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The association between immune-inflammatory indexes and lower urinary tract symptoms: an analysis of cross-sectional data from the US National Health and Nutrition Examination Survey (2005–2008)

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Abstract

Objective This study aimed to systematically investigate the relationship between immune-inflammatory indexes with lower urinary tract symptoms (LUTS).

Design Cross-sectional study.

Setting National Health and Nutrition Examination Survey (NHANES) (2005–2008).

Participants A total of 2,709 men with complete information for immune-inflammatory indexes and LUTS were included from NHANES 2005–2008.

Outcomes and analyses Automated hematology analyzing devices are used to measure blood cell counts, and LUTS were presented by standard questionnaires. Nonlinear and logistic regression analysis were used to estimate their association after adjustment for confounders.

Results Multivariate logistic regression showed that PIV (OR[95%CI] = 1.60[1.14–2.23]), SIRI (OR[95%CI] = 1.82[1.21–2.73]), NLR (OR[95%CI] = 1.81[1.31–2.49]), dNLR (OR[95%CI] = 1.91[1.35–2.70]), and CRP (OR[95%CI] = 1.71[1.05–2.79]) was positively associated with LUTS. Additionally, composite immune-inflammation markers exhibited a stronger association with LUTS

than any single index, with the ORs for high SIRI+high CRP, high NLR+high CRP, and high dNLR+high CRP being 2.26, 2.44, and 2.16, respectively (All $P < 0.05$). Furthermore, subgroup analyses revealed that age, smoking status, and hypertension have different effects on the relationship between immune-inflammatory markers and LUTS.

Conclusions This study indicated that high levels of immune-inflammatory markers were associated with an increased risk of clinical LUTS. The combination of CRP with SIRI, NLR, and dNLR respectively showed a stronger positive correlation with clinical LUTS compared to any single index.

Keywords: NHANES; Lower urinary tract symptoms; prostatic hyperplasia; immune-inflammatory index; inflammation

STRENGTHS AND LIMITATIONS OF THIS STUDY

The NHANES dataset, representing the national population, enhances the generalizability of our findings to a broader context.

This study investigates the positive correlation between various immune-inflammatory indexes and lower urinary tract symptoms (LUTS).

Composite immune-inflammation markers exhibit a more robust association with LUTS compared to individual indexes.

It's important to note that drawing causal conclusions from cross-sectional analyses presents challenges.

Introduction

Lower urinary tract symptoms (LUTS) are a common complaint among aging men, with approximately 80% experiencing at least one urine symptom by the age of 80(1). LUTS is now widely recognized as a term that encompasses various urinary symptoms, including storage, voiding, postmicturition, and nocturia, negatively impacting on patients' quality of life(2, 3). In the United States (US), nearly $194 million is spent annually on LUTS drugs, which can impose a heavy strain on the economy and public health(4, 5). Thus, it is essential to identify the factors that contribute to the development and progression of LUTS in aging men.

Several inflammatory markers, including the pan-immune-inflammation value (PIV), systemic inflammation response index (SIRI), systemic immune-inflammation index (SII),

neutrophil/lymphocyte ratio (NLR), derived neutrophil/lymphocyte ratio (dNLR), monocyte/lymphocyte ratio (MLR), platelet/lymphocyte ratio (PLR), and C-reactive protein (CRP), have been considered in the development and progression of inflammatory and infectious diseases(6-10). Interestingly, studies have also identified positive associations between inflammatory markers, such as CRP(10-12)and NLR(13, 14), and the risk of LUTS, suggesting that inflammation may play an important role in the development of LUTS. For instance, prostate tissue samples taken from individuals with benign prostatic hyperplasia (BPH), a condition often associated with LUTS resulting from bladder outlet obstruction, commonly exhibit acute and chronic inflammation(2, 15, 16). Additionally, inflammation may contribute to overactive bladder, which is another cause of LUTS(2, 17).

In recent years, a number of new inflammatory markers, such as PIV(18), SIRI(19), and SII(19), have been developed, yet no study has explored their relationship with LUTS. Furthermore, using these markers as single risk factors for LUTS could be limited by their low discriminatory power. Since the interplay between immunity, inflammation, and diseases involve complex networks, composite markers would be a more accurate and meaningful approach to capture the overall inflammatory status and reflect various immuno-inflammatory populations(20-22). Therefore, this study aims to systematically investigate the relationship between blood immune-inflammatory indexes and their combinations with LUTS, using representative NHANES data. This study sought to advance the understanding of the pathogenesis of LUTS and provide insights for potential interventions.

Methods

Study design and participants

The NHANES is a cross-sectional survey that employs a sophisticated multistage sample methodology to investigate the health and nutritional status of the non-institutionalized population in the US. The demographic information used in this study was obtained from the NHANES, and the protocol was approved by the National Center for Health Statistics Ethics Review Board. Written informed consent was obtained from all participants, and all NHANES data is publicly available on the relevant website(23).

In this study, we used publicly accessible data from two 2-year cycles of NHANES (2005-2006, 2007-2008) and restricted the analysis cohort to men aged 40 years or older. Initially, there were 3,506 man participants aged 40 years and older in our data. We excluded 417 participants with incomplete

LUTS status and 150 participants with a history of prostate cancer. Additionally, 230 participants with incomplete variables data were excluded. Finally, 2,709 participants were included in this study (Supplementary Fig. 1).

Questionnaire Data Assessment

LUTS were assessed by four questions, including: (1) "Do you usually have trouble starting to urinate (pass water)?" (hesitancy, defined as the answer is yes); (2) "After urinating (passing water), does your bladder feel empty?" (incomplete emptying, defined as the answer is no); (3) "How often do you have urinary leakage?" (urinary frequency, defined as the answer is 1 or greater); (4) "During the past 30 days, how many times per night did you most typically get up to urinate, from the time you went to bed at night until the time you got up in the morning?" (nocturia, defined as an answer is 2 or greater). Daytime LUTS was defined as a participant with one or more of the first three symptoms listed above. Clinical LUTS was defined as a participant having two or more of the mentioned symptoms(1).

Definition of Immune-Inflammation indexes

Automated hematology analyzing devices (Coulter DxH 800 analyzer) are used to measure lymphocyte, neutrophil, monocyte, and platelet count, which are presented as $\times 10^{®}3$ cells/μl. The Behring Nephelometer is used to measure serum CRP levels by latex-enhanced nephelometry, with a lower limit of detection (LLOD) of 0.2 mg/L. The immune-inflammatory indexes in our study were calculated as follows: PIV = platelet × neutrophil × monocyte /lymphocyte(18); SIRI = platelet × monocyte/lymphocyte(19); SII = platelet × neutrophil/lymphocyte(24); NLR = neutrophil/lymphocyte(24); dNLR = neutrophil/(leukocyte-neutrophil)(25); MLR = monocyte/lymphocyte; PLR = platelet/lymphocyte(24).

Ascertainment of covariates

Our study considered several covariates that could potentially influence the association between immune-inflammatory indexes and clinical LUTS, daytime LUTS, and nocturia. These covariates included age, race, education level, smoking status, alcohol use, body mass index (BMI, kg/m^2), blood total cholesterol concentration, and history of hypertension and diabetes. Hypertension was defined as a mean systolic blood pressure greater than 140 mmHg, or a mean diastolic blood pressure less than 90 mmHg, or a self-reported history of hypertension. Diabetes was defined as the use of antidiabetic treatment, an HbA1c level of ≥ 6.5%, or a self-reported history of diabetes.

Statistical analysis

To obtain nationally representative findings for the men population aged 40 and over in the US, survey weights were included in the analysis in accordance with NHANES standards. Baseline feature indicators were presented as weighted mean and standard error (SE) for continuous data and weighted ratio for classified data. The difference between baseline characteristics was assessed using the student's t-test on continuous data and the Chi-square test on classified data. We used restricted cubic splines with three nodes at the 5th, 50th, and 95th percentiles to evaluate the nonlinear correlation between immune-inflammatory indexes and clinical LUTS, daytime LUTS and nocturia. Multivariate logistic regression was utilized in three models to explore the association between immune-inflammatory indexes and clinical LUTS, daytime LUTS and nocturia. Covariates were not adjusted in model 1, age, race, education level, smoking status, alcohol use, and BMI were adjusted in model 2, and model 3 was further adjusted for blood total cholesterol, and a history of diabetes and hypertension. Additionally, we conducted multivariate logistic ordinal regression analyses to verify the association of immune-inflammatory indexes with the number of positive symptoms associated with clinical LUTS (0, 1, 2, 3, 4). Furthermore, multiple logistics regression was used to explore whether there is a stronger correlation between SIRI + CRP, NLR + CRP, dNLR + CRP and clinical LUTS. Subgroup analyses were performed for the association between immune-inflammatory indexes and clinical LUTS, stratified by age, smoking, and a history of hypertension, and multiplicative interaction terms were used to test for interactions.

All statistical analyses were performed using R (version 4.2.2, http://www.r-project.org/). Statistical significance was defined as a two-sided *P*-value < 0.05.

Patient and public involvement

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

Results

Baseline characteristics

As shown in Table 1, we included 2709 men participants aged 40 and above with complete information, including 399 men who met the diagnostic criteria of clinical LUTS, 675 men who met the diagnostic criteria of daytime LUTS, and 946 men who had nocturia symptoms. Compared to men without clinical LUTS, men with clinical LUTS were older, less educated, smokers, and non-alcohol

users, more prone to have lower blood cholesterol concentration, and higher hypertension, diabetes, PIV, SIRI, SII, NLR, dNLR and MLR values (all $P < 0.05$). Similarly, compared to men without daytime LUTS, men with daytime LUTS were older, non-alcohol users, more likely to have hypertension, diabetes, and higher PIV, SIRI, NLR, dNLR and MLR values (all $P < 0.05$). Furthermore, compared to men without nocturia, men with nocturia were found to be older, non-Hispanic Black, less educated, smokers, and non-alcohol users, more prone to have lower blood cholesterol concentration, and higher BMI, hypertension, diabetes, PIV, SIRI, NLR and MLR values (all $P < 0.05$).

Dose-response relationships between immune-inflammatory indexes and LUTS

We used restricted cubic splines to assess the non-linear correlation between immune-inflammatory indexes and LUTS. After adjusting for covariates, we found that PIV, SIRI, SII, NLR, dNLR, MLR, and CRP had a linear relationship with clinical LUTS, daytime LUTS, and nocturia (all P for non-linearity > 0.05). Specifically, the prevalence of clinical LUTS increased by 14%, 22%, 16%, 24%, 21% and 21% per standard deviation of PIV, SIRI, SII, NLR, dNLR and CRP, respectively (all $P < 0.05$) (Fig. 1). The prevalence of daytime LUTS increased by 15%, 23%, 20%, and 15% per standard deviation of SIRI, NLR, dNLR and CRP, respectively (all $P < 0.05$) (Supplementary Fig. 2). The prevalence of nocturia increased by 15%, 12%, 19%, and 23% per standard deviation of SIRI, NLR, MLR and CRP, respectively (all $P < 0.05$) (Supplementary Fig. 3).

Multivariate logistic regression analyses between immune-inflammatory indexes and LUTS

To further clarify the relationship between immune-inflammatory indexes and LUTS, we classified each index into quartiles (Q1, Q2, Q3, Q4) and performed multiple logistic regression analyses with the Q1 group as reference. Our results showed that Q4 groups of PIV, SIRI, NLR, dNLR and CRP were positively correlated with clinical LUTS in all three models (all $P < 0.05$, all P for trend < 0.05). After adjustment for all confounders, PIV (OR = 1.60, 95%CI = 1.14–2.23), SIRI (OR = 1.82, 95%CI = 1.21–2.73), NLR (OR = 1.81, 95%CI = 1.31–2.49), dNLR (OR = 1.91, 95%CI = 1.35–2.70), and CRP (OR = 1.71, 95%CI = 1.05–2.79) in the Q4 group were significant risk factors for clinical LUTS in model 2. In the crude model, we also found that SII (OR = 1.45, 95%CI = 1.02–2.06) and MLR (OR = 1.96, 95%CI = 1.17–3.28) in the Q4 group were positively correlated with LUTS (Table 2). Furthermore, to confirm the linear relationship between these immune-inflammatory indexes and LUTS, we conducted a multiple ordinal logistic regression analysis and found a significant positive

correlation between SIRI, SII, NLR, dNLR, MLR, and CRP and the number of positive symptoms associated with clinical LUTS (Supplementary table 1).

Regarding the presence of daytime LUTS, we found a significant association between NLR (Q4, OR = 1.82, 95%CI = 1.21–2.74), dNLR (Q4, OR = 1.81, 95%CI = 1.20–2.71), and SIRI (Q4, OR = 1.82, 95%CI = 1.05–3.17) and increased risk of daytime LUTS (Supplementary table 2). In contrast, in the outcome of nocturia, MLR (Q4, OR = 1.49, 95%CI = 1.07–2.08) and CRP (Q4, OR = 1.59, 95%CI = 1.08–2.34) were significantly associated with nocturia (Supplementary table 3). Given the varying associations between immune-inflammatory indexes and different LUTS characteristics, we combined different indexes based on the results in Table 2. We selected cut-off values of 1.14, 2.08, 1.84, and 0.43 for SIRI, NLR, dNLR, and CRP, respectively, and divided them into high and low-level groups. We then combined SIRI, NLR, and dNLR with CRP in pairs to explore the correlation between the combined markers and clinical LUTS. The reference groups were the low CRP + low SIRI, low CRP + low NLR, and low CRP + low dNLR groups. As expected, when combined in pairs, the markers showed a stronger association with clinical LUTS than any single index alone, with the ORs for high SIRI + high CRP, high NLR + high CRP, and high dNLR + high CRP being 2.26 (95%CI = 1.56–3.26), 2.44 (95%CI = 1.60–3.71), and 2.16 (95%CI = 1.21–3.87), respectively, and there was a significant increasing trend for the prevalence of clinical LUTS (all $P < 0.05$) (Table 3).

Subgroup analyses

In our subgroup analyses, we examined the impact of age, smoking, and hypertension on the relationship between immune-inflammatory indexes and LUTS (Fig. 2). Using the Q1 group as a reference, we found a more pronounced positive association between PIV, SIRI, SII, NLR, dNLR, MLR, CRP and clinical LUTS in older men aged 60 years and older in the Q4 group compared to those under 60 years (all P <0.05, all P for interaction <0.05). Similarly, smokers exhibited a stronger positive correlation between PIV, SIRI, NLR, CRP and clinical LUTS in the Q4 group than non-smokers (all P <0.05, all P for interaction <0.05). Additionally, hypertensive men in the Q4 group showed a significantly positive association between SIRI, NLR, dNLR and clinical LUTS than those without a history of hypertension (all P <0.05, all P for interaction <0.05). These findings suggested that age, smoking, and hypertension might modify the impact of immune-inflammatory status on clinical LUTS, and should be taken into consideration in clinical practice.

Discussion

This study represents the first attempt to systematically investigate the association between different immune-inflammatory markers and LUTS risk, and to explore the potential effects of combining them. These findings revealed strong positive linear correlations between PIV, SIRI, NLR, dNLR, and CRP with clinical LUTS. Interestingly, when CRP was combined with SIRI, NLR, and dNLR respectively, the positive correlations with clinical LUTS became even stronger compared to any of the individual indexes alone. Additionally, subgroup analysis found that the effects of age, smoking, and history of hypertension varied in their influence on the relationship between immune-inflammatory indexes and clinical LUTS.

Previous studies have investigated the mechanisms underlying the association between inflammation and LUTS. As a common disease in aging men that can contribute to LUTS, the development and progression of BPH are closely related to prostatic inflammation(2, 3). In fact, Theyer et al. reported that human BPH tissue had a substantial influx of activated T cells, which secret various growth factors that facilitate prostate stromal and glandular hyperplasia(26). Additionally, stromal cells in BPH patients can stimulate the production of proinflammatory cytokines and chemotherapeutic kinases in a state of inflammation(27), such as IL-2, IL-4, IL-7, IL-17, and IFNy(28-30). Moreover, chronic inflammation in BPH is linked to the focal overexpression of cyclooxygenase 2 in the glandular epithelium, which results in the production of proinflammatory prostaglandins and prostate cell proliferation(27, 31). Furthermore, the pathogenesis of LUTS may involve different types of bladder dysfunction, such as detrusor overactivity or underactivity(2). There is a possible connection between inflammation and overactive bladder, which could be due to inflammation-induced remodeling of extracellular matrix and an increase in tissue stiffness(3). All the above studies have shown that there is a certain relationship between immune inflammation and LUTS.

The risk of LUTS has been found to be associated with immune-inflammation indexes, which are readily available and inexpensive biomarkers. Although Rohrmann et al. did not find a positive correlation between CRP and LUTS using NHANESIII data(32), several studies revealed that an elevated level of CRP was related to an increased risk of LUTS(10-12, 33), consistent with our findings. The discrepancy in results may be due to differences in CRP classification criteria. Additionally, previous small-scale studies have identified a link between elevated NLR levels and the progression of LUTS/BPH without performing multivariable analysis(13, 14). In contrast, our study provides strong evidence for a significant relationship between NLR and the prevalence of LUTS,

regardless of whether NLR was treated as a continuous or categorical variable in multivariable regression analysis. Specially, we found that elevated levels of CPR were primarily associated with nocturia, while NLR, dNLR, and SIRI were associated with daytime LUTS. Given that previous studies have combined inflammatory markers to better reflect their relationship with disease(20-22), we attempted to combine CRP with NLR, dNLR, and SIRI. Our findings highlight a stronger linear correlation between the combination of these indexes and the risk of LUTS, indicating that composite immune-inflammation markers may be more effective in reflecting the risk of LUTS.

In our study, we discovered for the first time that several immune-inflammation biomarkers, namely PIV, SIRI, and dNLR, were positively correlated with the presence of clinical LUTS. Among these biomarkers, PIV stands out for its comprehensive nature, as it comprises peripheral blood counts of neutrophils, monocytes, lymphocytes, and platelets(18), making it a promising prognostic biomarker for various cancers(34). Similarly, SIRI and SII have been established as a prognostic indicator for different types of tumors(35-37) and inflammation-related diseases(38-40), as they reflect the balance between the immune response and inflammation. After adjusting for covariates, we found that SIRI was positively associated with LUTS while SII was not, which might be due to the weak relationship between platelets and LUTS. Among these pro-inflammatory cells, NLR has been the most extensively validated. However, dNLR, which replaces the denominator of NLR with (WBC-neutrophils), has emerged as an alternative in cases where lymphocyte information is unavailable(41). Proctor et al. found that both NLR and dNLR have equal reliability for the prognostic value in patients with cancer(41). Our study revealed a significant correlation between NLR and the prevalence of LUTS, as well as a comparable association between dNLR and LUTS. Since both indexes include neutrophils, it emphasizes the strong and intimate link between neutrophils and LUTS, relative to other pro-inflammatory cells.

Subgroup analyses revealed that the positive association between inflammation and clinical LUTS was stronger among the elderly, smokers, and hypertensive patients, highlighting the potential role of excessive production and release of inflammatory factors in these populations, leading to increased levels of inflammation(42-44). Additionally, factors such as physical aging, smoking, and hypertension may contribute to a higher prevalence of LUTS through mechanisms such as prostate and bladder aging, impaired renal function, and damage to blood vessels and nerves(45-47). Thus, it is important to closely monitor the inflammation levels in these populations suffering from LUTS, and providing anti-

inflammatory interventions for those with high inflammation levels might be a promising treatment option.

This study has several advantages. Firstly, this is the first study to systematically explore the relationship between immune-inflammation indexes and LUTS, emphasizing the importance of monitoring inflammation levels in individuals with LUTS. Secondly, the NHANES dataset comprises a representative sample of the national population, and we utilize NHANES-provided weights to ensure that our findings can be extrapolated to the broader population. Furthermore, multiple potential confounders were adjusted to ensure reliable results. However, this study also has several limitations. Firstly, peripheral blood was tested only once rather than repeatedly, which may not accurately reflect a person's long-term peripheral blood status. Secondly, the questionnaire survey may have been subject to recall bias and reporting bias. Finally, it is difficult to draw causal conclusions from such cross-sectional analyses.

Conclusions

In conclusion, this study emphasized that high levels of immune-inflammatory indexes such as PIV, SIRI, NLR, dNLR, and CRP were independent risk factors for clinical LUTS. The combination of CRP with SIRI, NLR, and dNLR respectively showed a stronger positive correlation with clinical LUTS compared to any of the individual indexes alone. Furthermore, the impact of age, smoking, and history of hypertension on the relationship between immune-inflammatory indexes and LUTS was significant. Further research, including multi-center studies, is needed to confirm the relationship between immune-inflammatory indexes and LUTS and to provide additional evidence for the management and treatment of clinical LUTS.

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Contributors

W-L: conceptualization, methodology, data analysis, manuscript writing; J-W: methodology, data collection, data analysis, manuscript writing; MM-W: methodology, data collection, data analysis; M-W: data analysis, manuscript writing; X-D: methodology, supervision; M-L: conceptualization, supervision, manuscript editing, funding acquisition.

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Competing interests

None declared

Patient consent for publication

Not applicable.

Ethical statement

Ethical review and approval for the research involving human participants were obtained from the Ethics Review Board of the NCHS (Protocol #98-12). The current analysis, which is based on publicly available data, did not necessitate any further ethics approval. Written informed consent was obtained from all patients or participants who were part of the study.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be downloaded here: https://www.cdc.gov/nchs/nhanes/ (NHANES 2005-2006 and 2007-2008).

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Figure legend

Fig. 1 Dose-response relationships between blood immune-inflammatory indexes and clinical LUTS (A) PIV and clinical LUTS; (B) SIRI and LUTS; (C) SII and LUTS; (D) NLR and LUTS; (E) dNLR and LUTS; (F) MLR and LUTS; (G) PLR and LUTS; (H) CRP and LUTS. They are adjusted for age, race/ethnicity, education level, smoking status, alcohol use, and BMI, total cholesterol, and a history of

diabetes and hypertension. The shaded part represents the 95% CI. Abbreviations: OR, odds ratio; LUTS, lower urinary tract symptoms; PIV, pan-immune-inflammation value; SIRI, system inflammation response index; SII, systemic immune-inflammation index; NLR, neutrophil to lymphocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio; MLR, monocyte to lymphocyte ratio; PLR, platelet to lymphocyte ratio; CRP, C-reactive protein.

Fig. 2 Associations between blood immune-inflammatory indexes and clinical LUTS in subgroup analyses. They are adjusted for age, race/ethnicity, education level, smoking status, alcohol use, and BMI, total cholesterol, and a history of diabetes and hypertension, if not already stratified. Abbreviations: OR, odds ratio; LUTS, lower urinary tract symptoms; PIV, pan-immune-inflammation value; SIRI, system inflammation response index; SII, systemic immune-inflammation index; NLR, neutrophil to lymphocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio; MLR, monocyte to lymphocyte ratio; PLR, platelet to lymphocyte ratio; CRP, C-reactive protein.

Supplementary Fig. 1 Study flowchart. Of 20,497 participants in the 2005–2008 National Health and Nutrition Examination Survey (NHANES), 2,709 remained after fulfilling inclusion and exclusion criteria

Supplementary Fig. 2 Dose-response relationships between blood immune-inflammatory indexes and daytime LUTS (A) PIV and LUTS; (B) SIRI and LUTS; (C) SII and LUTS; (D) NLR and LUTS; (E) dNLR and LUTS; (F) MLR and LUTS; (G) PLR and LUTS; (H) CRP and LUTS. They are adjusted for age, race/ethnicity, education level, smoking status, alcohol use, and BMI, total cholesterol, and a history of diabetes and hypertension. The shaded part represents the 95% CI. Abbreviations: OR, odds ratio; LUTS, lower urinary tract symptoms; PIV, pan-immune-inflammation value; SIRI, system inflammation response index; SII, systemic immune-inflammation index; NLR, neutrophil to lymphocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio; MLR, monocyte to lymphocyte ratio; PLR, platelet to lymphocyte ratio; CRP, C-reactive protein.

Supplementary Fig. 3 Dose-response relationships between blood immune-inflammatory indexes and nocturia (A) PIV and LUTS; (B) SIRI and LUTS; (C) SII and LUTS; (D) NLR and LUTS; (E) dNLR and LUTS; (F) MLR and LUTS; (G) PLR and LUTS; (H) CRP and LUTS. They are adjusted for age, race/ethnicity, education level, smoking status, alcohol use, and BMI, total cholesterol, and a history of diabetes and hypertension. The shaded part represents the 95% CI. Abbreviations: OR, odds ratio; LUTS, lower urinary tract symptoms; PIV, pan-immune-inflammation value; SIRI, system inflammation response index; SII, systemic immune-inflammation index; NLR, neutrophil to lymphocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio; MLR, monocyte to lymphocyte ratio; PLR, platelet to lymphocyte ratio; CRP, C-reactive protein.

Table 1. Demographic and clinic characteristics according to clinical LUTS, daytime LUTS, and nocturia. NHANES 2005-2008*

Characteristics	Total Adults (N = 2709)	Clinical LUTS			Daytime LUTS			Nocturia		
		No (N = 2310)	Yes (N = 399)	*P* value	No (N = 2034)	Yes (N = 675)	*P* value	No (N = 1763)	Yes (N = 946)	*P* value
Age, years, n (%)				< 0.01			< 0.01			< 0.01

< 60	1362(64.90)	1240(67.84)	122(43.46)		1110(68.60)	252(52.09)		1045(72.17)	317(44.88)	
≥ 60	1347(35.10)	1070(32.16)	277(56.54)		924(31.40)	423(47.91)		718(27.83)	629(55.12)	
Race/ethnicity, n (%)				0.94			0.67			< 0.01
Non-Hispanic White	1502(78.06)	1261(77.96)	241(78.77)		1108(77.87)	394(78.71)		1003(80.02)	499(72.63)	
Non-Hispanic Black	508(8.82)	435(8.90)	73(8.22)		388(9.15)	120(7.66)		298(7.34)	210(12.88)	
Mexican	433(6.14)	379(6.19)	54(5.81)		334(6.24)	99(5.81)		272(5.46)	161(8.03)	
Other	266(6.99)	235(6.96)	31(7.20)		204(6.75)	62(7.83)		190(7.18)	76(6.46)	
Education, n (%)				< 0.01			0.08			< 0.01
Grades 0–12	821(17.80)	675(16.73)	146(25.63)		599(16.85)	222(21.10)		460(14.50)	361(26.89)	
High school graduate/GED	651(25.61)	555(25.53)	96(26.19)		487(25.22)	164(26.98)		433(25.75)	218(25.23)	
Some college or above	1237(56.59)	1080(57.74)	157(48.18)		948(57.94)	289(51.91)		870(59.75)	367(47.88)	
Smoking†, n (%)				< 0.01			0.06			< 0.01
Yes	1681(59.25)	1390(57.37)	291(72.99)		1227(58.41)	454(62.18)		1036(55.58)	645(69.37)	
No	1028(40.75)	920(42.63)	108(27.01)		807(41.59)	221(37.82)		727(44.42)	301(30.63)	
Alcohol use‡, n (%)				< 0.01			< 0.01			< 0.01
Yes	1776(72.69)	1550(74.51)	226(59.41)		1376(75.21)	400(63.98)		1213(75.41)	563(65.20)	
No	933(27.31)	760(25.49)	173(40.59)		658(24.79)	275(36.02)		550(24.59)	383(34.80)	
BMI§, kg/m², n (%)				0.94			0.83			0.02
< 25	627(21.53)	527(21.42)	100(22.29)		463(21.25)	164(22.47)		397(21.78)	230(20.82)	
25–29.9	1139(43.17)	982(43.14)	157(43.42)		863(43.03)	276(43.65)		783(45.19)	356(37.61)	
≥ 30	943(35.30)	801(35.44)	142(34.29)		708(35.71)	235(33.88)		583(33.03)	360(41.57)	
Total cholesterol, mmol/L, n (%)				0.02			0.38			< 0.01
< 5.02	1370(47.14)	1137(46.02)	233(55.31)		1006(46.51)	364(49.31)		833(44.22)	537(55.18)	
≥ 5.02	1339(52.86)	1173(53.98)	166(44.69)		1028(53.49)	311(50.69)		930(55.78)	409(44.82)	
Hypertension, n (%)				< 0.01			< 0.01			< 0.01
Yes	1441(49.14)	1188(47.25)	253(62.93)		1029(46.53)	412(58.20)		833(44.00)	608(63.32)	
No	1268(50.86)	1122(52.75)	146(37.07)		1005(53.47)	263(41.80)		930(56.00)	338(36.68)	
Diabetes, n (%)				< 0.01			0.01			< 0.01
Yes	558(15.16)	453(13.93)	105(24.17)		395(13.54)	163(20.78)		292(11.97)	266(23.97)	
No	2151(84.84)	1857(86.07)	294(75.83)		1639(86.46)	512(79.22)		1471(88.03)	680(76.03)	
WBC, 1000 cells/ul, mean (SE)	7.28(0.07)	7.22(0.07)	7.74(0.18)	0.01	7.25(0.08)	7.41(0.11)	0.22	7.25(0.08)	7.38(0.12)	0.41
Neu, 1000 cells/ul, mean (SE)	4.36(0.05)	4.31(0.06)	4.72(0.09)	< 0.01	4.31(0.06)	4.51(0.08)	0.05	4.33(0.07)	4.42(0.08)	0.38
Lym, 1000 cells/ul, mean (SE)	2.07(0.03)	2.07(0.02)	2.13(0.12)	0.63	2.09(0.03)	2.03(0.07)	0.41	2.08(0.02)	2.06(0.06)	0.83
Mono, 1000	0.59(0.0	0.59(0.0	0.62(0.0	0.06	0.59(0.0	0.59(0.0	0.51	0.58(0.0	0.61(0.0	0.02

cells/ul, mean (SE)	1)	1)	2)		1)	1)		1)	1)	
PLT, 1000 cells/ul, mean (SE)	252.30(1.74)	253.68(1.92)	242.25(3.78)	0.01	254.55(1.70)	244.53(3.97)	0.02	255.35(2.23)	243.91(2.51)	< 0.01
CRP, mg/dl, mean (SE)	0.38(0.02)	0.35(0.02)	0.63(0.14)	0.06	0.35(0.02)	0.51(0.08)	0.06	0.32(0.01)	0.55(0.08)	0.01
PIV, mean (SE)	352.79(8.51)	345.11(8.45)	408.87(18.25)	< 0.01	345.06(9.09)	379.59(14.17)	0.02	342.07(8.07)	382.35(14.59)	< 0.01
SIRI, mean (SE)	1.38(0.03)	1.34(0.03)	1.66(0.06)	< 0.01	1.33(0.03)	1.53(0.04)	< 0.01	1.32(0.03)	1.53(0.05)	< 0.01
SII, mean (SE)	586.41(10.55)	577.92(11.21)	648.46(25.42)	0.01	575.69(12.23)	623.61(20.14)	0.05	578.16(11.65)	609.18(16.11)	0.08
NLR, mean (SE)	2.32(0.04)	2.27(0.04)	2.67(0.08)	< 0.01	2.25(0.04)	2.56(0.07)	< 0.01	2.26(0.04)	2.47(0.05)	< 0.01
dNLR, mean (SE)	1.58(0.02)	1.55(0.02)	1.73(0.04)	< 0.01	1.54(0.02)	1.69(0.03)	< 0.01	1.56(0.02)	1.62(0.03)	0.08
MLR, mean (SE)	0.31(0.00)	0.31(0.00)	0.34(0.01)	< 0.01	0.30(0.00)	0.33(0.01)	< 0.01	0.30(0.00)	0.34(0.01)	< 0.01
PLR, mean (SE)	134.99(1.58)	134.75(1.66)	136.73(4.45)	0.67	133.75(1.47)	139.26(4.43)	0.24	134.33(1.89)	136.79(2.68)	0.45

Abbreviations: LUTS, lower urinary tract symptoms NHANES, National Health and Nutrition Examination Survey; SE, standard error; GED, General Equivalency Diploma; BMI, body mass index; WBC, leukocyte; Neu, neutrophil; Lym, lymphocyte; Mono, monocyte; PLT, platelet; CRP, C-reactive protein; PIV, pan-immune-inflammation value; SIRI, system inflammation response index; SII, systemic immune-inflammation index; NLR, neutrophil to lymphocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio; MLR, monocyte to lymphocyte ratio; PLR, platelet to lymphocyte ratio.
*Means and percentages were adjusted for survey weights of NHANES.
†Smoking was defined as smoking at least 100 cigarettes during their lifetime.
‡Alcohol use was defined as having at least 12 alcohol drinks in any given year.
§BMI was calculated by dividing weight in kilograms (kg) by height in meters squared (m^2). Participants were classified as normal weight (< 25 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥ 30 kg/m^2).

Table 2. *OR* (95% *CI*) for LUTS across quartiles of blood immune-inflammatory indexes*

	Crude Model	*P* value	Model 1	*P* value	Model 2	*P* value
PIV						
Q1 (< 181.50)	1[Reference]		1[Reference]		1[Reference]	
Q2 (181.50–276.64)	1.15(0.73,1.80)	0.53	1.11(0.69,1.79)	0.65	1.14(0.71,1.85)	0.56
Q3 (276.65–421.83)	0.86(0.59,1.24)	0.39	0.79(0.54,1.17)	0.22	0.82(0.57,1.18)	0.26
Q4 (≥ 421.84)	1.85(1.34,2.56)	< 0.01	1.59(1.14,2.24)	0.01	1.60(1.14,2.23)	0.01
P for trend		< 0.01		0.01		0.02
SIRI						
Q1 (< 0.80)	1[Reference]		1[Reference]		1[Reference]	
Q2 (0.80–1.14)	1.01(0.58,1.73)	0.98	0.98(0.56,1.70)	0.93	0.97(0.55,1.72)	0.92
Q3 (1.15–1.65)	1.39(1.06,1.84)	0.02	1.26(0.94,1.69)	0.12	1.23(0.91,1.66)	0.17
Q4 (≥ 1.66)	2.35(1.61,3.44)	< 0.01	1.91(1.30,2.82)	< 0.01	1.82(1.21,2.73)	0.01
P for trend		< 0.01		< 0.01		< 0.01
SII						
Q1 (< 356.13)	1[Reference]		1[Reference]		1[Reference]	
Q2 (356.13–500.41)	0.97(0.68,1.39)	0.86	0.97(0.65,1.43)	0.86	1.02(0.71,1.48)	0.89
Q3 (500.42–702.31)	0.98(0.67,1.43)	0.91	1.00(0.66,1.51)	0.99	1.04(0.71,1.54)	0.82
Q4 (≥ 702.32)	1.45(1.02,2.06)	0.04	1.37(0.94,2.00)	0.09	1.40(0.97,2.04)	0.07
P for trend		< 0.01		0.03		0.03
NLR						
Q1 (< 1.56)	1[Reference]		1[Reference]		1[Reference]	
Q2 (1.56–2.08)	1.08(0.74,1.60)	0.67	1.15(0.76,1.75)	0.50	1.16(0.75,1.80)	0.48
Q3 (2.09–2.72)	1.75(1.16,2.63)	0.01	1.73(1.12,2.66)	0.02	1.71(1.10,2.66)	0.02
Q4 (≥ 2.73)	2.21(1.60,3.04)	< 0.01	1.89(1.39,2.56)	< 0.01	1.81(1.31,2.49)	< 0.01

P for trend		< 0.01		< 0.01		< 0.01
dNLR						
Q1 (< 1.13)	1[Reference]		1[Reference]		1[Reference]	
Q2 (1.13–1.44)	1.09(0.80,1.49)	0.55	1.09(0.80,1.50)	0.56	1.10(0.80,1.51)	0.55
Q3 (1.45–1.84)	1.32(0.92,1.89)	0.12	1.32(0.92,1.89)	0.12	1.33(0.92,1.90)	0.12
Q4 (≥ 1.85)	2.17(1.55,3.04)	< 0.01	1.98(1.42,2.77)	< 0.01	1.91(1.35,2.70)	< 0.01
P for trend		< 0.01		< 0.01		< 0.01
MLR						
Q1 (< 0.22)	1[Reference]		1[Reference]		1[Reference]	
Q2 (0.22–0.29)	1.27(0.72,2.24)	0.39	1.24(0.69,2.25)	0.45	1.25(0.69,2.27)	0.43
Q3 (0.30–0.37)	1.49(0.87,2.56)	0.14	1.38(0.79,2.41)	0.24	1.38(0.77,2.46)	0.26
Q4 (≥ 0.38)	1.96(1.17,3.28)	0.01	1.51(0.89,2.57)	0.12	1.44(0.82,2.53)	0.18
P for trend		< 0.01		0.09		0.16
PLR						
Q1 (< 97.90)	1[Reference]		1[Reference]		1[Reference]	
Q2 (97.90–124.74)	0.94(0.59,1.49)	0.79	0.97(0.61,1.55)	0.90	1.00(0.62,1.62)	0.98
Q3 (124.75–159.41)	0.70(0.49,0.99)	0.04	0.81(0.56,1.18)	0.26	0.86(0.58,1.27)	0.41
Q4 (≥ 159.42)	1.09(0.72,1.63)	0.68	1.09(0.73,1.64)	0.65	1.14(0.74,1.74)	0.53
P for trend		0.77		0.70		0.57
CRP, mg/dl						
Q1 (< 0.09)	1[Reference]		1[Reference]		1[Reference]	
Q2 (0.09–0.20)	0.88(0.56,1.38)	0.57	0.84(0.53,1.34)	0.45	0.83(0.51,1.34)	0.41
Q3 (0.21–0.43)	1.12(0.66,1.92)	0.66	1.05(0.59,1.88)	0.86	1.05(0.58,1.88)	0.87
Q4 (≥ 0.43)	2.03(1.28,3.22)	< 0.01	1.78(1.09,2.90)	0.02	1.71(1.05,2.79)	0.03
P for trend		< 0.01		< 0.01		< 0.01

Abbreviations: *OR*, odds ratio; *CI*, confidence interval; PIV, pan-immune-inflammation value; SIRI, system inflammation response index; SII, systemic immune-inflammation index; NLR, neutrophil to lymphocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio; MLR, monocyte to lymphocyte ratio; PLR, platelet to lymphocyte ratio; CRP, C-reactive protein.
*Values are numerical values or weighted *OR* (95% *CI*).
Model 1 was adjusted for age, race/ethnicity, education level, smoking status, alcohol use, and BMI;
Model 2 was additionally adjusted for total cholesterol, and a history of diabetes and hypertension

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Table 3. *OR* (95% *CI*) for clinical LUTS across combined blood immune-inflammatory indexes*

	Crude Model	***P* value**	**Model 1**	***P* value**	**Model 2**	***P* value**
SIRI+CRP (Low SIRI < 1.14, High SIRI ≥ 1.14; Low CRP < 0.43, High CRP ≥ 0.43)						
Low SIRI and Low CRP	1[Reference]		1[Reference]		1[Reference]	
High SIRI and Low CRP	1.83(1.34,2.50)	< 0.01	1.60(1.13,2.25)	0.01	1.56(1.10,2.21)	0.02
Low SIRI and High CRP	2.28(1.28,4.07)	0.01	2.15(1.12,4.14)	0.02	2.10(1.09,4.03)	0.03
High SIRI and High CRP	2.90(2.04,4.12)	< 0.01	2.39(1.65,3.48)	< 0.01	2.26(1.56,3.26)	< 0.01
NLR+CRP (Low NLR < 2.08, High NLR ≥ 2.08)						
Low NLR and Low CRP	1[Reference]		1[Reference]		1[Reference]	
High NLR and Low CRP	2.06(1.54,2.77)	< 0.01	1.82(1.37,2.41)	< 0.01	1.78(1.33,2.38)	< 0.01
Low NLR and High CRP	2.69(1.57,4.62)	< 0.01	2.40(1.33,4.32)	0.01	2.31(1.29,4.14)	0.01
High NLR and High CRP	3.07(2.11,4.46)	< 0.01	2.59(1.73,3.86)	< 0.01	2.44(1.60,3.71)	< 0.01
dNLR+CRP (Low dNLR < 1.84, High dNLR ≥ 1.84)						
Low dNLR and Low CRP	1[Reference]		1[Reference]		1[Reference]	
High dNLR and Low CRP	2.03(1.39,2.97)	< 0.01	1.88(1.24,2.84)	< 0.01	1.87(1.22,2.87)	0.01
Low dNLR and High CRP	2.16(1.37,3.41)	< 0.01	2.01(1.23,3.26)	0.01	1.99(1.23,3.23)	0.01

High dNLR and High CRP	2.84(1.66,4.87)	< 0.01	2.38(1.35,4.21)	< 0.01	2.16(1.21,3.87)	0.01

Abbreviations: *OR*, odds ratio; *CI*, confidence interval; SIRI, system inflammation response index; NLR, neutrophil to lymphocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio; CRP, C-reactive protein.
*Values are numerical values or weighted *OR* (95% *CI*).
Model 1 was adjusted for age, race/ethnicity, education level, smoking status, alcohol use, and BMI;
Model 2 was additionally adjusted for total cholesterol, and a history of diabetes and hypertension.

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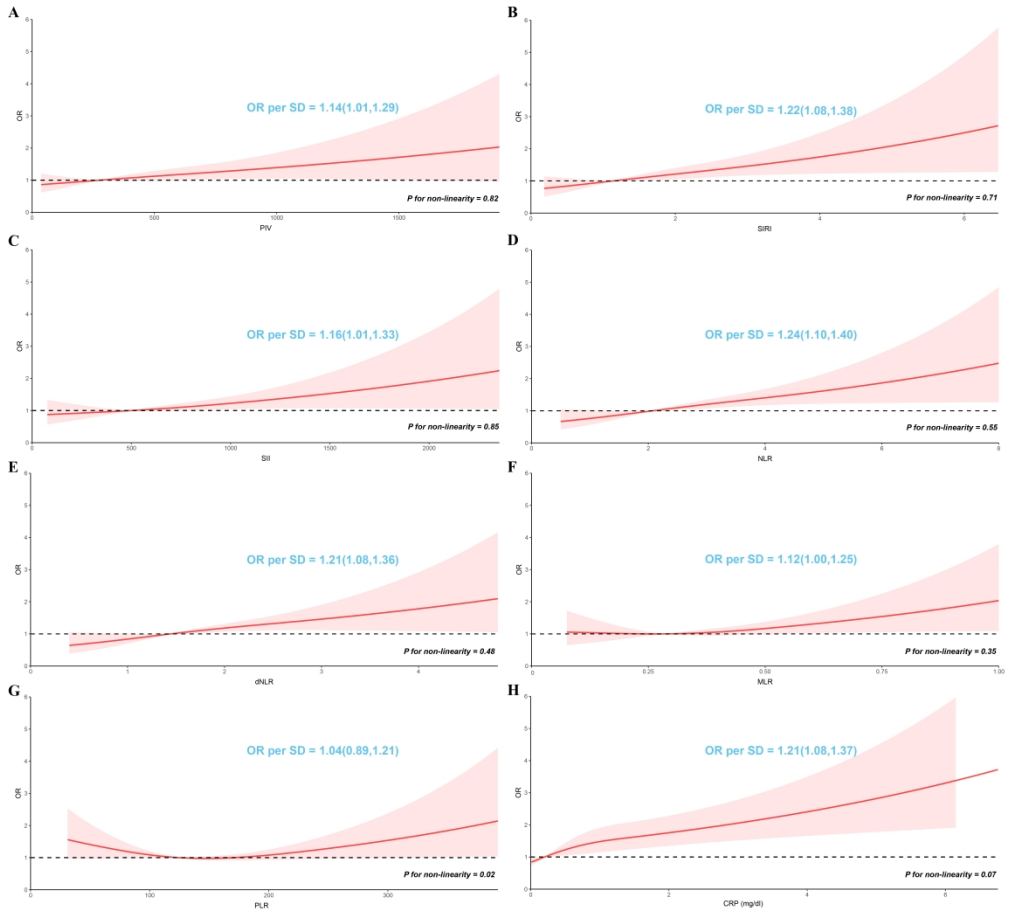

Fig. 1 Dose-response relationships between blood immune-inflammatory indexes and clinical LUTS (A) PIV and clinical LUTS; (B) SIRI and LUTS; (C) SII and LUTS; (D) NLR and LUTS; (E) dNLR and LUTS; (F) MLR and LUTS; (G) PLR and LUTS; (H) CRP and LUTS. They are adjusted for age, race/ethnicity, education level, smoking status, alcohol use, and BMI, total cholesterol, and a history of diabetes and hypertension. The shaded part represents the 95% CI. Abbreviations: OR, odds ratio; LUTS, lower urinary tract symptoms; PIV, pan-immune-inflammation value; SIRI, system inflammation response index; SII, systemic immune-inflammation index; NLR, neutrophil to lymphocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio; MLR, monocyte to lymphocyte ratio; PLR, platelet to lymphocyte ratio; CRP, C-reactive protein.

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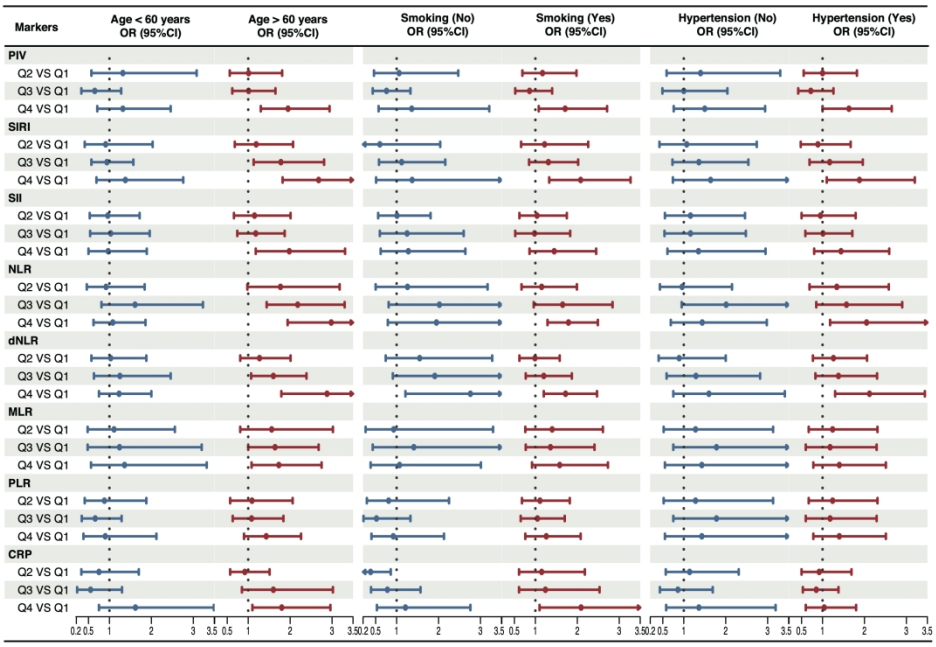

Fig. 2 Associations between blood immune-inflammatory indexes and clinical LUTS in subgroup analyses. They are adjusted for age, race/ethnicity, education level, smoking status, alcohol use, and BMI, total cholesterol, and a history of diabetes and hypertension, if not already stratified. Abbreviations: OR, odds ratio; LUTS, lower urinary tract symptoms; PIV, pan-immune-inflammation value; SIRI, system inflammation response index; SII, systemic immune-inflammation index; NLR, neutrophil to lymphocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio; MLR, monocyte to lymphocyte ratio; PLR, platelet to lymphocyte ratio; CRP, C-reactive protein.

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Supplementary table 1. Multivariate logistic ordinal regression analysis of the blood immune-inflammatory indexes among the number of positive symptoms associated with clinical LUTS*

	Crude Model	*P* value	Model 1	*P* value	Model 2	*P* value
PIV	1.15(1.06,1.24)	< 0.01	1.10(1.02,1.19)	0.02	1.08(1.00,1.18)	0.06
SIRI	1.27(1.17,1.37)	< 0.01	1.18(1.09,1.28)	< 0.01	1.16(1.06,1.26)	< 0.01
SII	1.13(1.03,1.24)	0.01	1.12(1.02,1.22)	0.02	1.10(1.01,1.21)	0.03
NLR	1.28(1.15,1.42)	< 0.01	1.22(1.11,1.34)	< 0.01	1.20(1.10,1.32)	< 0.01
dNLR	1.18(1.06,1.31)	< 0.01	1.16(1.06,1.28)	< 0.01	1.15(1.05,1.25)	< 0.01
MLR	1.27(1.17,1.37)	< 0.01	1.17(1.06,1.28)	< 0.01	1.16(1.05,1.27)	< 0.01
PLR	1.09(1.06,1.24)	< 0.01	1.09(0.98,1.20)	0.10	1.10(1.00,1.22)	0.06
CRP, mg/dl	1.20(1.13,1.27)	< 0.01	1.20(1.13,1.26)	< 0.01	1.19(1.12,1.27)	< 0.01

Abbreviations: *OR*, odds ratio; *CI*, confidence interval; PIV, pan-immune-inflammation value; SIRI, system inflammation response index; SII, systemic immune-inflammation index; NLR, neutrophil to lymphocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio; MLR, monocyte to lymphocyte ratio; PLR, platelet to lymphocyte ratio; CRP, C-reactive protein.
*Values are numerical values or weighted *OR* (95% *CI*).
Model 1 was adjusted for age, race/ethnicity, education level, smoking status, alcohol use, and BMI;
Model 2 was additionally adjusted for total cholesterol, and a history of diabetes and hypertension.

Supplementary table 2. *OR* (95% *CI*) for daytime LUTS across quartiles of blood immune-inflammatory indexes*

	Crude Model	*P* value	Model 1	*P* value	Model 2	*P* value
PIV						
Q1 (< 181.50)	1[Reference]		1[Reference]		1[Reference]	
Q2 (181.50–276.64)	1.20(0.83,1.71)	0.32	1.16(0.79,1.69)	0.44	1.17(0.80,1.71)	0.39
Q3 (276.65–421.83)	0.95(0.65,1.40)	0.81	0.91(0.62,1.34)	0.62	0.93(0.63,1.35)	0.67
Q4 (≥ 421.84)	1.46(0.96,2.21)	0.07	1.33(0.87,2.03)	0.17	1.32(0.85,2.03)	0.20
P for trend		0.07		0.16		0.22
SIRI						
Q1 (< 0.80)	1[Reference]		1[Reference]		1[Reference]	
Q2 (0.80–1.14)	1.08(0.62,1.88)	0.77	1.05(0.60,1.86)	0.85	1.04(0.58,1.86)	0.88
Q3 (1.15–1.65)	1.14(0.76,1.71)	0.51	1.05(0.68,1.62)	0.81	1.01(0.66,1.57)	0.94
Q4 (≥ 1.66)	1.82(1.05,3.17)	0.03	1.59(0.89,2.85)	0.11	1.52(0.83,2.80)	0.16
P for trend		< 0.01		0.04		0.07
SII						
Q1 (< 356.13)	1[Reference]		1[Reference]		1[Reference]	
Q2 (356.13–500.41)	1.00(0.72,1.39)	0.99	0.99(0.69,1.42)	0.96	1.03(0.73,1.45)	0.86
Q3 (500.42–702.31)	1.03(0.71,1.49)	0.86	1.02(0.70,1.51)	0.90	1.05(0.71,1.54)	0.81
Q4 (≥ 702.32)	1.32(0.89,1.95)	0.16	1.27(0.84,1.93)	0.25	1.28(0.83,1.96)	0.24
P for trend		0.11		0.17		0.19
NLR						
Q1 (< 1.56)	1[Reference]		1[Reference]		1[Reference]	
Q2 (1.56–2.08)	1.18(0.92,1.52)	0.19	1.19(0.90,1.57)	0.20	1.18(0.89,1.58)	0.23
Q3 (2.09–2.72)	1.41(0.91,2.18)	0.12	1.34(0.85,2.10)	0.19	1.32(0.83,2.09)	0.22
Q4 (≥ 2.73)	2.10(1.44,3.05)	< 0.01	1.87(1.26,2.78)	< 0.01	1.82(1.21,2.73)	0.01
P for trend		< 0.01		< 0.01		< 0.01
dNLR						
Q1 (< 1.13)	1[Reference]		1[Reference]		1[Reference]	
Q2 (1.13–1.44)	1.25(0.98,1.61)	0.07	1.23(0.95,1.59)	0.11	1.23(0.95,1.59)	0.11
Q3 (1.45–1.84)	1.20(0.78,1.83)	0.39	1.15(0.74,1.78)	0.51	1.15(0.74,1.79)	0.51
Q4 (≥ 1.85)	1.99(1.35,2.93)	< 0.01	1.86(1.25,2.75)	< 0.01	1.81(1.20,2.71)	0.01
P for trend		< 0.01		< 0.01		0.01
MLR						
Q1 (< 0.22)	1[Reference]		1[Reference]		1[Reference]	
Q2 (0.22–0.29)	1.17(0.81,1.69)	0.38	1.13(0.77,1.66)	0.50	1.13(0.77,1.66)	0.49
Q3 (0.30–0.37)	1.32(0.85,2.06)	0.20	1.23(0.77,1.96)	0.36	1.22(0.75,1.98)	0.40
Q4 (≥ 0.38)	1.66(1.14,2.42)	0.01	1.38(0.93,2.04)	0.10	1.35(0.89,2.03)	0.15
P for trend		0.01		0.13		0.19
PLR						
Q1 (< 97.90)	1[Reference]		1[Reference]		1[Reference]	
Q2 (97.90–124.74)	0.92(0.65,1.30)	0.63	0.93(0.66,1.32)	0.68	0.94(0.66,1.34)	0.71
Q3 (124.75–159.41)	0.76(0.60,0.96)	0.02	0.81(0.64,1.04)	0.09	0.83(0.65,1.07	0.14
Q4 (≥ 159.42)	1.13(0.82,1.57)	0.44	1.11(0.80,1.55)	0.50	1.13(0.80,1.60)	0.45
P for trend		0.47		0.52		0.45
CRP, mg/dl						
Q1 (< 0.09)	1[Reference]		1[Reference]		1[Reference]	

Q2 (0.09–0.20)	0.84(0.62,1.15)	0.28	0.83(0.59,1.16)	0.26	0.82(0.58,1.16)	0.23
Q3 (0.21–0.43)	0.95(0.66,1.37)	0.79	0.95(0.64,1.39)	0.76	0.92(0.63,1.36)	0.66
Q4 (≥ 0.43)	1.36(0.97,1.91)	0.07	1.29(0.90,1.85)	0.15	1.22(0.86,1.74)	0.25
P for trend		0.02		0.03		0.05

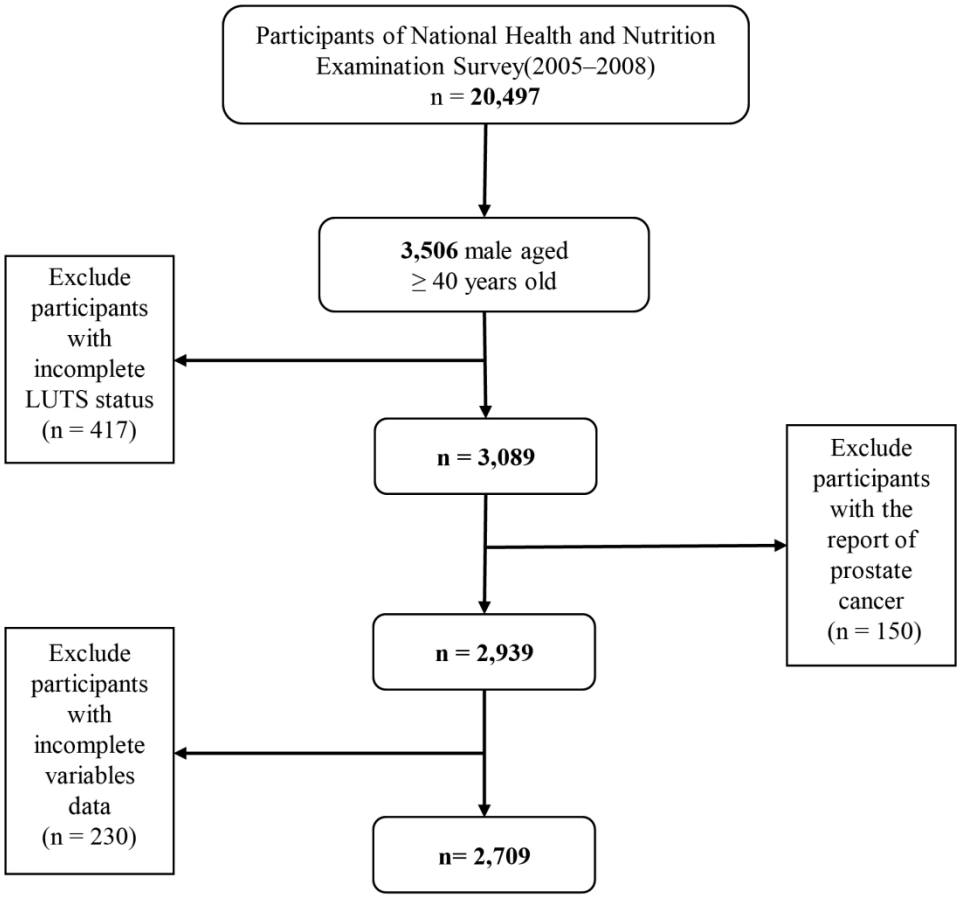
Abbreviations: *OR*, odds ratio; *CI*, confidence interval; PIV, pan-immune-inflammation value; SIRI, system inflammation response index; SII, systemic immune-inflammation index; NLR, neutrophil to lymphocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio; MLR, monocyte to lymphocyte ratio; PLR, platelet to lymphocyte ratio; CRP, C-reactive protein.
*Values are numerical values or weighted *OR* (95% *CI*).
Model 1 was adjusted for age, race/ethnicity, education level, smoking status, alcohol use, and BMI;
Model 2 was additionally adjusted for total cholesterol, and a history of diabetes and hypertension.

Supplementary table 3. *OR* (95% *CI*) for nocturia across quartiles of blood immune-inflammatory indexes*

	Crude Model	*P* value	Model 1	*P* value	Model 2	*P* value
PIV						
Q1 (< 181.50)	1[Reference]		1[Reference]		1[Reference]	
Q2 (181.50–276.64)	0.95(0.66,1.36)	0.77	0.96(0.65,1.43)	0.84	0.98(0.65,1.50)	0.93
Q3 (276.65–421.83)	0.91(0.63,1.33)	0.63	0.88(0.58,1.34)	0.55	0.91(0.59,1.41)	0.65
Q4 (≥ 421.84)	1.34(1.02,1.77)	0.04	1.26(0.94,1.70)	0.12	1.25(0.91,1.71)	0.15
P for trend		0.01		0.06		0.10
SIRI						
Q1 (< 0.80)	1[Reference]		1[Reference]		1[Reference]	
Q2 (0.80–1.14)	0.84(0.61,1.15)	0.27	0.87(0.61,1.22)	0.39	0.86(0.60,1.22)	0.36
Q3 (1.15–1.65)	1.26(0.89,1.77)	0.18	1.20(0.80,1.80)	0.36	1.17(0.76,1.81)	0.45
Q4 (≥ 1.66)	1.58(1.16,2.16)	0.01	1.39(1.00,1.94)	0.05	1.30(0.92,1.84)	0.12
P for trend		< 0.01		0.01		0.04
SII						
Q1 (< 356.13)	1[Reference]		1[Reference]		1[Reference]	
Q2 (356.13–500.41)	0.78(0.57,1.07)	0.12	0.78(0.57,1.08)	0.12	0.82(0.60,1.12)	0.19
Q3 (500.42–702.31)	0.79(0.60,1.04)	0.10	0.85(0.63,1.14)	0.26	0.87(0.65,1.17)	0.35
Q4 (≥ 702.32)	1.03(0.78,1.38)	0.81	1.03(0.78,1.37)	0.81	1.04(0.78,1.40)	0.76
P for trend		0.39		0.36		0.39
NLR						
Q1 (< 1.56)	1[Reference]		1[Reference]		1[Reference]	
Q2 (1.56–2.08)	0.83(0.54,1.27)	0.37	0.95(0.61,1.47)	0.81	0.94(0.59,1.48)	0.77
Q3 (2.09–2.72)	1.20(0.86,1.66)	0.27	1.25(0.88,1.79)	0.20	1.23(0.86,1.76)	0.25
Q4 (≥ 2.73)	1.45(1.04,2.02)	0.03	1.32(0.94,1.87)	0.10	1.25(0.88,1.77)	0.20
P for trend		< 0.01		0.03		0.06
dNLR						
Q1 (< 1.13)	1[Reference]		1[Reference]		1[Reference]	
Q2 (1.13–1.44)	0.97(0.69,1.37)	0.85	1.03(0.70,1.51)	0.88	1.02(0.68,1.53)	0.91
Q3 (1.45–1.84)	1.04(0.75,1.44)	0.83	1.11(0.78,1.60)	0.53	1.11(0.78,1.59)	0.54
Q4 (≥ 1.85)	1.24(0.88,1.76)	0.22	1.18(0.82,1.70)	0.36	1.13(0.77,1.65)	0.51
P for trend		0.16		0.29		0.44
MLR						
Q1 (< 0.22)	1[Reference]		1[Reference]		1[Reference]	
Q2 (0.22–0.29)	0.88(0.62,1.24)	0.45	0.92(0.65,1.30)	0.62	0.92(0.65,1.30)	0.60
Q3 (0.30–0.37)	1.34(0.97,1.87)	0.08	1.37(1.00,1.87)	0.05	1.37(0.98,1.89)	0.06
Q4 (≥ 0.38)	1.83(1.32,2.53)	< 0.01	1.56(1.13,2.16)	0.01	1.49(1.07,2.08)	0.02
P for trend		< 0.01		< 0.01		< 0.01
PLR						
Q1 (< 97.90)	1[Reference]		1[Reference]		1[Reference]	
Q2 (97.90–124.74)	0.79(0.56,1.11)	0.17	0.80(0.56,1.15)	0.21	0.84(0.57,1.24)	0.36
Q3 (124.75–159.41)	0.80(0.62,1.04)	0.09	0.94(0.74,1.20)	0.62	1.02(0.79,1.32)	0.86
Q4 (≥ 159.42)	1.01(0.70,1.45)	0.96	1.02(0.72,1.45)	0.91	1.08(0.74,1.56)	0.67
P for trend		0.74		0.54		0.40
CRP, mg/dl						
Q1 (< 0.09)	1[Reference]		1[Reference]		1[Reference]	

Q2 (0.09–0.20)	1.13(0.80,1.61)	0.47	1.07(0.76,1.51)	0.70	1.04(0.75,1.46)	0.23
Q3 (0.21–0.43)	1.39(0.98,1.98)	0.06	1.18(0.81,1.71	0.38	1.16(0.80,1.69)	0.66
Q4 (≥ 0.43)	2.19(1.61,2.98)	< 0.01	1.67(1.14,2.43)	0.01	1.59(1.08,2.34)	0.02
P for trend		< 0.01		< 0.01		< 0.01

Abbreviations: *OR*, odds ratio; *CI*, confidence interval; PIV, pan-immune-inflammation value; SIRI, system inflammation response index; SII, systemic immune-inflammation index; NLR, neutrophil to lymphocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio; MLR, monocyte to lymphocyte ratio; PLR, platelet to lymphocyte ratio; CRP, C-reactive protein.
*Values are numerical values or weighted *OR* (95% *CI*).
Model 1 was adjusted for age, race/ethnicity, education level, smoking status, alcohol use, and BMI;
Model 2 was additionally adjusted for total cholesterol, and a history of diabetes and hypertension.



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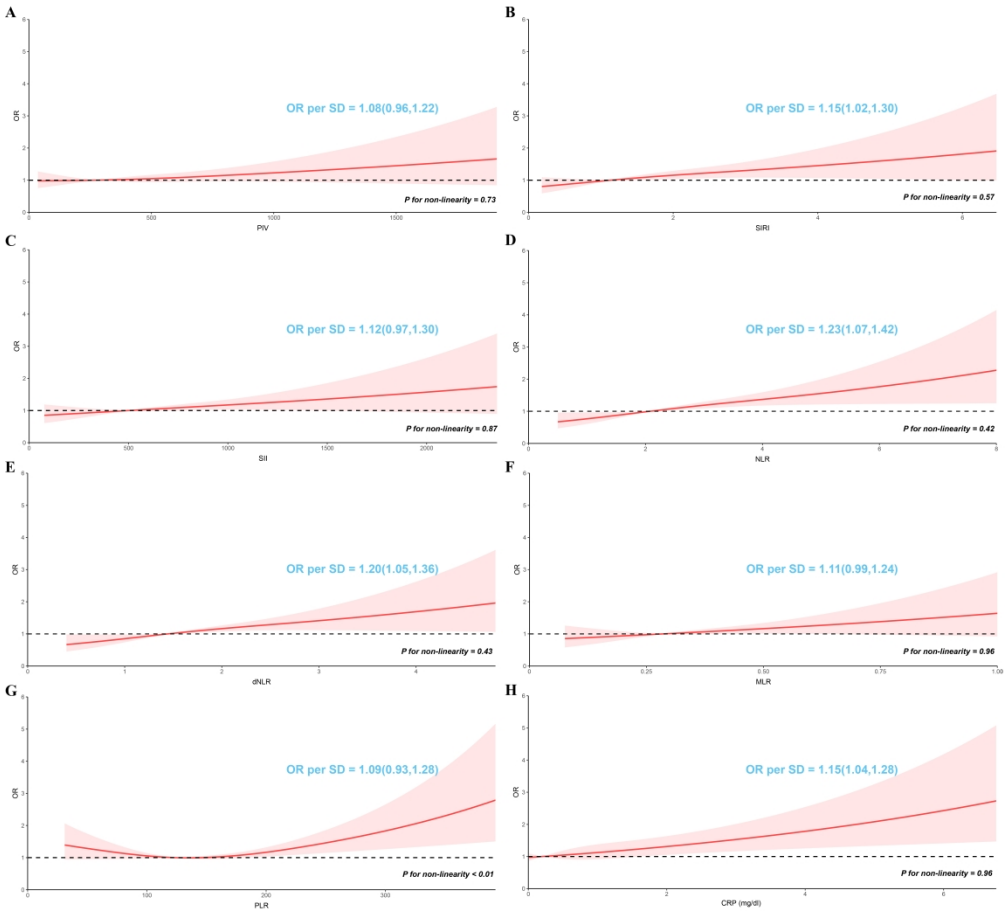

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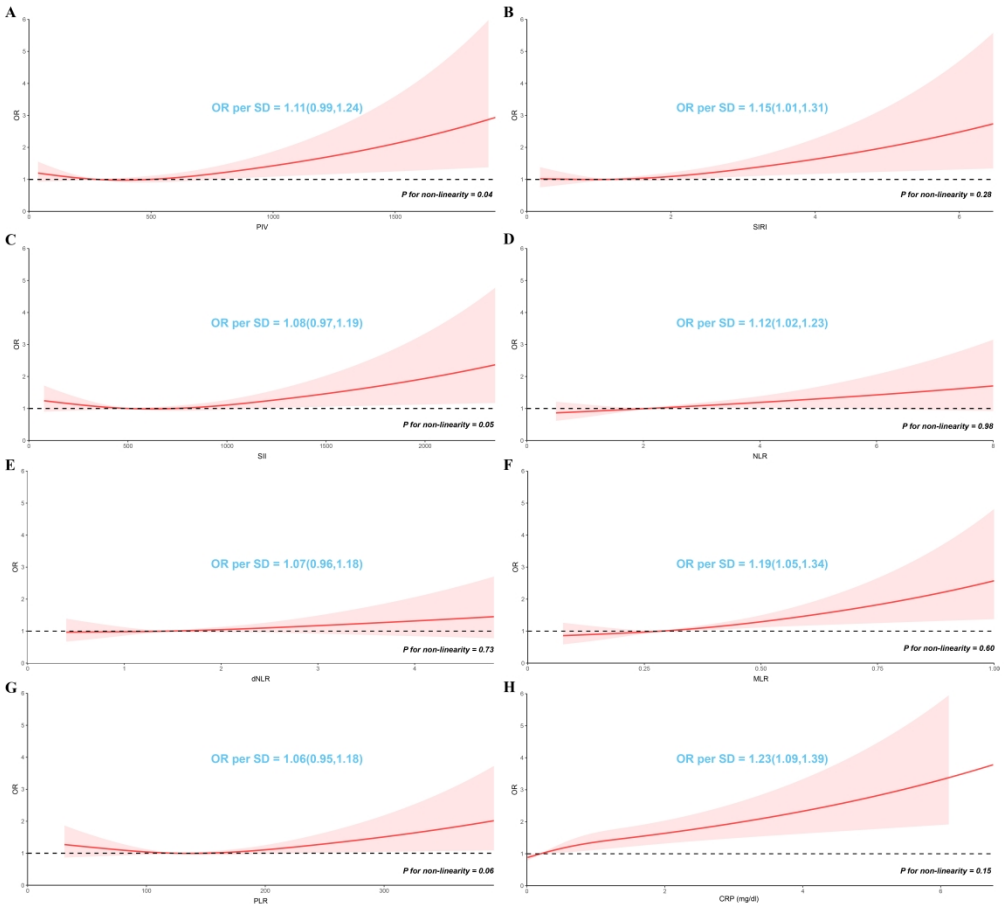

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

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

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5
		(b) Indicate number of participants with missing data for each variable of interest	5
Outcome data	15*	Report numbers of outcome events or summary measures	5-7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5-7
		(*b*) Report category boundaries when continuous variables were categorized	5-7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	5-7
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8-10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	8-10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

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

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

BMJ Open

Association between immune-inflammatory indexes and lower urinary tract symptoms: an analysis of cross-sectional data from the US National Health and Nutrition Examination Survey (2005–2008)

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Primary Subject Heading:	Urology
Secondary Subject Heading:	Urology
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Association between immune-inflammatory indexes and lower urinary tract symptoms: an analysis of cross-sectional data from the US National Health and Nutrition Examination Survey (2005–2008)

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Abstract

Objective This study aimed to systematically investigate the relationship between immune-inflammatory indexes with lower urinary tract symptoms (LUTS).

Design Cross-sectional study.

Setting National Health and Nutrition Examination Survey (NHANES) (2005–2008).

Participants A total of 2,709 men with complete information for immune-inflammatory indexes and LUTS were included from NHANES 2005–2008.

Outcomes and analyses Automated haematology analysing devices are used to measure blood cell

counts, and LUTS were presented by standard questionnaires. Nonlinear and logistic regression analysis were used to estimate their association after adjustment for confounders.

Results Multivariate logistic regression showed that PIV (OR [95% CI] = 1.60 [1.14–2.23]), SIRI (OR [95% CI] = 1.82 [1.21–2.73]), NLR (OR [95% CI] = 1.81 [1.31–2.49]), dNLR (OR [95% CI] = 1.91 [1.35–2.70]), and CRP (OR [95% CI] = 1.71 [1.05–2.79]) was positively associated with LUTS. Additionally, composite immune-inflammation markers exhibited a stronger association with LUTS than any single index, with the ORs for high SIRI+high CRP, high NLR+high CRP, and high dNLR+high CRP being 2.26, 2.44, and 2.16, respectively (All $P < 0.05$). Furthermore, subgroup analyses revealed that age, smoking status, and hypertension have different effects on the relationship between immune-inflammatory markers and LUTS.

Conclusions This study indicated that high levels of immune-inflammatory markers were associated with an increased risk of clinical LUTS. The combination of CRP with SIRI, NLR, and dNLR respectively showed a stronger positive correlation with clinical LUTS compared to any single index.

Keywords: NHANES; Lower urinary tract symptoms; prostatic hyperplasia; immune-inflammatory index; inflammation

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The NHANES dataset, representing the national population, enhances the generalisability of our findings to a broader context.
- This study investigated the correlation between various immune-inflammatory indexes, as well as composite markers, and lower urinary tract symptoms (LUTS).
- It is important to recognise that drawing causal conclusions from cross-sectional analyses presents challenges.

INTRODUCTION

Lower urinary tract symptoms (LUTS) are a common complaint among aging men, with approximately 80% experiencing at least one urine symptom by the age of 80(1). LUTS is now widely recognised as a term that encompasses various urinary symptoms, including storage, voiding, postmicturition, and nocturia, negatively impacting on patients' quality of life(2, 3). In the United States (US), nearly $194

million is spent annually on LUTS drugs, which can impose a heavy strain on the economy and public health(4, 5). Thus, it is essential to identify the factors that contribute to the development and progression of LUTS in aging men.

Several inflammatory markers, including the pan-immune-inflammation value (PIV), systemic inflammation response index (SIRI), systemic immune-inflammation index (SII), neutrophil/lymphocyte ratio (NLR), derived neutrophil/lymphocyte ratio (dNLR), monocyte/lymphocyte ratio (MLR), platelet/lymphocyte ratio (PLR), and C-reactive protein (CRP), have been considered in the development and progression of inflammatory and infectious diseases(6-10). Interestingly, studies have also identified positive associations between inflammatory markers, such as CRP(10-12)and NLR(13, 14), and the risk of LUTS, suggesting that inflammation may play an important role in the development of LUTS. For instance, prostate tissue samples taken from individuals with benign prostatic hyperplasia (BPH), a condition often associated with LUTS resulting from bladder outlet obstruction, commonly exhibit acute and chronic inflammation(2, 15, 16). Additionally, inflammation may contribute to overactive bladder, which is another cause of LUTS(2, 17).

In recent years, a number of new inflammatory markers, such as PIV(18), SIRI(19), and SII(19), have been developed, yet no study has explored their relationship with LUTS. Furthermore, using these markers as single risk factors for LUTS could be limited by their low discriminatory power. Since the interplay between immunity, inflammation, and diseases involve complex networks, composite markers would be a more accurate and meaningful approach to capture the overall inflammatory status and reflect various immuno-inflammatory populations(20-22). Therefore, this study aims to systematically investigate the relationship between blood immune-inflammatory indexes and their combinations with LUTS, using representative NHANES data. This study sought to advance the understanding of the pathogenesis of LUTS and provide insights for potential interventions.

METHODS

Study design and participants

The NHANES is a cross-sectional survey that employs a sophisticated multistage sample methodology to investigate the health and nutritional status of the non-institutionalised population in the US. The demographic information used in this study was obtained from the NHANES, and the protocol was approved by the National Center for Health Statistics Ethics Review Board. Written informed consent

was obtained from all participants, and all NHANES data is publicly available on the relevant website(23).

In this study, we used publicly accessible data from two 2-year cycles of NHANES (2005-2006, 2007-2008) and restricted the analysis cohort to men aged 40 years or older. Initially, there were 3,506 male participants aged 40 years and older in our data. We excluded 417 participants with incomplete LUTS status and 150 participants with a history of prostate cancer. Additionally, 230 participants with incomplete variables data were excluded. Finally, 2,709 participants were included in this study (Supplementary Figure 1).

Questionnaire data assessment

LUTS were assessed by four questions, including: (1) "Do you usually have trouble starting to urinate (pass water)?" (hesitancy, defined as the answer is yes); (2) "After urinating (passing water), does your bladder feel empty?" (incomplete emptying, defined as the answer is no); (3) "How often do you have urinary leakage?" (urinary frequency, defined as the answer is 1 or greater); (4) "During the past 30 days, how many times per night did you most typically get up to urinate, from the time you went to bed at night until the time you got up in the morning?" (nocturia, defined as an answer is 2 or greater). Daytime LUTS was defined as a participant with one or more of the first three symptoms listed above. Clinical LUTS was defined as a participant having two or more of the mentioned symptoms(1).

Definition of immune-inflammation indexes

Automated haematology analysing devices (Coulter DxH 800 analyzer) are used to measure lymphocyte, neutrophil, monocyte, and platelet count, which are presented as $\times 10^{®}3$ cells/μl. The Behring Nephelometer is used to measure serum CRP levels by latex-enhanced nephelometry, with a lower limit of detection (LLOD) of 0.2 mg/L. The immune-inflammatory indexes in our study were calculated as follows: PIV = platelet × neutrophil × monocyte /lymphocyte(18); SIRI = neutrophil × monocyte/lymphocyte(19); SII = platelet × neutrophil/lymphocyte(24); NLR = neutrophil/lymphocyte(24); dNLR = neutrophil/(leukocyte-neutrophil)(25); MLR = monocyte/lymphocyte; PLR = platelet/lymphocyte(24).

Ascertainment of covariates

Our study considered several covariates that could potentially influence the association between immune-inflammatory indexes and clinical LUTS, daytime LUTS, and nocturia. These covariates included age, race, education level, smoking status, alcohol use, body mass index (BMI, kg/m^2), blood

total cholesterol concentration, and history of hypertension and diabetes. Hypertension was defined as a mean systolic blood pressure greater than 140 mmHg, or a mean diastolic blood pressure less than 90 mmHg, or a self-reported history of hypertension. Diabetes was defined as the use of antidiabetic treatment, an HbA1c level of ≥ 6.5%, or a self-reported history of diabetes.

Statistical analysis

To obtain nationally representative findings for the men population aged 40 and over in the US, survey weights were included in the analysis in accordance with NHANES standards. Baseline feature indicators were presented as weighted mean and standard error (SE) for continuous data and weighted ratio for classified data. The difference between baseline characteristics was assessed using the student's t-test on continuous data and the Chi-square test on classified data. We used restricted cubic splines with three nodes at the 5th, 50th, and 95th percentiles to evaluate the nonlinear correlation between immune-inflammatory indexes and clinical LUTS, daytime LUTS and nocturia. Multivariate logistic regression was utilised in three models to explore the association between immune-inflammatory indexes and clinical LUTS, daytime LUTS and nocturia. Covariates were not adjusted in crude model, age, race, education level, smoking status, alcohol use, and BMI were adjusted in model 1, and model 2 was further adjusted for blood total cholesterol, and a history of diabetes and hypertension. Additionally, we conducted multivariate logistic ordinal regression analyses to verify the association of immune-inflammatory indexes with the number of positive symptoms associated with clinical LUTS (0, 1, 2, 3, 4). Furthermore, multiple logistics regression was used to explore whether there is a stronger correlation between SIRI + CRP, NLR + CRP, dNLR + CRP and clinical LUTS. Subgroup analyses were performed for the association between immune-inflammatory indexes and clinical LUTS, stratified by age, smoking, and a history of hypertension, and multiplicative interaction terms were used to test for interactions.

All statistical analyses were performed using R (version 4.2.2, http://www.r-project.org/). Statistical significance was defined as a two-sided *P*-value < 0.05.

Patient and public involvement

None.

RESULTS

Baseline characteristics

As shown in Table 1, we included 2709 men participants aged 40 and above with complete

information, including 399 men who met the diagnostic criteria of clinical LUTS, 675 men who met the diagnostic criteria of daytime LUTS, and 946 men who had nocturia symptoms. Compared to men without clinical LUTS, men with clinical LUTS were older, less educated, smokers, and non-alcohol users, more prone to have lower blood cholesterol concentration, and higher hypertension, diabetes, PIV, SIRI, SII, NLR, dNLR and MLR values (all $P < 0.05$). Similarly, compared to men without daytime LUTS, men with daytime LUTS were older, non-alcohol users, more likely to have hypertension, diabetes, and higher PIV, SIRI, NLR, dNLR and MLR values (all $P < 0.05$). Furthermore, compared to men without nocturia, men with nocturia were found to be older, non-Hispanic Black, less educated, smokers, and non-alcohol users, more prone to have lower blood cholesterol concentration, and higher BMI, hypertension, diabetes, PIV, SIRI, NLR and MLR values (all $P < 0.05$).

Dose-response relationships between immune-inflammatory indexes and LUTS

We used restricted cubic splines to assess the non-linear correlation between immune-inflammatory indexes and LUTS. After adjusting for covariates, we found that PIV, SIRI, SII, NLR, dNLR, MLR, and CRP had a linear relationship with clinical LUTS, daytime LUTS, and nocturia (all P for non-linearity > 0.05). Specifically, the prevalence of clinical LUTS increased by 14%, 22%, 16%, 24%, 21% and 21% per standard deviation of PIV, SIRI, SII, NLR, dNLR and CRP, respectively (all $P < 0.05$) (Figure 1). The prevalence of daytime LUTS increased by 15%, 23%, 20%, and 15% per standard deviation of SIRI, NLR, dNLR and CRP, respectively (all $P < 0.05$) (Supplementary Figure 2). The prevalence of nocturia increased by 15%, 12%, 19%, and 23% per standard deviation of SIRI, NLR, MLR and CRP, respectively (all $P < 0.05$) (Supplementary Figure 3).

Multivariate logistic regression analyses between immune-inflammatory indexes and LUTS

To further clarify the relationship between immune-inflammatory indexes and LUTS, we classified each index into quartiles (Q1, Q2, Q3, Q4) and performed multiple logistic regression analyses with the Q1 group as reference. Our results showed that Q4 groups of PIV, SIRI, NLR, dNLR and CRP were positively correlated with clinical LUTS in all three models (all $P < 0.05$, all P for trend < 0.05). After adjustment for all confounders, PIV (*OR* = 1.60, 95% *CI* = 1.14–2.23), SIRI (*OR* = 1.82, 95% *CI* = 1.21–2.73), NLR (*OR* = 1.81, 95% *CI* = 1.31–2.49), dNLR (*OR* = 1.91, 95% *CI* = 1.35–2.70), and CRP (*OR* = 1.71, 95 %*CI* = 1.05–2.79) in the Q4 group were significant risk factors for clinical LUTS in model 2. In the crude model, we also found that SII (*OR* = 1.45, 95% *CI* = 1.02–2.06) and MLR (*OR* =

1.96, 95% *CI* = 1.17–3.28) in the Q4 group were positively correlated with LUTS (Table 2). Furthermore, to confirm the linear relationship between these immune-inflammatory indexes and LUTS, we conducted a multiple ordinal logistic regression analysis and found a significant positive correlation between SIRI, SII, NLR, dNLR, MLR, and CRP and the number of positive symptoms associated with clinical LUTS (Supplementary table 1).

Regarding the presence of daytime LUTS, we found a significant association between NLR (Q4, OR = 1.82, 95% CI = 1.21–2.74), dNLR (Q4, OR = 1.81, 95% CI = 1.20–2.71), and SIRI (Q4, OR = 1.82, 95% CI = 1.05–3.17) and increased risk of daytime LUTS (Supplementary table 2). By contrast, in the outcome of nocturia, MLR (Q4, OR = 1.49, 95% CI = 1.07–2.08) and CRP (Q4, OR = 1.59, 95% CI = 1.08–2.34) were significantly associated with nocturia (Supplementary table 3). Given the varying associations between immune-inflammatory indexes and different LUTS characteristics, we combined different indexes based on the results in Table 2. We selected cut-off values of 1.14, 2.08, 1.84, and 0.43 for SIRI, NLR, dNLR, and CRP, respectively, and divided them into high and low-level groups. We then combined SIRI, NLR, and dNLR with CRP in pairs to explore the correlation between the combined markers and clinical LUTS. The reference groups were the low CRP + low SIRI, low CRP + low NLR, and low CRP + low dNLR groups. As expected, when combined in pairs, the markers showed a stronger association with clinical LUTS than any single index alone, with the ORs for high SIRI + high CRP, high NLR + high CRP, and high dNLR + high CRP being 2.26 (95% CI = 1.56–3.26), 2.44 (95% CI = 1.60–3.71), and 2.16 (95% CI = 1.21–3.87), respectively, and there was a significant increasing trend for the prevalence of clinical LUTS (all $P < 0.05$) (Table 3).

Subgroup analyses

In our subgroup analyses, we examined the impact of age, smoking, and hypertension on the relationship between immune-inflammatory indexes and LUTS (Figure 2). Using the Q1 group as a reference, we found a more pronounced positive association between PIV, SIRI, SII, NLR, dNLR, MLR, CRP and clinical LUTS in older men aged 60 years and older in the Q4 group compared to those under 60 years (all P <0.05, all P for interaction <0.05). Similarly, smokers exhibited a stronger positive correlation between PIV, SIRI, NLR, CRP and clinical LUTS in the Q4 group than non-smokers (all P <0.05, all P for interaction <0.05). Additionally, hypertensive men in the Q4 group showed a significantly positive association between SIRI, NLR, dNLR and clinical LUTS than those without a history of hypertension (all P <0.05, all P for interaction <0.05). These findings suggested

that age, smoking, and hypertension might modify the impact of immune-inflammatory status on clinical LUTS and should be taken into consideration in clinical practice.

DISCUSSION

This study represents the first attempt to systematically investigate the association between different immune-inflammatory markers and LUTS risk, and to explore the potential effects of combining them. These findings revealed strong positive linear correlations between PIV, SIRI, NLR, dNLR, and CRP with clinical LUTS. Interestingly, when CRP was combined with SIRI, NLR, and dNLR respectively, the positive correlations with clinical LUTS became even stronger compared to any of the individual indexes alone. Additionally, subgroup analysis found that the effects of age, smoking, and history of hypertension varied in their influence on the relationship between immune-inflammatory indexes and clinical LUTS.

Previous studies have investigated the mechanisms underlying the association between inflammation and LUTS. As a common disease in aging men that can contribute to LUTS, the development and progression of BPH are closely related to prostatic inflammation(2, 3). In fact, Theyer et al. reported that human BPH tissue had a substantial influx of activated T cells, which secret various growth factors that facilitate prostate stromal and glandular hyperplasia(26). Additionally, stromal cells in BPH patients can stimulate the production of proinflammatory cytokines and chemotherapeutic kinases in a state of inflammation(27), such as IL-2, IL-4, IL-7, IL-17, and IFNy(28-30). Moreover, chronic inflammation in BPH is linked to the focal overexpression of cyclooxygenase 2 in the glandular epithelium, which results in the production of proinflammatory prostaglandins and prostate cell proliferation(27, 31). Furthermore, the pathogenesis of LUTS may involve different types of bladder dysfunction, such as detrusor overactivity or underactivity(2). There is a possible connection between inflammation and overactive bladder, which could be due to inflammation-induced remodelling of extracellular matrix and an increase in tissue stiffness(3). All the above studies have shown that there is a certain relationship between immune inflammation and LUTS.

The risk of LUTS has been found to be associated with immune-inflammation indexes, which are readily available and inexpensive biomarkers. Although Rohrmann et al. did not find a positive correlation between CRP and LUTS using NHANESIII data(32), several studies revealed that an elevated level of CRP was related to an increased risk of LUTS(10-12, 33), consistent with our findings. The discrepancy in results may be due to differences in CRP classification criteria.

Additionally, previous small-scale studies have identified a link between elevated NLR levels and the progression of LUTS/BPH without performing multivariable analysis(13, 14). By contrast, our study provides strong evidence for a significant relationship between NLR and the prevalence of LUTS, regardless of whether NLR was treated as a continuous or categorical variable in multivariable regression analysis. Specially, we found that elevated levels of CPR were primarily associated with nocturia, while NLR, dNLR, and SIRI were associated with daytime LUTS. Given that previous studies have combined inflammatory markers to better reflect their relationship with disease(20-22), we attempted to combine CRP with NLR, dNLR, and SIRI. Our findings highlight a stronger linear correlation between the combination of these indexes and the risk of LUTS, indicating that composite immune-inflammation markers may be more effective in reflecting the risk of LUTS.

In our study, we discovered for the first time that several immune-inflammation biomarkers, namely PIV, SIRI, and dNLR, were positively correlated with the presence of clinical LUTS. Among these biomarkers, PIV stands out for its comprehensive nature, as it comprises peripheral blood counts of neutrophils, monocytes, lymphocytes, and platelets(18), making it a promising prognostic biomarker for various cancers(34). Similarly, SIRI and SII have been established as a prognostic indicator for different types of tumors(35-37) and inflammation-related diseases(38-40), as they reflect the balance between the immune response and inflammation. After adjusting for covariates, we found that SIRI was positively associated with LUTS while SII was not, which might be due to the weak relationship between platelets and LUTS. Among these pro-inflammatory cells, NLR has been the most extensively validated. However, dNLR, which replaces the denominator of NLR with (WBC-neutrophils), has emerged as an alternative in cases where lymphocyte information is unavailable(41). Proctor et al. found that both NLR and dNLR have equal reliability for the prognostic value in patients with cancer(41). Our study revealed a significant correlation between NLR and the prevalence of LUTS, as well as a comparable association between dNLR and LUTS. Since both indexes include neutrophils, it emphasises the strong and intimate link between neutrophils and LUTS, relative to other pro-inflammatory cells.

Subgroup analyses revealed that the positive association between inflammation and clinical LUTS was stronger among the elderly, smokers, and hypertensive patients, highlighting the potential role of excessive production and release of inflammatory factors in these populations, leading to increased levels of inflammation(42-44). Additionally, factors such as physical aging, smoking, and hypertension

may contribute to a higher prevalence of LUTS through mechanisms such as prostate and bladder aging, impaired renal function, and damage to blood vessels and nerves(45-47). Thus, it is important to closely monitor the inflammation levels in these populations suffering from LUTS, and providing anti-inflammatory interventions for those with high inflammation levels might be a promising treatment option.

This study has several advantages. Firstly, this is the first study to systematically explore the relationship between immune-inflammation indexes and LUTS, emphasising the importance of monitoring inflammation levels in individuals with LUTS. Secondly, the NHANES dataset comprises a representative sample of the national population, and we utilise NHANES-provided weights to ensure that our findings can be extrapolated to the broader population. Furthermore, multiple potential confounders were adjusted to ensure reliable results. However, this study also has several limitations. First, it is important to recognise that drawing causal conclusions from cross-sectional analyses presents challenges. Second, peripheral blood was tested only once rather than repeatedly, which may not accurately reflect a person's long-term peripheral blood status. Third, the questionnaire survey may have been subject to recall bias and reporting bias. Finally, the evaluation of LUTS relies on four questionnaire items from NHANES, which may not provide a thorough assessment of storage and voiding conditions, as well as the need for treatment.

CONCLUSIONS

In conclusion, this study emphasised that high levels of immune-inflammatory indexes such as PIV, SIRI, NLR, dNLR, and CRP were independent risk factors for clinical LUTS. The combination of CRP with SIRI, NLR, and dNLR respectively showed a stronger positive correlation with clinical LUTS compared to any of the individual indexes alone. Furthermore, the impact of age, smoking, and history of hypertension on the relationship between immune-inflammatory indexes and LUTS was significant. Further research, including multicentre studies, is needed to confirm the relationship between immune-inflammatory indexes and LUTS and to provide additional evidence for the management and treatment of clinical LUTS.

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Contributors

W-L: conceptualisation, methodology, data analysis, manuscript writing; J-W: methodology, data collection, data analysis, manuscript writing; MM-W: methodology, data collection, data analysis; M-W: data analysis, manuscript writing; X-D: methodology, supervision; M-L: conceptualisation, supervision, manuscript editing, funding acquisition.

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Competing interests

None declared.

Patient consent for publication

Not applicable.

Ethical statement

Ethical review and approval for the research involving human participants were obtained from the Ethics Review Board of the NCHS (Protocol #98-12). Written informed consent was obtained from all patients or participants who were part of the study. The current analysis, which is based on publicly available data, did not necessitate any further ethics approval.

Data availability statement

Publicly available datasets were analysed in this study. This data can be downloaded from https://www.cdc.gov/nchs/nhanes/ (NHANES 2005-2006 and 2007-2008).

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Figure legends

Figure 1. Dose-response relationships between blood immune-inflammatory indexes and clinical LUTS (A) PIV and clinical LUTS; (B) SIRI and LUTS; (C) SII and LUTS; (D) NLR and LUTS; (E) dNLR and LUTS; (F) MLR and LUTS; (G) PLR and LUTS; (H) CRP and LUTS. They are adjusted for age, race/ethnicity, education level, smoking status, alcohol use, and BMI, total cholesterol, and a history of diabetes and hypertension. The shaded part represents the 95% CI. Abbreviations: OR, odds ratio; LUTS, lower urinary tract symptoms; PIV, pan-immune-inflammation value; SIRI, system inflammation response index; SII, systemic immune-inflammation index; NLR, neutrophil to lymphocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio; MLR, monocyte to lymphocyte ratio; PLR, platelet to lymphocyte ratio; CRP, C-reactive protein.

Figure 2. Associations between blood immune-inflammatory indexes and clinical LUTS in subgroup analyses. They are adjusted for age, race/ethnicity, education level, smoking status, alcohol use, and BMI, total cholesterol, and a history of diabetes and hypertension, if not already stratified. Abbreviations: OR, odds ratio; LUTS, lower urinary tract symptoms; PIV, pan-immune-inflammation value; SIRI, system inflammation response index; SII, systemic immune-inflammation index; NLR, neutrophil to lymphocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio; MLR, monocyte to lymphocyte ratio; PLR, platelet to lymphocyte ratio; CRP, C-reactive protein.

Supplementary Figure 1. Study flowchart. Of 20,497 participants in the 2005–2008 National Health and Nutrition Examination Survey (NHANES), 2,709 remained after fulfilling inclusion and exclusion criteria

Supplementary Figure 2. Dose-response relationships between blood immune-inflammatory indexes and daytime LUTS (A) PIV and LUTS; (B) SIRI and LUTS; (C) SII and LUTS; (D) NLR and LUTS; (E) dNLR and LUTS; (F) MLR and LUTS; (G) PLR and LUTS; (H) CRP and LUTS. They are adjusted for age, race/ethnicity, education level, smoking status, alcohol use, and BMI, total cholesterol, and a history of diabetes and hypertension. The shaded part represents the 95% CI. Abbreviations: OR, odds ratio; LUTS, lower urinary tract symptoms; PIV, pan-immune-inflammation value; SIRI, system inflammation response index; SII, systemic immune-inflammation index; NLR, neutrophil to lymphocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio; MLR, monocyte to lymphocyte ratio; PLR, platelet to lymphocyte ratio; CRP, C-reactive protein.

Supplementary Figure 3. Dose-response relationships between blood immune-inflammatory indexes and nocturia (A) PIV and LUTS; (B) SIRI and LUTS; (C) SII and LUTS; (D) NLR and LUTS; (E) dNLR and LUTS; (F) MLR and LUTS; (G) PLR and LUTS; (H) CRP and LUTS. They are adjusted for age, race/ethnicity, education level, smoking status, alcohol use, and BMI, total cholesterol, and a history of diabetes and hypertension. The shaded part represents the 95% CI. Abbreviations: OR, odds ratio; LUTS, lower urinary tract symptoms; PIV, pan-immune-inflammation value; SIRI, system inflammation response index; SII, systemic immune-inflammation index; NLR, neutrophil to lymphocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio; MLR, monocyte to lymphocyte ratio;

PLR, platelet to lymphocyte ratio; CRP, C-reactive protein.

Table 1. Demographic and clinic characteristics according to clinical LUTS, daytime LUTS, and nocturia. NHANES 2005-2008*

Characteristics	Total Adults (N = 2709)	Clinical LUTS		*P* value	Daytime LUTS		*P* value	Nocturia		*P* value
		No (N = 2310)	Yes (N = 399)		No (N = 2034)	Yes (N = 675)		No (N = 1763)	Yes (N = 946)	
Age, years, n (%)				< 0.01			< 0.01			< 0.01
< 60	1362(64.90)	1240(67.84)	122(43.46)		1110(68.60)	252(52.09)		1045(72.17)	317(44.88)	
≥ 60	1347(35.10)	1070(32.16)	277(56.54)		924(31.40)	423(47.91)		718(27.83)	629(55.12)	
Race/ethnicity, n (%)				0.94			0.67			< 0.01
Non-Hispanic White	1502(78.06)	1261(77.96)	241(78.77)		1108(77.87)	394(78.71)		1003(80.02)	499(72.63)	
Non-Hispanic Black	508(8.82)	435(8.90)	73(8.22)		388(9.15)	120(7.66)		298(7.34)	210(12.88)	
Mexican	433(6.14)	379(6.19)	54(5.81)		334(6.24)	99(5.81)		272(5.46)	161(8.03)	
Other	266(6.99)	235(6.96)	31(7.20)		204(6.75)	62(7.83)		190(7.18)	76(6.46)	
Education, n (%)				< 0.01			0.08			< 0.01
Grades 0–12	821(17.80)	675(16.73)	146(25.63)		599(16.85)	222(21.10)		460(14.50)	361(26.89)	
High school graduate/GED	651(25.61)	555(25.53)	96(26.19)		487(25.22)	164(26.98)		433(25.75)	218(25.23)	
Some college or above	1237(56.59)	1080(57.74)	157(48.18)		948(57.94)	289(51.91)		870(59.75)	367(47.88)	
Smoking†, n (%)				< 0.01			0.06			< 0.01
Yes	1681(59.25)	1390(57.37)	291(72.99)		1227(58.41)	454(62.18)		1036(55.58)	645(69.37)	
No	1028(40.75)	920(42.63)	108(27.01)		807(41.59)	221(37.82)		727(44.42)	301(30.63)	
Alcohol use‡, n (%)				< 0.01			< 0.01			< 0.01
Yes	1776(72.69)	1550(74.51)	226(59.41)		1376(75.21)	400(63.98)		1213(75.41)	563(65.20)	
No	933(27.31)	760(25.49)	173(40.59)		658(24.79)	275(36.02)		550(24.59)	383(34.80)	
BMI§, kg/m², n (%)				0.94			0.83			0.02
< 25	627(21.53)	527(21.42)	100(22.29)		463(21.25)	164(22.47)		397(21.78)	230(20.82)	
25–29.9	1139(43.17)	982(43.14)	157(43.42)		863(43.03)	276(43.65)		783(45.19)	356(37.61)	
≥ 30	943(35.30)	801(35.44)	142(34.29)		708(35.71)	235(33.88)		583(33.03)	360(41.57)	
Total cholesterol, mmol/L, n (%)				0.02			0.38			< 0.01
< 5.02	1370(47.14)	1137(46.02)	233(55.31)		1006(46.51)	364(49.31)		833(44.22)	537(55.18)	
≥ 5.02	1339(52.86)	1173(53.98)	166(44.69)		1028(53.49)	311(50.69)		930(55.78)	409(44.82)	
Hypertension, n (%)				< 0.01			< 0.01			< 0.01
Yes	1441(49.14)	1188(47.25)	253(62.93)		1029(46.53)	412(58.20)		833(44.00)	608(63.32)	
No	1268(50.86)	1122(52.75)	146(37.07)		1005(53.47)	263(41.80)		930(56.00)	338(36.68)	
Diabetes, n (%)				< 0.01			0.01			< 0.01

Yes	558(15.16)	453(13.93)	105(24.17)		395(13.54)	163(20.78)		292(11.97)	266(23.97)	
No	2151(84.84)	1857(86.07)	294(75.83)		1639(86.46)	512(79.22)		1471(88.03)	680(76.03)	
WBC, 1000 cells/ul, mean (SE)	7.28(0.07)	7.22(0.07)	7.74(0.18)	0.01	7.25(0.08)	7.41(0.11)	0.22	7.25(0.08)	7.38(0.12)	0.41
Neu, 1000 cells/ul, mean (SE)	4.36(0.05)	4.31(0.06)	4.72(0.09)	< 0.01	4.31(0.06)	4.51(0.08)	0.05	4.33(0.07)	4.42(0.08)	0.38
Lym, 1000 cells/ul, mean (SE)	2.07(0.03)	2.07(0.02)	2.13(0.12)	0.63	2.09(0.03)	2.03(0.07)	0.41	2.08(0.02)	2.06(0.06)	0.83
Mono, 1000 cells/ul, mean (SE)	0.59(0.01)	0.59(0.01)	0.62(0.02)	0.06	0.59(0.01)	0.59(0.01)	0.51	0.58(0.01)	0.61(0.01)	0.02
PLT, 1000 cells/ul, mean (SE)	252.30(1.74)	253.68(1.92)	242.25(3.78)	0.01	254.55(1.70)	244.53(3.97)	0.02	255.35(2.23)	243.91(2.51)	< 0.01
CRP, mg/dl, mean (SE)	0.38(0.02)	0.35(0.02)	0.63(0.14)	0.06	0.35(0.02)	0.51(0.08)	0.06	0.32(0.01)	0.55(0.08)	0.01
PIV, mean (SE)	352.79(8.51)	345.11(8.45)	408.87(18.25)	< 0.01	345.06(9.09)	379.59(14.17)	0.02	342.07(8.07)	382.35(14.59)	< 0.01
SIRI, mean (SE)	1.38(0.03)	1.34(0.03)	1.66(0.06)	< 0.01	1.33(0.03)	1.53(0.04)	< 0.01	1.32(0.03)	1.53(0.05)	< 0.01
SII, mean (SE)	586.41(10.55)	577.92(11.21)	648.46(25.42)	0.01	575.69(12.23)	623.61(20.14)	0.05	578.16(11.65)	609.18(16.11)	0.08
NLR, mean (SE)	2.32(0.04)	2.27(0.04)	2.67(0.08)	< 0.01	2.25(0.04)	2.56(0.07)	< 0.01	2.26(0.04)	2.47(0.05)	< 0.01
dNLR, mean (SE)	1.58(0.02)	1.55(0.02)	1.73(0.04)	< 0.01	1.54(0.02)	1.69(0.03)	< 0.01	1.56(0.02)	1.62(0.03)	0.08
MLR, mean (SE)	0.31(0.00)	0.31(0.00)	0.34(0.01)	< 0.01	0.30(0.00)	0.33(0.01)	< 0.01	0.30(0.00)	0.34(0.01)	< 0.01
PLR, mean (SE)	134.99(1.58)	134.75(1.66)	136.73(4.45)	0.67	133.75(1.47)	139.26(4.43)	0.24	134.33(1.89)	136.79(2.68)	0.45

Abbreviations: LUTS, lower urinary tract symptoms NHANES, National Health and Nutrition Examination Survey; SE, standard error; GED, General Equivalency Diploma; BMI, body mass index; WBC, leukocyte; Neu, neutrophil; Lym, lymphocyte; Mono, monocyte; PLT, platelet; CRP, C-reactive protein; PIV, pan-immune-inflammation value; SIRI, system inflammation response index; SII, systemic immune-inflammation index; NLR, neutrophil to lymphocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio; MLR, monocyte to lymphocyte ratio; PLR, platelet to lymphocyte ratio.
*Means and percentages were adjusted for survey weights of NHANES.
†Smoking was defined as smoking at least 100 cigarettes during their lifetime.
‡Alcohol use was defined as having at least 12 alcohol drinks in any given year.
§BMI was calculated by dividing weight in kilograms (kg) by height in meters squared (m^2). Participants were classified as normal weight (< 25 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥ 30 kg/m^2).

Table 2. *OR* (95% *CI*) for LUTS across quartiles of blood immune-inflammatory indexes*

	Crude Model	*P* value	Model 1	*P* value	Model 2	*P* value
PIV						
Q1 (< 181.50)	1[Reference]		1[Reference]		1[Reference]	
Q2 (181.50–276.64)	1.15(0.73,1.80)	0.53	1.11(0.69,1.79)	0.65	1.14(0.71,1.85)	0.56
Q3 (276.65–421.83)	0.86(0.59,1.24)	0.39	0.79(0.54,1.17)	0.22	0.82(0.57,1.18)	0.26
Q4 (≥ 421.84)	1.85(1.34,2.56)	< 0.01	1.59(1.14,2.24)	0.01	1.60(1.14,2.23)	0.01
P for trend		< 0.01		0.01		0.02
SIRI						
Q1 (< 0.80)	1[Reference]		1[Reference]		1[Reference]	
Q2 (0.80–1.14)	1.01(0.58,1.73)	0.98	0.98(0.56,1.70)	0.93	0.97(0.55,1.72)	0.92
Q3 (1.15–1.65)	1.39(1.06,1.84)	0.02	1.26(0.94,1.69)	0.12	1.23(0.91,1.66)	0.17
Q4 (≥ 1.66)	2.35(1.61,3.44)	< 0.01	1.91(1.30,2.82)	< 0.01	1.82(1.21,2.73)	0.01
P for trend		< 0.01		< 0.01		< 0.01
SII						
Q1 (< 356.13)	1[Reference]		1[Reference]		1[Reference]	

Q2 (356.13–500.41)	0.97(0.68,1.39)	0.86	0.97(0.65,1.43)	0.86	1.02(0.71,1.48)	0.89
Q3 (500.42–702.31)	0.98(0.67,1.43)	0.91	1.00(0.66,1.51)	0.99	1.04(0.71,1.54)	0.82
Q4 (≥ 702.32)	1.45(1.02,2.06)	0.04	1.37(0.94,2.00)	0.09	1.40(0.97,2.04)	0.07
P for trend		< 0.01		0.03		0.03
NLR						
Q1 (< 1.56)	1[Reference]		1[Reference]		1[Reference]	
Q2 (1.56–2.08)	1.08(0.74,1.60)	0.67	1.15(0.76,1.75)	0.50	1.16(0.75,1.80)	0.48
Q3 (2.09–2.72)	1.75(1.16,2.63)	0.01	1.73(1.12,2.66)	0.02	1.71(1.10,2.66)	0.02
Q4 (≥ 2.73)	2.21(1.60,3.04)	< 0.01	1.89(1.39,2.56)	< 0.01	1.81(1.31,2.49)	< 0.01
P for trend		< 0.01		< 0.01		< 0.01
dNLR						
Q1 (< 1.13)	1[Reference]		1[Reference]		1[Reference]	
Q2 (1.13–1.44)	1.09(0.80,1.49)	0.55	1.09(0.80,1.50)	0.56	1.10(0.80,1.51)	0.55
Q3 (1.45–1.84)	1.32(0.92,1.89)	0.12	1.32(0.92,1.89)	0.12	1.33(0.92,1.90)	0.12
Q4 (≥ 1.85)	2.17(1.55,3.04)	< 0.01	1.98(1.42,2.77)	< 0.01	1.91(1.35,2.70)	< 0.01
P for trend		< 0.01		< 0.01		< 0.01
MLR						
Q1 (< 0.22)	1[Reference]		1[Reference]		1[Reference]	
Q2 (0.22–0.29)	1.27(0.72,2.24)	0.39	1.24(0.69,2.25)	0.45	1.25(0.69,2.27)	0.43
Q3 (0.30–0.37)	1.49(0.87,2.56)	0.14	1.38(0.79,2.41)	0.24	1.38(0.77,2.46)	0.26
Q4 (≥ 0.38)	1.96(1.17,3.28)	0.01	1.51(0.89,2.57)	0.12	1.44(0.82,2.53)	0.18
P for trend		< 0.01		0.09		0.16
PLR						
Q1 (< 97.90)	1[Reference]		1[Reference]		1[Reference]	
Q2 (97.90–124.74)	0.94(0.59,1.49)	0.79	0.97(0.61,1.55)	0.90	1.00(0.62,1.62)	0.98
Q3 (124.75–159.41)	0.70(0.49,0.99)	0.04	0.81(0.56,1.18)	0.26	0.86(0.58,1.27)	0.41
Q4 (≥ 159.42)	1.09(0.72,1.63)	0.68	1.09(0.73,1.64)	0.65	1.14(0.74,1.74)	0.53
P for trend		0.77		0.70		0.57
CRP, mg/dl						
Q1 (< 0.09)	1[Reference]		1[Reference]		1[Reference]	
Q2 (0.09–0.20)	0.88(0.56,1.38)	0.57	0.84(0.53,1.34)	0.45	0.83(0.51,1.34)	0.41
Q3 (0.21–0.43)	1.12(0.66,1.92)	0.66	1.05(0.59,1.88)	0.86	1.05(0.58,1.88)	0.87
Q4 (≥ 0.43)	2.03(1.28,3.22)	< 0.01	1.78(1.09,2.90)	0.02	1.71(1.05,2.79)	0.03
P for trend		< 0.01		< 0.01		< 0.01

Abbreviations: *OR*, odds ratio; *CI*, confidence interval; PIV, pan-immune-inflammation value; SIRI, system inflammation response index; SII, systemic immune-inflammation index; NLR, neutrophil to lymphocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio; MLR, monocyte to lymphocyte ratio; PLR, platelet to lymphocyte ratio; CRP, C-reactive protein.
*Values are numerical values or weighted *OR* (95% *CI*).
Model 1 was adjusted for age, race/ethnicity, education level, smoking status, alcohol use, and BMI.
Model 2 was additionally adjusted for total cholesterol, and a history of diabetes and hypertension.

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Table 3. *OR* (95% *CI*) for clinical LUTS across combined blood immune-inflammatory indexes*

	Crude Model	*P* value	Model 1	*P* value	Model 2	*P* value
SIRI+CRP (Low SIRI < 1.14, High SIRI ≥ 1.14; Low CRP < 0.43, High CRP ≥ 0.43)						
Low SIRI and Low CRP	1[Reference]		1[Reference]		1[Reference]	
High SIRI and Low CRP	1.83(1.34,2.50)	< 0.01	1.60(1.13,2.25)	0.01	1.56(1.10,2.21)	0.02
Low SIRI and High CRP	2.28(1.28,4.07)	0.01	2.15(1.12,4.14)	0.02	2.10(1.09,4.03)	0.03
High SIRI and High CRP	2.90(2.04,4.12)	< 0.01	2.39(1.65,3.48)	< 0.01	2.26(1.56,3.26)	< 0.01

NLR+CRP (Low NLR < 2.08, High NLR ≥ 2.08)						
Low NLR and Low CRP	1[Reference]		1[Reference]		1[Reference]	
High NLR and Low CRP	2.06(1.54,2.77)	< 0.01	1.82(1.37,2.41)	< 0.01	1.78(1.33,2.38)	< 0.01
Low NLR and High CRP	2.69(1.57,4.62)	< 0.01	2.40(1.33,4.32)	0.01	2.31(1.29,4.14)	0.01
High NLR and High CRP	3.07(2.11,4.46)	< 0.01	2.59(1.73,3.86)	< 0.01	2.44(1.60,3.71)	< 0.01
dNLR+CRP (Low dNLR < 1.84, High dNLR ≥ 1.84)						
Low dNLR and Low CRP	1[Reference]		1[Reference]		1[Reference]	
High dNLR and Low CRP	2.03(1.39,2.97)	< 0.01	1.88(1.24,2.84)	< 0.01	1.87(1.22,2.87)	0.01
Low dNLR and High CRP	2.16(1.37,3.41)	< 0.01	2.01(1.23,3.26)	0.01	1.99(1.23,3.23)	0.01
High dNLR and High CRP	2.84(1.66,4.87)	< 0.01	2.38(1.35,4.21)	< 0.01	2.16(1.21,3.87)	0.01

Abbreviations: *OR*, odds ratio; *CI*, confidence interval; SIRI, system inflammation response index; NLR, neutrophil to lymphocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio; CRP, C-reactive protein.
*Values are numerical values or weighted *OR* (95% *CI*).
Model 1 was adjusted for age, race/ethnicity, education level, smoking status, alcohol use, and BMI.
Model 2 was additionally adjusted for total cholesterol, and a history of diabetes and hypertension.

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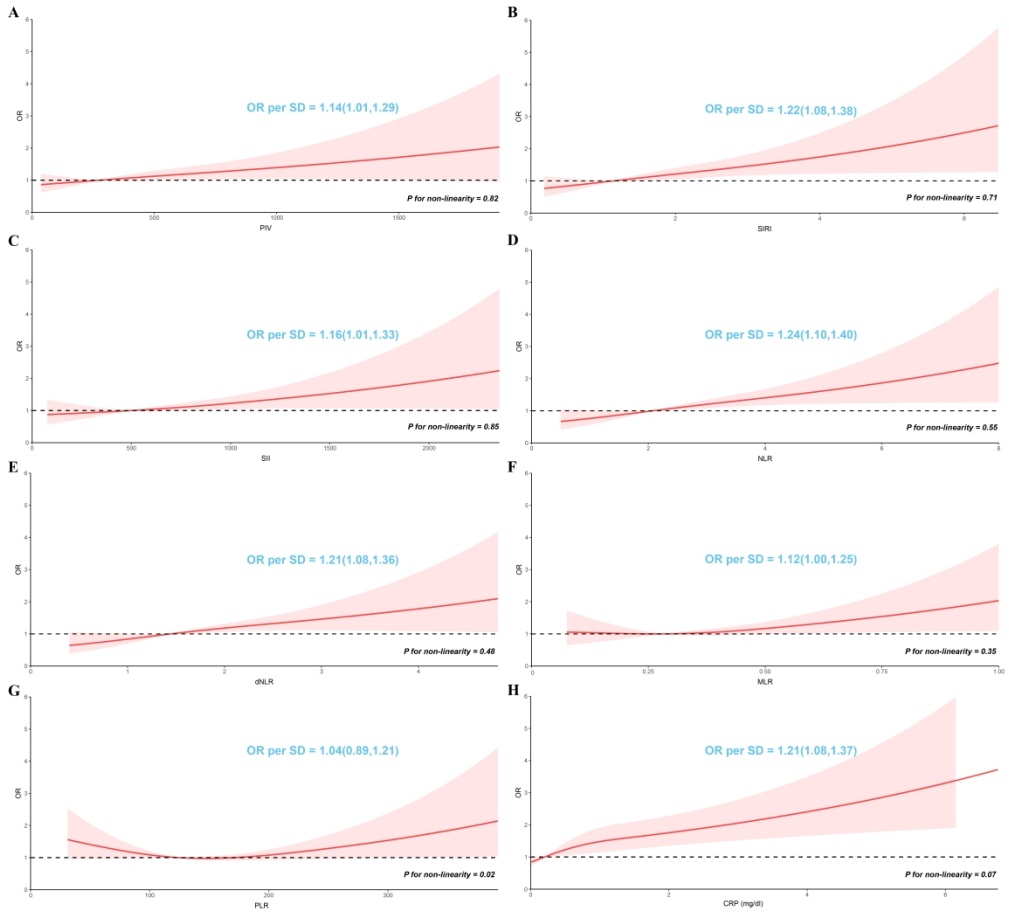

Fig. 1 Dose-response relationships between blood immune-inflammatory indexes and clinical LUTS (A) PIV and clinical LUTS; (B) SIRI and LUTS; (C) SII and LUTS; (D) NLR and LUTS; (E) dNLR and LUTS; (F) MLR and LUTS; (G) PLR and LUTS; (H) CRP and LUTS. They are adjusted for age, race/ethnicity, education level, smoking status, alcohol use, and BMI, total cholesterol, and a history of diabetes and hypertension. The shaded part represents the 95% CI. Abbreviations: OR, odds ratio; LUTS, lower urinary tract symptoms; PIV, pan-immune-inflammation value; SIRI, system inflammation response index; SII, systemic immune-inflammation index; NLR, neutrophil to lymphocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio; MLR, monocyte to lymphocyte ratio; PLR, platelet to lymphocyte ratio; CRP, C-reactive protein.

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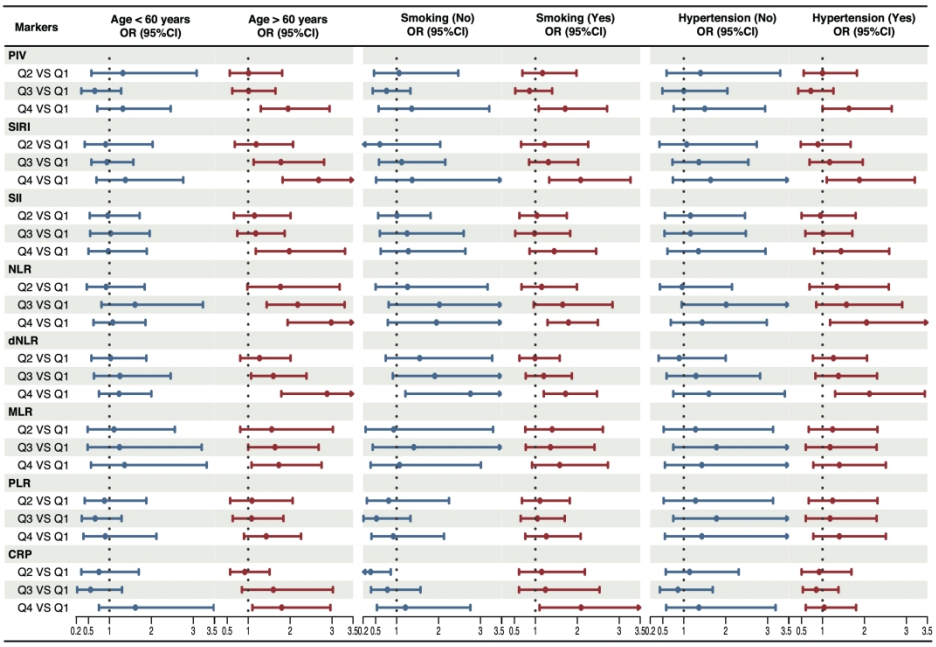

Fig. 2 Associations between blood immune-inflammatory indexes and clinical LUTS in subgroup analyses. They are adjusted for age, race/ethnicity, education level, smoking status, alcohol use, and BMI, total cholesterol, and a history of diabetes and hypertension, if not already stratified. Abbreviations: OR, odds ratio; LUTS, lower urinary tract symptoms; PIV, pan-immune-inflammation value; SIRI, system inflammation response index; SII, systemic immune-inflammation index; NLR, neutrophil to lymphocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio; MLR, monocyte to lymphocyte ratio; PLR, platelet to lymphocyte ratio; CRP, C-reactive protein.

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Supplementary table 1. Multivariate logistic ordinal regression analysis of the blood immune-inflammatory indexes among the number of positive symptoms associated with clinical LUTS*

	Crude Model	*P* value	Model 1	*P* value	Model 2	*P* value
PIV	1.15(1.06,1.24)	< 0.01	1.10(1.02,1.19)	0.02	1.08(1.00,1.18)	0.06
SIRI	1.27(1.17,1.37)	< 0.01	1.18(1.09,1.28)	< 0.01	1.16(1.06,1.26)	< 0.01
SII	1.13(1.03,1.24)	0.01	1.12(1.02,1.22)	0.02	1.10(1.01,1.21)	0.03
NLR	1.28(1.15,1.42)	< 0.01	1.22(1.11,1.34)	< 0.01	1.20(1.10,1.32)	< 0.01
dNLR	1.18(1.06,1.31)	< 0.01	1.16(1.06,1.28)	< 0.01	1.15(1.05,1.25)	< 0.01
MLR	1.27(1.17,1.37)	< 0.01	1.17(1.06,1.28)	< 0.01	1.16(1.05,1.27)	< 0.01
PLR	1.09(1.06,1.24)	< 0.01	1.09(0.98,1.20)	0.10	1.10(1.00,1.22)	0.06
CRP, mg/dl	1.20(1.13,1.27)	< 0.01	1.20(1.13,1.26)	< 0.01	1.19(1.12,1.27)	< 0.01

Abbreviations: *OR*, odds ratio; *CI*, confidence interval; PIV, pan-immune-inflammation value; SIRI, system inflammation response index; SII, systemic immune-inflammation index; NLR, neutrophil to lymphocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio; MLR, monocyte to lymphocyte ratio; PLR, platelet to lymphocyte ratio; CRP, C-reactive protein.
*Values are numerical values or weighted *OR* (95% *CI*).
Model 1 was adjusted for age, race/ethnicity, education level, smoking status, alcohol use, and BMI;
Model 2 was additionally adjusted for total cholesterol, and a history of diabetes and hypertension.

Supplementary table 2. *OR* (95% *CI*) for daytime LUTS across quartiles of blood immune-inflammatory indexes*

	Crude Model	*P* value	Model 1	*P* value	Model 2	*P* value
PIV						
Q1 (< 181.50)	1[Reference]		1[Reference]		1[Reference]	
Q2 (181.50–276.64)	1.20(0.83,1.71)	0.32	1.16(0.79,1.69)	0.44	1.17(0.80,1.71)	0.39
Q3 (276.65–421.83)	0.95(0.65,1.40)	0.81	0.91(0.62,1.34)	0.62	0.93(0.63,1.35)	0.67
Q4 (≥ 421.84)	1.46(0.96,2.21)	0.07	1.33(0.87,2.03)	0.17	1.32(0.85,2.03)	0.20
P for trend		0.07		0.16		0.22
SIRI						
Q1 (< 0.80)	1[Reference]		1[Reference]		1[Reference]	
Q2 (0.80–1.14)	1.08(0.62,1.88)	0.77	1.05(0.60,1.86)	0.85	1.04(0.58,1.86)	0.88
Q3 (1.15–1.65)	1.14(0.76,1.71)	0.51	1.05(0.68,1.62)	0.81	1.01(0.66,1.57)	0.94
Q4 (≥ 1.66)	1.82(1.05,3.17)	0.03	1.59(0.89,2.85)	0.11	1.52(0.83,2.80)	0.16
P for trend		< 0.01		0.04		0.07
SII						
Q1 (< 356.13)	1[Reference]		1[Reference]		1[Reference]	
Q2 (356.13–500.41)	1.00(0.72,1.39)	0.99	0.99(0.69,1.42)	0.96	1.03(0.73,1.45)	0.86
Q3 (500.42–702.31)	1.03(0.71,1.49)	0.86	1.02(0.70,1.51)	0.90	1.05(0.71,1.54)	0.81
Q4 (≥ 702.32)	1.32(0.89,1.95)	0.16	1.27(0.84,1.93)	0.25	1.28(0.83,1.96)	0.24
P for trend		0.11		0.17		0.19
NLR						
Q1 (< 1.56)	1[Reference]		1[Reference]		1[Reference]	
Q2 (1.56–2.08)	1.18(0.92,1.52)	0.19	1.19(0.90,1.57)	0.20	1.18(0.89,1.58)	0.23
Q3 (2.09–2.72)	1.41(0.91,2.18)	0.12	1.34(0.85,2.10)	0.19	1.32(0.83,2.09)	0.22
Q4 (≥ 2.73)	2.10(1.44,3.05)	< 0.01	1.87(1.26,2.78)	< 0.01	1.82(1.21,2.73)	0.01
P for trend		< 0.01		< 0.01		< 0.01
dNLR						
Q1 (< 1.13)	1[Reference]		1[Reference]		1[Reference]	
Q2 (1.13–1.44)	1.25(0.98,1.61)	0.07	1.23(0.95,1.59)	0.11	1.23(0.95,1.59)	0.11
Q3 (1.45–1.84)	1.20(0.78,1.83)	0.39	1.15(0.74,1.78)	0.51	1.15(0.74,1.79)	0.51
Q4 (≥ 1.85)	1.99(1.35,2.93)	< 0.01	1.86(1.25,2.75)	< 0.01	1.81(1.20,2.71)	0.01
P for trend		< 0.01		< 0.01		0.01
MLR						
Q1 (< 0.22)	1[Reference]		1[Reference]		1[Reference]	
Q2 (0.22–0.29)	1.17(0.81,1.69)	0.38	1.13(0.77,1.66)	0.50	1.13(0.77,1.66)	0.49
Q3 (0.30–0.37)	1.32(0.85,2.06)	0.20	1.23(0.77,1.96)	0.36	1.22(0.75,1.98)	0.40
Q4 (≥ 0.38)	1.66(1.14,2.42)	0.01	1.38(0.93,2.04)	0.10	1.35(0.89,2.03)	0.15
P for trend		0.01		0.13		0.19
PLR						
Q1 (< 97.90)	1[Reference]		1[Reference]		1[Reference]	
Q2 (97.90–124.74)	0.92(0.65,1.30)	0.63	0.93(0.66,1.32)	0.68	0.94(0.66,1.34)	0.71
Q3 (124.75–159.41)	0.76(0.60,0.96)	0.02	0.81(0.64,1.04)	0.09	0.83(0.65,1.07	0.14
Q4 (≥ 159.42)	1.13(0.82,1.57)	0.44	1.11(0.80,1.55)	0.50	1.13(0.80,1.60)	0.45
P for trend		0.47		0.52		0.45
CRP, mg/dl						
Q1 (< 0.09)	1[Reference]		1[Reference]		1[Reference]	

Q2 (0.09–0.20)	0.84(0.62,1.15)	0.28	0.83(0.59,1.16)	0.26	0.82(0.58,1.16)	0.23
Q3 (0.21–0.43)	0.95(0.66,1.37)	0.79	0.95(0.64,1.39)	0.76	0.92(0.63,1.36)	0.66
Q4 (≥ 0.43)	1.36(0.97,1.91)	0.07	1.29(0.90,1.85)	0.15	1.22(0.86,1.74)	0.25
P for trend		0.02		0.03		0.05

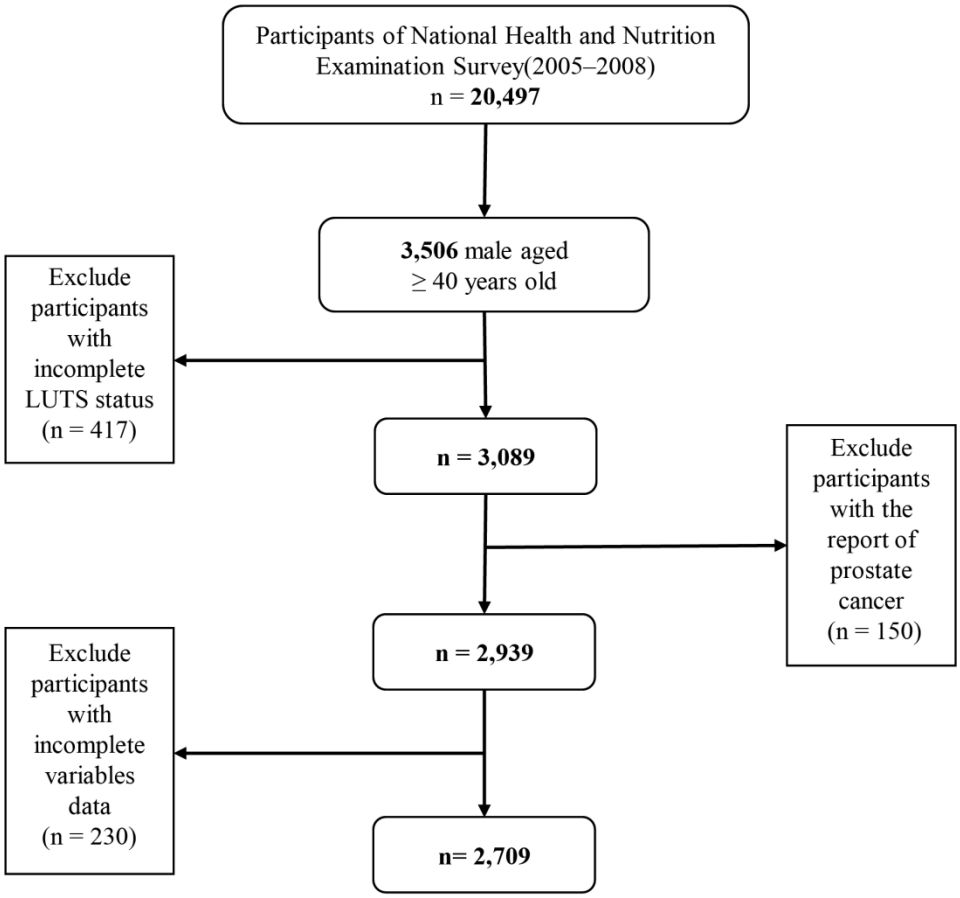
Abbreviations: *OR*, odds ratio; *CI*, confidence interval; PIV, pan-immune-inflammation value; SIRI, system inflammation response index; SII, systemic immune-inflammation index; NLR, neutrophil to lymphocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio; MLR, monocyte to lymphocyte ratio; PLR, platelet to lymphocyte ratio; CRP, C-reactive protein.
*Values are numerical values or weighted *OR* (95% *CI*).
Model 1 was adjusted for age, race/ethnicity, education level, smoking status, alcohol use, and BMI;
Model 2 was additionally adjusted for total cholesterol, and a history of diabetes and hypertension.

Supplementary table 3. *OR* (95% *CI*) for nocturia across quartiles of blood immune-inflammatory indexes*

	Crude Model	*P* value	Model 1	*P* value	Model 2	*P* value
PIV						
Q1 (< 181.50)	1[Reference]		1[Reference]		1[Reference]	
Q2 (181.50–276.64)	0.95(0.66,1.36)	0.77	0.96(0.65,1.43)	0.84	0.98(0.65,1.50)	0.93
Q3 (276.65–421.83)	0.91(0.63,1.33)	0.63	0.88(0.58,1.34)	0.55	0.91(0.59,1.41)	0.65
Q4 (≥ 421.84)	1.34(1.02,1.77)	0.04	1.26(0.94,1.70)	0.12	1.25(0.91,1.71)	0.15
P for trend		0.01		0.06		0.10
SIRI						
Q1 (< 0.80)	1[Reference]		1[Reference]		1[Reference]	
Q2 (0.80–1.14)	0.84(0.61,1.15)	0.27	0.87(0.61,1.22)	0.39	0.86(0.60,1.22)	0.36
Q3 (1.15–1.65)	1.26(0.89,1.77)	0.18	1.20(0.80,1.80)	0.36	1.17(0.76,1.81)	0.45
Q4 (≥ 1.66)	1.58(1.16,2.16)	0.01	1.39(1.00,1.94)	0.05	1.30(0.92,1.84)	0.12
P for trend		< 0.01		0.01		0.04
SII						
Q1 (< 356.13)	1[Reference]		1[Reference]		1[Reference]	
Q2 (356.13–500.41)	0.78(0.57,1.07)	0.12	0.78(0.57,1.08)	0.12	0.82(0.60,1.12)	0.19
Q3 (500.42–702.31)	0.79(0.60,1.04)	0.10	0.85(0.63,1.14)	0.26	0.87(0.65,1.17)	0.35
Q4 (≥ 702.32)	1.03(0.78,1.38)	0.81	1.03(0.78,1.37)	0.81	1.04(0.78,1.40)	0.76
P for trend		0.39		0.36		0.39
NLR						
Q1 (< 1.56)	1[Reference]		1[Reference]		1[Reference]	
Q2 (1.56–2.08)	0.83(0.54,1.27)	0.37	0.95(0.61,1.47)	0.81	0.94(0.59,1.48)	0.77
Q3 (2.09–2.72)	1.20(0.86,1.66)	0.27	1.25(0.88,1.79)	0.20	1.23(0.86,1.76)	0.25
Q4 (≥ 2.73)	1.45(1.04,2.02)	0.03	1.32(0.94,1.87)	0.10	1.25(0.88,1.77)	0.20
P for trend		< 0.01		0.03		0.06
dNLR						
Q1 (< 1.13)	1[Reference]		1[Reference]		1[Reference]	
Q2 (1.13–1.44)	0.97(0.69,1.37)	0.85	1.03(0.70,1.51)	0.88	1.02(0.68,1.53)	0.91
Q3 (1.45–1.84)	1.04(0.75,1.44)	0.83	1.11(0.78,1.60)	0.53	1.11(0.78,1.59)	0.54
Q4 (≥ 1.85)	1.24(0.88,1.76)	0.22	1.18(0.82,1.70)	0.36	1.13(0.77,1.65)	0.51
P for trend		0.16		0.29		0.44
MLR						
Q1 (< 0.22)	1[Reference]		1[Reference]		1[Reference]	
Q2 (0.22–0.29)	0.88(0.62,1.24)	0.45	0.92(0.65,1.30)	0.62	0.92(0.65,1.30)	0.60
Q3 (0.30–0.37)	1.34(0.97,1.87)	0.08	1.37(1.00,1.87)	0.05	1.37(0.98,1.89)	0.06
Q4 (≥ 0.38)	1.83(1.32,2.53)	< 0.01	1.56(1.13,2.16)	0.01	1.49(1.07,2.08)	0.02
P for trend		< 0.01		< 0.01		< 0.01
PLR						
Q1 (< 97.90)	1[Reference]		1[Reference]		1[Reference]	
Q2 (97.90–124.74)	0.79(0.56,1.11)	0.17	0.80(0.56,1.15)	0.21	0.84(0.57,1.24)	0.36
Q3 (124.75–159.41)	0.80(0.62,1.04)	0.09	0.94(0.74,1.20)	0.62	1.02(0.79,1.32)	0.86
Q4 (≥ 159.42)	1.01(0.70,1.45)	0.96	1.02(0.72,1.45)	0.91	1.08(0.74,1.56)	0.67
P for trend		0.74		0.54		0.40
CRP, mg/dl						
Q1 (< 0.09)	1[Reference]		1[Reference]		1[Reference]	

Q2 (0.09–0.20)	1.13(0.80,1.61)	0.47	1.07(0.76,1.51)	0.70	1.04(0.75,1.46)	0.23
Q3 (0.21–0.43)	1.39(0.98,1.98)	0.06	1.18(0.81,1.71	0.38	1.16(0.80,1.69)	0.66
Q4 (≥ 0.43)	2.19(1.61,2.98)	< 0.01	1.67(1.14,2.43)	0.01	1.59(1.08,2.34)	0.02
P for trend		< 0.01		< 0.01		< 0.01

Abbreviations: *OR*, odds ratio; *CI*, confidence interval; PIV, pan-immune-inflammation value; SIRI, system inflammation response index; SII, systemic immune-inflammation index; NLR, neutrophil to lymphocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio; MLR, monocyte to lymphocyte ratio; PLR, platelet to lymphocyte ratio; CRP, C-reactive protein.
*Values are numerical values or weighted *OR* (95% *CI*).
Model 1 was adjusted for age, race/ethnicity, education level, smoking status, alcohol use, and BMI;
Model 2 was additionally adjusted for total cholesterol, and a history of diabetes and hypertension.



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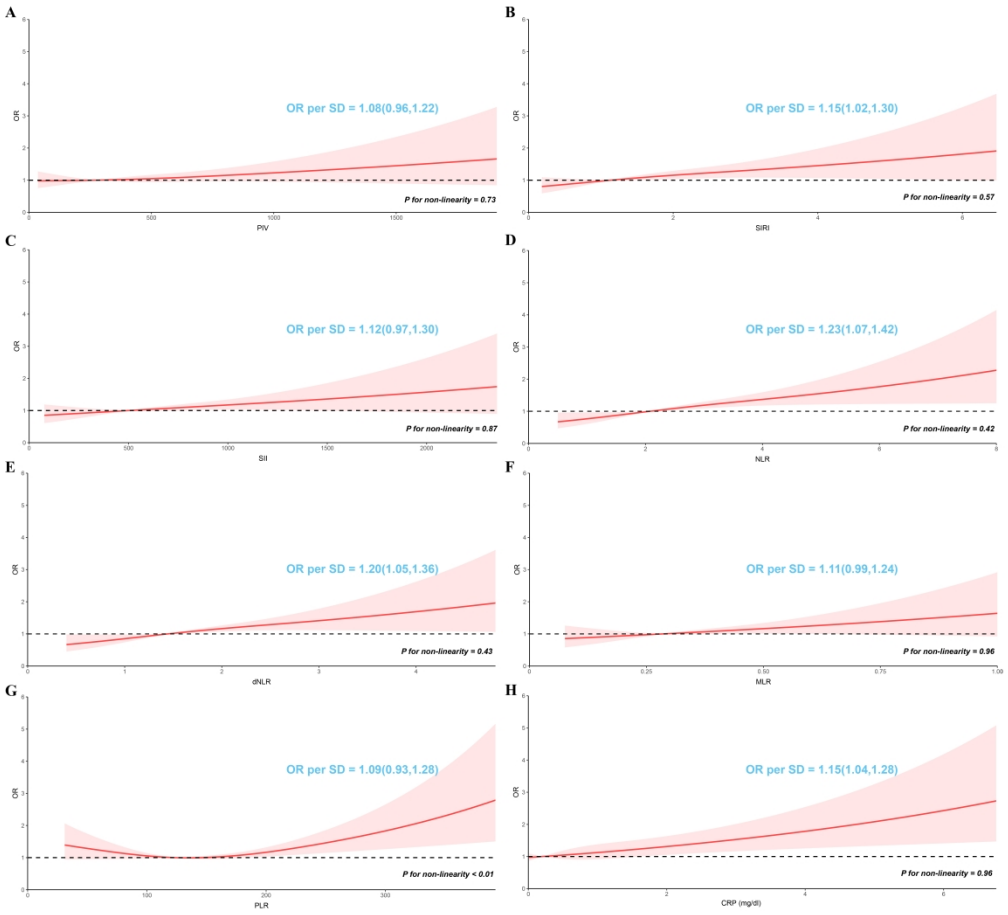

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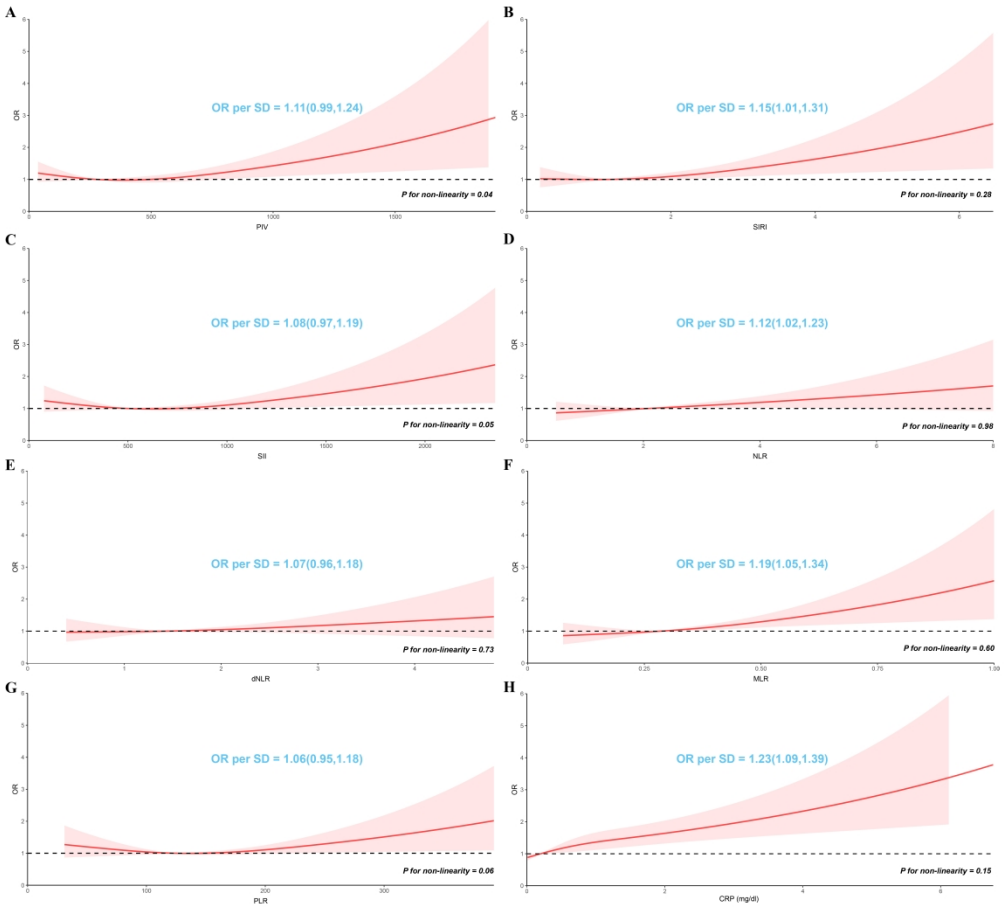

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

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

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5
		(b) Indicate number of participants with missing data for each variable of interest	5
Outcome data	15*	Report numbers of outcome events or summary measures	5-7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5-7
		(*b*) Report category boundaries when continuous variables were categorized	5-7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	5-7
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8-10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	8-10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

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

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