ARTICLE

Identification of a plausible serum uric acid cut-off value as prognostic marker of stroke: the Uric Acid Right for Heart Health (URRAH) study

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The Working Group on Uric Acid and Cardiovascular Risk of the Italian Society of Hypertension conceived and designed an ad hoc study aimed at searching for prognostic cut-off values of serum uric acid (SUA) in predicting combined (fatal and non-fatal) cerebrovascular (CBV) events in the whole database. The URic acid Right for heArt Health study is a nationwide, multicenter, observational cohort study involving data on subjects aged 18–95 years recruited on a regional community basis from all the territory of Italy under the patronage of the Italian Society of Hypertension with a mean follow-up period of 120.7 ± 61.8 months. A total of 14,588 subjects were included in the analysis. A prognostic cut-off value of SUA able to discriminate combined CBV events (>4.79 mg/dL or >284.91 µmol/L) was identified by means of receiver operating characteristic curve in the whole database. Multivariate Cox regression analysis adjusted for confounders (age, sex, arterial hypertension, diabetes, chronic kidney disease, smoking habit, ethanol intake, body mass index, low-density lipoprotein cholesterol, and use of diuretics) identified an independent association between SUA and combined CBV events in the whole database (HR 1.249, 95% confidence interval, 1.041–1.497, $p = 0.016$). The results of the present study confirm that SUA is an independent risk marker for CBV events after adjusting for potential confounding variables, including arterial hypertension, and demonstrate that >4.79 mg/dL is a valid prognostic cut-off value.

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INTRODUCTION

Uric acid is the final product of purine metabolism in humans. The association between serum uric acid (SUA) and cardiovascular disease has been investigated for almost 50 years [1] and the role of SUA as a cardiovascular risk factor or indicator is growing, especially due to convincing epidemiological evidences [2–5]. Although the pathogenetic role for SUA in cardiovascular diseases remain to be elucidated, experimental studies have shown that hyperuricemia is associated with endothelial dysfunction, increased oxidative stress, thrombus formation, and elevated circulating levels of systemic inflammatory mediators [6–8].

Two recent metanalyses of prospective observational studies suggest that hyperuricemia is significantly associated with cerebrovascular (CBV) morbidity and mortality [9, 10]. However,

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no univocal definition for hyperuricemia exists, even though SUA >6.8 mg/dL (>404.46 µmol/L), i.e., the limit of urate solubility, is generally used. On two metanalytical reviews, a wide between-study range of SUA cut-off value (from 5.0 to 11.0 mg/dL or from 297.4 to 654.28 µmol/L) was observed, indicating that the relation between SUA and stroke is relevant to SUA levels usually considered in the normal-to-high range.

The Working Group on Uric Acid and Cardiovascular Risk of the Italian Society of Hypertension conceived and designed a nationwide ad hoc protocol involving a great number of Italian people, aimed at finding, if any, the cut-off value of SUA able to stratify subjects into having or having not an increased risk of CBV events. The URic acid Right for heArt Health (URRAH) intends to clarify if SUA is associated with stroke, if a univariate cut-off level of SUA exists and can be confirmed being accepted in multivariate Cox regression models adjusted for confounders.

MATERIALS AND METHODS

Database and study protocol

The database called URRAH is a multicenter retrospective observational cohort study that involves data on subjects aged 18–95 years collected on a regional community basis from all the territory of Italy under the patronage of the Italian Society of Hypertension with a median follow-up period of 136 months (interquartile range from 72 to 160 months) up to July 31, 2017. Participant centers that collected the data included in the general database are listed under Acknowledgements. The study protocol has been previously extensively described [11–14]. In brief, a nationwide Italian database was built on a regional basis by collecting data on subjects from representative cohorts having SUA measurement and complete information about several variables including outcomes. For all subjects, a standardized set of items was recorded, including demographics, anthropometric measures, metabolic parameters, smoking habit, systolic and diastolic arterial blood pressure (BP), kidney function, concomitant treatments, and outcomes. Low-density lipoprotein cholesterol (LDLC) was calculated as: total cholesterol – HDL cholesterol levels, minus triglyceride level divided by 5, if the triglyceride level was <400 mg/dL. Diabetes mellitus was defined by treatment with antidiabetic drugs, fasting plasma glucose ≥126 mg/dL, or hemoglobin A1c ≥48 mmol/mol. Systolic and diastolic BP was measured twice, in a quiet room, after 5 min resting and with the participant in sitting position. The second measure was used for all analyses. According to ESH-ESC guidelines, arterial hypertension was defined as BP ≥140 or ≥90 mmHg or by the presence of antihypertensive treatment. Kidney function was evaluated through estimation of the glomerular filtration rate, using a standardized serum creatinine assay and according to the Chronic Kidney Disease Epidemiology Collaboration equation [15]. Chronic kidney disease (CKD) was defined for estimated glomerular filtration rate values <60 mL/min per 1.73 m^2.

Ethics

The study data were collected routinely or ad hoc in previously authorized studies. Subjects underwent no extra tests or interventions, and there was no impact on subjects' care or outcome. The URRAH was performed according to the Declaration of Helsinki for Human Research (41st World Medical Assembly, 1990). The processing of the patients' personal data collected in this study complies with the European Directive on the Privacy of Data. All data to be collected, stored, and processed are anonymized, and all study-related documents are retained in a secure location. No personal information is stored on local personal computers. Approval was sought from the Ethical Committee of the Coordinating Center at the Division of Internal Medicine of the University of Bologna (No. 77/2018/Oss/AOUBo). Informed consent was obtained from all subjects at recruitment.

Outcomes

Incidence of any fatal and non-fatal ischemic and hemorrhagic stroke was evaluated at the time of the first CBV event for non-fatal events and at the end of follow-up for fatal events, based on the International Classification of Diseases Tenth Revision codes I61, I62, I63, I65-I67, I69, and F01. Information about death was obtained from hospital records or death certificates. Follow-up data were censored at the time of the first CBV event or, for subjects lost during follow-up, at the last date they were known to be alive.

Statistics

General description. The SAS package version 9.4 (SAS Institute, Cary, NC) was used for statistical analysis (software information: SAS 9.4 TS level 1M4; X64_10PRO platform). A preliminary power analysis based on differences from stratified values of uric acid for $\alpha = 0.05$ and power $(1 - \beta) = 0.80$ was performed. To our knowledge, no study exists about possible cut-off values of SUA discriminating subjects into doomed to and not doomed to develop any CBV event. Consequently, based on previous work of our research staff [16, 17], we considered 1 mg/dL SUA as a possible difference able to stratify subjects according to the above-mentioned outcome. Power analysis showed that the number of subjects in the database ($n = 14{,}588$) represented a sample largely sufficient to avoid β error. The Kolmogorov–Smirnov normality test was performed. Continuous variables were expressed as mean (standard deviation) and compared among classes or categories by the analysis of covariance adjusted time to time for proper confounders and followed by Bonferroni's post hoc test. Categorical variables were compared by means of the Pearson χ^2 test. In multivariate analyses, the covariables that were not independent from each other were previously log-transformed. The null hypothesis was rejected for values of $p < 0.05$.

Preliminary Cox analysis. SUA as a continuous item (in mg/dL) was used as independent variable in Cox analyses having all combined CBV events (fatal + non-fatal) as dichotomic-dependent variable, and sex, age, arterial hypertension, diabetes mellitus, CKD, smoking habit, ethanol intake, body mass index, LDLC and use of diuretics as possible confounders. We tested interactions of SUA with age, gender, diabetes mellitus, arterial hypertension, ethanol intake, CKD, and diuretics by incorporating corresponding interaction terms in the analysis. Hazard ratios (HR) with 95% confidence intervals (CI) were produced. The null hypothesis was rejected for values of $p < 0.05$.

Univariate prognostic cut-off value. The receiver operating characteristic (ROC) curves method was used to search for prognostic cut-off of SUA for combined CBV events in the whole database and by diabetic status. SUA was used as basic variable and all CBV events as dichotomic classification variables. The De Long et al. method [18] was used. Ratio of cases in the positive group (prevalence), sensitivity, and specificity were calculated. ROC curves were generated in the whole database, and a prognostic cut-off value was identified as the curve point nearest to the 100% of axis of the ordinates [19]. In practical terms, this was made by identifying the SUA value associated with the highest values of the sum sensitivity + specificity. Youden's index [20] defined for all points of ROC curves was used as a criterion for selecting the optimum cut-off. The area under the curve was also shown for each ROC curves analysis [21].

Validation of the prognostic cut-off value. The cut-off value of SUA identified by mean of the ROC curves was used as independent variable in multivariate Cox analyses adjusted for the confounders already identified, having combined CBV events as dichotomic-dependent variable in the whole database. A cut-off value identified via the ROC curves method was considered as valid if accepted in the model being the null hypothesis rejected, otherwise it was considered a false cut-off. The corresponding HR with 95% CI were obtained.

CBV events in relation to cut-off value. In the whole database, the validated cut-off value was used to stratify combined CBV events in descriptive analysis and for generating outcome curves according to the Kaplan–Meier non-parametric estimator of limit product. Log-rank tests were used to assess differences between curves. Finally, as sensitivity analysis, a multivariate Cox analysis having combined CBV events as dependent variable and the validated cut-off as independent variable was performed, adjusting for the confounders already identified and the interaction term cuff-off value × age. Quintiles of age were calculated for using them in this sensitivity analysis.

RESULTS

Descriptive statistics

The general characteristics of the 14,588 subjects are shown in Table 1. In the overall study population, median follow-up was 136.0 months (5th–95th percentile interval: 6.5–194.0 months). During 142,896 person-years of follow-up, 305 participants experienced fatal CBV events (2.13 per 1000 age-adjusted person-years),

Table 1. General characteristics of the study database.

Variables	Whole database ($n = 14,588$)	Females ($n = 7748$)	Males ($n = 6840$)	p values between sexes
Age (years)	58.4 (14.7)	58.7 (15.0)	58.0 (14.3)	0.003
Serum uric acid (mg/dL)	4.99 (1.38)	4.82 (1.37)	5.18 (1.37)	<0.0001
Waist circumference (cm)	88.8 (12.6)	85.8 (12.8)	92.2 (11.5)	<0.0001
Heart rate (bpm)	71.5 (11.2)	72.2 (11.1)	70.7 (11.3)	<0.0001
Systolic BP (mmHg)	143.9 (23.9)	144.2 (25.0)	143.7 (22.7)	0.27
Diastolic BP (mmHg)	85.2 (12.7)	85.3 (12.9)	85.1 (12.4)	0.50
Body mass index (kg/m^2)	26.6 (4.3)	26.7 (4.5)	26.5 (4.0)	0.003
Azotaemia (mg/dL)	33.6 (9.6)	33.0 (9.4)	32.2 (9.9)	0.0003
Serum creatinine (mg/dL)	0.93 (0.22)	0.90 (0.24)	0.96 (0.20)	<0.0001
Serum glucose (mg/dL)	98.6 (24.7)	99.3 (26.8)	97.9 (22.2)	0.0025
LDLC (mg/dL)	136.0 (35.7)	136.3 (35.3)	135.7 (36.1)	0.29
Smoking habit (yes, %)	22.3	19.5	25.5	<0.0001
Ethanol intake (yes, %)	61.6	60.0	63.3	<0.0001
Diabetes (yes, %)	9.2	10.0	8.3	0.0005
Hypertension (yes, %)	66.8	66.5	67.2	0.37
CKD (yes, %)	20.3	21.4	19.1	0.0006
Gout (yes, %)	1.1	0.5	1.9	<0.0001
Diuretics use (yes, %)	16.2	17.7	14.6	<0.0001
Allopurinol use (yes, %)	1.1	0.6	1.7	<0.0001
Statin use (yes, %)	4.2	4.0	4.5	0.18

Continuous variables are expressed as mean (standard deviation). Categorical variables are in %.
BP arterial blood pressure, *LDLC* low-density lipoprotein serum cholesterol, *CKD* chronic kidney disease.

and 285 non-fatal CBV events (2.00 per 1000 age-adjusted person-years).

Multivariate analysis

Preliminary Cox models having combined CBV events as dependent variable showed that, in the whole cohort, SUA as a continuous variable was associated with CBV events (HR 1.105, 95% CI 1.041–1.173, $p = 0.001$), being age, diabetes mellitus, hypertension, and ethanol intake significant confounders (Table 2). Six interaction terms were tested (SUA × age, SUA × gender, SUA × diabetes mellitus, SUA × arterial hypertension, SUA × ethanol intake, SUA × CKD, and SUA × diuretics). Only SUA × age and SUA × diabetes mellitus were significant when included in the model (HR 0.992, 95% CI 0.986–0.997, $p = 0.004$ and HR 1.146, 95% CI 1.00–1.31, $p = 0.04$, respectively).

Search for cut-off value

ROC curve furnished a plausible univariate cut-off value of SUA for combined CBV events (>4.79 mg/dL). The ROC curve for the whole cohort is shown in Fig. 1, and ROC curve parameters are summarized in Table 3.

Furthermore, in multivariate Cox analyses performed in all subjects and adjusted for sex, age, arterial hypertension, diabetes mellitus, CKD, smoking habit, ethanol intake, body mass index [22], LDLC, and use of diuretics [23], the cut-off value of SUA for combined CBV events was accepted in the model (HR 1.249, CI 1.041–1.497, $p = 0.016$) (Table 4). Age, diabetes, hypertension, and ethanol intake directly contributed to incident CBV events.

Due to the significant interaction term SUA × diabetes, we searched for possible cut-off values by diabetes status. ROC curve furnished plausible univariate cut-off value of SUA for CBV events in non-diabetic subjects only (>4.79 mg/dL) (Supplementary Table 1).

Table 2. Cox model for combined cerebrovascular events using serum uric acid as a continuous independent variable in the whole cohort.

Independent variables	HR	95% CI	p value
Serum uric acid (mg/dL)	1.105	1.041–1.173	0.0011
Age (years)	1.063	1.054–1.072	<0.0001
Diabetes (1 = yes, 0 = no)	2.051	1.674–2.512	<0.0001
Smoking (1 = yes, 0 = no)	1.016	0.819–1.261	0.88
Sex (1 = men, 0 = women)	1.146	0.968–1.358	0.11
Body mass index (kg/m^2)	1.002	0.982–1.023	0.84
LDLC (mg/dL)	1.001	0.999–1.003	0.40
Hypertension (1 = yes, 0 = no)	1.329	1.053–1.677	0.017
CKD (1 = yes, 0 = no)	1.123	0.925–1.364	0.24
Ethanol (1 = yes, 0 = no)	1.478	1.202–1.817	0.0002
Use of diuretics (1 = yes, 0 = no)	1.124	0.905–1.397	0.29

HR hazard ratio, *CI* confidence interval, *LDLC* low-density lipoprotein serum cholesterol, *CKD* chronic kidney disease.

Application of the confirmed cut-off to the study database

Kaplan–Meier curves in the whole database are shown in Fig. 2. The curves of subjects having SUA ≤ cut-off and SUA > cut-off were clearly separate.

Sensitivity analysis

In the preliminary Cox analysis, the interaction term SUA × age was accepted in the model with a negative parameter estimates (beta = –0.00813 ± 0.00271, $p = 0.0027$). We therefore performed in all subjects a further multivariate Cox analysis having combined CBV events as dependent variable, and cut-off of SUA as independent variable, adjusting for the interaction term cuff-off SUA × age and the confounders already identified. The interaction

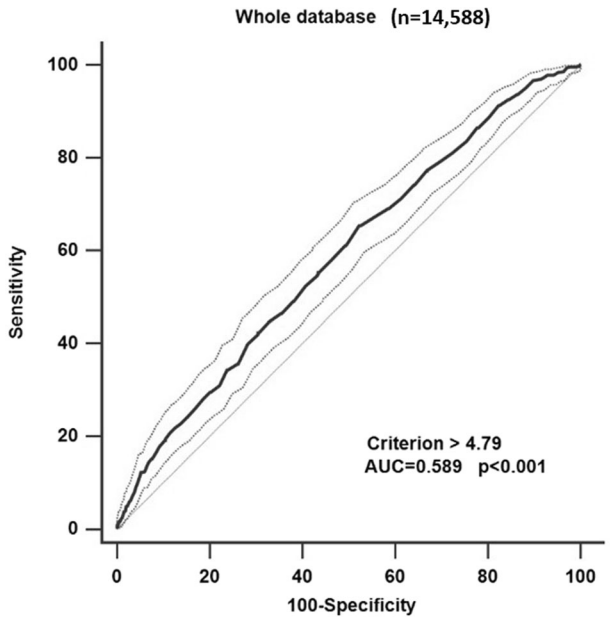

Fig. 1 Receiver-operator-characteristic (ROC) curves of combined cerebrovascular events. 95% confidential intervals are shown (thin lines). AUC area under the curve, p criterion for rejection of the null hypothesis.

Table 3. ROC curve parameters of the cut-off value for combined cerebrovascular events in a regional community-based cohort of 14,588 subjects.

	All ($n = 14,588$)
Cut-off (CI[a])	>4.79 mg/dL (4.66–5.89)
AUC (SE, CI)	0.589 (0.013, 0.580–0.598)
Youden index (CI)	0.1299 (0.0937–0.1646)
Sensitivity, % (CI)	65.3 (61.0–69.4)
Specificity, % (CI)	47.7 (46.8–48.6)
Z statistics, *p*	7.028, <0.0001

CI confidence interval, *AUC* area under the curve, *SE* standard error.
[a]Bootstrap confidence intervals (1000 iterations).

Table 4. Hazard ratios of the cut-off value of serum uric acid for combined cerebrovascular events in the whole database.

Independent variables	HR	95% CI	*p* value
Specific cut-off of SUA (>4.79 mg/dL)	1.249	1.041–1.497	0.016
Age (years)	1.064	1.054–1.073	<0.0001
Smoking (1 = yes, 0 = no)	1.023	0.824–1.271	0.83
Diabetes (1 = yes, 0 = no)	2.075	1.692–2.545	<0.0001
Sex (1 = men, 0 = women)	1.153	0.972–1.367	0.10
Body mass index (kg/m^2)	1.004	0.983–1.025	0.70
LDLC (mg/dL)	1.001	0.999–1.003	0.41
Ethanol (1 = yes, 0 = no)	1.489	1.210–1.833	0.0002
Hypertension (1 = yes, 0 = no)	1.337	1.058–1.689	0.014
CKD (1 = yes, 0 = no)	1.140	0.938–1.384	0.18
Use of diuretics (1 = yes, 0 = no)	1.142	0.919–1.420	0.23

HR hazard ratio, *CI* confidence interval, *SUA* serum uric acid, *LDLC* low-density lipoprotein serum cholesterol, *CKD* chronic kidney disease.

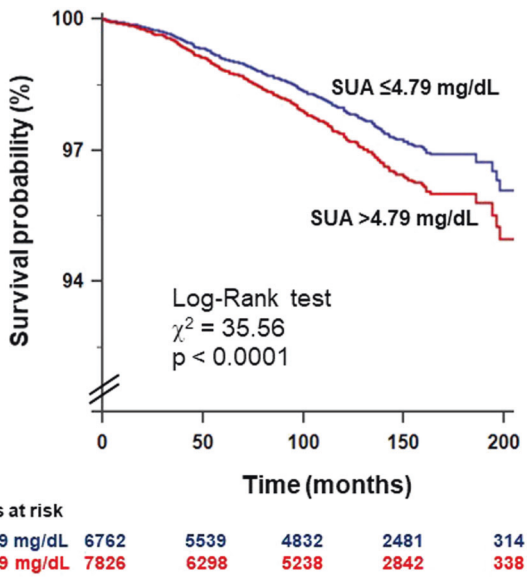

Fig. 2 Kaplan–Meier curves of survival probability for combined cerebrovascular events in the overall population. Trends of subjects having serum uric acid > cut-off (red line) and ≤ cut-off (blue line) are shown. Numbers of subjects at risk are shown in the two footnotes. SUA serum uric acid.

term was significantly accepted in the model (HR 0.974, 95% CI 0.958–0.991, $p = 0.003$). We then calculated the HR with 95% CI of combined CBV events for cut-off value of SUA > 4.79 mg/dL by quintiles of age (Fig. 3).

DISCUSSION

The results of the present study confirm that SUA is an independent marker associated with combined CBV events after adjusting for potential confounding variables including hypertension [24, 25], i.e., in our cohort with each increase of 1 mg/dL of SUA, the HR of combined CBV increases by 10.5%. These results are consistent with a series of studies showing positive association between hyperuricemia and risk of stroke incidence and mortality [9, 10, 26]. Results from a metanalysis of 16 prospective studies, including 238,449 adults and adjusting for multivariate risk factors, suggested that hyperuricemia was associated with a significantly increased risk of stroke incidence and mortality (+47% and +26%, respectively) [10]. In an updated metanalysis of 15 prospective studies, including 1,042,358 participants, hyperuricemia was associated with a significantly greater risk of both stroke incidence (22%) and mortality (33%) [9].

Up to date, there was no clear threshold above which SUA becomes abnormal on a prognostic point of view. We demonstrated in our study that a prognostic cut-off value able to separate the subjects at risk of developing the CBV events from those free from those events can be identified (>4.79 mg/dL). This is the first report in a large Italian database of a defined prognostic cut-off value of SUA predicting the risk of developing a CBV events. This cut-off value is much lower than the SUA values commonly associated with gout [27]. Indeed, as we already published [12–14], the commonly used cut-off value of 6.8 mg/dL [28], corresponding to the super-saturation value of uric acid, appears to be inappropriate when referred to other cardiovascular events. However, this should be further investigated before promoting treatments that might not be clinically indicated.

Concerning sex, the literature suggests that a difference exists between men and women as regards SUA [1, 29]. In our data, SUA was 7% lower in women than in men but the interaction term SUA

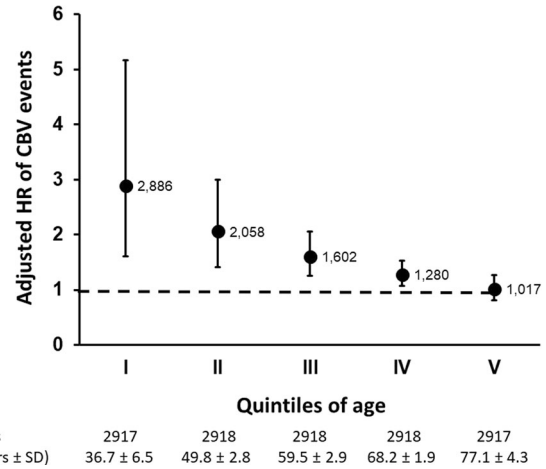

Fig. 3 Adjusted hazard ratios with 95% confidence intervals of the combined cerebrovascular events for having serum uric acid >4.79 mg/dL by quintiles of age in models including the interaction term cut-off value of SUA × age and other covariates. Reference = 1 for every class age. HR hazard ratio, SUA serum uric acid, CBV cerebrovascular events.

× gender was rejected from the Cox model. In agreement with this evidence, the authors of recent metanalyses on hyperuricemia and risk of stroke observed that gender was a non-significant source of heterogeneity [9, 10, 26].

A positive interaction term was observed between SUA and diabetes status, indicating that only non-diabetic subjects accumulate the risk of CBV events with SUA above the cut-off value of 4.79 mg/dL. This is in line with a metanalysis by Xu et al. including 20,891 patients with type 2 diabetes, where elevated SUA was as an independent predictor of vascular complications and mortality in those patients but not in Italian population (HR 1.25; 95% CI 0.97–1.62) [30]. In another metanalysis of 23 case–control studies, type 2 diabetes patients with concomitant stroke exhibited SUA levels 29% higher than those detected in subjects without stroke [31], indicating an unclear role of SUA in predicting stroke in diabetes patients.

In sensitivity analysis, the significant interaction term between the cut-off value of SUA with age indicates that, in those subjects with SUA value over 4.79 mg/dL, the HR of the combined CBV events tended to decrease with increasing age disappearing after 77 years of age. This could explain the reported inconsistency on the relationship between the SUA level and strokes observed on several epidemiological studies [9, 10].

Thiazide diuretics are first-line antihypertensive drugs, essential in reducing morbidity and mortality related to stroke in patients with hypertension [32]. However, thiazide diuretics are associated with elevated SUA levels, increasing direct urate reabsorption in the proximal renal tubules. In our data, we found no impact of the interaction term SUA × diuretics on the Cox model. This result has been already discussed in a specific paper by our group demonstrating that diuretic-related hyperuricemia carries a similar risk of CV events and all-cause mortality than hyperuricemia without diuretic [23].

The mechanisms underlying the association between SUA and the development of stroke are not completely understood. Several potential pathophysiological mechanisms have been proposed. Soluble uric acid has been shown to act as a pro-oxidant, as well as a facilitator of free radical production [33]. Uric acid can crystallize, resulting in the formation of monosodium urate crystals that tend to precipitate in various tissues, triggering local inflammatory responses. It has also been demonstrated that human atherosclerosis plaque contains more uric acid than do control arteries [34]. SUA can stimulate oxidative stress, induce endothelial dysfunction, inflammation, stimulating vascular smooth cell proliferation, vasoconstriction, and promote platelet adhesiveness [35, 36]. Moreover, SUA concentrations were also found to promote oxygenation of LDLC and to facilitate lipid peroxidation [37]. Each of these pathophysiological factors plays a crucial role in the progression of atherosclerosis and may potentially contribute to the development of stroke.

The strength of the study shown herein is that, to our knowledge, it is the first aimed at finding prognostic cut-off values of SUA for the development of CBV events in a large nationwide database analyzed longitudinally with a long-lasting follow-up. The limitations are represented by the fact that this was a retrospective evaluation, data are partially derived from a selected sample of patients referred by general practitioners to specialized centers, an underestimation of morbid events is quite likely as in other cohort studies, the analysis was based on a single SUA measurement without taking into consideration the dilution bias, and the design was fit to demonstrate an association but not a causality in the relationship between SUA and CBV events. Moreover, we were unable to distinguish between ischemic and hemorrhagic CBV events. Also, dietary intake assessment was not implemented in our study, and thus we had no information about the type of food consumed that may affect SUA level. The URRAH study was entirely composed of a cohort of Caucasian ethnicity. Consequently, further studies are needed to confirm that the thresholds of SUA emerging from our analyses are valid also in general populations and in other ethnicities. Finally, the echogenetic context was not analyzed [38].

In conclusion, measurement of the SUA level might provide significant prognostic information about incident CBV events, in addition to the evaluation of conventional risk factors in daily clinical practice. These thresholds are lower than those commonly associated with an increased risk of gout, suggesting the adoption of more stringent normality ranges for SUA.

Summary table

What is known about this topic

- The role of serum uric acid (SUA) as a cardiovascular risk factor or indicator is growing.
- Hyperuricemia is significantly associated with cerebrovascular morbidity and mortality.

What this study adds

- Identification of a validated cut-off value of SUA for combined cerebrovascular events.
- The measurement of the SUA level might provide significant prognostic information in addition to the evaluation of conventional risk factors in daily clinical practice.

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Conception and design: VT, EC. Acquisition of data: VT, EC, PS, CMB, MB, AFGC, MC, PC, GD, LD, CF, FG, LG, CG, GI, FM, AM, SM, AM, MLM, PN, PP, GP, RP, FQ-T, MR, GR, MS, GT, AU, PV, FV, AV, MV, GG, CB. Analysis and interpretation of data: VT, EC. Drafting of the manuscript or revising it critically for important intellectual content: VT, EC, GB, CF, FG, CG, FM, MLM, PP, GP, RP, AU, PV, AV, MV, GG, CB. Final approval of the manuscript submitted: VT, EC, PS, CMB, MB, AFGC, MC, PC, GD, LD, CF, FG, LG, CG, GI, FM, AM, SM, AM, MLM, PN, PP, GP, RP, FQ-T, MR, GR, MS, GT, AU, PV, FV, AV, MV, GG, GB.

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The authors declare no competing interests.

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