四川大学学报（医学版） 2024，55（3）：671－679
J Sichuan Univ（Med Sci） doi: 10.12182/20240560108

在线全文

全身炎症综合指数与白蛋白尿的关联：基于2007–2018年国家健康与营养调查的横断面研究*

孙丽荣[1,2]，霍醒伟[1]，贾珊珊[1]，陈晓平[1△]

1. 四川大学华西医院 心内科（成都 610041）；2. 西藏民族大学附属医院（咸阳 712000）

【摘要】 目的 探讨美国成人全身炎症综合指数（aggregate index of systemic inflammation, AISI）与白蛋白尿之间的关联。**方法** 研究使用了2007–2018年美国国家健康与营养调查（National Health and Nutrition Examination Survey, NHANES）的数据，排除了怀孕妇女和18岁以下的个体，缺少AISI、尿白蛋白浓度及其他共变量数据的病例也被排除。AISI的计算公式为：AISI=（血小板计数×中性粒细胞计数×单核细胞计数）/淋巴细胞计数，并根据$\log_2$AISI三分位数将研究变量分为3组，即Q1（4.94～7.49），Q2（7.49～8.29），Q3（8.29～10.85）。白蛋白尿是指尿白蛋白与肌酐比值超过30 mg/g。通过加权多变量逻辑回归和亚组分析研究AISI与白蛋白尿之间的独立关系。广义相加模型用于检验非线性关联。**结果** 本研究共分析了32 273名参与者。白蛋白尿的患病率为9.64%。按AISI水平分类的基线特征显示随着AISI水平的增加，白蛋白尿的患病率相应增加。在完全调整模型中，加权多变量逻辑回归揭示了与最低AISI水平相比，更高AISI水平的个体患白蛋白尿风险更高〔比值比（odds ratio, OR）=1.37，95%置信区间（confidence interval, CI）：1.21～1.55，P<0.001〕；AISI与大量白蛋白尿风险间的关系强调了这一正向关系的稳健性。广义相加模型结果表明AISI与白蛋白尿之间存在非线性关系。阈值效应分析提示当$\log_2$AISI小于7.25时，$\log_2$AISI的增加并不增加白蛋白尿的风险，但当$\log_2$AISI超过7.25时，$\log_2$AISI的增加显著增加白蛋白尿的风险。亚组分析和交互作用提示性别、血压、体质量指数、吸烟和饮酒与AISI存在交互作用，影响蛋白尿的风险。**结论** 美国成人AISI与白蛋白尿风险之间存在稳健的正向关联。然而，有必要通过大规模前瞻性研究进一步验证该结论。

【关键词】 全身炎症综合指数 白蛋白尿 肌酐 阈值效应 横断面研究

Association Between the Aggregate Index of Systemic Inflammation and Albuminuria: A Cross-Sectional Study of National Health and Nutrition Examination Survey 2007-2018

SUN Lirong[1,2], *HUO Xingwei*[1], *JIA Shanshan*[1], *CHEN Xiaoping*[1△].

1. *Department of Cardiology, West China Hospital, Sichuan University*, Chengdu 610041, China; 2. *Affiliated Hospital of Xizang Minzu University*, Xianyang 712000, China

△ Corresponding author, E-mail: xiaopingchen13@126.com

【Abstract】 Objective Prior studies have established a connection between albuminuria and various inflammatory reactions, highlighting that an increase in C-reactive protein by 1 mg/L increases the likelihood of albuminuria by 2%. Recent investigations indicate a positive correlation between the systemic immune-inflammation index (SII) and increased urinary protein excretion. In addition, elevated levels of the systemic inflammatory response index (SIRI) also correlate with a higher prevalence of albuminuria. The aggregate index of systemic inflammation (AISI) offers a more comprehensive indicator of inflammation, providing an extensive assessment of systemic inflammatory status compared to SII and SIRI. Yet, the specific relationship between AISI and albuminuria remains unclear. This study aims to explore this association in U.S. adults. **Methods** We analyzed data from the National Health and Nutrition Examination Survey (NHANES) for 2007-2018, excluding pregnant women and individuals under 18. Cases with missing data on AISI, urinary albumin concentration, and other covariates were also excluded. AISI was computed using the formula: AISI=(platelet count×neutrophil count×monocyte count)/lymphocyte count. Albuminuria was defined as the urinary albumin-to-creatinine ratio exceeding 30 mg/g. Continuous variables were presented in the form of the mean±standard error, and categorical variables in percentages. We utilized weighted *t*-tests and chi-square tests for baseline comparisons. We applied weighted multivariable logistic regression and generalized additive models (GAM) to explore the association between AISI and albuminuria and to assess potential nonlinear relationships. **Results** The study included 32 273 participants, with an average age of (46.75±0.24) years old. The cohort comprised 48.73% males and 51.27% females. The prevalence of albuminuria was 9.64%. The average logarithmic value of $\log_2$AISI was 7.95±0.01, and were categorized into tertiles as follows: Quartile 1 (Q1) (4.94 to 7.49), Q2 (7.49 to 8.29), and Q3 (8.29 to 10.85). As

* 西藏自治区科技计划项目（No. XZ202303ZY0004G）资助

△ 通信作者，E-mail: xiaopingchen13@126.com

出版日期：2024-05-20

log_2AISI increased, so did the prevalence of hypertension, diabetes, congestive heart failure, and albuminuria, all showing statistically significant increases (P<0.001). Similarly, the use of antihypertensive, lipid-lowering, and hypoglycemic drugs was also more prevalent (P<0.001). Statistically significant differences were observed across the three groups concerning age, race and ethnicity, formal education, alcohol consumption, smoking status, systolic and diastolic blood pressures, body mass index, estimated glomerular filtration rate, HbA1c, alanine aminotransferase, aspartate aminotransferase, albumin, creatinine, uric acid, and high-density lipoprotein cholesterol (P<0.05). However, no significant differences were noted in the total cholesterol or the sex ratios among the groups. The association between log_2AISI and albuminuria was assessed using weighted multivariable logistic regression, and the detailed results are presented in Table 2. In model 1, without adjusting for covariates, each unit increase in log_2AISI was associated with a 32% increase in the risk of albuminuria (odds ratio [OR]=1.32, 95% confidence interval [CI]: 1.27-1.38, P<0.001). Model 2 was adjusted for age, gender, race, and education level, and showed a similar trend, with each unit increase in log_2AISI associated with a 31% increased risk (OR=1.31, 95% CI: 1.26-1.37, P<0.001). Model 3, which was further adjusted for all covariates, revealed that each unit increase in log_2AISI was associated with a 20% increase in the risk of albuminuria (OR=1.20, 95% CI: 1.15-1.26, P<0.001). The study also transformed log_2AISI from a continuous to a categorical variable for analysis. Compared with Q1, the risk of albuminuria in Q3, after adjusting for all covariates, significantly increased (OR=1.37, 95% CI: 1.22-1.55, P<0.001). Q2 also demonstrated a higher risk compared with Q1 (OR=1.13, 95% CI: 1.06-1.36, P=0.004). The trend test indicated a dose-effect relationship between increasing log_2AISI and the rising risk of albuminuria. GAM revealed a nonlinear relationship between log_2AISI and albuminuria, with distinct trends noted between sexes. Segmented regression based on turning points showed significant effects among women, although the slope difference between the segments was not significant. In men, a significant threshold effect was observed; below the log_2AISI of 7.25, increases in log_2AISI did not enhance the risk of albuminuria, but above this threshold, the risk significantly increased. As part of a sensitivity analysis, weighted multivariable logistic regression was performed by changing the outcome variable to macroalbuminuria and adjusting for all covariates. The analysis showed that for every unit increase in log_2AISI, the risk of developing macroalbuminuria increased by 31% (OR=1.31, 95% CI: 1.15-1.49, P<0.001). Compared with Q1, the risk of albuminuria in Q3 increased by 69% (OR=1.69, 95% CI: 1.27-2.25, P<0.001), and in Q2, it increased by 40% (OR=1.40, 95% CI: 1.03-1.92, P=0.030). Subgroup analysis and interaction results showed that the positive association between AISI and proteinuria risk was stronger in men than in women. Similarly, the association was stronger in people with hypertension compared with those with normal blood pressure, and higher in overweight people compared with those of normal weight. Furthermore, smokers and drinkers showed a stronger positive association between AISI and the risk of proteinuria than non-smokers and non-drinkers do. These results suggest that sex, blood pressure, body mass index, smoking, and alcohol consumption interact with AISI to influence the risk of proteinuria. **Conclusion** There is a robust positive association between AISI and increased risks of albuminuria in US adults. As log_2AISI increases, so does the risk of albuminuria. However, further validation of this conclusion through large-scale prospective studies is warranted.

【Key words】 Aggregate index of systemic inflammation Albuminuria Creatinine Threshold effect Cross-sectional study

白蛋白尿是由于肾脏滤过屏障损伤导致尿液中异常排泄白蛋白的结果[1]。它通过随机尿液白蛋白与肌酐比值(urinary albumin-to-creatinine ratio, uACR)来量化,超过30 mg/g表明存在白蛋白尿[2]。它被用作特定的筛查和诊断工具,用于早期识别肾脏损伤[3]。众多研究一致显示,白蛋白尿是高血压、糖尿病、心力衰竭和冠心病等多种疾病不良预后的强有力的预测因素[4]。然而,临床实践中对白蛋白尿筛查的应用不足。在美国进行的一项针对高血压或糖尿病患者的全国性队列研究显示,uACR检测的应用明显不足,约有三分之二的潜在白蛋白尿病例未被检出[5]。这可能导致延迟给予适当的药物治疗,血压控制不佳,以及心血管并发症风险增加[6-7]。因此,白蛋白尿的早期筛查在医学领域可能具有重要的意义[8-10]。

已有研究报告显示白蛋白尿与多种炎症反应有关,一项基于2015–2018年美国国家健康和营养检查调查(National Health and Nutrition Examination Survey, NHANES)的横断面研究表明:超敏C反应蛋白(high sensitivity C-reactive protein, hs-CRP)升高可能与蛋白尿异常有关[11]。一项包括2 661名参与者的研究显示,肿瘤坏死因子α(tumor necrosis factor α, TNF-α)、白细胞介素(interleukin, IL)-6、肿瘤坏死因子受体-2(tumor necrosis factor receptor 2, TNFR2)和骨保护素与白蛋白尿显著相关[12]。此外,炎症基因变异也与白蛋白尿相关[12]。一项涉及2 927名日本人的研究发现,*IL-6*和CC趋化因子配体

1(CC chemokine ligand 1, CCL1)基因中的单核苷酸多态性与白蛋白尿相关[13]。研究还表明NLR家族pyrin结构域含有3个炎症小体可以增加尿蛋白风险[14]。

最新研究表明, 全身免疫炎症指数(systemic immune-inflammation index, SII)与尿蛋白排泄增加呈正相关[15]; 全身炎症反应指数(systemic inflammatory response index, SIRI)水平升高与白蛋白尿患病率升高相关[16]。与SII、SIRI相比, 全身炎症综合指数(aggregate index of systemic inflammation, AISI)是一个更全面的炎症指标, 可以更全面地评估全身炎症状态, 然而, AISI与白蛋白尿之间的关联尚不明确。因此, 本研究利用NHANES的数据, 探讨AISI与白蛋白尿风险之间的相关性。

1　资料与方法

1.1　数据来源和受试者

本研究使用的所有数据均来源于NHANES数据库。该研究已获得美国国家卫生统计中心研究伦理审查委员会的批准。NHANES每年访问约5 000名各年龄段的人群。受访者必须签署同意书, 同意参加家庭访谈、体格检查和实验室检测。公开数据进行了匿名处理, 不包含个人信息。见图1。本研究使用了2007–2018年59 842名参与者的数据。排除年龄小于18岁、怀孕、缺少白蛋白尿数据和缺少AISI数据的情况后, 最终纳入32 273名参与者。

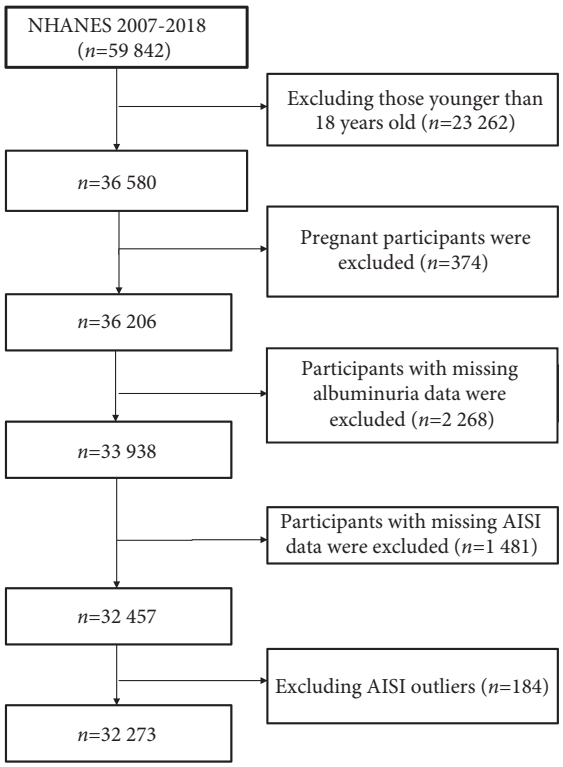

图 1 流程图

Fig 1 Flow chart of participant enrollment

1.2　AISI的评估

研究的暴露变量为AISI, 它通过4种血细胞计数计算得出: AISI=(血小板计数×中性粒细胞计数×单核细胞计数)/淋巴细胞计数。如果参与者患有血友病、在检查前4周内接受过化疗, 或由于伤口、麻痹、萎缩、水肿、烧伤、疤痕、石膏或其他疾病导致手臂不适合静脉穿刺, 则排除其参与血液采集。血液测试使用贝克曼库尔特MAXM仪器进行。由于AISI的分布呈偏态(左偏), 本研究在分析前应用对数变换($\log_2$)使数据接近正态分布。

1.3　白蛋白尿的评估

研究的结果变量为白蛋白尿, 当uACR超过30 mg/g时即被诊断。尿样收集后, 严格存放在−30 ℃下, 并运送至实验室进行检测。尿液收集过程遵循了严格的标准化协议。此外, 为了评估AISI与白蛋白尿关联的稳健性, 本研究还使用大量白蛋白尿作为替代标准来检查结果, 其定义为uACR超过300 mg/g。

1.4　协变量

协变量包括年龄、性别、教育水平、种族和族群、收缩压(systolic blood pressure, SBP)、舒张压(diastolic blood pressure, DBP)、体重指数(body mass index, BMI)、吸烟、饮酒、医疗状况(糖尿病、高血压和充血性心力衰竭)、估算肾小球滤过率(estimate glomerular filtration rate, eGFR)、糖化血红蛋白(glycosylated hemoglobin, HbA1c)、总胆固醇(total cholesterol, TC)、高密度脂蛋白胆固醇(high density lipoprotein cholesterol, HDL-C)、尿酸、肌酐、谷丙转氨酶(alanine transaminase, ALT)、谷草转氨酶(aspartate transaminase, AST)和白蛋白[15, 17]。同时记录了包括降压药、降脂药和降糖药在内的药物使用情况。吸烟者定义为终生累计吸烟≥100支烟的个体。高血压的定义为医生明确诊断为高血压或者根据移动检查中心(Mobile Examination Center, MEC)工作人员至少3次标准测量, 平均收缩压>140 mmHg(1 mmHg=0.133 kPa)或舒张压>90 mmHg。参与者如果符合以下任一标准则被诊断为糖尿病: 医生明确诊断为糖尿病、空腹血清葡萄糖≥126 mg/dL、随机血清葡萄糖>11.1 mmol/L、HBA1c≥6.5%或餐后2 h血糖≥200 mg/dL。采用慢性肾脏病流行病学合作组织(Chronic Kidney Disease Epidemiology Collaboration, CKD-EPI)基于肌酐、年龄、性别和种族和族群的方程计算估计肾小球滤过率(estimated glomerular filtration rate, eGFR)[18]。

1.5　统计学方法

根据美国疾病控制与预防中心(Centers for Disease

Control and Prevention, CDC)的指南,所有统计分析应考虑NHANES复杂的抽样设计,并在统计分析中使用适当的抽样权重。连续变量以均值〔标准误(standard error, SE)〕表示,分类变量以百分比例显示。加权*t*检验和加权卡方检验用于比较各组之间的基线差异。为了研究AISI与白蛋白尿之间的关联,使用加权多变量逻辑回归。构建了3个模型:模型1不调整协变量;模型2调整年龄、性别、种族和族群和教育水平;模型3进一步调整所有协变量。此外,广义相加模型(GAM)用于评估潜在的非线性关系。两段线性回归模型用于探索转折点和阈值效应分析。同时,进行了亚组分析和交互作用分析,并检验了AISI与大量白蛋白尿之间的关联作为敏感性分析。对于缺失数据,连续变量使用均值插补,分类变量使用众数插补。复杂抽样分析使用R软件版本4.2.1进行。双侧$P<0.05$为差异有统计学意义。

2 结果

2.1 参与者基线特征

所有基线信息均展示在表1中。共有32 273名参与者入选。平均年龄为(46.75±0.24)岁。其中男性占48.73%,

表1 根据AISI分层划分的基线特征

Table 1 Baseline characteristics according to the AISI tertiles

Variable	Total (*n*=32 273)	Q1 (*n*=10 758)	Q2 (*n*=10 757)	Q3 (*n*=10 758)	*P*
Age/yr.	46.75 (0.24)	45.26 (0.31)	46.55 (0.27)	48.24 (0.31)	<0.001
Sex/%					0.730
Female	51.27 (0.01)	51.70 (0.64)	50.98 (0.57)	51.18 (0.65)	
Male	48.73 (0.01)	48.30 (0.64)	49.02 (0.57)	48.82 (0.65)	
Race and ethnicity/%					<0.001
Black	10.80 (0.01)	17.17 (1.10)	9.06 (0.62)	6.96 (0.53)	
Hispanic	5.98 (0.00)	5.99 (0.51)	6.24 (0.54)	5.73 (0.54)	
Mexican	8.84 (0.01)	9.13 (0.76)	8.81 (0.82)	8.61 (0.81)	
Other	8.11 (0.00)	10.04 (0.65)	7.77 (0.52)	6.75 (0.44)	
White	66.27 (0.03)	57.67 (1.64)	68.12 (1.43)	71.94 (1.37)	
Educational attainment/%					<0.001
Less than high school	16.37 (0.01)	16.50 (0.72)	15.42 (0.65)	17.18 (0.70)	
High school or GED	23.44 (0.01)	21.73 (0.64)	22.69 (0.70)	25.67 (0.77)	
Above high school	60.19 (0.02)	61.78 (1.08)	61.88 (1.00)	57.15 (1.09)	
Alcohol consumption/%	89.80 (0.02)	89.17 (0.56)	89.42 (0.56)	90.72 (0.44)	0.010
Smoking/%	43.00 (0.01)	37.58 (0.83)	41.65 (0.75)	49.06 (0.78)	<0.001
Hypertension/%	36.90 (0.01)	31.00 (0.72)	35.96 (0.80)	42.96 (0.78)	<0.001
DM/%	14.19 (0.00)	11.84 (0.44)	12.90 (0.43)	17.50 (0.52)	<0.001
CHF/%	2.20 (0.00)	1.61 (0.13)	1.72 (0.15)	3.19 (0.22)	<0.001
Albuminuria/%	9.64 (0.00)	7.56 (0.30)	9.14 (0.34)	11.94 (0.41)	<0.001
Antihypertensive/%	26.71 (0.01)	21.78 (0.59)	25.17 (0.57)	32.52 (0.67)	<0.001
Antihyperlipidemic/%	18.15 (0.01)	14.67 (0.50)	18.19 (0.56)	21.16 (0.64)	<0.001
Antidiabetic/%	8.83 (0.00)	6.77 (0.34)	8.04 (0.29)	11.39 (0.41)	<0.001
SBP/mmHg	121.78 (0.20)	120.17 (0.26)	121.57 (0.26)	123.41 (0.27)	<0.001
DBP/mmHg	70.67 (0.20)	70.29 (0.21)	70.83 (0.23)	70.85 (0.26)	0.010
BMI/(kg/m^2)	28.98 (0.08)	27.72 (0.11)	28.95 (0.12)	30.10 (0.10)	<0.001
HbA1c/%	5.63 (0.01)	5.58 (0.01)	5.60 (0.01)	5.71 (0.01)	<0.001
TC/(mmol/L)	4.97 (0.01)	4.96 (0.02)	4.99 (0.02)	4.95 (0.02)	0.070
HDL-C/(mmol/L)	1.38 (0.01)	1.43 (0.01)	1.37 (0.01)	1.34 (0.01)	<0.001
ALT/(mmol/L)	25.13 (0.14)	24.64 (0.22)	25.09 (0.22)	25.58 (0.25)	0.010
AST/(mmol/L)	25.17 (0.11)	25.64 (0.19)	24.82 (0.17)	25.10 (0.18)	0.010
Albumin/(g/L)	42.73 (0.06)	42.99 (0.06)	42.87 (0.07)	42.37 (0.06)	<0.001
Creatine/(μmol/L)	77.75 (0.22)	77.09 (0.30)	77.32 (0.29)	78.75 (0.39)	<0.001
Uric acid/(μmol/L)	322.65 (0.78)	314.38 (1.19)	322.08 (1.08)	330.41 (1.29)	<0.001
eGFR/(mL/[min·1.73 m^2])	95.23 (0.31)	97.19 (0.39)	95.28 (0.34)	93.47 (0.40)	<0.001

The data are expressed as mean (standard error). The $\log_2$AISI values were divided into three tertiles: Q1 (4.94-7.49), Q2 (7.49-8.29), and Q3 (8.29-10.85). GED: General Educational Development; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; HbA1c: hemoglobin A1C; DM: diabetes mellitus; CHF: congestive heart failure; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

女性占51.27%。白蛋白尿患病率为9.64%。平均log_2AISI为7.95±0.01，根据三分位数分为3组：Q1（4.94 ~ 7.49），Q2（7.49 ~ 8.29），Q3（8.29 ~ 10.85）。随着log_2AISI的增加，高血压、糖尿病、充血性心力衰竭和白蛋白尿的患病率增加（P<0.001），同时使用降压药、降脂药和降糖药的比例也增加（P<0.001）。3组之间在年龄、种族和族群、教育水平、饮酒、吸烟、SBP、DBP、BMI、eGFR、HbA1c、ALT、AST、白蛋白、肌酐、尿酸和HDL-C等指标上差异均有统计学意义（P<0.05）。而在TC和性别构成上，3组间差异无统计学意义。

2.2　多变量回归分析

使用加权多变量逻辑回归评估了log_2AISI与白蛋白尿之间的关系，结果见表2。在模型1中，未调整任何协变量，log_2AISI每增加一个单位，白蛋白尿的风险增加32%〔比值比（odds ratio, OR）=1.32, 95%置信区间（confidence interval, CI）：1.27 ~ 1.38, P<0.001〕。在模型2中，调整了年龄、性别、种族和族群及教育水平后，log_2AISI每增加一个单位，白蛋白尿的风险增加31%（OR=1.31, 95%CI: 1.26 ~ 1.37, P<0.001）。模型3进一步调整了所有协变量，log_2AISI每增加一个单位，白蛋白尿的风险增加20%（OR=1.20, 95%CI: 1.15 ~ 1.26, P<0.001）。本研究还将log_2AISI从连续变量转换为分类变量进行分析。与Q1相比，调整所有协变量后，Q3的白蛋白尿风险增加（OR=1.37, 95%CI: 1.21 ~ 1.55, P<0.001）。此外，Q2与Q1相比，也显示出更高的白蛋白尿风险（OR=1.20, 95%CI: 1.06 ~ 1.36, P=0.004）。趋势检验的结果提示随着AISI的增加，白蛋白尿风险增加。

2.3　非线性分析

结果见图2、表3。GAM的结果表明log_2AISI与白蛋白尿之间存在非线性关系，并且男性与女性之间的趋势有所不同。基于转折点进行分段回归，并使用似然比检验比较前后斜率的差异。虽然在女性中分段回归

表 2　log_2AISI与白蛋白尿的关系

Table 2　Relationship between log_2AISI and albuminuria

Variable	Model 1		Model 2		Model 3	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Continuous variable	1.32 (1.27-1.38)	<0.001	1.31 (1.26-1.37)	<0.001	1.20 (1.15-1.26)	<0.001
Categorical variable						
Q1	Ref.		Ref.		Ref.	
Q2	1.23 (1.10-1.37)	<0.001	1.27 (1.14-1.41)	<0.001	1.20 (1.06-1.36)	0.004
Q3	1.66 (1.50-1.83)	<0.001	1.65 (1.48-1.83)	<0.001	1.37 (1.21-1.55)	<0.001
P-trend (categorical variable)	<0.001		<0.001		<0.001	

Model 1 was adjusted for none; model 2 was adjusted for age, gender, race, and education; model 3 was adjusted for hypertension, diabetes, heart failure, smoking, alcohol consumption, systolic blood pressure, diastolic blood pressure, body mass index, estimated glomerular filtration rate, high-density lipoprotein cholesterol, creatinine, total cholesterol, uric acid, glycated hemoglobin, alanine aminotransferase, aspartate aminotransferase, albumin, use of antihypertensive drugs, and use of antidiabetic drugs, and the use of lipid-lowering drugs was further adjusted. OR: odds ratio; CI: confidence interval.

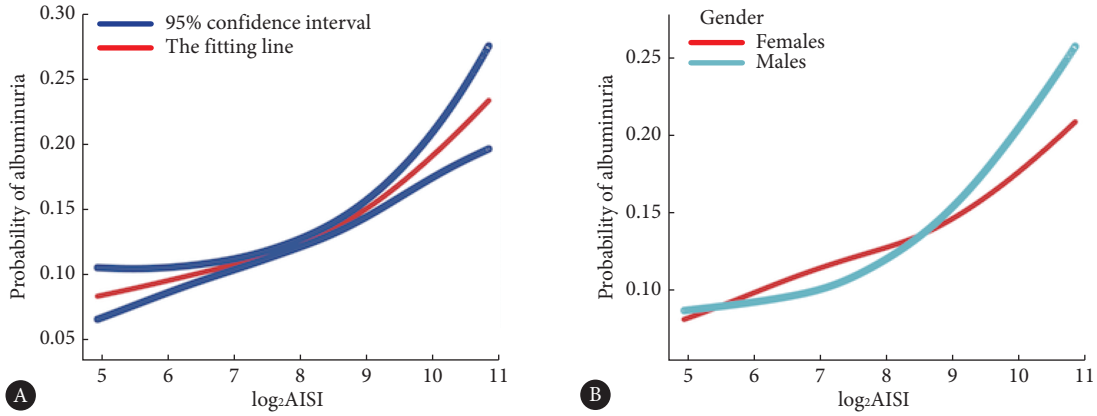

图 2　log_2AISI与白蛋白尿风险关系曲线

Fig 2　log_2AISI and albuminuria risk relationship curve

A shows the relationship curve between AISI and albuminuria in the total population. B shows the relationship curve between AISI and albuminuria after dividing the population into male and female groups.

表 3 AISI与白蛋白尿的分段回归分析

Table 3 Segmented regression of AISI and albuminuria

Piecewise regression	Female	Male	Total
Inflection point (K)	8.69	7.25	8.46
<K effect 1*	1.13 (1.05-1.22)	0.93 (0.77-1.13)	1.14 (1.08-1.21)
P	<0.001	0.464	<0.001
>K effect 2*	1.35 (1.15-1.60)	1.34 (1.25-1.45)	1.39 (1.26-1.53)
P	<0.001	<0.001	<0.001
Effect 2-1*	1.19 (0.97-1.47)	1.44 (1.14-1.82)	1.22 (1.07-1.39)
P	0.092	0.002	0.004
Likelihood ratio test	0.094	0.002	0.004

* The data are expressed as OR (95% CI).

效应显著,但两个分段之间的斜率差异并不显著。然而,在男性中,存在显著的阈值效应。当log_2AISI小于7.25时,log_2AISI的增加并不增加白蛋白尿的风险,但当log_2AISI超过7.25时,log_2AISI的增加显著增加白蛋白尿的风险。

2.4 敏感性分析

作为敏感性分析,本研究进行了加权多变量逻辑回归,将结果变量更改为大量白蛋白尿,并校正了所有协变量。结果表明,log_2AISI每增加一个单位,发展成大量白蛋白尿的风险增加20%(OR=1.20, 95%CI: 1.15 ~ 1.26, *P*<0.001)。与Q1相比,Q3的白蛋白尿风险增加了69%(OR=1.69, 95%CI: 1.27 ~ 2.25, *P*<0.001),Q2增加了40%(OR=1.40, 95%CI: 1.03 ~ 1.92, *P*=0.030)。见表4。

表 4 log_2AISI与大量蛋白尿的关系

Table 4 The relationship between log_2AISI and massive proteinuria

Variable	Model 1		Model 2		Model 3	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Continuous variable	1.32 (1.27-1.38)	<0.000 1	1.31 (1.26-1.37)	<0.000 1	1.20 (1.15-1.26)	<0.000 1
Categorical variable						
Q1	Ref.		Ref.		Ref.	
Q2	1.44 (1.08-1.92)	0.010	1.55 (1.16-2.06)	0.003	1.40 (1.03-1.92)	0.030
Q3	2.40 (1.88-3.06)	<0.000 1	2.52 (1.97-3.23)	<0.000 1	1.69 (1.27-2.25)	<0.001
P-trend (categorical variable)	<0.000 1		<0.000 1		<0.001	

Model 1 was djusts for none; model 2 was adjusted for age, gender, race, and education; model 3 was adjusted for hypertension, diabetes, heart failure, smoking, alcohol consumption, systolic blood pressure, diastolic blood pressure, body mass index, estimated glomerular filtration rate, high-density lipoprotein cholesterol, creatinine, total cholesterol, uric acid, glycated hemoglobin, alanine aminotransferase, aspartate aminotransferase, albumin, use of antihypertensive drugs, and use of antidiabetic drugs, and the use of lipid-lowering drugs was further adjusted. OR: odds ratio; CI: confidence interval.

2.5 亚组分析

见图3。为了检验不同人群背景之间的关系,本研究根据年龄、性别、种族和族群、BMI、吸烟情况、饮酒习惯、高血压、糖尿病和eGFR进行了亚组分析和交互作用分析。结果表明:与女性相比,男性AISI与蛋白尿风险之间的正向关系更为明显。同样,与血压正常者相比,高血压患者的这种关联性更强;与体质量正常者相比,超重者的这种关联性更强。此外,吸烟者和饮酒者分别比不吸烟者和不饮酒者表现出AISI与蛋白尿风险之间更明显的正向关系。这些发现表明,性别、血压、BMI、吸烟和饮酒与AISI存在交互作用,影响蛋白尿的风险。

3 讨论

本研究首次利用NHANES数据探讨了log_2AISI与白蛋白尿之间的关系。作为一项横断面研究,共纳入32 273名参与者,研究发现log_2AISI较高的参与者更容易患有白蛋白尿。GAM和分段回归分析表明存在阈值效应,且性别差异明显,特别是在男性中存在显著的阈值效应。当log_2AISI超过7.25时,即AISI超过2.86,蛋白尿的风险显著增加。亚组分析表明,这一关联在不同人群中是稳定

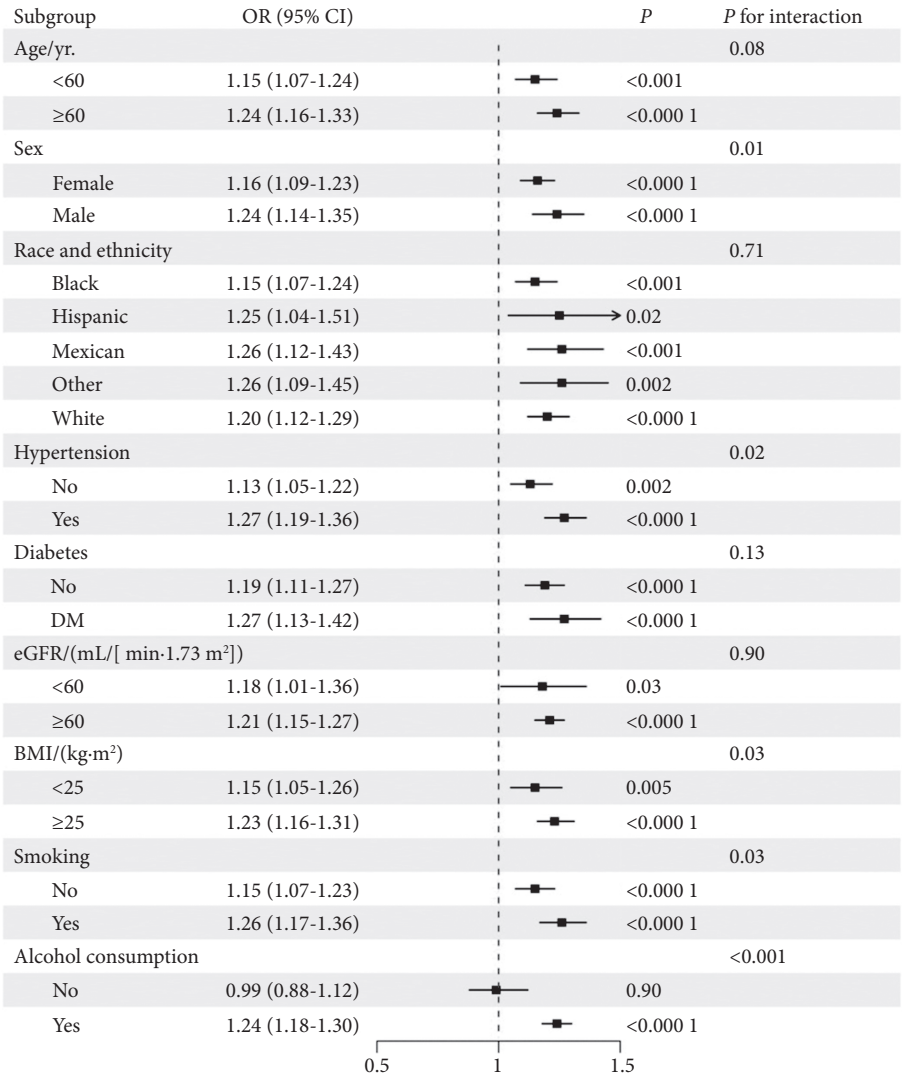

图 3 亚组分析和交互作用分析

Fig 3 Subgroup analysis and interaction analysis

的。性别、吸烟情况、饮酒习惯、高血压和BMI与AISI存在交互作用。敏感性分析进一步证实了这一关联的稳定性。该发现强调了监测和控制体内炎症水平对预防和管理肾脏疾病的重要性。此外，这一发现也为未来的临床治疗提供了潜在的治疗靶点，即通过降低AISI来减少白蛋白尿的发生，从而保护肾脏健康。

既往研究主要集中在AISI与慢性肾脏病（chronic kidney disease, CKD）患者预后之间的关联。一项研究纳入了369例接受透析治疗的患者，中位随访时间32.83个月，发现在调整混杂因素后，AISI较高的患者存活率较低[19]。高血压也是导致肾脏损伤的重要原因，而且人们认为白蛋白尿与高血压引起的肾小球内皮损伤有关[20]。一项使用NHANES数据的队列研究发现，在有高血压的成年人中，更高的AISI与心血管死亡风险增加相关[17]。上述研究进一步支持本研究的发现，即AISI与肾脏损伤有关。

肾脏拥有驻留的免疫细胞，包括巨噬细胞和淋巴细胞，它们在维持肾功能和体内环境稳态中起着重要作用[21]。然而，炎症诱因导致炎症细胞增殖，细胞因子释放以及循环中炎症细胞的招募[22]。这会通过促进肾小球结构的破坏和肾间质的纤维化，损害肾脏的重吸收和过滤功能。此外，炎症会激活肾素-血管紧张素-醛固酮系统，减少血管活性物质的释放，以及肾小球滤过压力的异常[23]。而且，炎症因子可以抑制如胆红素、过氧化物酶体增殖激活受体伽马共激活蛋白-1α等肾脏保护因子的合成和释放，以及如IL-10等抗炎相关细胞因子[24-25]。

目前的研究还发现，抑制炎症信号传导可以减少尿白蛋白排泄。TNF-α和核因子-κB在肾损伤中扮演重要角色。动物实验中发现，抑制它们可减少尿白蛋白排泄[26-27]。此外，抗炎治疗可能对高炎症负荷人群也有效。在一项

开放标签、前瞻性、单中心、随机对照研究中,262例稳定冠状动脉疾病患者被随机分组,并随访1年,观察二十碳五烯酸(eicosapentaenoic acid, EPA)和二十二碳六烯酸(docosahexaenoic acid, DHA)补充对其白蛋白尿的影响,结果表明ω-3可以减少患者的白蛋白尿;这些患者有高炎症负荷,ω-3脂肪酸通过治疗炎症来防止冠状动脉斑块进展[28]。在RIDKER等[29]的研究中,对于接受稳定他汀治疗的9151例心肌梗死后患者,使用IL-1β抗体的抗炎治疗在CKD患者中比正常肾功能患者具有更优越的心血管效益。

综上,AISI与白蛋白尿风险之间存在正向的关联。但本研究尚存局限:首先,这是一项横断面研究,不能建立因果推论。其次,本研究的样本基于美国人口,因此将结论应用到其他人群可能存在局限性。需要更广泛的队列研究来观察AISI与白蛋白尿之间的关系。

* * *

作者贡献声明 孙丽荣负责论文构思、数据审编、正式分析、调查研究、软件、可视化和初稿写作,霍醒伟负责论文构思、研究方法、提供资源和审读与编辑写作,贾珊珊负责正式分析、研究项目管理和验证,陈晓平负责经费获取、监督指导和审读与编辑写作。所有作者已经同意将文章提交给本刊,且对将要发表的版本进行最终定稿,并同意对工作的所有方面负责。

Author Contribution SUN Lirong is responsible for conceptualization, data curation, formal analysis, investigation, software, visualization, and writing--original draft. HUO Xingwei is responsible for conceptualization, methodology, resources, and writing--review and editing. JIA Shanshan is responsible for formal analysis, project administration, and validation. CHEN Xiaoping is responsible for funding acquisition, supervision, and writing--review and editing. All authors consented to the submission of the article to the Journal. All authors approved the final version to be published and agreed to take responsibility for all aspects of the work.

利益冲突 所有作者均声明不存在利益冲突

Declaration of Conflicting Interests All authors declare no competing interests.

致谢 感谢所有NHANES的工作人员和美国疾病预防控制中心(CDC)的支持。

参 考 文 献

[1] DAEHN I S, DUFFIELD J S. The glomerular filtration barrier: a structural target for novel kidney therapies. Nat Rev Drug Discov, 2021, 20(10): 770–788. doi: 10.1038/s41573-021-00242-0.

[2] ORTIZ A, Asociación Información Enfermedades Renales Genéticas (AIRG-E), European Kidney Patients' Federation (EKPF), *et al*. RICORS2040: the need for collaborative research in chronic kidney disease. Clin Kidney J, 2022, 15(3): 372–387. doi: 10.1093/ckj/sfab170.

[3] Writing Group for the CKD Prognosis Consortium, GRAMS M E, CORESH J, *et al*. Estimated glomerular filtration rate, albuminuria, and adverse outcomes: an individual-participant data meta-analysis. JAMA, 2023, 330(13): 1266–1277. doi: 10.1001/jama.2023.17002.

[4] KÜHN A, Van der GIET M, KUHLMANN M K, *et al*. Kidney function as risk factor and predictor of cardiovascular outcomes and mortality among older adults . Am J Kidney Dis, 2021, 77(3): 386-396. e1. doi: 10.1053/j.ajkd.2020.09.015.

[5] CHU C D, XIA F, DU Y, *et al*. Estimated prevalence and testing for albuminuria in US adults at risk for chronic kidney disease. JAMA Netw Open, 2023, 6(7): e2326230. doi: 10.1001/jamanetworkopen.2023.26230.

[6] QIAO Y, SHIN J I, CHEN T K, *et al*. Association of albuminuria levels with the prescription of renin-angiotensin system blockade. Hypertension, 2020, 76(6): 1762–1768. doi: 10.1161/HYPERTENSIONAHA.120.15956.

[7] CHU C D, POWE N R, SHLIPAK M G, *et al*. Albuminuria testing and nephrology care among insured US adults with chronic kidney disease: a missed opportunity. BMC Prim Care, 2022, 23(1): 299. doi: 10.1186/s12875-022-01910-9.

[8] MCGILL J B, HALLER H, ROY-CHAUDHURY P, *et al*. Making an impact on kidney disease in people with type 2 diabetes: the importance of screening for albuminuria. BMJ Open Diabetes Res Care, 2022, 10(4): e002806. doi: 10.1136/bmjdrc-2022-002806.

[9] WILLIAMSON T, GOMEZ-ESPINOSA E, STEWART F, *et al*. Poor adherence to clinical practice guidelines: a call to action for increased albuminuria testing in patients with type 2 diabetes. J Diabetes Complications, 2023, 37(8): 108548. doi: 10.1016/j.jdiacomp.2023.108548.

[10] CUSICK M M, TISDALE R L, CHERTOW G M, *et al*. Population- w ide screening for chronic kidney disease: a cost-effectiveness analysis. Ann Intern Med, 2023, 176(6): 788–797. doi: 10.7326/M22-3228.

[11] KASPAR C D W, LU J. Hyperuricemia, elevated body mass index, female sex, and albuminuria increase the probability of elevated high-sensitivity C-reactive protein: results from the National Health and Nutrition Examination Survey 2015-2018. Front Public Health, 2021, 9: 689219. doi: 10.3389/fpubh.2021.689219.

[12] UPADHYAY A, LARSON M G, GUO C Y, *et al*. Inflammation, kidney function and albuminuria in the Framingham Offspring cohort. Nephrol Dial Transplant, 2011, 26(3): 920–926. doi: 10.1093/ndt/gfq471.

[13] MASHIMA Y, KONTA T, KUDO K, *et al*. Polymorphism of proinflammatory cytokine genes and albuminuria in the Japanese general population: the Takahata study. Nephrol Dial Transplant, 2011, 26(12): 3902–3907. doi: 10.1093/ndt/gfr105.

[14] SHAHZAD K, FATIMA S, KHAWAJA H, *et al*. Podocyte-specific Nlrp3 inflammasome activation promotes diabetic kidney disease. Kidney Int, 2022, 102(4): 766–779. doi: 10.1016/j.kint.2022.06.010.

[15] QIN Z, LI H, WANG L, *et al*. Systemic immune-inflammation index is associated with increased urinary albumin excretion: a population-based study. Front Immunol, 2022, 13: 863640. doi: 10.3389/fimmu.2022.863640.

[16] LI X, CUI L, XU H. Association between systemic inflammation response index and chronic kidney disease: a population-based study. Front

Endocrinol (Lausanne), 2024, 15: 1329256. doi: 10.3389/fendo.2024.1329256.

[17] XIU J, LIN X, CHEN Q, *et al*. The aggregate index of systemic inflammation (AISI): a novel predictor for hypertension. Front Cardiovasc Med, 2023, 10: 1163900. doi: 10.3389/fcvm.2023.1163900.

[18] DELANAYE P, CAVALIER E, POTTEL H, *et al*. New and old GFR equations: a European perspective. Clin Kidney J, 2023, 16(9): 1375–1383. doi: 10.1093/ckj/sfad039.

[19] YANG Y, XU Y, LIU S, *et al*. The systemic inflammation indexes predict all-cause mortality in peritoneal dialysis patients. Ren Fail, 2023, 45(1): 2160348. doi: 10.1080/0886022X.2022.2160348.

[20] SUN D, WANG J, SHAO W, *et al*. Pathogenesis and damage targets of hypertensive kidney injury. J Transl Int Med, 2020, 8(4): 205–209. doi: 10.2478/jtim-2020-0033.

[21] LI J, YANG Y, WANG Y, *et al*. Metabolic signatures of immune cells in chronic kidney disease. Expert Rev Mol Med, 2022, 24: e40. doi: 10.1017/erm.2022.35.

[22] KANY S, VOLLRATH J T, RELJA B. Cytokines in inflammatory disease. Int J Mol Sci, 2019, 20(23): 6008. doi: 10.3390/ijms20236008.

[23] SATOU R, PENROSE H, NAVAR L G. Inflammation as a regulator of the renin-angiotensin system and blood pressure. Curr Hypertens Rep, 2018, 20(12): 100. doi: 10.1007/s11906-018-0900-0.

[24] ABRAHAM C R, LI A. Aging-suppressor klotho: prospects in diagnostics and therapeutics. Ageing Res Rev, 2022, 82: 101766. doi: 10.1016/j.arr.2022.101766.

[25] WEI W, ZHAO Y, ZHANG Y, *et al*. The role of IL-10 in kidney disease. Int Immunopharmacol, 2022, 108: 108917. doi: 10.1016/j.intimp.2022.108917.

[26] OPAZO-RÍOS L, PLAZA A, SÁNCHEZ MATUS Y, *et al*. Targeting NF-κB by the cell-permeable NEMO-binding domain peptide improves albuminuria and renal lesions in an experimental model of type 2 diabetic nephropathy. Int J Mol Sci, 2020, 21(12): 4225. doi: 10.3390/ijms21124225.

[27] SHEN J, DAI Z, LI Y, *et al*. TLR9 regulates NLRP3 inflammasome activation via the NF-κB signaling pathway in diabetic nephropathy. Diabetol Metab Syndr, 2022, 14(1): 26. doi: 10.1186/s13098-021-00780-y.

[28] ELAJAMI T K, ALFADDAGH A, LAKSHMINARAYAN D, *et al*. Eicosapentaenoic and docosahexaenoic acids attenuate progression of albuminuria in patients with type 2 diabetes mellitus and coronary artery disease. J Am Heart Assoc, 2017, 6(7): e004740. doi: 10.1161/JAHA.116.004740.

[29] RIDKER P M, TUTTLE K R, PERKOVIC V, *et al*. Inflammation drives residual risk in chronic kidney disease: a CANTOS substudy. Eur Heart J, 2022, 43(46): 4832–4844. doi: 10.1093/eurheartj/ehac444.

（2023 – 11 – 26收稿, 2024 – 05 – 12修回）

编辑　余　琳