senescence”, which is a common feature of the elderly.²⁵ Due to gradual changes in immune function, older people tend to

have higher SII values. At the same time, gender and pregnancy status can lead to differences in SII levels due to differences in hormone levels, especially in women, where sex hormones (estrogen and progesterone) regulate immune cells such as lymphocytes and neutrophils.²⁶ This elevated inflammatory state is often closely associated with changes in biomarker levels in a variety of disease processes. Several previous studies have pointed out the potential role of SII and inflammatory markers in CA125-affected diseases, and elevated SII may be associated with high levels of CA125. In the context of oncologic diseases, SII is a more effective tool for predicting survival outcomes in patients with colorectal cancer, and it may be useful in identifying high-risk patients among those with the same TNM stage.¹⁴ Secondly, SII is a strong predictor of adverse outcomes in patients with hepatocellular carcinoma, and elevated SII is associated with higher levels of circulating tumor cells.¹⁵ In a large prospective cohort study, SII, NLR, and PLR were positively associated with the risk of lung and rectal cancers; among inflammatory markers, SII usually has the strongest correlation with cancer risk.²⁷ Previous studies have suggested that higher levels of SII in pre-treatment prostate cancer patients may be associated with poorer OS and PFS.^{28,29} CA125 is the most widely used and talked-about biomarker in ovarian cancer screening and is involved in the development and progression of ovarian cancer.¹ In addition, CA125 is an important and independent prognostic factor in patients with colorectal cancer and is a better prognostic marker than CEA and CA19-9.³⁰ Some studies have identified elevated CA125 levels as a risk factor for the early recurrence of pancreatic cancer.³¹ In a retrospective analysis by Sui et al, serum CA125 was noted to be an independent risk factor for the progression of gastrointestinal mesenchymal tumors and for its importance as a serum biomarker in the overall management of patients with gastrointestinal mesenchymal tumors.³² Many of these studies fail to adequately consider the interplay between inflammatory processes and tumor dynamics, focusing instead on isolated marker effects. By integrating our findings with evidence from prior research, we propose that there may be a synergistic effect between the SII and CA125 in both the development and prognosis of tumor diseases. Our study highlights the importance of examining combined biomarker effects to gain a more comprehensive understanding of their roles in oncology.

There is a synergistic effect between SII and CA125, so adding SII levels to the consideration of the effect of CA125 levels on tumor-associated disease may reduce bias. Previous studies have also suggested that CA125 in combination with inflammatory cells would have better predictive value. Kim et al used a combination of neutrophils and CA125 for the prediction of endometrial cancer and suggested that it was a simple, accurate, and cost-effective predictive method.³³ Similarly, it has been reported that CA125, NLR, and PLR levels are strongly associated with the nature of junctional epithelial ovarian tumors and the malignant progression of malignant epithelial ovarian tumors; however, the combination of CA125, NLR, and PLR is more accurate in identifying the nature of malignant epithelial ovarian tumors than the combination alone or in duo.³⁴ In addition, a study evaluated by logistic regression analysis and ROC curves indicated that serum D-dimer, NLR, and CA125 are potential screening indicators for ovarian cancer, and that the combined measurement of D-dimer, NLR, and CA125 may provide a convenient screening method.³⁵ Overall, by jointly monitoring SII and CA125, we can more accurately identify and assess fluctuations in biomarker levels due to changes in inflammatory status, especially in the diagnosis and surveillance of tumors that are closely associated with CA125, such as ovarian cancer. This approach not only facilitates risk assessment in situations where conventional testing methods do not provide a definitive answer, but also supports personalized disease management strategies. For example, in older female patients who show elevated SII and CA125 simultaneously, physicians can adjust treatment regimens and follow-up strategies based on the results of monitoring, which may include more frequent monitoring and more aggressive interventions. In addition, changes in SII can be used as an adjunctive indicator of disease progression and treatment efficacy in patients with diagnosed cancers. Combined monitoring can help physicians more accurately understand a patient's disease state and thus make more appropriate clinical decisions.

Furthermore, a strong link has been found between SII and the worsening of some non-cancerous conditions, such as cardiovascular disease,³⁶ liver fibrosis,¹⁹ diabetes mellitus,³⁷ low bone mineral density,¹⁸ and protein excretion in the urine.³⁸ According to a prospective study, CA125 has demonstrated superior efficacy as a marker for acute heart failure in comparison to NT-proBNP.³⁹ A case-control study found that serum CA125 levels were higher in preeclamptic pregnancies compared to normotensive pregnancies. This suggests that CA125 may be a biomarker of how bad eclampsia is.⁴⁰ In a retrospective cohort study, it was observed that patients with acute pancreatitis had unfavorable clinical outcomes when their CA125 levels exceeded 35 U/mL.⁴¹ Still, not a lot of research has been done on the link between

a group of SII-related markers and CA125 in diseases other than oncology that do not affect the genital area. Further prospective or retrospective studies are warranted to explore this relationship in greater depth.

The correlation between SII and CA125 exhibited significant variations based on subgroup analyses and interaction tests, with notably higher associations observed in lower BMI subgroups. These findings align with previous research results. Serum CA125 levels decreased with increasing BMI in a retrospective analysis of 11,234 women.⁴² In the same way, the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO), which looked at 26,981 women who had gone through menopause, found that lower BMI was linked to higher levels of CA125.⁴³

Findings from prior research indicate that there is a connection between heightened levels of inflammatory biomarkers, disease severity, and an increase in specific tumor markers.⁴⁴ Additionally, it has been observed that activated lymphocytes express numerous genes that serve as tumor-specific markers.^{45,46} Inflammatory factors such as LPS, IL-6, IL-8, and TNF- α can increase the expression and release of CA125, which may play a role in activating the MAPK signaling pathway by inducing the expression of molecules such as JNK, p38, ERK, and NF- κ B in the downstream cascade.⁴⁷ When studying and using tumor biomarkers, systemic inflammation can make things more complicated. To rule out other possible biomarkers, all of them should be checked to see how well they work in inflammatory conditions.⁴⁸

This study has several advantages. First, our study is based on NHANES data with the appropriate NHANES sample weights considered to make the analyzed sample representative. Secondly, previous studies have reported that CA125 levels in premenopausal women are strongly influenced by hormone levels. Therefore, to minimize the effect of this confounding factor, the premenopausal female population was excluded from the inclusion of variables in this study. However, there are some limitations to our study as well. First, in our study, we could not further distinguish between causal relationships due to the inherent limitations of cross-sectional surveys. Therefore, prospective cohort studies are still needed to confirm this causal relationship. Second, due to database limitations, although we tried to adjust for some potential covariates as much as possible, we could not completely exclude the effects of other possible confounders. Third, because the outcome variable CA125 was only fully documented in 2001–2002 in the NHANES database, only older women over the age of 60 were included in order to exclude the effect of hormone levels on CA125. Although this approach helps to minimize confounding by hormonal fluctuations, it also means that our findings may not be generalizable to younger women or postmenopausal women outside of this age group. Future studies are necessary to explore this association in more diverse populations, including premenopausal women, to better understand the impact of endocrine changes on SII levels. Fourth, our survey is based on the NHANES database, which is limited to people in the United States and is therefore geographically restricted.

Conclusion

In this study, we confirmed the clinical value of the combined use of these two biomarkers in elderly women by analyzing the association between SII and CA125. Our findings emphasize that in older women, especially in the diagnosis and surveillance of ovarian cancer, SII and CA125 can be used together as an effective tool to improve diagnostic accuracy and sensitivity of disease surveillance. It is hoped that more clinical trials and studies will be facilitated to explore the combined use of SII and CA125 in disease prediction, diagnosis, and treatment, ultimately leading to the optimization and personalization of disease management for older women.

Institutional Review Board Statement

This study was approved by the Traditional Chinese Medicine Ethics Committee (2024-057) of Jinjiang Hospital of Traditional Chinese Medicine. This committee waived approval for studies using publicly available data.

Data Sharing Statement

All data are available at the NHANES website <https://www.cdc.gov/nchs/nhanes/index.htm>.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report there are no competing interests to declare.

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