·临床研究·

高尿酸血症与类风湿关节炎患者全因死亡率的相关性

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【摘 要】 目的 探讨高尿酸血症(HUA)与类风湿关节炎(RA)患者全因死亡率的相关性。**方法** 基于2001年至2018年美国国家健康与营养检查调查,选取1 507例基线患有RA的患者为研究对象。根据随访终点时患者的生存状态,分为生存组1 035例和死亡组472例。根据是否合并HUA,分为HUA组418例和非HUA组1 089例。采用R软件4.1.0版本进行统计分析。采用限制性立方样条(RCS)、多变量Cox回归模型以及Kaplan-Meier生存曲线分析HUA与RA患者全因死亡率之间的关系,并针对年龄和性别进行亚组分析。**结果** 两组患者年龄、种族、家庭年收入、婚姻状况、受教育程度及体质量指数比较,差异均有统计学意义(均$P<0.05$)。与生存组相比,死亡组患者高血压患病率、SUA水平和尿白蛋白水平显著升高,25-羟维生素D和尿肌酐水平显著降低,差异均有统计学意义(均$P<0.05$)。RA患者SUA水平每增加10 μmol/L,全因死亡风险增加1%($HR=1.01$,95%CI 1.01~1.02)。性别分层分析显示,女性RA患者SUA水平与全因死亡率呈显著正相关($HR=1.02$,95%CI 1.01~1.04)。年龄分层分析显示,≥60岁RA患者SUA水平每增加10 μmol/L,全因死亡风险增加1%($HR=1.01$,95%CI 1.00~1.03),其中≥60岁女性RA患者显示出较强关联性,SUA水平每增加10 μmol/L,全因死亡风险增加2%($HR=1.02$,95%CI 1.01~1.04)。HUA组患者全因死亡风险较非HUA组增加33%($HR=1.33$,95%CI 1.08~1.62)。性别分层分析显示,HUA组女性患者的全因死亡风险增加69%($HR=1.69$,95%CI 1.23~2.33)。年龄分层分析显示,HUA组≥60岁患者的全因死亡风险增加39%($HR=1.39$,95%CI 1.12~1.73),其中≥60岁女性患者的全因死亡风险增加最为显著($HR=1.76$,95%CI 1.26~2.45)。Kaplan-Meier生存分析显示,HUA可能与较低的生存率相关,且HUA组的累计死亡率显著高于非HUA组($P<0.05$)。RCS分析显示,在所有RA患者中,当SUA>350.9 μmol/L时,SUA水平与全因死亡率呈非线性正相关($P=0.017$)。而在≥60岁女性RA患者中,当SUA>333.1 μmol/L时,SUA水平与全因死亡率呈非线性正相关($P=0.004$)。**结论** HUA与RA患者全因死亡风险显著相关,尤其影响老年女性患者。建议对SUA≥333.1 μmol/L的老年女性RA患者,开展更密切的随访监测。

【关键词】 血清尿酸;类风湿关节炎;死亡率;美国国家健康与营养调查
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Correlation between hyperuricemia and all-cause mortality in patients with rheumatoid arthritis

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【Abstract】 Objective To investigate the correlation between hyperuricemia (HUA) and all-cause mortality in rheumatoid arthritis (RA) patients. **Methods** Based on data from the 2001 to 2018 National Health and Nutritional Examination Survey (NHANES), 1 507 RA patients at baseline were enrolled. According to survival status at follow-up endpoint, participants were divided into a survival group ($n=1\,035$) and a death group ($n=472$). They were further divided into a hyperuricemia (HUA) group ($n=418$) and a non-HUA group ($n=1\,089$) based on HUA comorbidity. Statistical analysis was conducted using R software (version 4.1.0). Restricted cubic spline (RCS) models, multivariable Cox proportional hazards regression, and Kaplan-Meier survival analysis were employed to assess the relationship between HUA and all-cause mortality in RA patients. Subgroup analyses were conducted according to age and sex. **Results** There were statistically significant differences between the two groups in age, race, family annual income, marital status, education level, and body mass index (all $P<0.05$). Compared with the survival group, the death group had significantly increased prevalence of hypertension, SUA levels, and urinary albumin levels, but significantly decreased 25 hydroxyvitamin D and urinary creatinine levels, with statistically significant differences (all $P<0.05$). For every 10 μmol/L increase in SUA in RA patients, the risk of all-cause mortality increased by 1% ($HR=1.01$, 95%CI 1.01-1.02). Sex-stratified analysis showed a significant positive correlation between SUA levels and all-cause mortality in female RA patients ($HR=1.02$, 95%CI 1.01-1.04). Age-stratified analysis

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showed that for RA patients aged ≥ 60 years, an increase of 10 μmol/L in SUA levels raised the risk of all-cause mortality by 1% (*HR*= 1.01, 95% *CI* 1.00-1.03), and that female RA patients aged ≥ 60 years had a strong association, with an increase of 10 μmol/L in SUA levels raising the risk of all-cause mortality by 2% (*HR*=1.02, 95%*CI* 1.01-1.04). The mortality risk of patients in the HUA group was 33% higher than that in the non-HUA group (*HR*=1.33, 95%*CI* 1.08-1.62). Sex-stratified analysis showed that the mortality risk of female patients in the HUA group increased by 69% (*HR*=1.69, 95%*CI* 1.23-2.33). Age-stratified analysis showed that patients aged ≥ 60 years in the HUA group had a 39% increased risk of mortality (*HR*=1.39, 95%*CI* 1.12-1.73), with the most significant increase in risk observed in the subgroup of females aged ≥ 60 years (*HR*=1.76, 95%*CI* 1.26-2.45). Kaplan Meier survival analysis showed that HUA may be associated with lower survival rates, and cumulative mortality was significantly higher in the HUA group than in the non-HUA group ($P<0.05$). RCS analysis showed that a non-linear positive correlation between SUA levels and all-cause mortality when SUA>350.9 μmol/L among all RA patients ($P=0.017$) and when SUA>333.1 μmol/L in female RA patients aged ≥ 60 years ($P=0.004$). **Conclusion** HUA is significantly associated with increased all-cause mortality risk in RA patients, particularly affecting elderly female populations. Closer monitoring is recommended for elderly female RA patients with higher SUA levels (≥333.1 μmol/L).

【**Key words**】 serum uric acid; rheumatoid arthritis; mortality; National Health and Nutritional Examination Survey

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类风湿关节炎(rheumatoid arthritis,RA)是一种慢性自身免疫性疾病,主要表现为关节侵蚀性炎症,好发于中老年女性,全球患病率为 0.25%~1.00%[1]。RA 肢体残疾率较普通人群高 3.81%,死亡风险增加 40%~50%,预期寿命缩短 3~18 年[2-4]。然而,导致 RA 死亡风险增加的潜在机制尚未完全明确,其中高尿酸血症(hyperuricemia,HUA)可能是一项重要但未被充分研究的因素。HUA 是嘌呤代谢异常导致的综合征,定义为非同日两次血清尿酸(serum uric acid,SUA)水平>420 μmol/L。尿酸(uric acid,UA)作为嘌呤代谢终产物,是重要的内源性抗氧化剂,在血压调节和神经保护中发挥关键作用[5]。UA 水平异常可能参与了多种疾病的发病机制[6,7]。HUA 诱导尿酸盐晶体沉淀可激活 NOD 样受体热蛋白结构域蛋白 3,不仅会导致痛风,还可激活成纤维细胞样滑膜细胞,加重 RA 关节炎症[8-10]。因此,本研究基于美国国家健康与营养检查调查(National Health and Nutritional Examination Survey,NHANES)数据库,探究 HUA 与 RA 患者全因死亡率的相关性。

1 对象与方法

1.1 研究对象

NHANES 是一项采用多阶段概率抽样的全国性横断面研究,选择美国非制度化平民人口为研究对象。本研究基于 NHANES 数据库,最终纳入 2001 年至 2018 年 9 个周期共计 1 507 例 RA 患者为研究对象。根据随访终点时患者的生存状态,分为生存组 1 035 例和死亡组472例。根据是否合并 HUA,分为 HUA 组 418 例和非 HUA 组 1 089 例。纳入标准:(1)年龄≥20 岁;(2)访谈所收集的信息包括 RA 诊断信息和人口学信息。RA 的诊断基于以下连续问题:"是否曾经被医师或其他医疗专业人员告知患有关节炎?"、"是哪种类型的关节炎?"。将对第二个问题回答为"类风湿关节炎"者,归为 RA 患者;(3)有完整的 SUA 检测结果且有可随访的死亡结局数据。排除标准:(1)年龄<20 岁;(2)研究指标数据缺失。本研究获美国国家卫生统计中心伦理审查委员会批准。所有参与者均签署知情同意书。

1.2 方法

1.2.1 资料收集方法 (1)社会人口学特征:性别、年龄、种族、家庭收入、婚姻、教育水平及体质量指数(body mass index,BMI)等;(2)合并症:糖尿病、高血压及肾衰等;(3)实验室指标:25-羟维生素 D[25-hydroxyvitamin D, 25(OH)D]、SUA、总胆固醇、尿白蛋白及尿肌酐等。

1.2.2 随访方法 随访起点为患者首次纳入 NHANES 调查并完成基线检查的时间点。随访终点为 2019 年 12 月 31 日或参与者全因死亡时间点(以先发生者为准)。随访时间中位数为 80(1~225)个月。死亡信息通过 NHANES 与国家死亡指数数据库的链接获得。

1.3 统计学处理

采用 R 软件 4.1.0 版本进行统计分析。计量资料呈正态分布者以均数±标准差($\bar{x}\pm s$)表示,组间比较采用 t 检验;呈非正态分布者以中位数(四分位数间距)[$M(Q_1, Q_3)$]表示,组间比较采用 Kruskal-Wallis 检验。计数资料以例数(百分率)表示,组间比较采用 χ^2 检验。为降低混杂因素和选择偏倚,采用倾向性评分匹配。采用 R 语言的'MatchIt'包,运用最近邻匹配算法(卡尺宽度设为倾向性评分 logit 值标准差的 0.2 倍)进行 1:3 匹配。采用 Cox 回归模型估计死亡风险比(*HR*)并计算 95%置信区间(*CI*),HUA 作为分类变量纳入模型,并进行年龄和性别亚组分析。采用基于限制性立方样条(restricted

cubic spline,RCS)的 Cox 回归模型对 SUA 水平与 RA 全因死亡率的非线性关系进行可视化,亚组分析控制人口学和临床协变量。$P<0.05$ 为差异有统计学意义。

2 结 果

2.1 两组患者基线资料比较

两组患者年龄、种族、家庭年收入、婚姻状况、受教育程度及 BMI 比较,差异均有统计学意义($P<0.05$)。与生存组相比,死亡组患者高血压患病率、SUA 水平和尿白蛋白水平显著升高,25(OH)D 和尿肌酐水平显著降低,差异均有统计学意义(均 $P<0.05$;表 1)。

2.2 SUA 水平与 RA 患者全因死亡的 Cox 回归分析

RA 患者 SUA 每增加 10 μmol/L,全因死亡风险增加 1%($HR=1.01$,95%CI 1.01~1.02)。性别分层分析显示,女性 RA 患者中 SUA 水平与全因死亡率呈显著正相关($HR=1.02$,95%CI 1.01~1.04),而男性患者中该关联未达到统计学显著水平。年龄分层分析显示,≥60 岁 RA 患者 SUA 水平每增加 10 μmol/L,全因死亡风险增加 1%($HR=1.01$,95%CI 1.00~1.03),其中≥60 岁女性 RA 患者显示出较强关联性,SUA 水平每增加 10 μmol/L,全因死亡风险增加 2%($HR=1.02$,95%CI 1.01~1.04)。

HUA 组患者死亡风险较非 HUA 组增加 33%($HR=1.33$,95%CI 1.08~1.62)。性别分层分析显示,HUA 组女性患者的死亡风险增加 69%($HR=1.69$,95%CI 1.23~2.33),而男性患者中该关联未达到统计学显著水平。年龄分层分析表明,HUA 组≥60 岁的患者死亡风险增加 39%($HR=1.39$,95%CI 1.12~1.73),其中≥60 岁女性亚组的风险增加最为显著($HR=1.76$,95% CI 1.26~2.45)。详见表 2。

2.3 HUA 水平与 RA 患者生存率的 Kaplan-Meier 生存分析

Kaplan-Meier 生存分析显示,HUA 可能与较低的生存率相关,且 HUA 组的累计死亡率显著高于非 HUA 组($P<0.05$;图 1)。

2.4 SUA 水平与 RA 患者全因死亡率的剂量反应关系

RCS 分析显示,在所有 RA 患者中,当 SUA>350.9 μmol/L 时,SUA 水平与全因死亡率呈非线性正相关($P=0.017$;图 2A)。而在≥60 岁女性 RA 患者中,SUA>333.1 μmol/L 时,SUA 水平与全因死亡率呈非线性正相关($P=0.004$;图 2B)。

表 1 两组患者基线资料比较

Table 1 Comparison of baseline data between two groups

Item	Survival group($n=1\,035$)	Death group($n=472$)	P value
Female[n(%)]	442(42.7)	201(42.6)	1
Age[years,$M(Q_1, Q_3)$]	61.00(52.00,69.00)	74.00(65.00,80.00)	<0.001
Race[n(%)]			<0.001
Mexican American	113(10.9)	31(6.6)	
Other Hispanic	63(6.1)	10(2.1)	
Non-Hispanic white	390(37.7)	279(59.1)	
Non-Hispanic black	373(36.0)	137(29.0)	
Other race	96(9.3)	15(3.2)	
Family annual income[n(%)]			<0.001
<$44,000	648(62.6)	369(78.2)	
$44,000-$75,00	231(22.3)	89(18.8)	
≥$75,000	156(15.1)	14(3.0)	
Marital status[n(%)]			<0.001
Married/cohabiting	609(58.9)	214(45.3)	
Widowed/divorced/separated	343(33.1)	234(49.6)	
Unmarried	83(8.0)	24(5.1)	
Education level[n(%)]			<0.001
Under high school	305(29.5)	207(43.9)	
High school or equivalent	236(22.8)	128(27.1)	
Above high school	494(47.7)	137(29.0)	
BMI[kg/m^2, $M(Q_1, Q_3)$]	29.90(25.80,35.00)	28.45(24.38,32.81)	<0.001
Diabetes mellitus[n(%)]			0.613
No	731(70.6)	323(68.4)	
Boderline	36(3.5)	20(4.3)	
Yes	268(25.9)	129(27.3)	
Hypertension[n(%)]	647(62.5)	336(71.2)	0.001
Failing kidneys[n(%)]	80(7.7)	51(10.8)	0.062
25(OH)D[nmol/L, $M(Q_1, Q_3)$]	61.80(44.35,81.82)	56.55(37.50,73.00)	<0.001
Serum uric acid(μmol/L, $\bar{x}\pm s$)	357.49±97.28	377.88±101.53	<0.001
Total cholesterol[mmol/L,$M(Q_1, Q_3)$]	4.94(4.27,5.66)	4.89(4.08,5.74)	0.275
Urinary albumin[mg/L, $M(Q_1, Q_3)$]	9.80(4.90,23.65)	15.60(6.57,46.85)	<0.001
Urine creatinine[μmol/L, $M(Q_1, Q_3)$]	10 166.00(6 188.00,15 470.00)	9 193.50(5 812.00,13 790.00)	0.013

BMI: body mass index; 25(OH)D: 25-hydroxyvitamin D.

表 2 SUA 水平对不同性别和年龄 RA 患者全因死亡影响的 Cox 回归分析

Table 2 Cox regression analysis of influence of SUA levels on all-cause mortality in RA patients of different genders and ages

Group	For every 10 μmol/L increase in SUA		HUA	
	HR(95%*CI*)	*P* value	*HR*(95%*CI*)	*P* value
All RA patient	1.01(1.01-1.02)	0.004	1.33(1.08-1.62)	0.006
Male	1.00(0.99-1.02)	0.520	1.04(0.79-1.37)	0.754
Female	1.02(1.01-1.04)	0.003	1.69(1.23-2.33)	0.001
Age<60 years	1.01(0.99-1.04)	0.337	0.75(0.37-1.52)	0.430
Age≥60 years	1.01(1.00-1.03)	0.007	1.39(1.12-1.73)	0.003
Female, age≥60 years	1.02(1.01-1.04)	0.004	1.76(1.26-2.45)	<0.001

SUA: serum uric acid; RA: rheumatoid arthritis; HUA: hyperuricemia.

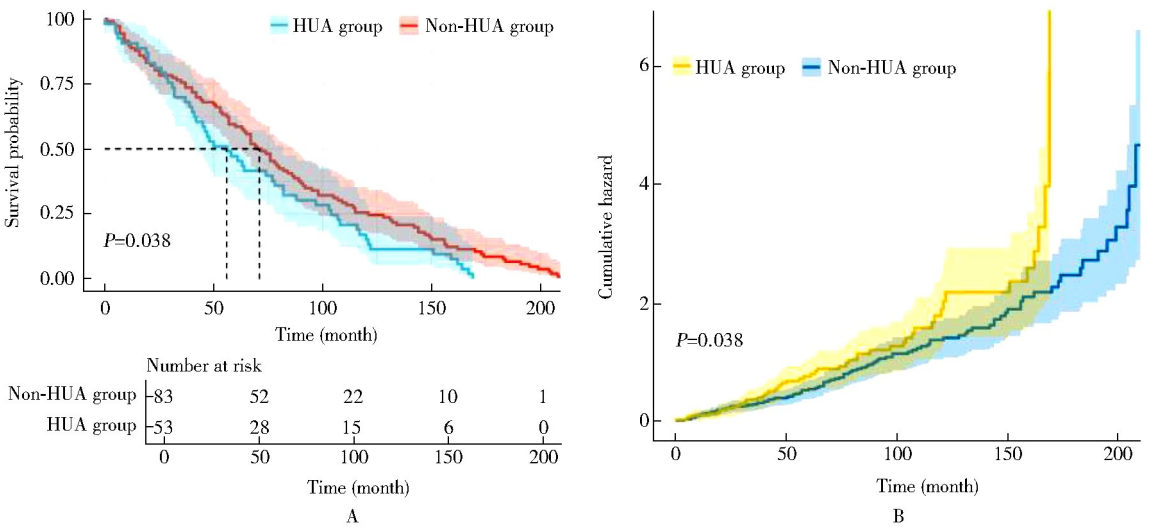


图 1 HUA 与 RA 患者累计生存率(A)及累计死亡率(B)的关系

Figure 1 Relationship between HUA and cumulative survival rate (A) and cumulative mortality rate (B) in patients with RA

HUA: hyperuricemia; RA: rheumatoid arthritis.

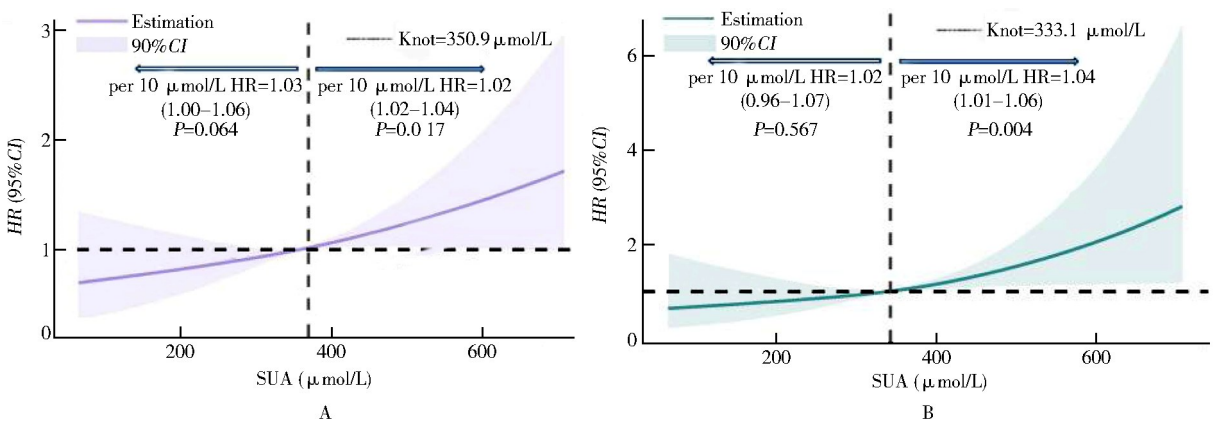


图 2 SUA 水平与 RA 患者(A)及≥60 岁女性 RA 患者(B)全因死亡率的剂量反应关系

Figure 2 Dose-response relationship between SUA levels and all-cause mortality in RA patients (A) and female RA patients aged ≥ 60 years (B)

SUA: serum uric acid; RA: rheumatoid arthritis. All models were adjusted for age, gender, race, family annual income, marital status, education level, body mass index, diabetes mellitus, hypertension, failing kidneys, total cholesterol, 25-hydroxyvitamin D, urinary albumin, and urine creatinine.

3 讨 论

本研究基于NHANES数据库,历时9年随访得出的结果提示,RA患者合并HUA的患病情况值得临床高度关注。进一步分析显示,SUA显著增加了RA患者的全因死亡风险,这一关联在≥60岁女性患者中表现尤为显著。经多变量调整后发现,HUA组患者全因死亡风险较非HUA组增加33%,表明HUA是RA患者死亡风险的独立预测因子。已有证据显示高水平SUA与RA患者心血管疾病相关死亡风险显著相关[11]。本研究亚组分析进一步揭示,女性HUA患者的死亡风险增加69%,其中≥60岁女性患者的死亡风险增加最为显著,这一结果与我国基于中国老年人前瞻性队列研究得出的关于性别和年龄对UA代谢影响的发现相符[12]。一项涵盖3 205名健康体检人群的横断面研究证实了这一现象的病理生理学基础:虽然男性SUA水平总体高于女性,但女性50岁后SUA水平明显上升,而男性各年龄段相对稳定。同时,HUA与血糖、血脂代谢异常密切相关,提示绝经后女性UA代谢改变及其伴随的代谢紊乱可能是老年女性HUA患者死亡风险显著增加的重要机制[13]。

本研究发现,SUA与RA患者全因死亡率之间存在非线性关系和明确的阈值效应。在总体RA患者中,当SUA>350.9 μmol/L时呈显著正相关,而在老年女性RA患者中阈值进一步降低,提示老年女性可能对UA升高更为敏感,推测与绝经后激素变化有关。既往研究显示,雌激素加孕激素疗法可显著降低绝经后女性SUA水平,而使用其他激素治疗无明显作用[14]。另一项基于女性健康体检人群的研究进一步证实了性激素与UA代谢的密切关系。研究发现,SUA与雌二醇、孕酮呈显著负相关,与血糖、睾酮呈正相关,这为老年女性RA患者SUA阈值降低提供了激素水平变化的直接证据[15]。此外,肾功能的年龄相关性下降也可能是重要因素。一项针对中国中老年人的纵向研究证实,年龄增长是肾功能快速下降的独立危险因素,且女性患者中UA变化与肾功能下降的关联更为显著[16],提示老年女性肾脏对UA代谢异常敏感性更高。因此,老年女性RA患者SUA阈值降低可能是激素水平下降与肾功能衰退共同作用的结果。结合Tian等[17]基于中国河北省的大型前瞻性队列研究可发现,SUA的较高变异性与全因死亡风险独立相关,这一关联与一般人群的基线SUA水平和变异性方向无关。这一发现提示在RA患者的长期管理中,不仅要关注SUA的具体水平,更应重视其长期稳定性。鉴于RA患者存在较高的炎症负担及多种影响UA代谢的因素[18,19],建议对老年女性等高危人群建立SUA连续监测机制,将UA变异性纳入预后评估体系,以实现更精准的风险分层和个体化管理。

从病理机制角度而言,有体外实验证实,尿酸钠晶体能够直接激活成纤维细胞样滑膜细胞,显著增加白细胞介素-6、CXC趋化因子配体8和基质金属蛋白酶-1等炎症因子的释放,且与肿瘤坏死因子α或白细胞介素-1β联合作用时产生协同效应,通过细胞外信号调节蛋白激酶和c-Jun氨基末端激酶信号通路介导关节破坏[10]。这一发现表明HUA可作为RA疾病进展的主动参与者,与原有炎症状态相互放大,形成恶性循环,为本研究中HUA显著增加RA患者全因死亡风险提供了病理生理学基础。研究表明,甲氨蝶呤可通过阻断腺苷向UA转化降低SUA水平,且出现UA降低的RA患者疾病活动度控制更佳[20],而来氟米特则通过促进UA的肾脏排泄实现降UA作用[19]。横断面研究进一步显示,SUA水平与RA患者的心血管共病存在独立关联。合并高血压的RA患者SUA水平显著高于血压正常者(5.44和4.56 mg/dl;P<0.001),SUA每增加1 mg/dl,高血压风险增加59%(OR = 1.59;P = 0.001)[21];同时,合并心血管疾病的RA患者SUA水平亦显著升高(5.68和5.06 mg/dl,P = 0.001),SUA≥6.38 mg/dl者心血管疾病风险增加6倍(OR = 6.46,P = 0.007)[22]。这些发现均表明HUA可能通过加重高血压、心血管疾病等主要致死性合并症的负荷,成为影响RA患者长期生存的重要病理机制,为本研究中HUA独立增加全因死亡风险33%这一发现,提供了重要的共病机制支撑。

综上,本研究表明HUA可能是RA患者全因死亡的独立危险因素,SUA水平与老年女性RA患者的全因死亡率呈非线性正相关。本研究的优势在于大样本量(n = 1 507)及采用性别和年龄亚组分析,增强了结果的准确性和客观性。局限性在于横断面研究难以确定因果关系。未来需要开展严格设计的大样本前瞻性研究对结果进一步验证。鉴于目前相关研究较少,本研究提出的SUA阈值对预测RA患者死亡风险及指导临床管理具有重要参考价值。

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