Relationship between serum uric acid levels and pulmonary embolism: an age-based stratified analysis

Bin Yuan[1†], Lingyue Song[1†], Weiqing Su[2†], Xianbing Zeng[2], Jinqiang Su[2], Jie Sun[1], Jun Wu[1], Kaili Fu[1], Zhihai Huang[1], Qiaoyun Chen[1], Dingyu Guo[1], Xishi Sun[1*] and Lingpin Pang[1*]

Abstract

Background The association between uric acid and pulmonary embolism(PE) remains controversial, and there has been limited investigation into how uric acid influences pulmonary embolism across different age groups. Our study aimed to elucidate the relationship between uric acid levels and pulmonary embolism, considering variations across age groups.

Methods A total of 368 patients who underwent computed tomography pulmonary angiography from July 2018 to May 2022 were included in the analysis. Subsequently, the cohort was stratified by age, with separate univariate and multivariate logistic regression analyses conducted for the elderly (aged ≥ 60 years) and non-elderly (aged < 60 years), respectively.

Results The study revealed that patients with PE exhibited higher uric acid levels compared to those without (325.11 ± 137.02 vs. 298.26 ± 110.54 (umol/l), $p = 0.039$). This disparity persisted even after adjusting for multiple confounders (OR = 1.002, 95% CI 1.000-1.005, $p = 0.042$). Additionally, a notable age difference was observed between PE and non-PE patients (65.7 ± 16.12 vs. 61.42 ± 15.03 (umol/l), $p = 0.009$). Subsequently, upon age stratification, significant differences ($p < 0.05$) in serum uric acid were noted between PE and non-PE patients in both elderly and non-elderly populations. However, elevated uric acid levels were independently associated with PE only in the elderly following adjustment for multiple confounders (OR = 1.003, 95% CI 1.001–1.005, $p = 0.008$).

Conclusion High uric acid levels are an independent risk factor for pulmonary embolism in the elderly (≥ 60 years).

Keywords Pulmonary embolism, Uric acid, Age

†Bin Yuan, Lingyue Song and Weiqing Su contributed equally to this work.

*Correspondence:
Xishi Sun
1097213689@qq.com
Lingpin Pang
panglingpin@126.com
[1] Affiliated Hospital of Guangdong Medical University, Zhanjiang 524000, Guangdong, China
[2] Lianjiang People's Hospital, Zhanjiang 524400, Guangdong, China

Introduction

Pulmonary embolism (PE) manifests as a clinical syndrome triggered by endogenous or exogenous emboli obstructing the pulmonary artery, resulting in pulmonary circulation and right heart dysfunction. It ranks among the top three causes of cardiovascular death globally, following stroke and heart attack [1]. Symptoms include dyspnea, chest pain, syncope or dizziness, hemoptysis, and palpitations [2]. Risk factors encompass genetics, age, pregnancy, postpartum, cancer, recent surgery, trauma or fracture, and immobility [3]. In the United States alone, PE affects around 370,000 individuals annually and

Yuan *et al. Thrombosis Journal*   (2024) 22:87

Page 2 of 11

contributes to an estimated 60,000 to 100,000 deaths per year [3]. While the incidence of PE is on the rise, overall mortality rates are decreasing due to improved diagnostics, treatment, and interventions. Nonetheless, PE remains a prevalent and potentially fatal type of venous thromboembolism [4].

Uric acid (UA) is the end product of purine metabolism, and its serum levels are closely influenced by dietary habits, physical activity, and other factors [5]. The prevalence of hyperuricemia in China has been steadily rising over the years [6]. The development of hyperuricemia is notably associated with age [7], with mean uric acid levels and hyperuricemia prevalence tending to increase in individuals aged 60 years or older [8]. Elevated serum uric acid levels have demonstrated significant associations with the development and prognosis of various cardiovascular diseases, including coronary heart disease, chronic kidney disease, heart failure, hypertension, and atrial fibrillation, thereby increasing the risk of cardiovascular mortality [9].

Diagnosing pulmonary embolism poses a significant challenge, particularly in elderly patients. The nonspecific nature of its signs and symptoms makes it difficult to differentiate from other conditions with similar presentations, such as congestive heart failure and chronic obstructive pulmonary disease, based solely on clinical manifestations [10]. The discovery of effective biomarkers contributes to enhanced diagnosis and prevention strategies for pulmonary embolism. Numerous observational studies have identified a strong correlation between elevated serum uric acid levels and the risk of pulmonary embolism, independent of other confounding risk factors [11, 12]. Additionally, serum uric acid levels play a role in prognostic stratification among patients with pulmonary embolism [13, 14]. Despite several recent investigations into the relationship between uric acid levels and venous thromboembolism, controversy remains regarding its association with pulmonary embolism [15, 16]. Therefore, this study primarily aims to explore the relationship between uric acid levels and pulmonary embolism, as well as their correlation across different age groups, aiming to furnish a theoretical basis for the diagnosis, prevention, and prognosis of pulmonary embolism.

Methods
Population and study design
This study conducted a retrospective analysis of data obtained from patients who underwent computed tomography pulmonary angiography (CTPA) during their hospitalization at the Affiliated Hospital of Guangdong Medical University from July 2018 to May 2022. Approval for the study was granted by the Medical Ethics Committee of the Affiliated Hospital of Guangdong Medical University, adhering to the principles outlined in the Helsinki Declaration and its amendments (Ethical No.: YJYS2024188). Inclusion criteria comprised patients aged > 18 years who had been hospitalized for at least 3 days, had undergone CTPA displaying sufficient quality for definitive diagnosis or exclusion of pulmonary embolism (PE), and possessed a complete medical history, clinical presentation, and laboratory results. Exclusion criteria included patients previously diagnosed with PE or receiving prophylactic medication, those with incomplete clinical data, and pregnant women.

Diagnostic criteria for PE
CTPA examination reveals filling defects in the pulmonary artery and its branches. Pulmonary embolism arises when a filling defect is observed in the pulmonary artery or any of its branches, whereas non-pulmonary embolism is indicated when the pulmonary artery shows adequate filling or no alteration in the filling defect is observed [17].

Basic data collection
The demographic and clinical data of all enrolled patients in this study were retrospectively collected. This included admission time, gender, age, and various clinical symptoms such as syncope, impaired consciousness, coughing up sputum, hemoptysis, chest tightness and chest pain, palpitations/tachycardia, shortness of breath, unilateral lower extremity edema or pain, hypoxemia. Past medical history, including chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), hypertension, atrial fibrillation (AF), fracture, and recent trauma/surgery (within one month), was also recorded. Laboratory tests encompassed parameters such as white blood cell count (WBC), neutrophil proportion (NE), lymphocyte proportion (LY), monocyte proportion (MO), eosinophil proportion (EO), basophil proportion (BA), red blood cell count (RBC), hemoglobin (HGB), hematocrit (HCT), platelet volume distribution width (PDW), prothrombin time (PT), activated partial thromboplastin time (APTT), D-dimer (DD-i), alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine (Scr), uric acid (SUA), glucose (GLU), and triglycerides (TG). Additionally, lower extremity venous thrombosis and data from CTPA examinations were included.

Statistical methods
The Shapiro-Wilk test evaluates the normality of continuous variable distributions. For normally distributed measures, t-tests were utilized and presented as mean ± standard deviation; for non-normally distributed measures, rank sum tests were applied and presented as median (interquartile range). Count data were analyzed

Yuan *et al. Thrombosis Journal*   (2024) 22:87

Page 3 of 11

using the chi-square test and presented as frequencies (percentages). Univariate logistic regression analysis was conducted to estimate the odds ratio (OR) and corresponding 95% confidence interval (CI), followed by multivariate logistic regression analysis to examine the association between uric acid levels and pulmonary embolism development. To analyze the interaction between age and uric acid on pulmonary embolism. The ability of levels of SUA to predict PE was assessed by calculating the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. Pulmonary embolism served as the outcome variable, while predictor variables included those with $P < 0.05$ from univariate analysis or deemed clinically relevant. Model fit was assessed using the Hosmer–Lemeshow test. Statistical analyses were performed using SPSS 26.0 software, with significance evaluated using two-tailed P values. A threshold of < 0.05 was considered statistically significant.

Results
Baseline characteristics
According to our inclusion and exclusion criteria, 368 hospitalized patients who underwent CTPA were included, divided into 187 cases in the PE group and 181 cases in the non-PE group based on CTPA confirmation. Patients in the PE group were older (65.7 vs. 61.42, $P = 0.009$) and exhibited higher levels of WBC (9.27 ± 4.29 vs. 8.33 ± 4.02), NE (74.70 ± 12.39 vs. 69.57 ± 14.27), RBC (4.16 ± 0.84 vs. 3.93 ± 0.87), HCT (36.12 ± 6.76 vs. 34.08 ± 7.48), D-dimer [5.96 (2.55, 10.52) vs. 2.62 (1.01, 7.39)], SUA (325.11 ± 137.02 vs. 298.26 ± 110.54), GLU (6.40 ± 2.75 vs. 5.78 ± 1.89), recent (≤ 1 month) trauma or surgery (24.6% vs. 16.0%), palpitations/tachycardia (19.3% vs. 8.8%), shortness of breath (56.1% vs. 43.6%), unilateral lower extremity edema/pain (23.5% vs. 13.3%), hypoxemia (24.7% vs. 8.8%), and lower extremity venous thrombosis (37.3% vs. 25.3%) compared to non-PE patients ($P < 0.05$). Conversely, fracture (5.9% vs. 13.9%), LY (16.32 ± 11.55 vs. 19.38 ± 10.62), BA [0.26 (0.10, 0.40) vs. 0.30 (0.20, 0.50)], APTT (34.61 ± 9.50 vs. 37.92 ± 7.78), and TG (1.23 ± 0.66 vs. 1.42 ± 0.83) were significantly lower in the non-PE group ($P < 0.05$). Basic information is presented in Table 1.

Logistic regression analysis
To explore the impact of uric acid on pulmonary embolism, we examined clinically relevant variables with statistical significance ($P < 0.05$) and included them in both univariate and multivariate logistic regression analyses. Univariate logistic regression revealed that fracture, recent (≤ 1 month) trauma or surgery, palpitations/tachycardia, shortness of breath, unilateral lower extremity swelling/pain, hypoxemia, WBC, NE, LY, EO, RBC, HCT,

APTT, SUA, GLU, and TG could potentially influence pulmonary embolism ($P < 0.05$). To mitigate the influence of confounding factors, these variables were incorporated into multivariate logistic regression, which indicated that SUA were independent risk factors for pulmonary embolism ($P < 0.05$). For more details, refer to Table 2.

Comparison after stratification by age
In the clinical baseline data, a significant age difference was observed between patients with and without pulmonary embolism (65.7 vs. 61.42, $p < 0.01$). Subjects were categorized into 133 cases (age < 60 years) in the non-elderly group and 235 cases (age ≥ 60 years) in the elderly group, using 60 years as the cutoff. Variables screened for statistical significance ($p < 0.05$) or those clinically relevant continued to be compared, and differences between the groups were assessed within age subgroups.

It was notably higher in patients with pulmonary embolism than in non-pulmonary embolism patients exclusively in the elderly population (337.70 ± 144.84 vs. 291.32 ± 112.36, $p = 0.006$), with no statistically significant difference detected in the non-elderly population (299.73 ± 116.69 vs. 309.02 ± 107.57, $p = 0.673$). Further details are provided in Tables 3 and 4.

Logistic regression analysis after stratification by age
To investigate the impact of uric acid levels on pulmonary embolism across different age groups, we screened for statistically significant variables ($P < 0.05$) or those deemed clinically relevant for inclusion in logistic regression models for both univariate and multivariate analyses.

It appeared to potentially influence pulmonary embolism solely in the elderly population (OR = 1.003, 95% CI 1.001–1.005, $P = 0.008$), with no statistically significant association found in the non-elderly group (OR = 0.999, 95% CI 0.996–1.002, $P = 0.631$). Subsequent analysis after adjusting for confounders revealed uric acid as an independent risk factor for pulmonary embolism in the elderly (OR = 1.003, 95% CI 1.000-1.007, $P = 0.030$), whereas its significance was not established in the non-elderly (OR = 1.001, 95% CI 0.996–1.005, $P = 0.800$). Detailed results are presented in Tables 5 and 6.

P for Interaction between age and uric acid
The results showed that there was an interaction between age and uric acid, which doubled the risk of pulmonary embolism ($p = 0.002$). Old Age increased the risk of pulmonary embolism by 1.001 times($p = 0.008$). Detailed results are presented in Table 7.

Yuan *et al. Thrombosis Journal*   (2024) 22:87

Page 4 of 11

Table 1 Comparison of the characteristics of patients with pulmonary embolism and non-pulmonary embolism

		Non-PE (n = 181)	PE (n = 187)	T-value/χ²-value	P
Demographics					
Age (years)[a]		61.42 ± 15.03	65.7 ± 16.12	2.629	0.009*
sex	0	92(50.8%)	77(41.2%)	3.451	0.063
	1	89(49.2%)	110(58.8%)		
Past medical histories					
COPD		18(9.9%)	21(11.2%)	0.160	0.689
CHD		23(12.7%)	23(12.3%)	0.014	0.906
hypertension		57(31.5%)	56(29.9%)	0.103	0.748
AF		8(4.4%)	13(7.0%)	1.096	0.295
break		25(13.9%)	11(5.9%)	6.646	0.010*
Recent (less than or equal to 1 month) trauma or surgery		29(16.0%)	46(24.6%)	4.170	0.041*
Active stage of malignant tumor (except tumor has been removed or cured)		36(19.9%)	38(20.3%)	0.011	0.918
Clinical features					
syncope		4(2.2%)	7(3.8%)	0.810	0.368
Disturbance of consciousness		10(5.5%)	17(9.1%)	1.759	0.185
Cough and expectoration		90(49.7%)	85(45.5%)	0.672	0.412
hemoptysis		17(9.4%)	22(11.8%)	0.520	0.471
chest tightness and chest pain		64(35.4%)	66(35.5%)	0.001	0.980
Palpitations/tachycardia		16(8.8%)	36(19.3%)	8.217	0.004*
anhelation		79(43.6%)	105(56.1%)	5.752	0.016*
Unilateral lower extremity edema/pain		24(13.3%)	44(23.5%)	6.440	0.011*
hypoxemia		16(8.8%)	46(24.7%)	16.500	<0.001*
Laboratory					
WBC(*10^9/L)[a]		8.33 ± 4.02	9.27 ± 4.29	2.167	0.031*
NE(%)[a]		69.57 ± 14.27	74.70 ± 12.39	3.676	<0.001*
LY(%)[a]		19.38 ± 10.62	16.32 ± 11.55	2.651	0.008*
MO(%)[a]		7.96 ± 3.35	7.61 ± 3.08	1.044	0.297
EO(%)[b]		1.20(0.20, 2.50)	0.80(0.10, 2.00)	1.777	0.075
BA(%)[b]		0.30(0.20, 0.50)	0.26(0.10, 0.40)	2.041	0.041*
RBC(*10^9/L)[a]		3.93 ± 0.87	4.16 ± 0.84	2.592	0.010*
HGB(g/L)[a]		114.79 ± 26.36	119.47 ± 22.97	1.815	0.070
HCT(%)[a]		34.08 ± 7.48	36.12 ± 6.76	2.746	0.006*
PDW (%)[b]		11.50(9.70, 15.00)	11.70(10.20, 15.90)	1.856	0.063
PT(s)[a]		14 ± 2.01	13.70 ± 1.99	1.431	0.153
APTT(s)[a]		37.92 ± 7.78	34.61 ± 9.50	3.663	<0.001*
DD-i (mg/L)[b]		2.62(1.01, 7.39)	5.96(2.55, 10.52)	4.552	<0.001*
ALT(U/L)[b]		16.80(11.60, 31.20)	18.70(12.40, 31.10)	0.940	0.347
AST(U/L)[b]		23.30(16.50, 38.80)	22.50(17.20, 34.20)	0.315	0.753
Scr(umol/l)[a]		86.48 ± 73.53	83.76 ± 50.60	0.415	0.678
SUA(umol/l)[a]		298.26 ± 110.54	325.11 ± 137.02	2.072	0.039*
GLU(mmol/l)[a]		5.78 ± 1.89	6.40 ± 2.75	2.504	0.013*
TG(mmol/l)[a]		1.42 ± 0.83	1.23 ± 0.66	2.434	0.015*
Color Doppler Ultrasonography					
Lower extremity venous thrombosis		38(25.3%)	53(37.3%)	4.889	0.027*

Sex: 0 is female,1 is male

AF Atrial fibrillation, *WBC* White blood cell count, *NE* Neutrophil proportio, *LY* Lymphocyte proportion, *MO* Monocyte proportion, *EO* Eosinophil proportion, *BA* Basophil proportion, *RBC* Red blood cell count, *HGB* hemoglobin, *HCT* Hematocrit, *PDW* Platelet volume distribution width, *PT* Prothrombin time, *APTT* Partial thromboplastin time, *DD-I* D-dimer, *ALT* Alanine aminotransferase, *AST* Aspartate aminotransferase, *Scr* Serum creatinine, *SUA* Serum uric acid, *GLU* Glucose, *TG* Triglycerides

[a] data are presented as mean ± SD

Yuan *et al. Thrombosis Journal*   (2024) 22:87

Page 5 of 11

Table 2 Logistic regression of Uric Acid on Pulmonary Embolism

Variables	single-factor logistic regression		multifactor logistic regression	
	OR(95%CI)	*P*	OR(95%CI)	*P*
break	0.388(0.185, 0.813)	0.012*	0.149(0.053, 0.420)	< 0.001*
Recent (less than or equal to 1 month) trauma or surgery	1.710(1.018, 2.871)	0.042*	2.436(1.189, 4.990)	0.015*
Palpitations/tachycardia	2.459(1.311, 4.611)	0.005*	2.172(1.015, 4.649)	0.046*
anhelation	1.653(1.095, 2.486)	0.017*	1.113(0.666, 1.860)	0.683
Unilateral lower extremity edema/pain	2.013(1.165, 3.477)	0.012*	2.149(1.108, 4.166)	0.024*
hypoxemia	3.388(1.838, 6.247)	< 0.001*	2.929(1.371, 6.260)	0.006*
WBC(*10^9/L)	1.057(1.005, 1.111)	0.033*	0.999(0.930, 1.073)	0.978
NE(%)	1.030(1.013, 1.046)	< 0.001*	1.040(1.002, 1.079)	0.039*
LY(%)	0.974(0.955, 0.994)	0.010*	1.000(0.965, 1.037)	0.992
MO(%)	0.967(0.907, 1.030)	0.297	1.064(0.971, 1.167)	0.184
EO(%)	0.896(0.808, 0.992)	0.035*	0.992(0.852, 1.156)	0.922
BA(%)	0.978(0.681, 1.403)	0.903	1.313(0.676, 2.549)	0.421
RBC(*10^9/L)	1.378(1.076, 1.764)	0.011*	0.863(0.486, 1.534)	0.616
HGB(g/L)	1.008(0.999, 1.016)	0.071	0.968(0.927, 1.012)	0.151
HCT(%)	1.041(1.011, 1.072)	0.007*	1.179(0.987, 1.410)	0.070
PDW (%)	1.067(0.995, 1.143)	0.069	1.038(0.950, 1.135)	0.408
PT(s)	0.927(0.835, 1.029)	0.156	0.912(0.775, 1.072)	0.263
APTT(s)	0.954(0.929, 0.980)	0.001*	0.962(0.929, 0.996)	0.029*
DD-i (mg/L)	1.019(0.999, 1.038)	0.062	1.014(0.995, 1.034)	0.154
ALT(U/L)	1.005(0.999, 1.010)	0.076	1.011(1.003, 1.020)	0.007*
AST(U/L)	1.001(0.996, 1.006)	0.660	0.994(0.986, 1.002)	0.118
Scr(umol/l)	0.999(0.996, 1.003)	0.679	0.995(0.989, 1.000)	0.042*
SUA(umol/l)	1.002(1.000, 1.003)	0.041*	1.002(1.000, 1.005)	0.042*
GLU(mmol/l)	1.124(1.022, 1.237)	0.016*	1.206(1.064, 1.366)	0.003*
TG(mmol/l)	0.692(0.508, 0.943)	0.020*	0.552(0.380, 0.800)	0.002*

Multifactor logistic regression: Adjusted for WBC、NE、LY、MO、EO、BA、RBC、HGB、HCT、PDW、PT、APTT、DD-i、ALT、AST、Scr、SUA、GLU、TG、break 、Recent (less than or equal to 1 month) trauma or surgery、Palpitations/tachycardia、anhelation、Unilateral lower extremity edema/pain、hypoxemia

WBC White blood cell count, *NE* Neutrophil proportion, *LY* Lymphocyte proportion, *MO* Monocyte proportion, *EO* Eosinophil proportion, *BA* Basophil proportion, *RBC* Red blood cell count, *HGB* Hemoglobin, *HCT* Hematocrit, *PDW* Platelet volume distribution width, *PT* Prothrombin time, *APTT* Partial thromboplastin time, *DD-I* D-dimer, *ALT* Alanine aminotransferase, *AST* Aspartate aminotransferase, *Scr* Serum creatinine, *SUA* Serum uric acid, *GLU* Glucose, *TG* Triglycerides

* Indicates a statistically significant difference of *P* < 0.05

Receiver operator characteristic curves of old people

Receiver operator characteristics curve showed that SUA had an area under curve (AUC) of 0.577 (95% CI 0.504–0.640, *P* = 0.042). Detailed results are presented in Fig. 1. The optimal cutoff values for SUA that had the highest combined sensitivity and specificity for predicting PE was > 319 (48.8% sensitivity and 65.5% specificity).

Discussion

The objective of this study was to examine the relationship between serum uric acid levels and the occurrence of pulmonary embolism. The findings demonstrated that elevated uric acid levels independently increased the risk of pulmonary embolism, a correlation that persisted even after adjusting for various potential confounding factors. And, upon stratifying the subjects by age, notable differences in SUA were observed between patients with and without pulmonary embolism in both

Yuan *et al. Thrombosis Journal*   (2024) 22:87

Page 6 of 11

Table 3 Comparison of characteristics of patients with and without pulmonary embolism in the nonagenarian group

Variables	Non-PE (n = 71)	PE (n = 62)	T-value/χ^2 -value	P
WBC(*10^9/L)[a]	8.59 ± 4.23	9.75 ± 5.07	-1.433	0.154
NE(%)[a]	68.25 ± 15.23	75.22 ± 10.68	-3.088	0.002[*]
LY(%)[a]	20.27 ± 10.87	15.77 ± 8.90	2.593	0.011[*]
MO(%)[a]	8.25 ± 3.78	7.51 ± 2.64	1.328	0.186
EO(%)[b]	1.20(0.20, 2.10)	0.70(0.11, 1.70)	-0.959	0.337
BA(%)[b]	0.30(0.10, 0.40)	0.20(0.10, 0.40)	-0.725	0.469
RBC(*10^9/L)[a]	3.99 ± 0.96	3.97 ± 0.91	0.138	0.890
HGB(g/l)[a]	113 ± 30.39	114.22 ± 24.97	-0.141	0.888
HCT(%)[a]	34.00 ± 8.30	34.70 ± 7.20	-0.517	0.606
PDW(%)[b]	11.50(9.80,15.20)	12.05(10.60,15.60)	-1.550	0.121
PT(s)[a]	14.27 ± 2.43	13.90 ± 2.18	0.908	0.365
APTT(s)[a]	38.72 ± 9.24	35.24 ± 7.42	2.370	0.019[*]
DD-i(mg/L)[b]	0.79(2.44, 5.34)	2.61(5.15, 10.52)	-3.518	0.000[*]
ALT(U/L)[b]	18.40(12.00,32.70)	17.90(13.20,28.30)	-0.079	0.937
AST(U/L)[b]	21.50(15.40,36.25)	22.50(17.40,35.50)	-0.487	0.626
Scr(umol/l)[a]	82.97 ± 71.80	74.72 ± 32.60	0.832	0.407
SUA(umol/l)[a]	309.02 ± 107.57	299.73 ± 116.69	0.477	0.634
GLU(mmol/l)[a]	5.67 ± 2.34	6.67 ± 3.21	-2.028	0.045[*]
TG(mmol/l)[a]	1.60 ± 1.03	1.25 ± 0.81	2.161	0.033[*]
break	7(10.0%)	1(1.6%)	2.723	0.990
Recent (less than or equal to 1 month) trauma or surgery	15(21.1%)	15(24.2%)	0.178	0.673
Palpitations/tachycardia	9(12.7%)	11(17.7%)	0.665	0.415
anhelation	26(36.6%)	29(46.8%)	1.407	0.236
Unilateral lower extremity edema/pain	9(12.7%)	14(22.6%)	2.270	0.132
hypoxemia	4(5.6%)	11(18.9%)	5.008	0.025[*]
Lower extremity venous thrombosis	16(26.2%)	14(29.8%)	0.167	0.682

[a] data are presented as mean ± SD W

[b] indicates that the data are median and interquartile spacing; The rest of the data are data are presented as n (%

BC White blood cell count, *NE* Neutrophil proportion, *LY* Lymphocyte proportion, *MO* Monocyte proportion, *EO* Eosinophil proportion, *BA* Basophil proportion, *RBC* Red blood cell count, *HGB* Hemoglobin, *HCT* Hematocrit, *PDW* Platelet volume distribution width, *PT* Prothrombin time, *APTT* Partial thromboplastin time, *DD-I* D-dimer, *ALT* Alanine aminotransferase, *AST* Aspartate aminotransferase, *Scr* Serum creatinine, *SUA* Serum uric acid, *GLU* Glucose, *TG* Triglycerides

* Indicates a statistically significant difference of *P* < 0.05

the elderly (≥ 60 years) and non-elderly (< 60 years) cohorts. Interestingly, uric acid levels exhibited a significant association with pulmonary embolism solely in the elderly population following adjustments for multiple confounders. In addition, there is an interaction between age and uric acid, which increases the risk of pulmonary embolism.

Previous studies have shown that uric acid is strongly associated with the onset and recurrence of pulmonary embolism and that high levels of serum uric acid may be a potential risk factor for pulmonary embolism [12, 15, 18], which is consistent with our findings. To our knowledge, our study represents the first attempt to explore the impact of uric acid on pulmonary embolism occurrence

across different age groups. In a case-control analysis involving 368 hospitalized patients who underwent CTPA, we systematically screened numerous suspected risk factors and observed significantly higher uric acid levels in patients with pulmonary embolism compared to those without (325.11 ± 137.02 vs. 298.26 ± 110.54, *P* = 0.039). Furthermore, following adjustment for multiple confounding variables, multifactorial logistic regression analysis demonstrated that uric acid served as an independent risk factor for pulmonary embolism (OR = 1.002, 95% CI 1.000-1.005, *p* = 0.042).

After stratifying by age, elevated uric acid levels remained significant among elderly patients with pulmonary embolism. Upon adjusting for multiple confounders, heightened uric acid levels emerged as an

Yuan *et al. Thrombosis Journal*   (2024) 22:87

Page 7 of 11

Table 4 Comparison of characteristics of patients with and without pulmonary embolism in the elderly group

Variables	Non-PE (n=110)	PE (n=125)	T-value/χ^2 -value	P
WBC(*10^9/L)[a]	8.17±3.90	9.04±3.84	-1.724	0.086
NE(%)[a]	70.42±13.63	74.44±13.20	-2.292	0.023*
LY(%)[a]	18.81±10.47	16.59±12.69	1.454	0.147
MO(%)[a]	7.78±3.04	7.67±3.29	0.267	0.789
EO(%)[b]	1.25(0.20, 2.95)	0.90 (0.10, 2.15)	-1.608	0.108
BA(%)[b]	0.30 (0.20, 0.50)	0.27 (0.10, 0.50)	-2.007	0.045*
RBC(*10^9/L)[a]	3.89±0.81	4.25±0.79	-3.506	0.001*
HGB(g/l)[a]	115.61±23.52	122.07±21.55	-2.198	0.029*
HCT(%)[a]	34.13±6.94	36.82±6.45	-3.081	0.002*
PDW(%)[b]	11.50(9.60,14.20)	11.40(9.90,16.10)	-1.200	0.230
PT(s)[a]	13.83±1.68	13.60±1.89	0.960	0.338
APTT(s)[a]	37.40±6.66	34.29±10.40	2.761	0.006*
DD-i(mg/L)[b]	1.06 (2.75, 8.18)	2.43(6.60, 11.36)	-2.920	0.003*
ALT(U/L)[b]	16.55(11.30,28.30)	19.70(12.40,32.90)	-1.258	0.209
AST(U/L)[b]	24.30(17.10,38.80)	22.30(17.20,33.90)	-0.852	0.394
Scr(umol/l)[a]	88.75±74.87	88.24±57.06	0.059	0.953
SUA(umol/l)[a]	291.32±112.36	337.70±144.84	-2.759	0.006*
GLU(mmol/l)[a]	5.85±1.54	6.26±2.49	-1.520	0.130
TG(mmol/l)[a]	1.31±0.64	1.22±0.57	1.037	0.301
break	18(16.4%)	10(8.0%)	3.900	0.048*
Recent (less than or equal to 1 month) trauma or surgery	14(12.7%)	31(24.8%)	5.508	0.019*
Palpitations/tachycardia	7(6.4%)	25(20.0%)	9.250	0.002*
anhelation	53(48.2%)	76(60.8%)	3.762	0.052
Unilateral lower extremity edema/pain	15(13.6%)	30(24.0%)	4.059	0.044*
hypoxemia	12(10.9%)	35(28.0%)	10.682	0.001*
Lower extremity venous thrombosis	22(24.7%)	39(41.1%)	5.532	0.019*

[a] data are presented as mean±SD

[b] indicates that the data are median and interquartile spacing; The rest of the data are presented as n (%)

WBC White blood cell count, *NE* Neutrophil proportion, *LY* Lymphocyte proportion, *MO* Monocyte proportion, *EO* Eosinophil proportion, *BA* Basophil proportion, *RBC* Red blood cell count, *HGB* Hemoglobin, *HCT* Hematocrit, *PDW* Platelet volume distribution width, *PT* Prothrombin time, *APTT* Partial thromboplastin time, *DD-I* D-dimer, *ALT* Alanine aminotransferase, *AST* Aspartate aminotransferase, *Scr* Serum creatinine, *SUA* Serum uric acid, *GLU* Glucose, *TG* Triglycerides

* Indicates a statistically significant difference of *P* < 0.05

independent risk factor for pulmonary embolism development in the elderly (OR = 1.003, 95% CI 1.001–1.005, *P* = 0.008). Previous studies have consistently linked gout or elevated uric acid levels with venous thrombosis in the elderly [19–21]. Our findings are consistent with this.

The current study reveals a robust association between elevated uric acid levels and pulmonary embolism, shedding light on further investigations into their causal relationship. Recent years have witnessed a notable surge in pulmonary embolism incidence among the elderly, leading to increased utilization of late-stage resources, including long-term care facilities and home health services, among afflicted individuals in this demographic [22]. Unfortunately, elderly patients with acute pulmonary embolism often face poor prognoses [23], exacerbated by financial constraints [24]. Our study identified high uric acid levels as an independent risk factor for pulmonary embolism in the elderly, suggesting the potential for proactive interventions to mitigate its incidence and improve survival and quality of life in this population. Given the elderly population's susceptibility to various cardiovascular ailments, diagnosing pulmonary embolism based solely on symptoms can be challenging, resulting in delayed diagnosis and worse outcomes [25]. Clarifying the link between uric acid and pulmonary embolism risk in the elderly may facilitate early detection and intervention, thereby

Yuan *et al. Thrombosis Journal*   (2024) 22:87

Page 8 of 11

Table 5 One-way logistic regression of uric acid on pulmonary embolism stratified by age

Variables	non-elderly OR(95%CI)	P	elderly OR(95%CI)	P
break	0.148(0.018, 1.235)	0.078	0.444(0.196, 1.009)	0.053
Recent (less than or equal to 1 month) trauma or surgery	1.191(0.528, 2.689)	0.673	2.261(1.132, 4.519)	0.021*
Palpitations/tachycardia	1.486(0.571, 3.864)	0.417	3.679(1.523, 8.888)	0.004*
anhelation	1.521(0.760, 3.045)	0.236	1.668(0.993, 2.801)	0.053
Unilateral lower extremity edema/pain	2.009(0.802, 5.033)	0.136	2.000(1.011, 3.955)	0.046*
hypoxemia	3.685(1.1208, 12.254)	0.033*	3.176(1.553, 6.495)	0.002*
WBC(*10^9/L)	1.056(0.979, 1.139)	0.157	1.061(0.991, 1.137)	0.088
NE(%)	1.042(1.013, 1.072)	0.005*	1.023(1.003, 1.043)	0.025*
LY(%)	0.955(0.921, 0.990)	0.013*	0.983(0.961, 1.006)	0.155
MO(%)	0.932(0.837, 1.037)	0.198	0.989(0.912, 1.073)	0.788
EO(%)	0.930(0.790, 1.095)	0.383	0.870(0.763, 0.993)	0.038*
BA(%)	0.538(0.131, 2.204)	0.389	1.005(0.691, 1.462)	0.979
RBC(*10^9/L)	0.974(0.676, 1.405)	0.889	1.804(1.275, 2.554)	0.001*
HGB(g/l)	1.001(0.989, 1.013)	0.887	1.013(1.001, 1.025)	0.031*
HCT(%)	1.012(0.968, 1.057)	0.603	1.063(1.021, 1.107)	0.003*
PDW(%)	1.007(0.959, 1.211)	0.210	1.061(0.973, 1.157)	0.178
PT(s)	0.931(0.798, 1.087)	0.367	0.932(0.807, 1.077)	0.932
APTT(s)	0.942(0.894, 0.993)	0.027*	0.960(0.930, 0.990)	0.010*
DD-i(mg/L)	1.069(1.010, 1.132)	0.022*	1.007(0.987, 1.027)	0.505
ALT(U/L)	1.002(0.995, 1.009)	0.600	1.007(0.999, 1.016)	0.077
AST(U/L)	1.001(0.995, 1.008)	0.655	1.001(0.993, 1.009)	0.802
Scr(umol/l)	0.997(0.989, 1.005)	0.431	1.000(0.996, 1.004)	0.953
SUA(umol/l)	0.999(0.996, 1.002)	0.631	1.003(1.001, 1.005)	0.008*
GLU(mmol/l)	1.147(1.000, 1.317)	0.050*	1.102(0.966, 1.258)	0.147
TG(mmol/l)	0.601(0.363, 0.994)	0.047*	0.798(0.520, 1.224)	0.302

WBC White blood cell count, *NE* Neutrophil proportion, *LY* Lymphocyte proportion, *MO* Monocyte proportion, *EO* Eosinophil proportion, *BA* Basophil proportion, *RBC* Red blood cell count, *HGB* Hemoglobin, *HCT* Hematocrit, *PDW* Platelet volume distribution width, *PT* Prothrombin time, *APTT* Partial thromboplastin time, *DD-I* D-dimer, *ALT* Alanine aminotransferase, *AST* Aspartate aminotransferase, *Scr* Serum creatinine, *SUA* Serum uric acid, *GLU* Glucose, *TG* Triglycerides

* Indicates a statistically significant difference of $P < 0.05$

enhancing prognosis. Moreover, it may inspire novel strategies for pulmonary embolism prevention.

The pathogenesis linking uric acid and pulmonary embolism remains unclear, but most findings suggest that elevated uric acid levels activate inflammatory pathways, potentially associating SUA with PE. High uric acid levels correlate strongly with inflammatory factors like interleukin-6 (IL-6), interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP) [26]. Moreover, uric acid promotes cyclooxygenase-2 (COX-2) and reactive oxygen species (ROS) production, fostering inflammation and vascular smooth muscle cell proliferation [27]. Subsequently, inflammation disrupts the coagulation system by boosting coagulation, reducing anticoagulation activity, inhibiting fibrinolysis, and inducing endothelial dysfunction [28]. Studies have identified that activated endothelial cells contribute to coagulation by affecting TMEM16 proteins (TMEM16F and TMEM16E), which externalize phosphatidylserine in the vessel wall [29]. Research has further explored uric acid's role in this pathway, revealing that elevated uric acid induces phosphatidylserine exposure and particle release, thereby enhancing the procoagulant activity of erythrocytes and vascular endothelial cells via TMEM16F activation, thus promoting thrombosis [30, 31]. Moreover, the procoagulant activity of particles increases with age [32]. Consequently, we hypothesize that the serum uric acid level's role in promoting thrombosis through this pathway may be more pronounced in the elderly. Furthermore, experiments treating mouse and human umbilical vein endothelial cells with serum uric acid levels revealed that it inhibits myocyte enhancer factor (MEF2C) expression by upregulating let-7c expression,

Yuan *et al. Thrombosis Journal*   (2024) 22:87

Page 9 of 11

Table 6 Multifactorial logistic regression of uric acid on pulmonary embolism stratified by age

Variables	non-elderly OR(95%CI)	P	elderly OR(95%CI)	P
break	0.051(0.002, 1.144)	0.061	0.159(0.044, 0.577)	0.005*
Recent (less than or equal to 1 month) trauma or surgery	1.331(0.344, 5.154)	0.679	3.203(1.204, 8.520)	0.020*
Palpitations/tachycardia	1.028(0.246, 4.296)	0.970	2.594(0.887, 7.590)	0.082
anhelation	0.993(0.346, 2.848)	0.990	1.176(0.610, 2.267)	0.629
Unilateral lower extremity edema/pain	3.176(0.861, 11.715)	0.083	2.167(0.905, 5.188)	0.082
hypoxemia	4.742(0.825, 27.257)	0.081	3.007(1.208, 7.482)	0.018*
WBC(*10^9/L)	1.019(0.896, 1.159)	0.777	1.004(0.907, 1.113)	0.933
NE(%)	1.030(0.948, 1.119)	0.482	1.041(0.993, 1.092)	0.094
LY(%)	0.954(0.863, 1.053)	0.349	1.002(0.957, 1.048)	0.947
MO(%)	0.947(0.796, 1.126)	0.537	1.129(0.996, 1.280)	0.058
EO(%)	1.011(0.797, 1.283)	0.926	0.926(0.743, 1.154)	0.492
BA(%)	4.075(0.338, 49.095)	0.269	1.199(0.663, 2.166)	0.548
RBC(*10^9/L)	0.216(0.063, 0.749)	0.016*	1.188(0.572, 2.468)	0.644
HGB(g/l)	0.832(0.732, 0.945)	0.005*	0.997(0.956, 1.039)	0.870
HCT(%)	2.413(1.380, 4.219)	0.002*	1.037(0.883, 1.218)	0.657
PDW(%)	0.969(0.805, 1.166)	0.738	1.070(0.952, 1.202)	0.258
PT(s)	0.931(0.714, 1.215)	0.600	0.904(0.717, 1.140)	0.394
APTT(s)	0.976(0.900, 1.058)	0.554	0.956(0.914, 0.999)	0.047*
DD-i(mg/L)	1.048(0.977, 1.125)	0.187	1.005(0.980, 1.031)	0.671
ALT(U/L)	1.003(0.985, 1.020)	0.774	1.023(1.003, 1.043)	0.024*
AST(U/L)	0.995(0.983, 1.007)	0.423	0.980(0.962, 0.999)	0.041*
Scr(umol/l)	0.990(0.980, 1.001)	0.064	0.995(0.987, 1.003)	0.211
SUA(umol/l)	1.001(0.996, 1.005)	0.800	1.003(1.000, 1.007)	0.030*
GLU(mmol/l)	1.282(1.058, 1.553)	0.011*	1.195(0.987, 1.446)	0.067
TG(mmol/l)	0.544(0.291, 1.017)	0.056	0.649(0.373, 1.132)	0.128

Multifactor logistic regression: Adjusted for WBC、NE、LY、MO、EO、BA、RBC、HGB、HCT、PDW、PT、APTT、DD-i、ALT、AST、Scr、SUA、GLU、TG、break 、Recent (less than or equal to 1 month) trauma or surgery、Palpitations/tachycardia、anhelation、Unilateral lower extremity edema/pain、hypoxemia

WBC White blood cell count, *NE* Neutrophil proportion, *LY* Lymphocyte proportion, *MO* Monocyte proportion, *EO* Eosinophil proportion, *BA* Basophil proportion, *RBC* Red blood cell count, *HGB* Hemoglobin, *HCT* Hematocrit, *PDW* Platelet volume distribution width, *PT* Prothrombin time, *APTT* Partial thromboplastin time, *DD-I* D-dimer, *ALT* Alanine aminotransferase, *AST* Aspartate aminotransferase, *Scr* Serum creatinine, *SUA* Serum uric acid, *GLU* Glucose, *TG* Triglycerides

* Indicates a statistically significant difference of $P < 0.05$

Table 7 P for Interaction between age and uric acid

	OR	OR(95%CI)	P
SUA by age	1.000	(1.000,1.000)	0.002
SUA by age classification	1.001	(1.000,1.002)	0.008

SUA serum uric acid; age classification: The 60-year-old group and ≥60-year-old group were classified according to the age of 60

activating the NF-κB pathway, and ultimately leading to thrombosis [33].

There are several limitations to our study. Firstly, the serum uric acid level was assessed upon initial hospital admission, and the diagnosis of pulmonary embolism was made concurrently, preventing the determination of the sequence linking high uric acid levels to the onset of pulmonary embolism. As a result, we can only make preliminary etiological assumptions and cannot definitively establish a causal relationship between the two. Further prospective studies are required to verify this causal relationship. Secondly, the sample size of our study is relatively small and limited in scope, potentially contributing to a smaller odds ratio (OR). Thus, larger sample sizes in prospective studies are necessary for further validation. Additionally, certain potential confounding factors associated with pulmonary embolism, such as body mass index, blood pressure and CRP, were not included in the study due to high levels of missing data. Finally, because the mechanism of pulmonary embolism is complex, the reasons are diverse. Therefore, at the individual level, the
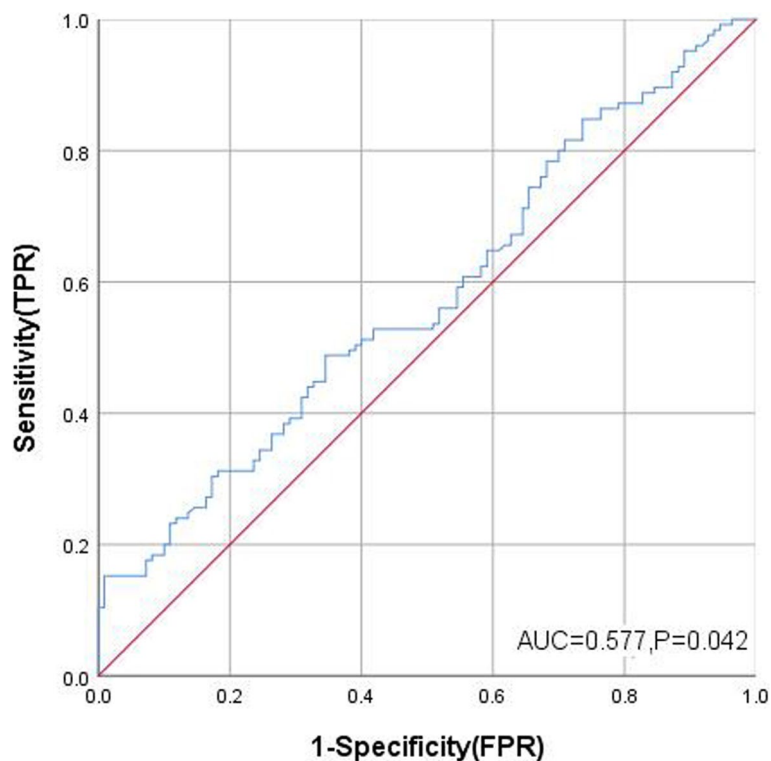
Fig. 1 Receiver operator characteristic curves of old people

change of uric acid level may have different effects on the occurrence of pulmonary embolism.

Conclusions

In conclusion, our study reveals that elevated uric acid levels constitute an independent risk factor for pulmonary embolism among the elderly (aged ≥ 60 years), thus offering valuable insights for clinical diagnosis and treatment. Moreover, further prospective investigations are warranted to determine if high uric acid levels can effectively identify individuals prone to pulmonary embolism and to elucidate the potential benefits of uric acid-lowering medications in preventing this condition.

Authors' contributions
Bin Yuan wrote the first draft; Lingyue Song, Weiqing Su and Xianbing Zeng designed the research methodology and statistical analysis; Jinqiang Su, Jie Sun and Jun Wu wrote the first draft of the statistical analysis and writing section; Kaili Fu, Zhihai Huang, qiaoyun Chen and Dingyu Guo software for data collection, data collation and call analysis; Xishi Sun for funding and revision; and Lingpin Pang for coordination and planning. All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

Data availability
The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Approval for the study was granted by the Medical Ethics Committee of the Affiliated Hospital of Guangdong Medical University, adhering to the principles outlined in the Helsinki Declaration and its amendments (Ethical No.: YJYS2024188).

Competing interests
The authors declare no competing interests.

References
1. Essien E-O, Rali P, Mathai SC. Pulmonary embolism. Med Clin North Am. 2019;103:549.
2. Dix C, Tran H. Pulmonary Embolus. Aust J Gen Pract. 2022;51:667.
3. Walter K. What is pulmonary embolism? JAMA. 2023;329:104.

Yuan *et al. Thrombosis Journal*   (2024) 22:87

Page 11 of 11

4.   Turetz M, Sideris AT, Friedman OA, Triphathi N, Horowitz JM. Epidemiology, pathophysiology, and Natural History of Pulmonary Embolism. Semin Intervent Rad. 2018;35:92.
5.   Piao W, Zhao L, Yang Y, Fang H, Ju L, Cai S, Yu D. The prevalence of hyperuricemia and its correlates among adults in China: results from CNHS 2015–2017. Nutrients. 2022;14:4095.
6.   Zhang M, et al. Prevalence of Hyperuricemia among Chinese adults: findings from two nationally representative cross-sectional surveys in 2015-16 and 2018-19. Front Immunol. 2021;12:791983.
7.   Liu H, Zhang X-M, Wang Y-L, Liu B-C. Prevalence of Hyperuricemia among Chinese adults: a National Cross-sectional Survey using Multistage, Stratified Sampling. J Nephrol. 2014;27:653.
8.   Wang R, Tang Z, Sun F, Diao LJ. Prevalence of hyperuricemia in the elderly in 7 areas of China. Zhonghua Liu Xing Bing Xue Za Zhi. 2018;39:286.
9.   Virdis A, et al. Identification of the uric acid thresholds predicting an increased total and cardiovascular mortality over 20 years. Hypertension. 2020;75:302.
10. Ma Y, Wang Y, Liu D, Ning Z, An M, Wu Q, Lin Y. A safe strategy to rule out pulmonary embolism: the combination of the wells score and D-imer test: one prospective study. Thromb Res. 2017;156:160.
11. Huang C-C, Huang P-H, Chen J-H, Lan J-L, Tsay GJ, Lin H-Y, Tseng C-H, Lin C-L, Hsu C-Y. An independent risk of gout on the development of deep vein thrombosis and pulmonary embolism: a nationwide, population-based cohort study. Med (Baltim). 2015;94:e2140.
12. Li L, McCormick N, Sayre EC, Esdaile JM, Lacaille D, Xie H, Choi HK, Aviña-Zubieta JA. Trends of venous thromboembolism risk before and after diagnosis of gout: a general population-based study. Rheumatology (Oxford). 2020;59:1099.
13. Lee JH, Huh JW, Hong S-B, Oh Y-M, Shim TS, Lim C-M, Lee S-D, Koh Y, Kim WS, Lee JS. Prognostic value of blood biomarkers in patients with unprovoked acute pulmonary embolism. Ann Thorac Med. 2019;14:248.
14. Ozsu S, Çoşar AM, Aksoy HB, Bülbül Y, Oztuna F, Karahan SC, Ozlu T. Prognostic value of uric acid for pulmonary thromboembolism. Resp Care. 2017;62:1091.
15. Weng H, et al. Association between uric acid and risk of venous thromboembolism in east asian populations: a cohort and mendelian randomization study. Lancet Reg Health West Pac. 2023;39:100848.
16. Ji L, Shu P. A mendelian randomization study of serum uric acid with the risk of venous thromboembolism. Arthritis Res Ther. 2023;25:122.
17. Subramaniam RM, Blair D, Gilbert K, Sleigh J, Karalus N. Computed tomography pulmonary angiogram diagnosis pulmonary embolism. Australas Radiol. 2006;50:193.
18. De Lucchi L, et al. Serum uric acid levels and the risk of recurrent venous thromboembolism. J Thromb Haemost. 2021;19:194.
19. Sultan AA, Muller S, Whittle R, Roddy E, Mallen C, Clarson L. Venous thromboembolism in patients with gout and the impact of hospital admission disease duration and urate-lowering therapy. CMAJ. 2019;191:E597.
20. Xu C, Wang H, Wang D, Wang Y, Chen M. Study on factors of deep vein thrombosis after percutaneous coronary intervention in elderly patients with atherosclerotic coronary heart disease. Chin J Clin. 2022;50:594–6.
21. Li ya. Zeng ping, Zhu Minglei, Liu Xiaohong, and Li Dongjing, clinical characteristics of gouty attacks and their complication with deep vein thrombosis of the lower extremities in elderly patients during hospitalization. Chin J Clin Health. 2018;21:398–401.
22. Pauley E, Orgel R, Rossi JS, Strassle PD. Age-Stratified natl trends pulmonary embolism admissions. Chest. 2019;156:733.
23. Zhai Z, et al. Trends in risk stratification, in-hospital management and mortality of patients with acute pulmonary embolism: an analysis from the China pUlmonary Thromboembolism REgistry Study (CURES). Eur Respir J. 2021;58:2002963.
24. Wadhera RK, Secemsky EA, Wang Y, Yeh RW, Goldhaber SZ. Association of socioeconomic disadvantage with mortality and readmissions among older adults hospitalized for pulmonary embolism in the United States. J Am Heart Assoc. 2021;10:e021117.
25. Mansella G, Keil C, Nickel CH, Eken C, Wirth C, Tzankov A, Peterson CJ, Aujesky D, Bingisser R. Delayed diagnosis in pulmonary embolism: frequency patient characteristics, and outcome. Respiration. 2020;99:589.
26. Lyngdoh T, Marques-Vidal P, Paccaud F, Preisig M, Waeber G, Bochud M, Vollenweider P. Elevated serum uric acid is associated with high circulating inflammatory cytokines in the population-based olaus study. PLoS ONE. 2011;6:e19901.
27. Oğuz N, Kırça M, Çetin A, Yeşilkaya A. Effect of uric acid on inflammatory COX-2 and ROS pathways in vascular smooth muscle cells. J Recept Signal Transduct Res. 2017;37:500.
28. Ţăpoi L, Şalaru DL, Sascău R, Stătescu C. Uric acid-an emergent risk marker for thrombosis? J Clin Med. 2021;10:2062.
29. Schmaier AA, et al. TMEM16E regulates endothelial cell procoagulant activity and thrombosis. J Clin Invest. 2023;133:e163808.
30. Yan M, et al. TMEM16F mediated phosphatidylserine exposure and microparticle release on erythrocyte contribute to hypercoagulable state in hyperuricemia. Blood Cell Mol Dis. 2022;96:102666.
31. Yu H, et al. Hyperuricemia enhances procoagulant activity of vascular endothelial cells through TMEM16F regulated phosphatidylserine exposure and microparticle release. FASEB J. 2021;35:e21808.
32. Owen BaL, Xue A, Heit JA, Owen WG. Procoagulant activity, but not number, of microparticles increases with age and in individuals after a single venous thromboembolism. Thromb Res. 2011;127:39.
33. Cheng X, Liu T, Ma L, Liu Z, Xin Y, Jia Z, Chen Y, Li C, Sun R. Prothrombotic effects of high uric acid in mice via activation of MEF2C-dependent NF-κB pathway by upregulating Let-7c. Aging (Albany NY). 2020;12:17976.

Publisher's note