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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 (LUTSs).

Design Cross-sectional study.

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

Participants A total of 2709 men with complete information for immune-inflammatory indexes and LUTSs were included from NHANES 2005–2008.

Outcomes and analyses Automated haematology analysing devices are used to measure blood cell counts, and LUTSs were presented by standard questionnaires. Non-linear and logistic regression analyses were used to estimate their association after adjustment for confounders.

Results Multivariate logistic regression showed that pan-immune-inflammation value (OR (95% CI)=1.60 (1.14 to 2.23)), systemic inflammation response index (SIRI) (OR (95% CI)=1.82 (1.21 to 2.73)), neutrophil/lymphocyte ratio (NLR) (OR (95% CI)=1.81 (1.31 to 2.49)), derived NLR (dNLR) (OR (95% CI)=1.91 (1.35 to 2.70)) and C reactive protein (CRP) (OR (95% CI)=1.71 (1.05 to 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 with any single index.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The National Health and Nutrition Examination Survey 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.
⇒ 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 ageing 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 USA), nearly US$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 ageing 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 NLR (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 involves 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 National Health and Nutrition Examination Survey (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 USA.[23]

In this study, we used publicly accessible data from two 2-year cycles of NHANES (2005–2006 and 2007–2008) and restricted the analysis cohort to men aged 40 years or older. Initially, there were 3506 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, 2709 participants were included in this study (online supplemental figure 1).

Questionnaire data assessment

LUTSs 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) and (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 analyser) are used to measure lymphocyte, neutrophil, monocyte and platelet count, which are presented as $x10^9$/L. The Behring Nephelometer is used to measure serum CRP levels by latex-enhanced nephelometry, with a lower limit of detection 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 and 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 mm Hg, or a mean diastolic blood pressure less than 90 mm Hg, or a self-reported history of hypertension. Diabetes was defined as the use of antidiabetic treatment, an glycated haemoglobin A1c (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 USA, survey weights were included in the analysis in accordance with NHANES standards. Baseline feature indicators were presented as weighted mean and 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 χ^2 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 used 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 (V.4.2.2, http://www.r-project.org/). Statistical significance was defined as a two-sided p<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 with 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 with 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 with 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 SD 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 SD of SIRI, NLR, dNLR and CRP, respectively (all p<0.05) (online supplemental figure 2). The prevalence of nocturia increased by 15%, 12%, 19% and 23% per SD of SIRI, NLR, MLR and CRP, respectively (all p<0.05) (online supplemental 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 a 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 to 2.23), SIRI (OR=1.82, 95% CI=1.21 to 2.73), NLR (OR=1.81, 95% CI=1.31 to 2.49), dNLR (OR=1.91, 95% CI=1.35 to 2.70) and CRP (OR=1.71, 95% CI=1.05 to 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 to 2.06) and MLR (OR=1.96, 95% CI=1.17 to 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 (online supplemental table 1).

Regarding the presence of daytime LUTS, we found a significant association between NLR (Q4, OR=1.82, 95% CI=1.21 to 2.74), dNLR (Q4, OR=1.81, 95% CI=1.20 to 2.71), and SIRI (Q4, OR=1.82, 95% CI=1.05 to 3.17) and increased risk of daytime LUTS (online supplemental table 2). By contrast, in the outcome of nocturia, MLR (Q4, OR=1.49, 95% CI=1.07 to 2.08) and CRP (Q4, OR=1.59, 95% CI=1.08 to 2.34) were significantly associated with nocturia (online supplemental 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 to 3.26), 2.44 (95% CI=1.60 to 3.71) and 2.16 (95% CI=1.21 to 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 with 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

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/m^2, 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)	
WCC, x10^9/L, 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, x10^9/L, 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

Continued

Table 1 Continued

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
Lym, x10^9/L, 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, x10^9/L, 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, x10^9/L, 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

*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 metres 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).
BMI, body mass index; CRP, C reactive protein; dNLR, derived NLR; GED, general equivalency diploma; LUTS, lower urinary tract symptoms; Lym, lymphocyte; MLR, monocyte to lymphocyte ratio; Mono, monocyte; Neu, neutrophil; NHANES, National Health and Nutrition Examination Survey; NLR, neutrophil to lymphocyte ratio; PIV, pan-immune-inflammation value; PLR, platelet to lymphocyte ratio; PLT, platelet; SII, systemic immune-inflammation index; SIRI, System Inflammation Response Index; WCC, white cell count.

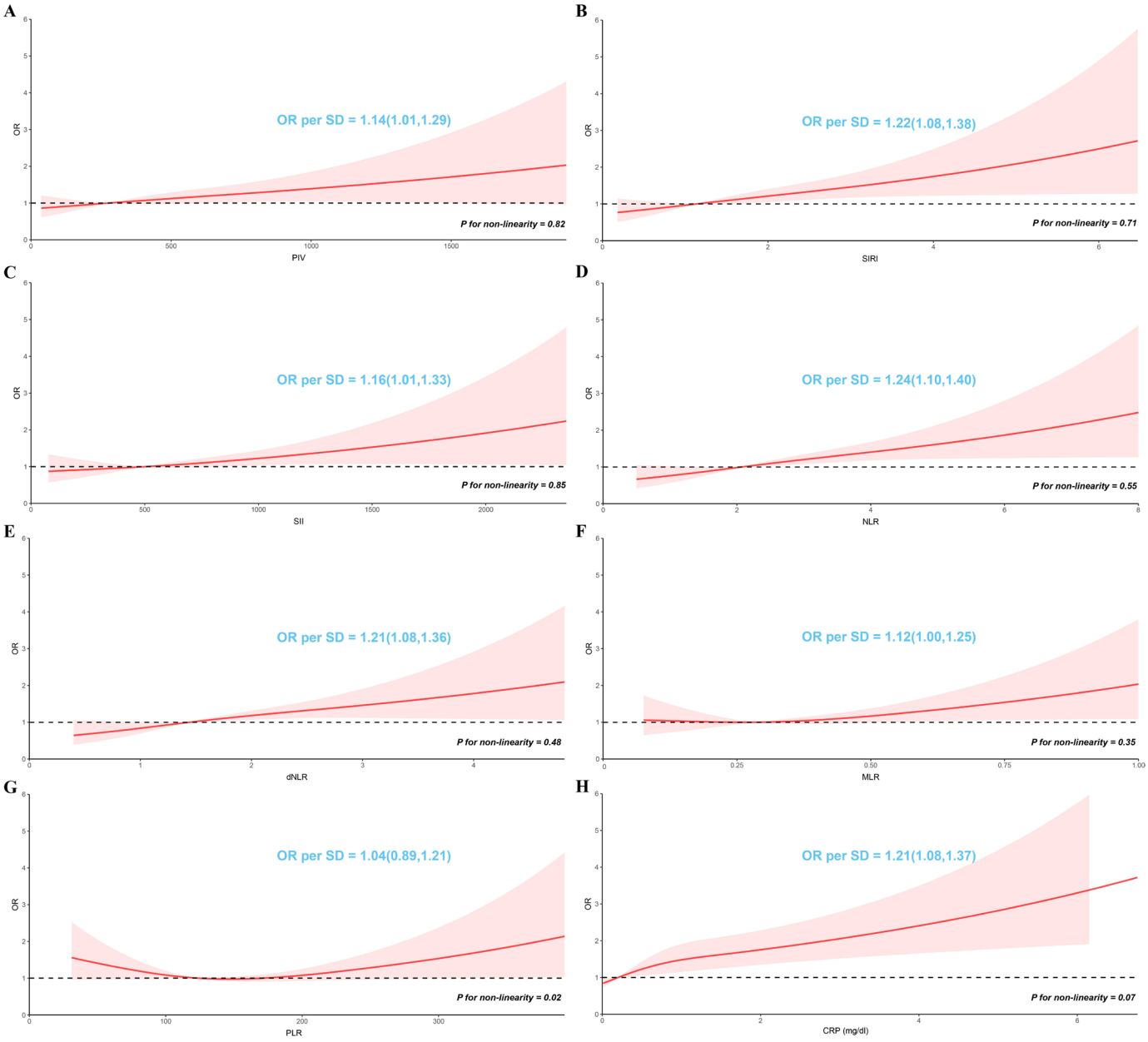

Figure 1 Dose–response relationships between blood immune-inflammatory indexes and clinical LUTS (A) PIV and clinical LUTS; (B) SIRI and LUTS; (C) SII and LUTS; (D) NLR and LUTS; (E) dNLR and LUTS; (F) MLR and LUTS; (G) PLR and LUTS; (H) CRP and LUTS. They are adjusted for age, race/ethnicity, education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

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 with any of the

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 to 1.80)	0.53	1.11 (0.69 to 1.79)	0.65	1.14 (0.71 to 1.85)	0.56
Q3 (276.65–421.83)	0.86 (0.59 to 1.24)	0.39	0.79 (0.54 to 1.17)	0.22	0.82 (0.57 to 1.18)	0.26
Q4 (≥421.84)	1.85 (1.34 to 2.56)	<0.01	1.59 (1.14 to 2.24)	0.01	1.60 (1.14 to 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 to 1.73)	0.98	0.98 (0.56 to 1.70)	0.93	0.97 (0.55 to 1.72)	0.92
Q3 (1.15–1.65)	1.39 (1.06 to 1.84)	0.02	1.26 (0.94 to 1.69)	0.12	1.23 (0.91 to 1.66)	0.17
Q4 (≥1.66)	2.35 (1.61 to 3.44)	<0.01	1.91 (1.30 to 2.82)	<0.01	1.82 (1.21 to 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 to 1.39)	0.86	0.97 (0.65 to 1.43)	0.86	1.02 (0.71 to 1.48)	0.89
Q3 (500.42–702.31)	0.98 (0.67 to 1.43)	0.91	1.00 (0.66 to 1.51)	0.99	1.04 (0.71 to 1.54)	0.82
Q4 (≥702.32)	1.45 (1.02 to 2.06)	0.04	1.37 (0.94 to 2.00)	0.09	1.40 (0.97 to 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 to 1.60)	0.67	1.15 (0.76 to 1.75)	0.50	1.16 (0.75 to 1.80)	0.48
Q3 (2.09–2.72)	1.75 (1.16 to 2.63)	0.01	1.73 (1.12 to 2.66)	0.02	1.71 (1.10 to 2.66)	0.02
Q4 (≥2.73)	2.21 (1.60 to 3.04)	<0.01	1.89 (1.39 to 2.56)	<0.01	1.81 (1.31 to 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 to 1.49)	0.55	1.09 (0.80 to 1.50)	0.56	1.10 (0.80 to 1.51)	0.55
Q3 (1.45–1.84)	1.32 (0.92 to 1.89)	0.12	1.32 (0.92 to 1.89)	0.12	1.33 (0.92 to 1.90)	0.12
Q4 (≥ 1.85)	2.17 (1.55 to 3.04)	<0.01	1.98 (1.42 to 2.77)	<0.01	1.91 (1.35 to 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 to 2.24)	0.39	1.24 (0.69 to 2.25)	0.45	1.25 (0.69 to 2.27)	0.43
Q3 (0.30–0.37)	1.49 (0.87 to 2.56)	0.14	1.38 (0.79 to 2.41)	0.24	1.38 (0.77 to 2.46)	0.26
Q4 (≥0.38)	1.96 (1.17 to 3.28)	0.01	1.51 (0.89 to 2.57)	0.12	1.44 (0.82 to 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 to 1.49)	0.79	0.97 (0.61 to 1.55)	0.90	1.00 (0.62 to 1.62)	0.98
Q3 (124.75–159.41)	0.70 (0.49 to 0.99)	0.04	0.81 (0.56 to 1.18)	0.26	0.86 (0.58 to 1.27)	0.41
Q4 (≥159.42)	1.09 (0.72 to 1.63)	0.68	1.09 (0.73 to 1.64)	0.65	1.14 (0.74 to 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 to 1.38)	0.57	0.84 (0.53 to 1.34)	0.45	0.83 (0.51 to 1.34)	0.41

Continued

Table 2 Continued

	Crude model	P value	Model 1	P value	Model 2	P value
Q3 (0.21–0.43)	1.12 (0.66 to 1.92)	0.66	1.05 (0.59 to 1.88)	0.86	1.05 (0.58 to 1.88)	0.87
Q4 (≥0.43)	2.03 (1.28 to 3.22)	<0.01	1.78 (1.09 to 2.90)	0.02	1.71 (1.05 to 2.79)	0.03
P for trend		<0.01		<0.01		<0.01

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.
*Values are numerical values or weighted OR (95% CI).
BMI, body mass index; CRP, C reactive protein; dNLR, derived NLR; LUTS, lower urinary tract symptoms; MLR, monocyte to lymphocyte ratio; NLR, neutrophil to lymphocyte ratio; PIV, pan-immune-inflammation value; PLR, platelet to lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index.

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 ageing 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 two 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

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 to 2.50)	<0.01	1.60 (1.13 to 2.25)	0.01	1.56 (1.10 to 2.21)	0.02
Low SIRI and high CRP	2.28 (1.28 to 4.07)	0.01	2.15 (1.12 to 4.14)	0.02	2.10 (1.09 to 4.03)	0.03
High SIRI and high CRP	2.90 (2.04 to 4.12)	<0.01	2.39 (1.65 to 3.48)	<0.01	2.26 (1.56 to 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 to 2.77)	<0.01	1.82 (1.37 to 2.41)	<0.01	1.78 (1.33 to 2.38)	<0.01
Low NLR and high CRP	2.69 (1.57 to 4.62)	<0.01	2.40 (1.33 to 4.32)	0.01	2.31 (1.29 to 4.14)	0.01
High NLR and high CRP	3.07 (2.11 to 4.46)	<0.01	2.59 (1.73 to 3.86)	<0.01	2.44 (1.60 to 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 to 2.97)	<0.01	1.88 (1.24 to 2.84)	<0.01	1.87 (1.22 to 2.87)	0.01
Low dNLR and high CRP	2.16 (1.37 to 3.41)	<0.01	2.01 (1.23 to 3.26)	0.01	1.99 (1.23 to 3.23)	0.01
High dNLR and high CRP	2.84 (1.66 to 4.87)	<0.01	2.38 (1.35 to4.21)	<0.01	2.16 (1.21 to 3.87)	0.01

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.
*Values are numerical values or weighted OR (95% CI).
BMI, body mass index; CRP, C reactive protein; dNLR, derived NLR; LUTS, lower urinary tract symptoms; NLR, neutrophil to lymphocyte ratio; SIRI, systemic inflammation response index.

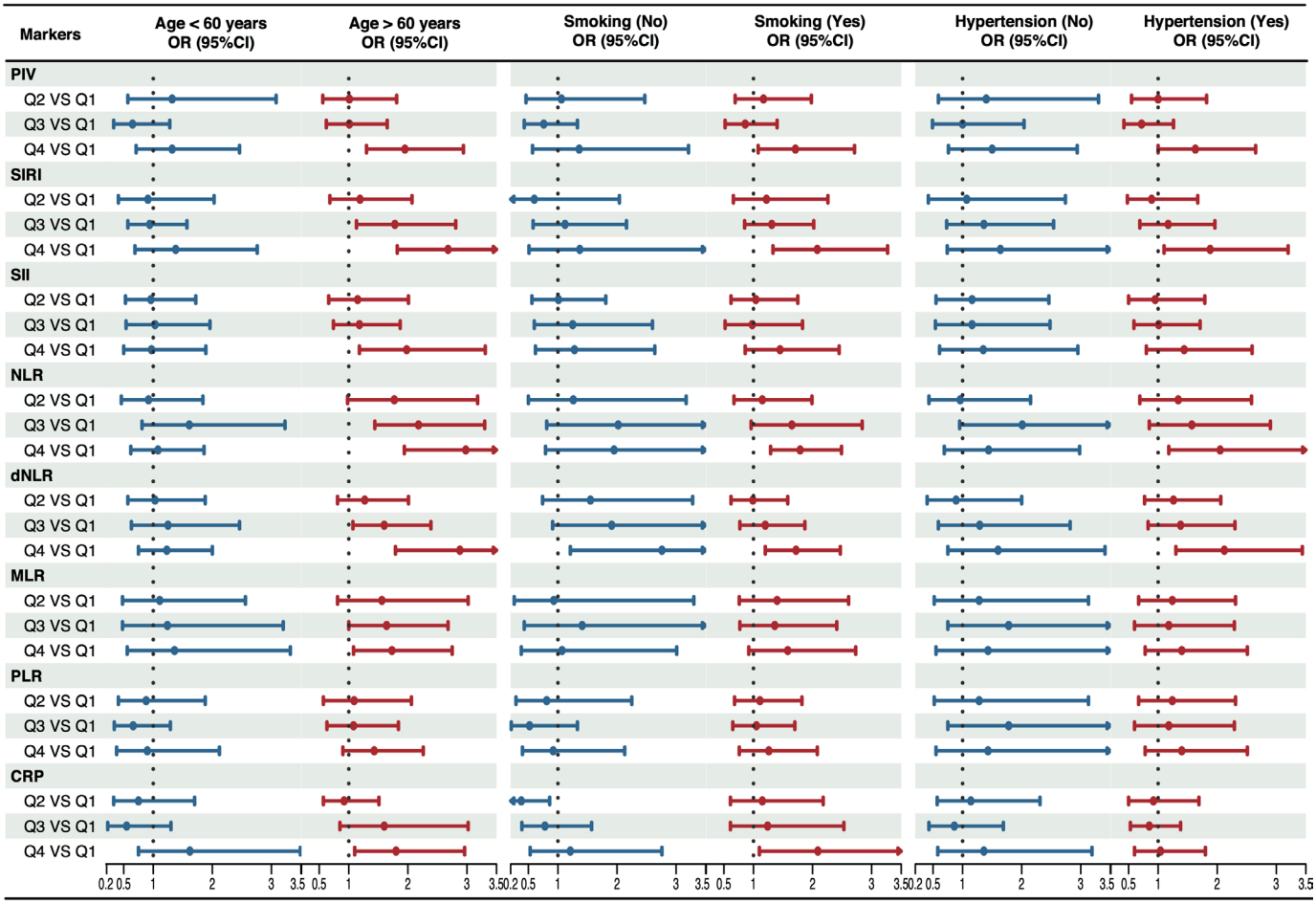

Figure 2 Associations between blood immune-inflammatory indexes and clinical LUTS in subgroup analyses. They are adjusted for age, race/ethnicity, education level, smoking status, alcohol use, and BMI, total cholesterol, and a history of diabetes and hypertension, if not already stratified. BMI, body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

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 tumours[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 proinflammatory cells, NLR has been the most extensively validated. However, dNLR, which replaces the denominator of NLR with (white cell count 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 proinflammatory 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 ageing, smoking and hypertension may contribute to a higher prevalence of LUTS through mechanisms such as prostate and bladder ageing, 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. First, 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. Second, the NHANES dataset comprises a representative sample of the national population, and we use 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 with 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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Patient consent for publication Not applicable.

Ethics approval 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.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Publicly available datasets were analysed in this study. These data can be downloaded here: https://www.cdc.gov/nchs/nhanes/ (NHANES 2005–2006 and 2007–2008).

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