Received: 17 July 2020 | Accepted: 9 October 2020

DOI: 10.1111/jth.15139

ORIGINAL ARTICLE

Serum uric acid levels and the risk of recurrent venous thromboembolism

Lara De Lucchi[1] | Chiara Nardin[1] | Alessandra Sponchiado[1] | Davide Raggi[2] | Elisabetta Faggin[3] | Elena Martini[1] | Valeria Pagliara[1] | Elena Callegari[1] | Livio Caberlotto[4] | Mario Plebani[3] | Paolo Pauletto[5] | Francesco Cinetto[1,3] | Carlo Agostini[1,3] | Sabina Villalta[6] | Marcello Rattazzi[1,3]

[1]Medicina Generale I^, Ca' Foncello University Hospital, Treviso, Italy

[2]Department of Economics, University of Bologna, Bologna, Italy

[3]Department of Medicine - DIMED, University of Padova, Padova, Italy

[4]Laboratory Medicine, Ca' Foncello University Hospital, Treviso, Italy

[5]ORAS Rehabilitation Hospital, Motta di Livenza, Treviso, Italy

[6]Medicina Generale, Castelfranco Veneto Hospital, Castelfranco Veneto, Italy

Correspondence
Marcello Rattazzi, Department of Medicine - DIMED, University of Padova, Medicina Generale I^, Ca' Foncello University Hospital, Via Ospedale 1, 31100 Treviso, Italy.
Emails: marcello.rattazzi@unipd.it; marcello.rattazzi@aulss2.veneto.it

Funding information
This work was supported by the Ministero della Salute (RF-2013-02358024 to MR).

Abstract

Background: The link between serum uric acid (SUA) and the risk of cardiovascular disease is well established. However, the impact of SUA levels on the risk of venous thromboembolism (VTE) recurrence is unknown.

Objectives: To investigate the association between SUA and the risk of VTE recurrence.

Patients and Methods: We performed a monocenter, prospective study on 280 patients with a previous episode of VTE that completed the oral anticoagulant period. SUA levels at enrollment were correlated with the risk of VTE recurrence (mean follow-up 71.1 ± 29.2 months).

Results: Patients were stratified according to SUA tertiles distribution at baseline (tertiles cut-off: I ≤ 4.37 mg/dL, II 4.38--5.54 mg/dL, III ≥ 5.55 mg/dL). Fifty episodes of VTE recurrence occurred during the follow-up and Kaplan-Meier survival analysis showed that subjects in the lower tertile of SUA distribution had significantly lower risk of future VTE recurrence ($P = .003$). No differences were seen among patients belonging to the second and the third tertile of SUA distribution. A multivariate Cox regression analysis showed that higher tertiles of SUA distribution had about threefold increase in the risk of VTE recurrence as compared to subjects with SUA ≤ 4.37, independently from potential confounders (hazard ratio [HR] 3.04, 95% confidence interval [CI] 1.15--8.05 $P = .025$). Moreover, we observed that the adjusted hazard of VTE recurrence increased by 30% for each additional unit of SUA (mg/dL; HR 1.30, 95% CI 1.01--1.22, $P = .040$).

Conclusion: Elevated SUA levels are associated with increased risk of future VTE recurrence independently from traditional risk factors.

KEYWORDS

deep vein thrombosis, glomerular filtration rate, pulmonary embolism, uric acid, venous thromboembolism

Manuscript handled by: Zhi-Cheng Jing

Final decision: Zhi-Cheng Jing, 9 October 2020

1 | INTRODUCTION

Uric acid is the final product of purine metabolism. In recent years, several population-based studies have reported an association between serum uric acid (SUA) levels and increased risk of cardiovascular (CV) disorders such as hypertension,[1] myocardial infarction,[2] stroke,[3] peripheral arterial disease,[4] and sudden cardiac death.[5,6] Despite the fact that a continuous relationship between SUA and all-cause and CV mortality has been suggested by many studies, more recently, data from the URRAH study (Uric Acid Right for Heart Health), allowed us to identify prognostic cut-off values for major adverse events.[6,7] Based on these findings SUA values of 4.7 and 5.7 mg/dL have been identified as optimal predictors, respectively, for all-cause mortality and fatal myocardial infarction.[6,7] These data further demonstrated that not only hyperuricemia, defined as SUA levels > 7 mg/dL in men or >6 mg/dL in women, but also lower SUA values are significantly associated with adverse CV outcomes.

Despite significant improvement in diagnosis and treatment, venous thromboembolism (VTE) still represents one of the most important causes of morbidity and mortality worldwide.[8] Given the well-established link between SUA and progression of atherosclerosis,[9,10] some authors have investigated whether elevated levels of SUA could be an independent risk factor for VTE, acting as an important linkage among endothelial dysfunction, inflammation, and pro-thrombotic state. The Atherosclerosis Risk in Community (ARIC) Study, involving 14 126 participants aged 45 to 64 years, first reported an association between high levels of SUA and increased risk of VTE.[11] Other authors demonstrated a role of SUA as an independent predictor of short-term mortality in pulmonary embolism[12] or as a risk factor for VTE in patients with gout.[13]

However, it is currently unknown whether SUA levels can predict the risk of VTE recurrence. To clarify this aspect, we performed a prospective study in a cohort of patients with a first episode of VTE, without history of recurrence, and that had completed the oral anticoagulant period.

Essentials

- Increase in serum uric acid (SUA) levels has been widely associated with higher risk of cardiovascular disease.
- We investigated the link between SUA levels and the risk of venous thromboembolism (VTE) recurrence.
- Patients with SUA levels ≥ 4.38 mg/dL showed a three-fold increase in the risk of VTE recurrence.
- Elevated SUA levels are associated with increased risk of recurrent VTE independently from traditional risk factors.

2 | MATERIALS AND METHODS

2.1 | Population and study design

We performed an observational perspective cohort study on 486 patients with a previous diagnosed episode of deep vein thrombosis (DVT) and/or pulmonary embolism (PE) who were referred between October 2010 and October 2019 to the Thrombosis Unit of the Cà Foncello University Hospital in Treviso, Italy. We included in the present study patients without history of VTE recurrence and not taking oral anticoagulants at enrollment (n = 236). We also considered for the present analysis all the subjects that stopped anticoagulants during the clinical follow-up (n = 44). All the clinical characteristics of the index VTE event were obtained from the medical record of the patients. At the time of the first event each patient was hospitalized and treated with either intravenous adjusted-dose of unfractionated heparin or fixed dose low molecular weight heparin (LMWH) followed by vitamin K antagonists (VKA) for at least 3 months (the decision to prolong the oral anticoagulation was made on an individual basis considering the risk of recurrent VTE). All the VTE events were classified as "unprovoked" in the absence of triggering factors and considered "provoked VTE" if the events were associated with at least one of the following conditions: surgery, trauma, bone fracture, immobilization, acute medical disease, oral contraceptives, hormonal replacement therapy, or pregnancy. We collected information about the site of DVT (proximal or distal), presence of PE, history of recurrence, and presence of thrombophilia. Results of the screening for thrombophilic conditions were available for 210 patients and included: anti-thrombin III (n = 1), factor V Leiden mutation (n = 28), prothrombin G20210A mutation (n = 21), protein C (n = 3) and protein S (n = 7) deficiency, and lupus anticoagulant (n = 1). We excluded from the present study patients with active or previous cancer. During the follow-up we contacted the patients annually or semi-annually by phone to ask about the occurrence of the following clinical events: VTE recurrence (DVT and/or PE), acute coronary syndrome (ACS), stroke/transient ischemic attack (TIA), and death. All the clinical information reported by the patients (or by the relatives) was then verified through a direct examination of the hospital/medical records (see Figure S1 in supporting information for study design).

All the subjects enrolled gave written informed consent and the study was approved by the local ethics committee.

2.2 | Clinical data collection and biochemical analysis at baseline

The following data were collected from each patient: age; sex; height; weight; body mass index (BMI, calculated as body weight [Kg] divided by the square of the height [m]); history of atherosclerotic cerebro-cardiovascular events (ischemic stroke, TIA, ACS); known diabetes; current use of antihypertensive drugs, antiplatelet drugs, and lipid lowering treatment. Blood pressure (BP) was measured at enrollment using a standard procedure (the mean of three measures 1 minute apart was considered to establish systolic BP

[SBP] and diastolic BP [DBP] values). Hypertension was defined as SBP ≥ 140 and/or DBP ≥ 90 or ongoing antihypertensive medications. All the subjects underwent fasting blood sampling to measure creatinine level and glomerular filtration rate (GFR) was estimated through the 2009 CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine equation. Blood serum samples were also collected from each patient and stored at −70°C until further analysis. SUA levels were measured using the uricase method (enzymatic–colorimetric assay on a Cobas C702, Roche Diagnostics) and expressed as mg/dL.

2.3 | Statistical analysis

Data have been expressed as mean ± standard deviation (SD) or as percentage. Patients were grouped according to tertiles of SUA distribution at baseline. Comparison between groups of continuous variables was performed by analysis of variance followed by least significant difference (LSD) post-hoc analysis. Chi-square test was used for the comparison of categorical variables.

A Kaplan-Meier survival analysis was then performed to investigate the association between the different tertiles and the risk of VTE recurrence. The log rank (Mantel-Cox) test was used for the comparison between survival curves of the three groups. Cox regression analysis was then conducted to estimate the association between the different SUA tertiles and the risk of recurrent VTE (considering the lowest tertile as a reference group). Univariate and multivariate Cox proportional hazards models were also computed considering SUA as a continuous variable and taking into account the following covariates: gender, age, BMI, hypertensive status, previous cardiovascular event, estimated GFR (eGFR), as well as the type of VTE index event. For all the models considered, the proportional hazard hypothesis is never rejected by the Schoenfeld residuals test. To graphically investigate the association between SUA levels and VTE recurrence risks, we used a restricted cubic spline model, based on five knots.

Statistical significance was considered as a two-tailed $P < .05$. All the analyses were performed by using STATA 16.

3 | RESULTS

3.1 | Population characteristics and baseline data

We enrolled a total of 280 subjects with a previous episode of VTE and not taking oral anticoagulants at enrollment visit. This cohort also includes 44 patients that completed the oral anticoagulation treatment during the follow-up (in this case the follow-up time was initiated at the time of therapy interruption). General characteristics of the cohort are shown in Table 1. For the present analysis the population was stratified according to SUA tertiles distribution. In particular, we identified three groups that were characterized by the following SUA cut-off values: first tertile ≤ 4.37 mg/dL (range 2.02--4.37, n = 95), second tertile 4.38--5.54 mg/dL (range 4.40--5.50, n = 88), third tertile ≥ 5.55 mg/dL (range 5.55--9.08, n = 97). Baseline clinical and biochemical characteristics of the three groups are summarized in Table 2. In particular, we observed that those with higher SUA were more likely to be male, older, to have higher BMI, higher BP levels, and lower eGFR values. No major differences were present between groups for the main characteristics of the VTE index event.

3.2 | Uric acid levels and the risk of VTE recurrence

The patients were followed for an average time of 71.1 ± 29.2 months (range 1--105 months) and during this time period 50 subjects (17.8%) experienced a symptomatic recurrence of VTE. As for the characteristics of the recurrent event we found that: 21 patients had ipsilateral DVT, 12 patients had contralateral DVT, isolated PE was observed in 3 cases, 11 patients had a combination of DVT/PE. Thirty-six subjects (72%) had an unprovoked recurrence, whereas in 14 cases the recurrent event was considered "provoked." Twelve patients died during the clinical follow-up and in four cases the death was ascribed to the recurrent VTE and in particular to fatal PE. Comparison of baseline characteristics between patients with or without recurrent VTE are shown in Table S1 in supporting information.

TABLE 1 Characteristics of the population

N	280
Age, years (SD)	57.0 (14.5)
Gender—male, n (%)	142 (50.7)
BMI, kg/m^2 (SD)	26.9 (4.3)
Mean SBP, mmHg (SD)	134.1 (20.4)
Mean DBP, mmHg (SD)	86.7 (10.9)
Hypertension (%)	167 (59)
Mean serum uric acid, mg/dL (SD)	5.06 (1.3)
Mean eGFR, mL/min/1.73 m^2 (SD)	87.1 (18.1)
Diabetes, n (%)	15 (5.4)
History of atherosclerotic events, n (%)	25 (8.9)
Therapy with statins, n (%)	44 (15.7)
Antiplatelet therapy, n (%)	40 (14.3)
Acid Uric lowering agents, n (%)	9 (3.2)
Gout, n (%)	11 (4.1)
VTE characteristics (first event)	
Type of VTE, unprovoked (%)	147 (52.5)
DVT site, proximal (%)	146 (52.1)
Pulmonary embolism, yes (%)	88 (31.4)
Thrombophilic defect, yes (%)[a]	61 (21.7)

Abbreviations: DPB, diastolic blood pressure; DVT, deep vein thrombosis; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; SD, standard deviation; VTE, venous thromboembolism.
[a]Data available for 210 patients.

TABLE 2 Baseline characteristics of the patients according to tertiles of serum uric acid levels

	Serum uric acid, mg/dL			
	≤4.37	4.38-5.54	≥5.55	*P*
N	97	88	95	
Mean age, years (SD)	53.1 (15.3)	58.7 (13.5)*	59.3 (13.8.)*	.005
Male sex, n (%)	18 (18.9)	48 (54.5)	76 (78.4)	<.0001
BMI (SD)	25.4 (3.7)	27.6 (5)*	28 (3.9)*	<.0001
Mean SBP, mmHg (SD)	127.8 (19.7)	137.9 (22.5)*	137 (17.2)*	.001
Mean DBP, mmHg (SD)	84.4 (10.7)	87.5 (11.8)*	88.6 (9.4)*	.019
Hypertension, n (%)	40 (42.1)	52 (59.1)	75 (77.3)	<.0001
Mean eGFR, mL/min/1.73m^2 (SD)	91.1 (19.9)	88.6 (13.9)	82.0 (18.4)	.001
Diabetes, n (%)	5 (5.3)	5 (5.7)	5 (5.2)	ns (.98)
Mean serum uric acid, mg/dL (SD)	3.67 (0.6)**,***	4.96 (0.28)*,***	6.51 (0.85)*,**	<.0001
Gout, n (%)	3 (3.2)	3 (3.6)	5 (5.4)	ns (.72)
Serum uric acid–lowering agents, n (%)	3 (2.0)	2 (2.3)	4 (4.1)	ns (.59)
History of atherosclerotic events, n (%)	2 (2.1)	10 (11.4)	13 (13.4)	.014
Therapy with statins, n (%)	6 (6.3)	17 (19.3)	21 (21.6)	.008
Antiplatelet therapy, n (%)	8 (8.4)	15 (17)	17 (17.5)	ns (.13)
Follow-up time, months (SD)	74.7 (30)	70.9 (28.3)	67.7 (29.2)	ns (.26)
VTE characteristics (first event)				
Type of VTE, unprovoked (%)	54 (56.8)	45 (51.1)	48 (49.5)	ns (.56)
DVT site, proximal (%)	40 (41.2)	53 (60.2)	53 (55.7)	ns (.15)
Thrombophilic defect, yes (%)[a]	15 (21.)	25 (37.3)	21 (28.4)	ns (.13)
Pulmonary embolism, yes (%)	32 (33.7)	26 (29.5)	30 (30.9)	ns (.82)

Abbreviations: BMI, body mass index; DPB, diastolic blood pressure; DVT, deep vein thrombosis; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; SD, standard deviation; SUA, serum uric acid; VTE, venous thromboembolism.

[a]Data were available for 210 patients (n = 69 in SUA ≤ 4.37 mg/dL, n = 67 in SUA 4.38-5.54 mg/dL, n = 74 in SUA ≥ 5.55 mg/dL).

*$P < .05$ vs SUA ≤ 4.37 mg/dL.

**$P < .05$ vs SUA 4.38-5.54 mg/dL.

***$P < .05$ vs SUA ≥ 5.55 mg/dL.

To investigate the association between SUA levels and the risk of VTE we plotted the Kaplan-Meier survival curves of the three groups of patients. As shown in Figure 1, the lowest risk of VTE recurrence was observed in the group of subjects belonging to the first tertile of SUA levels (≤4.37 mg/dL). On the contrary patients grouped in the second and third tertile of SUA distribution showed an overlap in the trend of the cumulative risk of recurrent VTE (Figure 1). The statistical comparison of the three curves confirmed that survival functions are equivalent for second and third tertile of SUA distribution ($P = .97$). On the other hand, second and third tertile both differ with respect to the first (first versus second tertile $P = .0015$, first versus third tertile $P = .0022$).

In Table 3 we summarize the hazard ratios (HRs) for VTE recurrence in the three tertiles of SUA. The analysis shows that the second and third tertile of SUA distribution have more than three-fold increase in the risk of VTE recurrence as compared to subjects with SUA ≤ 4.37 mg/dL. This increase in the risk was independent from several potential confounders, including age, gender, BMI, type of VTE, previous CV event, hypertension, and eGFR.

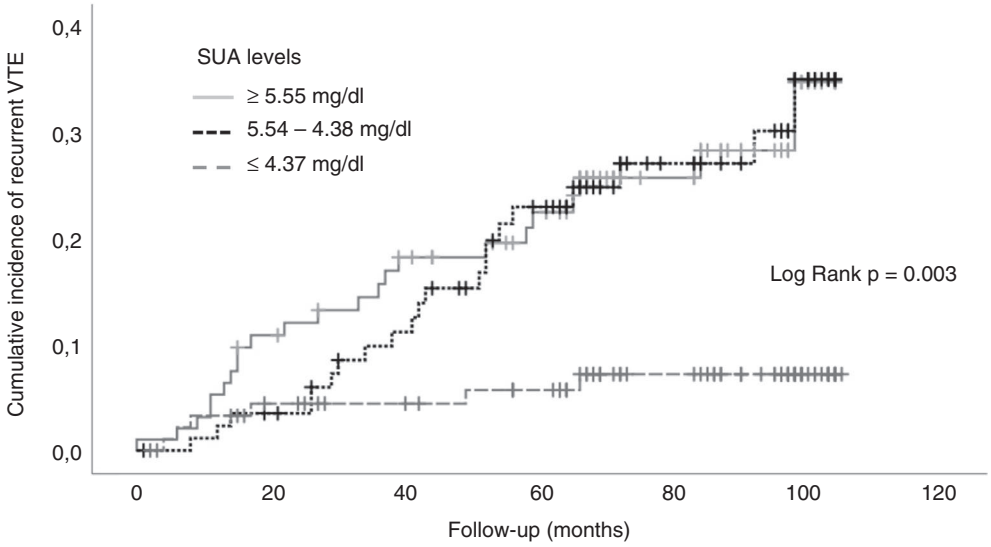

FIGURE 1 Risk of venous thromboembolism recurrence according to tertiles of serum uric acid (SUA) baseline values

TABLE 3 Hazard ratios (95% CI) for VTE recurrence according to serum uric acid level

	Serum uric acid (mg/dL)				
	≤4.37	4.38-5.54	*P*	≥5.55	*P*
Unadjusted	Ref.	3.92 (1.58--9.71)	.003	3.86 (1.56--9.54)	.003
Model 1	Ref.	3.68 (1.43--9.44)	.007	3.56 (1.34--9.45)	.011
Model 2	Ref.	3.80 (1.47--9.86)	.006	3.76 (1.39--10.16)	.009
Model 3	Ref.	3.87 (1.51--9.89)	.005	3.04 (1.15--8.05)	.025

Note: Model 1: Adjusted for age and gender; Model 2: Adjusted for age, gender, BMI and type of VTE; Model 3: Adjusted for age, gender, BMI, type of VTE, previous CV event, hypertension, and eGFR.

Abbreviations: BMI, body mass index; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; VTE, venous thromboembolism.

Based on results obtained from the analysis of survival curves and Cox regression, we decided to perform additional investigations to compare the risk of VTE recurrence between patients with baseline SUA levels higher or lower than 4.38 mg/dL. This analysis confirmed the significant increase in risk of VTE recurrence for patients with higher SUA levels independent from several baseline characteristics. In particular, the fully adjusted model showed that patients with SUA values ≥ 4.38 mg/dL had an HR for VTE recurrence of 3.48 (95% confidence interval [CI] 1.41--8.59, $P = .007$, Table S2 in supporting information). We also used this cut-off value to estimate the risk of thrombotic recurrence in different subgroups of our population. In particular, we found that SUA levels higher than 4.38 mg/dL remained significantly associated with the risk of VTE recurrence even when we limited the analysis to patients with history of unprovoked VTE (HR 3.73, 95% CI 1.2-11.1, $P = .018$). A similar finding was obtained when we grouped unprovoked VTE patients together with provoked VTE patients with "nonsurgical factors" (HR 3.96, 95% CI 1.31--11.9, $P = .014$). In addition, even when we excluded from the analysis patients that experienced a "provoked" recurrent event or subjects with ongoing oral anticoagulant use at enrollment, we found that SUA levels ≥ 4.38 mg/dL still remained associated with an increased risk of thrombotic recurrence (respectively, HR 3.78, 95% CI 1.27--11.2 $P = .017$, and HR 3.28, 95% CI 1.31--8.23, $P = .011$).

We also performed a univariate and multivariate Cox regression analysis to estimate the HRs for VTE recurrence considering SUA as a continuous variable (Table 4). The analysis showed that SUA levels were significantly associated with a higher risk of future VTE recurrence. In particular, we observed that for each additional unit of SUA (mg/dL) the hazard of recurrence increases by 37% (HR 1.37, 95% CI 1.12--1.68, $P = .002$). This association remained significant with an HR of 1.30 even after adjustment for age, gender, BMI, presence of hypertension, type of VTE, and renal function (95% CI 1.01--1.67, $P = .040$). The multivariate analysis also showed an independent significant association between the risk of future VTE recurrence and baseline eGFR values as well as history of unprovoked event (respectively, HR 0.97, 95% CI 0.96--0.99, $P = .030$ and HR 1.98, 95% CI 1.08--3.65, $P = .026$).

Based on the latter multivariate model (Table 4), we performed a further analysis to measure the in-sample association between HRs and SUA. As a reference (HR = 1) we considered a hypothetical patient with the following characteristics: SUA = 4.38 mg/dL, female, age 45 years, eGFR = 90 mL/min/1.72 m^2, previous provoked VTE, BMI = 21.5 kg/m^2, normotensive, no history of cardiovascular

TABLE 4 Univariate and multivariate Cox regression hazard ratios for VTE recurrence

Variable	Univariate HR (95% CI)	*P*	Multivariate HR (95% CI)	*P*
Age	1.01 (0.99-1.03)	.179	0.99 (0.96-1.01)	.551
Gender (male)	1.68 (0.95-2.98)	.070	1.32 (0.70-2.48)	.386
BMI	1.03 (0.97-1.09)	.250	1.03 (0.96-1.10)	.349
Hypertension	1.57 (0.87-2.86)	.132	1.02 (0.50-2.11)	.941
Unprovoked VTE	1.86 (1.02-3.37)	.041	1.98 (1.08-3.65)	.026
eGFR (mL/min/1.73 m^2)	0.97 (0.96-0.99)	.002	0.97 (0.96-0.99)	.030
Previous CV event	0.63 (0.19-2.02)	.406	0.36 (0.10-1.22)	.102
Serum uric acid (mg/dL)	1.37 (1.12-1.68)	.002	1.30 (1.01-1.67)	.040

Abbreviations: BMI, body mass index; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HR, hazard ratio; VTE, venous thromboembolism.

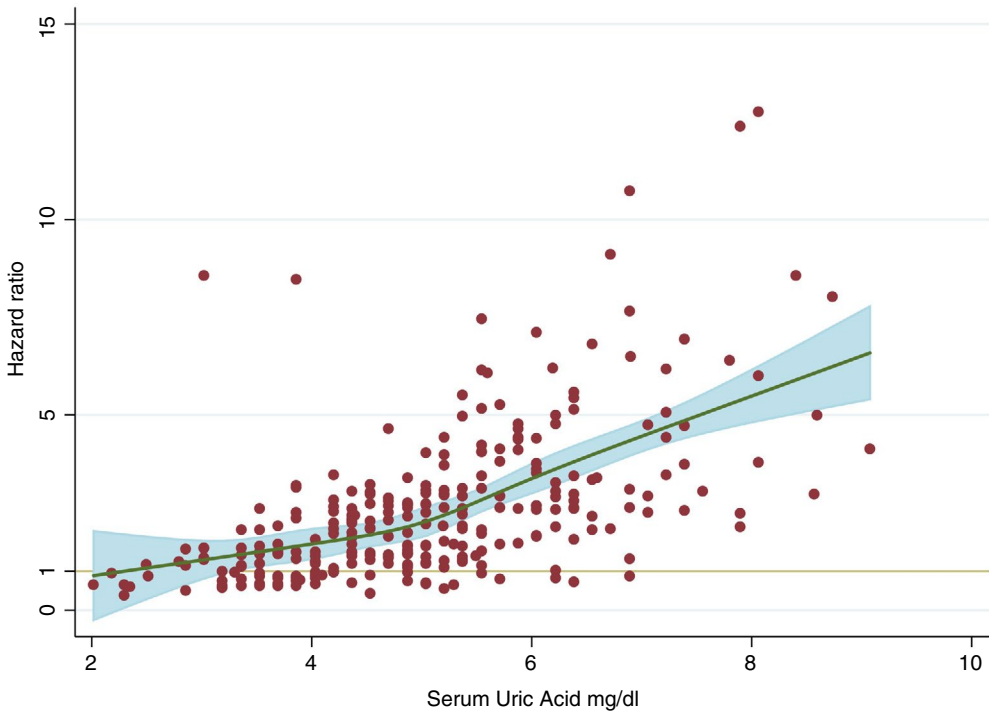

FIGURE 2 Association between venous thromboembolism recurrence risk and serum uric acid levels. Interpolation with restricted cubic spline is based on the multivariate model (Table 4). The solid green line is the estimated hazard ratio, the shaded blue area the 95% confidence interval whereas red points are the hazard ratios for each patient

events. Grounded on these results, we computed the HR for each patient considered in the study and estimated the non-linear relationship between HRs and SUA levels (Figure 2) through a restricted cubic spline. This analysis clearly showed a progressive increase in HRs for VTE recurrence in patients with higher baseline levels of SUA. This association tends to be stronger for levels of SUA larger than 5 mg/dL.

4 | DISCUSSION

The present study was undertaken to investigate the association between SUA levels and the risk of VTE recurrence. The major finding was that among patients with a first episode of VTE increased levels of SUA are associated with a higher risk of thrombotic recurrence. This correlation remained significant even after adjustment for age, gender, BMI, presence of hypertension, type of VTE, and renal function.

To the best of our knowledge this is the first study that investigated the impact of SUA levels on VTE recurrence. In the current study we followed-up 280 subjects with a previous episode of VTE for a mean period of 71.1 ± 29.2 months. Our results showed that SUA levels > 4.37 mg/dL (corresponding to the second and third tertile of SUA distribution in our population), were significantly associated with higher risk of future VTE recurrence. Relatively few investigators have analyzed the impact of SUA levels on VTE

occurrence and they mainly focused on the first episode of VTE. The ARIC study was the largest population-based study to investigate whether elevated SUA levels were associated with VTE in a large population of 14 126 subjects aged 45 to 64 years, without a history of VTE or gout and not using anticoagulants or SUA-lowering medications. The authors demonstrated a correlation between elevated SUA values and increased risk of VTE. This was observed also in patients with gout, although it was not statistically significant. Interestingly, in the ARIC study the positive trend was maintained across six different categories of SUA, with the lowest risk of incident VTE observed in subjects with SUA ≤ 4.9 mg/dL.[11] Our findings are in line with this previous study, and in particular with the observation that the lowest number of VTE recurrences occurred in patients with very low levels of SUA. Moreover, even when we set in our population a cut-off value for SUA at 4.9 mg/dL, we still observed a significant, independent increase in the risk of VTE recurrence among patients with higher SUA levels at enrolment (HR 2.05, 95% CI 1.05--4.00, $P = .034$). Overall, these data clearly indicate that the association between SUA and the risk of VTE remain significant even for SUA values lower than those used in clinical practice for defining hyperuricemia. More recently, Sultan and colleagues reported a 25% increased risk of developing VTE in patients with gout after the diagnosis.[13] In our study only 11 subjects had a history of gout and only 30 subjects showed SUA levels > 6.8 mg/dL, a value above which crystal deposition may occur leading to gout. Due to the limited number of patients with these characteristics we cannot establish whether very high levels of SUA can be associated with an additional risk for VTE recurrence. However, when the analysis was performed using SUA as a continuous variable, we observed a progressive increase in the risk for VTE recurrence that became more evident for SUA > 5 mg/dL (Figure 2).

In a previous study we reported a significant correlation between reduction in renal function and the risk of VTE recurrence.[14] This association was confirmed in the present analysis as we observed an inverse correlation between eGFR values and the risk of a second thrombotic event (HR 0.97, 95% CI 0.96--0.99, $P = .002$). Of interest, in the adjusted analysis, both SUA and the renal function remained independently associated with VTE recurrence, suggesting that the reduction in eGFR cannot fully explain the link between SUA and the thrombotic events.

Inflammation and oxidative stress are considered the major pathogenetic mechanisms driving the link between SUA and CV disease. SUA, even at physiologic concentrations, has been demonstrated to promote inflammatory response (such as increase in tumor necrosis factor alpha, interleukin 6, and C-reactive protein) as well as to impair proliferation/migration and nitric oxide (NO) release from human vascular cells.[15,16] Inflammation, therefore, might be a plausible linkage between UA and VTE. According to some investigators, the inflammatory activation of endothelial cells induced by oxygen reactive species derived from SUA metabolism could trigger a cascade reaction leading to endothelial injury, which is one of the initial triggers involved in the clotting formation (according to Virchow's triad).[17] Other studies also demonstrated that monosodium urate crystals can trigger inflammatory response[18] and the release of neutrophil extracellular traps (NETs) by neutrophils.[19] In animal models the occurrence of NETosis has been linked to the pathogenesis of thrombotic events, including VTE.[20] In addition, markers of NETosis are increased in subjects with acute VTE[21] and can be found in vivo within both arterial and venous thrombi.[22] Additional investigations are needed to establish which of the pathophysiological mechanisms listed above are preferentially driven by SUA and trigger venous thrombosis.

Our major findings, as well as data from subgroup analysis, can have significant clinical implications for the management of patients with VTE. Although some scores, based on D-dimer levels, age, hormone therapy, male gender, and site of VTE, have been validated to support the decision on prolonging oral anticoagulation after the first 3 months,[23,24] a certain degree of uncertainty still remains in the clinical approach to some groups of patients. Other clinical features, such as obesity, cancer, residual vein thrombosis, and hereditary thrombophilia are currently used in clinical practice to estimate the risk of VTE recurrence. The current study suggests that both renal function and SUA levels could be added to the list of tools to be used in the clinical evaluation of patients with a first episode of VTE. For instance, our subgroup analysis suggests that, even in the high-risk group of patients with a previous unprovoked VTE event, very low levels of SUA are associated with a low risk of VTE recurrence. Moreover, the observation that higher SUA levels remained associated with an increased risk of recurrence even after exclusion of "provoked" recurrent event further indicates that SUA could represent a potent predictor of unprovoked VTE recurrence. Thus, determination of SUA levels could support the clinical decision whether or not to extend oral anticoagulation beyond the first 3--6 months of treatment. Nevertheless, further investigations on larger population are needed to confirm our findings and to identify as well as validate cut-off values that can help physicians in their daily practice.

There are some limitations in the present study. First, SUA levels were measured only at enrolment and they were not available during the follow-up period. Thus, we cannot exclude the presence of confounding factors interfering with SUA levels and VTE recurrence during the follow-up period. Second, we did not collect data about inflammatory markers, thus we are not able to assess the impact of systemic inflammation on VTE recurrence and its correlation with SUA levels. The prospective and long-term design of our investigation represents the major strength of this study, which allows us to continue the follow-up period and the collection of data.

In conclusion, we found that SUA is an independent risk factor for recurrence of VTE after a first episode of DVT/PE. This observation might have significant implications in the management of oral anticoagulation in some groups of patients, although additional studies are needed to confirm these findings and identify SUA cut-off values that might drive clinical decisions.

ACKNOWLEDGMENTS

The authors are thankful for the support of FORIBICA.

CONFLICTS OF INTEREST

All the authors declared no competing interests.

AUTHOR CONTRIBUTIONS

M. Rattazzi, L. De Lucchi, and Sabina Villalta: designed the study and wrote the manuscript; A. Sponchiado, E. Martini, V. Pagliara, E. Callegari, C. Nardin recruited the patients and performed clinical follow-up; L. Caberlotto, M. Plebani, E. Faggin, performed laboratory investigations; D. Raggi and F. Cinetto performed statistical analysis; P. Pauletto and C. Agostini designed the study and participated in the interpretation of the findings.

REFERENCES

1. Wang J, Qin T, Chen J, et al. Hyperuricemia and risk of incident hypertension: a systematic review and meta-analysis of observational studies. *PLoS One*. 2014;9:1-18.
2. Holme I, Aastveit AH, Hammar N, Jungner I, Walldius G. Uric acid and risk of myocardial infarction, stroke and congestive heart failure in 417 734 men and women in the Apolipoprotein MOrtality RISk study (AMORIS). *J Intern Med*. 2009;266:558-570.
3. Bos MJ, Koudstaal PJ, Hofman A, Witteman JCM, Breteler MMB. Uric acid is a risk factor for myocardial infarction and stroke: the Rotterdam study. *Stroke*. 2006;37:1503-1507.
4. Sotoda Y, Hirooka S, Orita H, Wakabayashi I. Association of serum uric acid levels with leg ischemia in patients with peripheral arterial disease after treatment. *J Atheroscler Thromb*. 2017;24:725-734.
5. Kleber ME, Delgado G, Grammer TB, et al. Uric acid and cardiovascular events: a Mendelian randomization study. *J Am Soc Nephrol*. 2015;26:2831-2838.
6. Virdis A, Masi S, Casiglia E, et al. Identification of the uric acid thresholds predicting an increased total and cardiovascular mortality Over 20 years. *Hypertension*. 1979;2020(75):302-308.
7. Casiglia E, Tikhonoff V, Virdis A, et al. Serum uric acid and fatal myocardial infarction: detection of prognostic cut-off values: the URRAH (Uric Acid Right for Heart Health) study. *J Hypertens*. 2020;38:412-419.
8. Næss IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrøm J. Incidence and mortality of venous thrombosis: a population-based study. *J Thromb Haemost*. 2007;5:692-699.
9. Kanbay M, Segal M, Afsar B, Kang DH, Rodriguez-Iturbe B, Johnson RJ. The role of uric acid in the pathogenesis of human cardiovascular disease. *Heart*. 2013;99:759-766.
10. Erdogan D, Gullu H, Caliskan M, et al. Relationship of serum uric acid to measures of endothelial function and atherosclerosis in healthy adults. *Int J Clin Pract*. 2005;59:1276-1282.
11. Kubota Y, McAdams-Demarco M, Folsom AR. Serum uric acid, gout, and venous thromboembolism: the atherosclerosis risk in communities study. *Thromb Res*. 2016;144:144-148.
12. Ozsu S, Çoşar AM, Aksoy HB, et al. Prognostic value of uric acid for pulmonary thromboembolism. *Respir Care*. 2018;62:1091-1096.
13. 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-E603.
14. Rattazzi M, Villalta S, De Lucchi L, et al. Chronic kidney disease is associated with increased risk of venous thromboembolism recurrence. *Thromb Res*. 2017;160:32-37.
15. Kang DH, Park SK, Lee IK, Johnson RJ. Uric acid-induced C-reactive protein expression: Implication on cell proliferation and nitric oxide production of human vascular cells. *J Am Soc Nephrol*. 2005;16:3553-3562.
16. Lyngdoh T, Marques-Vidal P, Paccaud F, et al. Elevated serum uric acid is associated with high circulating inflammatory cytokines in the population-based colaus study. *PLoS One*. 2011;6:1-8.
17. Feig D, Kang DHJR. Uric acid and cardiovascular risk. *N Engl J Med*. 2008;309:1811-1821.
18. Martinon F, Pétrilli V, Mayor A, Tardivel A, Tschopp J. Gout-associated uric acid crystals activate the NALP3 inflammasome. *Nature*. 2006;440:237-241.
19. Chatfield SM, Grebe K, Whitehead LW, et al. Monosodium urate crystals generate nuclease-resistant neutrophil extracellular traps via a distinct molecular pathway. *J Immunol*. 2018;200:1802-1816.
20. Martinod K, Wagner DD. Thrombosis: tangled up in NETs. *Blood*. 2014;123:2768-2776.
21. Van Montfoort ML, Stephan F, Lauw MN, et al. Circulating nucleosomes and neutrophil activation as risk factors for deep vein thrombosis. *Arterioscler Thromb Vasc Biol*. 2013;33:147-151.
22. Pfeiler S, Stark K, Massberg S, Engelmann B. Propagation of thrombosis by neutrophils and extracellular nucleosome networks. *Haematologica*. 2017;102:206-213.
23. Tosetto A, Iorio A, Marcucci M, et al. Predicting disease recurrence in patients with previous unprovoked venous thromboembolism: a proposed prediction score (DASH). *J Thromb Haemost*. 2012;10:1019-1025.
24. Eichinger S, Heinze G, Jandeck LM, Kyrle PA. Risk assessment of recurrence in patients with unprovoked deep vein thrombosis or pulmonary embolism: The vienna prediction model. *Circulation*. 2010;121:1630-1636.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: De Lucchi L, Nardin C, Sponchiado A, et al. Serum uric acid levels and the risk of recurrent venous thromboembolism. *J Thromb Haemost*. 2021;19:194–201. https://doi.org/10.1111/jth.15139