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Original article



## Serum uric acid and left ventricular mass index independently predict cardiovascular mortality: The uric acid right for heart health (URRAH) project

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## ABSTRACT

A relationship between serum uric acid (SUA) and cardiovascular (CV) events has been documented in the Uric Acid Right for Heart Health (URRAH) study.

**Aim:** of this study was to investigate the association between SUA and left ventricular mass index (LVMI) and whether SUA and LVMI or their combination may predict the incidence of CV death.

**Methods:** Subjects with echocardiographic measurement of LVMI included in the URRAH study (n=10733) were part of this analysis. LV hypertrophy (LVH) was defined as LVMI > 95 g/m<sup>2</sup> in women and 115 g/m<sup>2</sup> in men.

**Results:** A significant association between SUA and LVMI was observed in multiple regression analysis in men: beta 0,095, F 5.47, P< 0.001 and women: beta 0,069, F 4.36, P<0.001. During follow-up 319 CV deaths occurred. Kaplan–Meier curves showed a significantly poorer survival rate in subjects with higher SUA (> 5.6 mg/dl in men and 5.1 mg/dl in women) and LVH (log-rank chi-square 298.105; P<0.0001). At multivariate Cox

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regression analysis in women LVH alone and the combination of higher SUA and LVH but not hyperuricemia alone, were associated with a higher risk of CV death, while in men hyperuricemia without LVH, LVH without hyperuricemia and their combination were all associated with a higher incidence of CV death.

**Conclusions:** Our findings demonstrate that SUA is independently associated with LVMI and suggest that the combination of hyperuricemia with LVH is an independent and powerful predictor for CV death both in men and women.

## 1. Introduction

The association between serum uric acid levels (SUA) and cardiovascular (CV) disease has been extensively investigated in the last 3 decades. A large number of epidemiological studies have confirmed the unfavorable impact of increased serum concentrations of SUA on the future development of CV diseases in general population samples and in selected groups of patients [1–3]. The cutoff definitions for hyperuricemia were quite different among these studies, ranging from 6 to 10 mg/dL. Recently, in the framework of the URRAH study, we were able to identify the SUA cut-off values for incident CV events [4], lower than 6 mg/dl, identifying the level of SUA that might be used in clinical practice to improve stratification of subjects at greater risk of CV events, as recently suggested by 2018 European guidelines [5].

In addition, many patients with hyperuricemia have comorbidities, such as obesity, diabetes mellitus (DM), hypertension (AH) and chronic kidney disease (CKD) [6]. All these conditions may influence the development of left ventricular hypertrophy (LVH). Uric acid might exert a detrimental influence on the heart [7–12], the kidney [13–15], the vasculature [16–18], and the brain [18] even when SUA is below the saturation limit, suggesting that the effect is only partially related to the precipitation of urate crystals [18]. In particular, an increased serum urate level is associated with higher mortality rate in patients with HF and normal renal function, thus excluding the surrogate role of reduced GFR as an intermediate proxy between cardiac dysfunction and increased levels of uric acid [18–21].

Several cross-sectional studies examining mostly hypertensive patients [7–13] have found an association between SUA and the presence of echocardiographic LVH. Other Authors did not confirm these findings, possibly because of demographic and clinical subjects differences [22–24]. Cuspidi et al were able to show that baseline SUA was related to the development of echocardiographic LVH independently of age, gender, baseline left ventricular (LV) mass index, 24-h systolic blood pressure, diabetes, hypercholesterolemia, creatinine, and the use of antihypertensive drugs [12]. It is interesting to note that the adjusted risk of incident LVH reached statistical significance in subjects with a SUA > 5.1 mg/dl, i.e. for a threshold similar to the one observed in the URRAH study for CV events [25].

In some studies, the prognostic role of both SUA and LV mass, and of their combination was tested, showing that SUA is independently associated with cardiac mass. The combination of hyperuricemia and LVH resulted as an independent and powerful predictor for CV death, suggesting that the association between SUA and CV events may be introduced in part because of a direct association of UA with LV mass index [11].

The Working Group on Uric Acid and Cardiovascular Risk of the Italian Society of Hypertension conceived and designed a nationwide ad hoc 15 protocol (URRAH - URic acid Right for heArt Health) involving a great number of Italian subjects recruited on a regional basis, aimed at finding, if any, the cut-off value of SUA able to stratify those exposed to an increased risk of CV events [4,25,26].

For the specific purpose of this analysis, we aimed to evaluate the prognostic role of SUA, of increased LV mass and of their combination on the incidence of CV deaths in the subset of URRAH database with available echocardiographic evaluation of LV mass [4,25,26].

## 2. Methods

### 2.1. Database and study protocol

The URRAH project is a multicenter retrospective observational cohort study collecting data obtained from subjects aged 18 to 95 years, recruited within the epidemiological network of the Italian Society of Hypertension and involving almost all the Italian regions. Caucasian patients attending hypertension clinics, as well as those enrolled in prospective observational cohort studies were included and followed for a mean period of  $10.7 \pm 5.4$  years (median 11.3 years) up to 31 July 2017. The study protocol has been previously described in detail [24, 25].

For all subjects, a standardized set of items was recorded, including demographics, metabolic parameters, smoking habit, systolic and diastolic blood pressure (BP), renal function, history of CV, renal and cerebrovascular disease, concomitant treatments and outcome.

We estimated GFR by the CKD-EPI equation as  $eGFR = 141 \times \min(\text{SCr}/k, 1)^a \times \max(\text{SCr}/k, 1)^{-1.209} \times 0.993^{\text{age}} \times 1.159$  (if black), where  $k$  is 0.7 for female patients and 0.9 for male patients,  $a$  is -0.329 for female patients and -0.411 for male patients;  $\min$  indicates the minimum of SCr/ $k$  or 1, and  $\max$  indicates the maximum of SCr/ $k$  or 1 [27]. We defined renal dysfunction as an eGFR of <60 mL/min, which corresponds to National Kidney Foundation KDOQI (Kidney Disease Outcomes Quality Initiative) stage 3 and 4 kidney disease [28].

Previously identified sex specific cut off values (5.6 mg/dl in men and 5.1 mg/dl in women) were used to define the presence of hyperuricemia [25].

Echocardiography was performed in a subset of the participants in this study. Studies were performed with M-mode and 2D capabilities. LV internal dimension and septal and posterior wall thickness were measured at end-diastole and end-systole according to the American Society of Echocardiography recommendations [29] and end-diastolic dimensions were used to calculate LV mass by a previously reported formula [29]. LV mass was considered an unadjusted variable and was normalized by body surface area and expressed as LV mass index, independently of the mathematical formula that was used as long as this was accepted by international guidelines [5]. All of the measurements were performed by a trained investigator who was blinded to the clinical data of the subjects.

### 2.2. Ethics

The study data were collected routinely or *ad hoc* in 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 comply 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.

### 2.3. Outcome

Diagnosis of CV death was obtained from hospital records or death certificates.

### 2.4. Statistics

General description. The SPSS package version 23 (IBM, Armonk, New York, USA) was used for statistical analysis.

Continuous variables were expressed as mean ± SD by the analysis of covariance adjusted to time for proper confounders and followed by the Bonferroni's post hoc test. Categorical variables were compared by means of the Pearson  $\chi^2$  test.

SUA as a continuous parameter (in mg/dL) was used as independent variable in Cox analyses having fatal CV events as dependent variables, and sex, age, systolic BP, diabetes, eGFR, smoking habit, ethanol intake, body mass index, hematocrit, low-density-lipoprotein cholesterol (LDL-C), previous diagnosis of CV disease and use of diuretics as possible confounders. Hazard ratios (HR) with 95% CI were produced. The null hypothesis was rejected for values of  $p < 0.05$ .

Kaplan Meier survival analysis was used to assess the event free survival in patients with LVH and/or increased SUA. The absence/presence of LVH and/or of increased SUA was tested as independent variable in multivariate Cox proportional hazard model analyses adjusted for the confounders, having fatal CV events as dichotomic dependent variables.

### 3. Results

Descriptive statistics. The baseline characteristics of the 10733 subjects with follow-up data are shown in Table 1. On average, subjects

**Table 1**

Baseline characteristics of the study participants

T test women vs men \*  $P < 0.01$ ; \*\*  $p < 0.001$  \*\*\*  $p < 0.0001$

Chisquare women vs men ¶  $P < 0.01$ ; ¶¶  $p < 0.001$ ; ¶¶¶  $p < 0.0001$

Variables	Whole database (n=10733)	Men N=5290	Women N=5443
Age (years)	54±14	54.1 ± 13.6	54.7 ±14 **
Body mass index (kg/m <sup>2</sup> )	26.5±4.12	26.4± 3.9	26.5±4.3
Waist circumference (cm)	89.5±12.7	94 ±11	85±12.8 ***
Obesity (%)	19	16	21 ¶¶¶
Systolic BP (mmHg)	144.2±22.5	145 ± 21	144 ± 24 *
Diastolic BP (mmHg)	88.4±12	89 ± 11	88 ± 12.5 **
Heart rate (bpm)	74±12.8	73 ± 13	74 ± 12 ***
Serum creatinine (mg/dL)	0.94±0.2	0.95±0.2	0.90±0.2 ***
Serum uric acid (mg/dL)	4.97±1.40	5.18 ± 1.40	4. 8 ± 1.4 ***
Serum glucose (mg/dL)	96.1±21	96 ± 20	96 ± 22
Total serum cholesterol (mg/dL)	210 ± 39.3	209 ± 39	212 ± 39 ***
Triglycerides (mg/dL)	126 ±77	128 ±78	124 ±75 ***
HDL serum cholesterol (mg/dL)	54 ±14.5	51 ± 13	55 ± 15 **
Smoking habit (yes, ex %)	24 /10	27/35	21 ¶¶¶/16 ¶¶¶
Diabetes (%)	7.4	7	8
Hypertension (%)	73.2	75	71 ¶¶¶
Chronic renal disease (%)	10.2	5.3	21 ¶¶¶
Gout (%)	0.8	1.0	0.6
Diuretics use (%)	21.5	21	22
ACE-inhibitors use (%)	21	19	22 ¶¶¶
Angiotensin receptor blockers use (%)	13.7	15	13 ¶¶
Calcium channel blockers use (%)	15.8	13	13
Beta-blockers use (%)	12.2	13	11 ¶¶
Statin use (%)	5.6	6	5
Allopurinol use (%)	1.3	2.2	1.1 ¶¶

were overweight, with a diagnosis of arterial hypertension in more than 70% of subjects, of diabetes mellitus in 7.4%, of CKD and of previous HF in 10.2 % and in 5.8 % of patients, respectively. The mean level of SUA (4.97 mg/dL) reflects the relatively low number of subjects with a diagnosis of gout (< 1% of the entire database) (Table 1). As compared with men, women were slightly older, with a greater prevalence of obesity and CKD, while the prevalence of hypertension and BP values were lower.

Prevalence of LVH was defined according to the presence of LV mass indexed by body surface area (BSA) > 95 g/m<sup>2</sup> in women and > 115 g/m<sup>2</sup> in men [5]. LVH prevalence was 41.3 % in the whole group, 30 % in men and 52 % in women. A significant correlation was observed between SUA and LV mass index ( $r=0.186$ ,  $p<0.0001$ ), with a higher correlation coefficient in women than in men ( $r=0.10$ ,  $p<0.0001$  and  $r=0.26$ ,  $p <0.0001$  in men and women, respectively). This correlation remained statistically significant after adjustment for confounders in multiple regression analysis in both sexes (men: beta 0,095, F 5.47,  $P < 0.001$ ; women: beta 0,069, F 4.36,  $P <0.001$ ) (Table 2).

In the overall analysis, the median follow-up duration was 130 months (range 1 to 360 months). During this period, 319 participants died for a CV event, including myocardial infarction, angina pectoris, congestive HF and cerebrovascular disease.

Patients with fatal CV disease were older, more frequently male, with a higher prevalence of hypertension, diabetes and CKD. At baseline triglycerides and SUA were higher in patients with fatal CV events as compared with those without. LV mass index and the prevalence of LVH were higher in patients who died for CV disease. (Table 3)

At the univariate Cox model, SUA was associated with an increased risk of CV death [hazard ratio, HR 1.29 (1.23–1.359),  $p < 0.0001$ ]; LV mass index was also associated with an higher incidence of CV mortality [HR 1.29 (1.23–1.359),  $p < 0.0001$ ]

The association between CV death and hyperuricemia and LVH remained highly significant even in models adjusted for confounders (HR = 1.751, 95%CI 1.394-2199,  $p=0.001$ ; HR = 2.050, 95%CI 1.576-2.668,  $p=0.001$ ); age, sex, diabetes mellitus, systolic BP, BMI, eGFR and smoke contributed significantly to CV death incidence while triglycerides and total cholesterol did not.

Previously identified sex specific cut off values (5.6 mg/dl in men and 5.1 mg/dl in women) and LVH were used to define 4 different groups (normal SUA and LV mass index, increased SUA and no LVH, normal SUA and LVH, increased SUA and LVH).

Kaplan–Meier curves showed a significantly poorer survival rate in the group with higher SUA and LV mass index (log-rank chi-square 298.105;  $P <0.0001$ ) (Fig 1).

**Table 2**

Multivariate analysis

Dependent variable: LV mass index

MEN	Beta	F	95% CI	Significance
Age	0.294	14.028	0.548; 0.726	0.000
BMI	0.122	7.423	0.651; 1.118	0.000
Smoke	0.007	0.430	-1.548; 2.419	Ns
SBP	0.230	13.912	0.266; 0.353	0.000
HR	-0.74	-4.757	-.226; -.353	0.000
Uric acid	0.095	5.467	1.220; 2.584	0.000
Glucose	.065	4.053	0.048; 0.139	0.000
Total Cholest	-.056	-3.423	-0.064; -0.017	0.01
eGFR EPI	.024	1.120	-0.029; 0.108	Ns
WOMEN	Beta	F	95% CI	Significance
Age	0.154	9.520	0.28; 0.43	0.000
BMI	0.101	6.755	0.552; 1.003	0.000
Smoke	0.048	3.447	1.600; 5.819	0.001
SBP	0.371	23.574	0.46; 0.54	0.000
HR	-.150	-10.192	-0.472; -0.329	0.000
Uric acid	0.069	4.357	0.920; 2.426	0.000
Glucose	.060	4.112	0.047; 0.131	0.000
Total Cholest	-.101	-6.830	-0.108; -0.060	0.011
eGFR EPI	-.085	-5.076	-0.200; -0.089	0.000

**Table 3**  
Demographic and clinical characteristics in patients with and without CV death.

Variables	No CV death (n=10414)	CV death (n=319)	Significance
Age (years)	54±14	69±11	0.0001
Sex male (%)	48	53	0.03
Smoking habit (yes, %)	25	23	ns
Diabetes (%)	6.4	22.6	0.0001
Hypertension (%)	72	88	0.0001
Chronic renal disease (%)	10.6	17.2	0.0001
Gout (%)	0.7	1.4	ns
Obesity (%)	18	22	ns
Body mass index (kg/m <sup>2</sup> )	26.4±4.1	26.6±4.3	ns
Waist circumference (cm)	88.4±12.7	93.01±11.6	0.0001
Systolic BP (mmHg)	144.1 ± 23	163.4 ± 25	0.0001
Diastolic BP (mmHg)	89.1±12	91 ± 12	ns
Heart rate (bpm)	75±13	76±12	0.0001
Serum creatinine (mg/dL)	0.93±0.2	1.03±0.3	0.0001
Serum uric acid (mg/dL)	4.9±1.4	5.7±1.5	0.0001
Serum glucose (mg/dL)	96.1±20	111±38	0.0001
Total serum cholesterol (mg/dL)	213±39	216±39	ns
Triglycerides (mg/dL)	127 ±78	140 ±75	0.002
HDL serum cholesterol (mg/dL)	53 ±14	53 ± 16	ns
LVMi (g/m <sup>2</sup> )	101.8± 31	128.9 ± 37.6	0.001
Antihypertensive treatment (%)	33	46	0.001
Allopurinol use (%)	1.0	2.3	0.001

Furthermore, in multivariate Cox analyses adjusted for sex, age, BMI, smoke, systolic BP, CKD, diabetes, total Cholesterol and triglycerides, the presence of hyperuricemia, the presence of LVH and the the combination of hyperuricemia and LVH were accepted in the model (Table 4) (Fig. 2A). Age, diabetes, systolic BP, smoke and CKD directly contributed to CV death, while female sex and BMI had a protective effect.

Multivariate Cox regression analysis showed that in women LVH alone [HR 2,25 (1.076 to 4,721);  $p=0.03$ ] and the combination of higher SUA and LVH [HR 3,785 (1.789 to 8.008);  $P=0.001$ ], but not hyperuricemia alone, were associated with a higher incidence of CV death (Fig. 2B), while in men hyperuricemia without LVH [HR 2.338 (1.292 to 4.232);  $P=0.005$ ], LVH without hyperuricemia [HR 3.008 (1.750 to 5.449);  $P=0.001$ ] and their combination [HR 5.273 (3.044 to 9.135);  $P=0.001$ ] were all associated with a higher risk of CV death (Fig. 2C).

#### 4. Discussion

The results of the present study add new data on the relationship

between SUA and LV mass, in a very large database of clinical data. We found a quite high prevalence of LVH, a well-recognized and independent risk factor for CV events, CV death and overall mortality [30,31]. We analyzed incident CV death, since it represents a hard outcome, and we were able to show a significant association between SUA, LVH and their combination and incident CV fatal events.

Previous studies have assessed the association between SUA and target organ damage (TOD) at cardiac [7–13,32,33], renal [13,14] and vascular [15–17,34,35] level in general population cohorts and in hypertensive patients. In fact, many patients with hyperuricemia have comorbidities, such as obesity, diabetes mellitus, hypertension and CKD [36,37]. All these conditions may influence the development of LVH. Uric acid might exert a detrimental influence on the heart, the vasculature, and the kidney even when SUA is below the saturation limit suggesting that the effect is only partially related to the precipitation of urate crystals.

Several cross-sectional studies examining mostly hypertensive patients [7–13] have found an association between SUA and the presence of echocardiographic LVH.

More recently, Visco et al [10] demonstrated that SUA directly correlates with LV mass index and that the cutoff of 5.6 mg/dl was able to identify patients with larger LV mass. The results, obtained in a small cohort, were confirmed in a much larger number of patients in the Campania region in Italy. The role of SUA in favoring the development of cardiac damage was underlined by Cuspidi et al. In the Pamela study, authors were able to show that baseline SUA was related to the development of echocardiographic LVH independently of age, gender, baseline LV mass index, 24-h systolic blood pressure, diabetes, hypercholesterolemia, creatinine, and the use of antihypertensive drugs [12]. It is interesting to note that the adjusted risk of incident LVH reached statistical significance in subjects with SUA > 5.1 mg/dl, i.e. for a threshold similar to the one observed in the URRAH study for CV events.

The association between SUA and LV mass index found in this study comes with low levels of  $r^2$ , thus indicating that the two parameters (SUA and LV mass index), although associated, may be influenced by other distinct mechanisms such as greater visceral fat accumulation, or increased large artery stiffness and augmentation index [34,35] usually common in the presence of insulin resistance or metabolic syndrome, which could not be explored by our study.

SUA levels might also reflect the degree of xanthine oxidase activity and resultant oxidative stress, which plays an essential role in the development of increased cardiac size. An increasing number of clinical

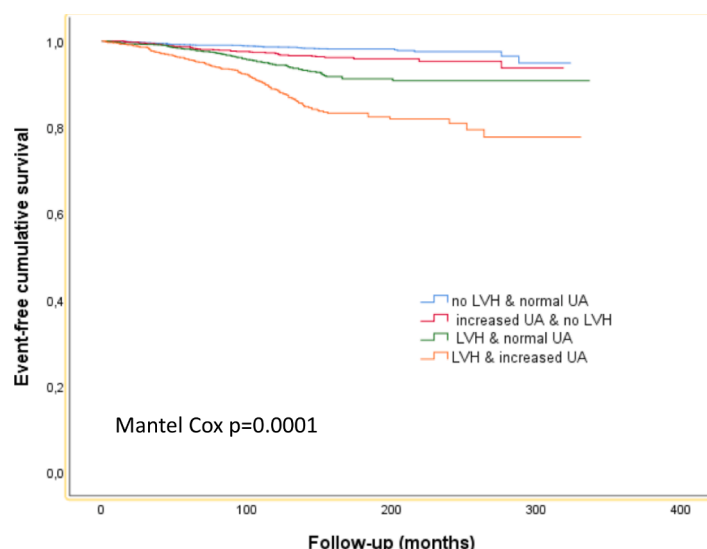
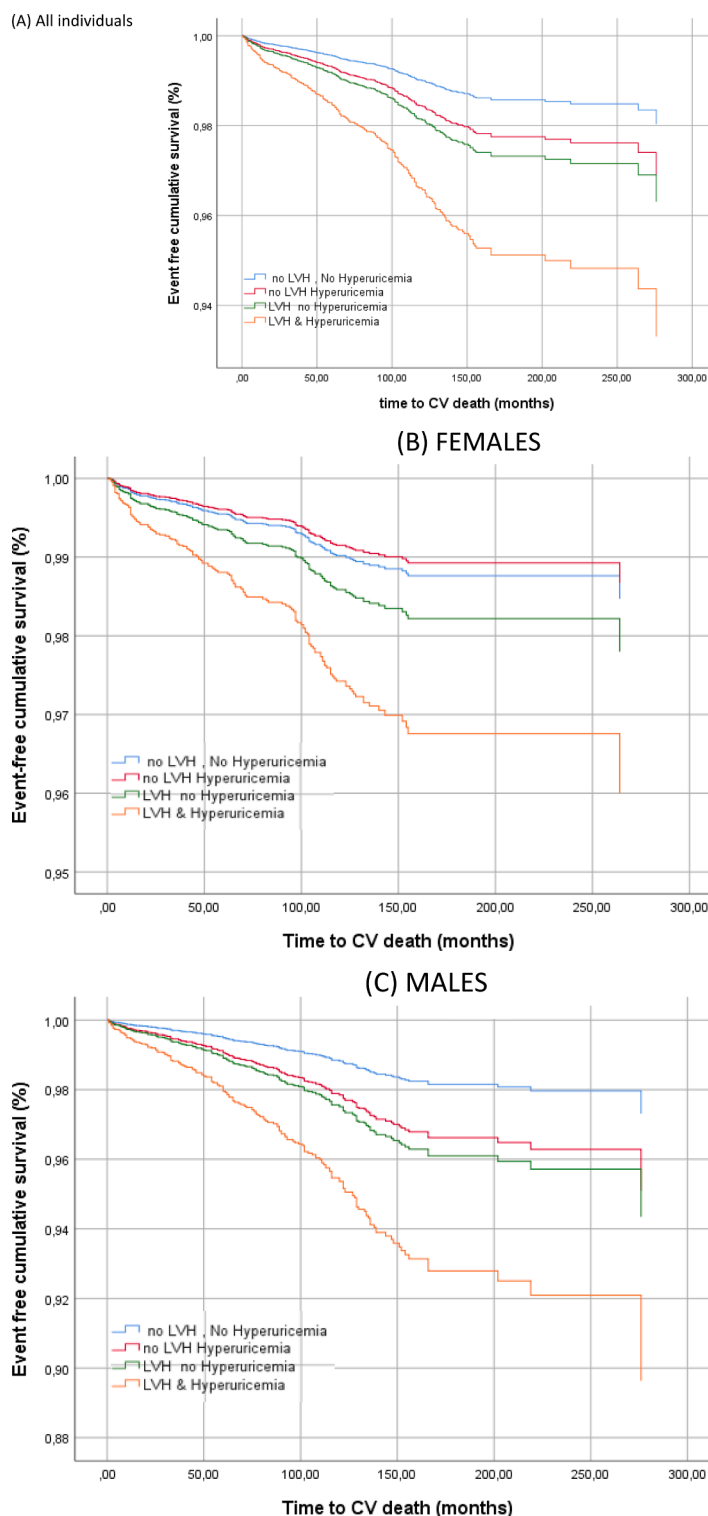


Fig. 1. Kaplan –Meier Curves according to the presence of LVH and /or Hyperuricemia



**Fig. 2.** Cox Multivariate Survival Analysis according to the presence of hyperuricemia and /or LVH in all subjects (A) and in women (panel B) and men (panel C) separately

studies have shown that allopurinol can improve LV mass reduction [38]. More recently, Gingles et al. reported the lack of LVH regression during uric acid reduction with allopurinol in normouricemic patients without established vascular disease, and therefore most likely with a low background oxidative stress or inflammation. These results suggest that reducing uric acid in normouricemic patients may impact on redox balance and change the anti-oxidant to pro-oxidant effect during allopurinol treatment [39].

Some observations confirming the association between uric acid and LV mass, found that this was gender related [40–42]. An increased prevalence and severity of TOD through tertiles of SUA was reported by Viazzi et al [8] in hypertensive women, but not in men. Catena et al [9] observed that increased uric acid levels were independently related to the LV mass in low risk hypertensive women without the metabolic syndrome. We have also observed a stronger correlation between SUA and LV mass index in women than in men. Hyperuricemia may result

**Table 4**

Cox models for CV death using the presence of hyperuricemia (no LVH & high SUA), presence of LVH (LVH & normal SUA) and the combination of hyperuricemia and LVH (LVH & high SUA).

Independent variables	HR	95% CI	p value
Age (years)	1.089	1.077-1.102	<0.0001
Male Sex	1.932	1.534-2.433	< 0.0001
Smoke (yes)	1.369	1.049-1.786	0.021
Diabetes (yes)	1.956	1.509-2.536	< 0.0001
SBP (mmHg)	1.010	1.006-1.015	< 0.0001
Total cholesterol (mg/dl)	0.998	0.995-1.001	0.14
Triglycerides mg/dl	1.001	0.999-1.002	0.22
CKD (yes)	1.621	1.252-2.099	< 0.0001
Body mass index (kg/m <sup>2</sup> )	0.961	0.933-0.990	0.009
Antihypertensive treatment (yes)	1.154	0.919-1.449	0.22
NoLVH & normal SUA	-		
NoLVH & high SUA	1.600	1.059-2.415	< 0.0001
LVH & normal SUA	1.888	1.330 - 2.680	< 0.0001
LVH & high SUA	3.456	2.459 - 4.856	< 0.0001

from an increase in the production of SUA mediated by the activity of the enzyme xanthine oxidase or reduced renal or intestinal excretion or by the combination of both mechanisms [37]. The alteration in urinary excretion of SUA is the mechanism mainly responsible for hyperuricemia in patients with gout, while SUA overproduction leading to oxidative stress can favor CV disease development or progression [38]. Campo et al. found that hyperuricemia was not an independent marker of LVH, grades 1-2 retinopathy, and proteinuria [43]. Interestingly in this study, conducted in a sample of 677 male hypertensives, it was observed that SUA predicted the presence of cardiac and vascular damage in patients with a low urate renal excretion, suggesting that hyperuricemia may be an indicator of TOD only in urate under-excreting patients.

In women the lack of the favourable effect of oestrogen on renal SUA excretion after menopause may represent a possible explanation for hyperuricemia. It has previously been reported that hyperuricemia has been associated with LV mass index in postmenopausal but not in premenopausal women [44]. In the URRAH database, we did not record menopausal age, although 50 % of women were older than 54 years, i.e., most likely in a postmenopausal state and with a reduced urinary excretion of uric acid, possibly explaining our findings. Other possible explanations are the genetic control of SUA metabolism, with sex differences in gene function or the increased activity of the sympathetic nervous system associated with reduced renal excretion of uric acid [45–47].

In few studies showing that SUA is independently associated with cardiac mass, the prognostic role of both SUA and LV mass, and of their combination was tested [11,48]. The combination of hyperuricemia and LV hypertrophy resulted as an independent and powerful predictor for CV death, suggesting that the association between SUA and CVD events may be introduced in part because of a direct association of SUA with LV mass index. It cannot be excluded, however, that the presence of a worse CV risk profile of patients with hyperuricemia might have contributed to the occurrence of clinical events

Our data are in accordance with the results of Iwashima et al. [11] and suggest that the combination of hyperuricemia and cardiac hypertrophy is a powerful predictor for CV death both in men and women, independently of most potential prevailing confounding variables.

The URRAH study found cutoff values for SUA which, while lower than previously thought, showed to be able to identify people at higher risk of CV diseases, stroke, myocardial infarction and HF [4,25]. Our findings extend those of previous studies on SUA and LV mass in a very large number of patients and subjects, and reinforce the evidence that the improvement in CV death risk stratification by SUA is linear and starts at concentrations well below the saturation limit corresponding to urate crystals precipitation.

Raised SUA could also be due to impaired renal clearance and increased production of urate and renal dysfunction has been associated

with CV outcomes [13,14]. However, the increased risk of CV death was independent of renal dysfunction, accurately estimated by eGFR according to the EPI-CKD equation and defining chronic kidney disease on eGFR values.

#### 4.1. Limitations

Our findings should be examined within the context of several potential limitations.

This is a retrospective analysis and SUA and LV mass index was measured only at baseline, therefore we cannot estimate the influence of changes in SUA and/or of LV mass during such a long follow-up on incidence of CV death. BP values were measured in the clinic and we lack of 24 hours BP values. The added value of SUA in the prediction of CV outcome, independent of 24 hours systolic BP, was recently shown in the ABP consortium [49]. We estimated eGFR by the EPI-CKD formula as suggested by 2018 ESH guidelines, although several clinical conditions may affect the accuracy of estimating glomerular filtration rate formulas [50].

We have not collected a detailed dietary intake in order to evaluate the influence of food/beverages that may affect SUA levels. Information on baseline treatment was available, but data on treatment changes during follow-up are lacking. In a clinical perspective, it could be possible to consider lifestyle and pharmacologic interventions aimed to reduce SUA levels and cardiac hypertrophy to prevent CV death. To this regard the recent evidence that the use of sodium–glucose cotransporter-2 inhibitors increases uric acid excretion, reduces circulating uric acid and improves cardiovascular prognosis, seems particularly promising, in addition to the effect of antihypertensive drugs on LV hypertrophy [51].

Moreover, our results refer to middle-aged Caucasian subjects and cannot be extended to other populations with different demographic and clinical features. The URRAH study includes subjects/patients with hypertension, diabetes mellitus, previous HF from different Italian regions enrolled in Hypertension Centers and therefore need confirmation in future studies.

#### 5. Conclusions

In conclusion, in a large database, it was demonstrated that SUA is independently associated with LV mass index. The combination of hyperuricemia with left ventricular hypertrophy represents an independent and powerful predictor for CV death both in men and women. The association between SUA and CVD events may be explained in part because of a direct association of SUA with LV mass index.

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#### Declaration of Competing Interest

None.

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