

Original article

Significance of serum uric acid levels on the risk of all-cause and cardiovascular mortality

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Abstract

Objective. To assess the associations between serum uric acid (SUA) level and mortality.**Methods.** The study included 354 110 subjects without a history of gout and whose SUA levels were tested at Chang Gung Memorial Hospital in Taiwan. Cox regression models were used to estimate hazard ratios and 95% CIs for mortality in six predefined SUA strata (≤ 0.17 , 0.18–0.29, 0.30–0.41, 0.42–0.53, 0.54–0.65 and ≥ 0.66 mmol/l), after adjusting for age, sex, SUA stratum, estimated glomerular filtration rate, fasting glucose, total cholesterol and history of hypertension, diabetes mellitus, coronary heart disease, stroke, heart failure or chronic kidney disease.**Results.** There were 33 562 all-cause deaths during the study period. Crude all-cause mortality rates across the SUA strata were 52.5, 19.7, 17.4, 20.0, 28.0 and 41.1 deaths per 1000 person-years. Using the stratum 3 of SUA as a reference, the age- and sex-adjusted hazard ratios (95% CIs) across SUA strata were 2.79 (2.62, 2.96), 1.32 (1.28, 1.36), 1.00, 1.10 (1.07, 1.14), 1.42 (1.37, 1.48) and 2.12 (2.01, 2.23) for all-cause mortality; 2.24 (1.93, 2.59), 1.18 (1.10, 1.27), 1.00, 1.21 (1.14, 1.29), 1.74 (1.60, 1.88) and 2.53 (2.28, 2.81) for cardiovascular mortality and 3.41 (3.11, 3.73), 1.48 (1.42, 1.55), 1.00, 0.88 (0.84, 0.92), 0.91 (0.85, 0.98) and 1.23 (1.11, 1.36) for cancer-related mortality.**Conclusion.** Individuals with SUA levels at either extremes are at higher risk for all-cause and cardiovascular mortality. SUA levels of 0.30–0.41 mmol/l were associated with the lowest mortality rate and should be regarded as optimal.**Key words:** uric acid, mortality, cardiovascular diseases, cancer.

Introduction

The relationships between serum uric acid (SUA) levels and clinical outcomes are complex, and current evidence is often contrasting and unclear. Increasing evidence has linked hyperuricaemia to cardiovascular [1, 2], metabolic [3, 4] and renal disorders [5] that may reduce the longevity

of the affected individuals. However, studies of the mortality risks associated with hyperuricaemia have yielded conflicting results. For example, although the First National Health and Nutrition Examination Survey (NHANES-1) revealed an independent association between high SUA and cardiovascular mortality [6], no such association was found in the Framingham Study [7].

The influence of low SUA levels on clinical outcomes has not been well studied; however, reports have indicated that low SUA levels may be detrimental to patient health and may result in poor outcomes, especially in elderly patients with diabetes mellitus (DM) [8], individuals who have experienced ischaemic stroke [9, 10] and subjects with chronic kidney disease (CKD) [11]. Moreover, reductions in SUA levels do not appear to promote a more positive outcome in patients with cardiovascular conditions [12, 13], and low SUA levels were found to be an independent mortality risk factor in subjects with CKD [11] and in those undergoing haemodialysis [14].

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Submitted 9 February 2012; revised version accepted 9 July 2012.

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However, the effect of low SUA levels has not been investigated in a large-scale study of a general population.

No clear explanation of the conflicting results of the studies investigating the effects of SUA levels on clinical outcomes has been proposed. In general, previous studies did not exclude gout patients from analysis; in these patients, the risk of cardiovascular disease is already high, while SUA levels are dependent on treatment. Thus, inclusion of these patients may result in the presentation of misleading conclusions. Moreover, it has been suggested that the baseline risk of study subjects affects the hazard predisposed by SUA [15, 16], and that the association between SUA and mortality risk is non-linear [8]. In addition, unadjusted confounders, such as renal function, may have further distorted the findings of previous studies. Therefore, in the present study, we aimed to explore the relationships between baseline SUA levels and long-term mortality risk, with exclusion of gout patients and by stratification of SUA levels.

Methods

This was a cohort study conducted using secondary data collected from the Chang Gung Memorial Hospital (CGMH, the largest hospital in Taiwan). This study was approved by the Institutional Review Board of CGMH and was conducted in full compliance with relevant local, national, ethical and regulatory guidelines.

Data source and participants

All individuals who had undergone SUA measurement at CGMH during the period from 2000 through 2007 were eligible for inclusion in the study. People with gout were not included in the analysis because they are often prescribed medications that affect SUA levels. An individual was excluded if they had been diagnosed with gout [International Classification of Diseases, Ninth Revision (ICD-9) code: 274.x] or if they had been using allopurinol, benzbromarone, probenecid or sulphinpyrazone—within 3 months of the index SUA measurement. Information pertaining to diagnoses and medications for each individual was collected from outpatient records at CGMH.

If multiple SUA measurements were performed for an individual, the result of the first SUA test was used. During the study period, 803 810 SUA measurements in 362 642 subjects were performed at the CGMH clinical laboratory. Patient identifiers were concealed before analysis to ensure anonymity during the entire study process.

Mortality and causes of death

Survival status and cause of death from 2000 through 2008 were ascertained using the National Death Registry of Taiwan, which records the deaths of all citizens. The accuracy of the coding has been validated by previous studies [17]. Causes of death, which are coded on death certificates, comprised death from any cause (ICD-9 codes: 001.x–998.x), death from cardiovascular diseases (ICD-9 codes: 390.x–459.x) and cancer-related death

(ICD-9 codes: 140.x–239.x). Leading cardiovascular causes of death, including coronary heart disease (CHD, ICD-9 codes: 410.x–414.x), ischaemic stroke (ICD-9 codes: 433.x, 434.x and 436.x), hypertensive heart disease (ICD-9 codes: 401.x–405.x) and heart failure (ICD-9 code: 428.x) were analysed separately.

Uric acid measurements

All blood specimens were sent to the clinical laboratory at CGMH, which is certified by the College of American Pathologists. SUA and creatinine were measured using a Hitachi 7470 autoanalyzer (Hitachi, Tokyo, Japan). SUA was measured using the uricase differential spectrophotometric method. At the CGMH laboratory, the coefficient of variation for repeated determinations of SUA level in known samples was $\leq 1.8\%$ throughout the year. Internal and external quality control procedures yielded consistently satisfactory results. External quality control was ensured by observing the guidelines promulgated by the College of American Pathologists and the National Quality Control Program of the government of Taiwan. As the limit of solubility of uric acid in serum is ~ 0.41 mmol/l, in this study, we defined hyperuricaemia as an SUA level exceeding 0.42 mmol/l. Subjects were further categorized into six baseline SUA strata: stratum 1, ≤ 0.17 mmol/l (≤ 2.9 mg/dl); stratum 2, 0.18–0.29 mmol/l (3.0–4.9 mg/dl); stratum 3, 0.30–0.41 mmol/l (5.0–6.9 mg/dl); stratum 4, 0.42–0.53 mmol/l (7.0–8.9 mg/dl); stratum 5, 0.54–0.65 mmol/l (9.0–10.9 mg/dl) and stratum 6, ≥ 0.66 mmol/l (≥ 11.0 mg/dl).

Other clinical and laboratory variables

Subjects were classified as having DM (ICD-9 code: 250.x), hypertension (ICD-9 codes: 401.x–405.x), CHD (ICD-9 codes: 410.x–414.x), stroke (ICD-9 codes: 430.x–438.x), heart failure (ICD-9 code: 428.x) and CKD (ICD-9 codes: 580.x–589.x) if the respective ICD-9 code was present in their outpatient medical record before SUA measurement.

Renal function is a major determinant of SUA levels [18]; therefore, we collected serum creatinine and used the estimated glomerular filtration rate (eGFR), which was estimated using the abbreviated Modification of Diet in Renal Disease equation, as a surrogate marker of renal function. Abnormal renal function was defined as an eGFR < 60 ml/min/1.73 m². We also collected data on fasting glucose level and total cholesterol levels, as the excesses of both are important cardiovascular risk factors [19, 20]. Hyperglycaemia was defined as a fasting glucose level > 5.55 mmol/l and hypercholesterolaemia as a total cholesterol level > 5.17 mmol/l.

Statistical analysis

Baseline characteristics of the study population were calculated, both overall and according to genders. Summary statistics were expressed as percentages for categorical data, and the mean \pm s.d. was used to describe approximately normally distributed continuous variables. Crude all-cause, cardiovascular and cancer-related mortality

rates, expressed as deaths per 1000 person-years, were calculated for the entire study population. Cox proportional hazards regression models with forward selection were used separately to investigate the relationships between SUA levels and all-cause and cardiovascular mortality. We used the first uric acid measurement as the study entry date, and enrolled individuals were observed from the entry date until the death date or 31 December 2008, whichever came first. Plots of log [−log (survival rate)] against log (survival time) were constructed to examine the appropriateness of the proportionality assumption. Hazard ratios (HRs) associated with each SUA stratum were calculated. For this analysis, stratum 3 (0.30–0.41 mmol/l) was used as a reference because the lowest rates for all-cause and cardiovascular mortality were observed in stratum 3. Therefore, we selected SUA stratum 3 as the reference stratum in analyses using Cox proportional hazards models to compare mortality among SUA strata. Different sets of explanatory variables were used in the Cox proportional hazards model analysis: unadjusted HRs used hyperuricaemia or SUA stratum as the sole explanatory variable; age- and sex-adjusted HRs and adjusted HRs used a set of explanatory variables that included age, sex, SUA stratum, eGFR, fasting glucose, total cholesterol and history of hypertension, DM, CHD, stroke, heart failure or CKD. A two-sided $P < 0.05$ was considered statistically significant. All analyses were performed using PASW Statistics, version 18, and PASW Modeller, version 13 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

After exclusion of gout patients ($n = 8532$), a total of 354 110 subjects were enrolled in the study during the 9-year study period. Mean age at the time of SUA measurement was 49.8 ± 16.4 years. The mean duration of follow-up was 4.6 ± 2.6 years. The prevalence of

hypertension and DM in this cohort was 14.7% ($n = 52\,005$) and 8.4% ($n = 29\,787$), respectively. There were 17 756 (5.0%), 15 301 (4.3%), 9231 (2.6%) and 13 059 (3.7%) subjects who had CHD, stroke, heart failure and CKD, respectively, at the time of SUA measurement. Overall, 81 928 (23.1%) individuals in the study cohort had at least one of the aforementioned chronic illnesses. Other clinical characteristics are shown in Table 1. Fig. 1 shows the distribution of individuals by SUA level. Men had a significantly higher mean SUA than did women (0.42 ± 0.21 vs 0.33 ± 0.13 mmol/l, $P < 0.001$). In both sexes, SUA stratum 3 had the highest proportion of individuals (men, $n = 84\,495$, 43.6%; women, $n = 66\,112$, 41.2%).

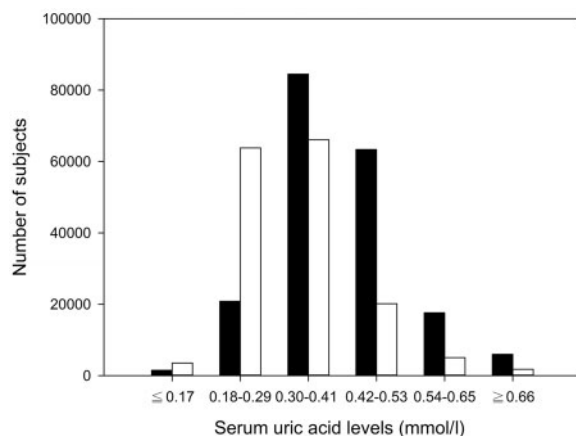
Associations between SUA levels and mortality rates

We further divided subjects by SUA level to explore the relative mortality risk across the SUA strata. Crude all-cause mortality rates across the SUA strata were 52.5, 19.7, 17.4, 20.0, 28.0 and 41.1 deaths per 1000 person-years, which showed a U-shaped association. Crude cardiovascular mortality rates across the SUA strata were 9.1, 3.6, 3.5, 4.6, 7.1 and 10.2 deaths per 1000 person-years. Cancer-related mortality rates across SUA strata were 24.6, 8.8, 7.3, 6.9, 7.6 and 10.1 deaths per 1000 person-years.

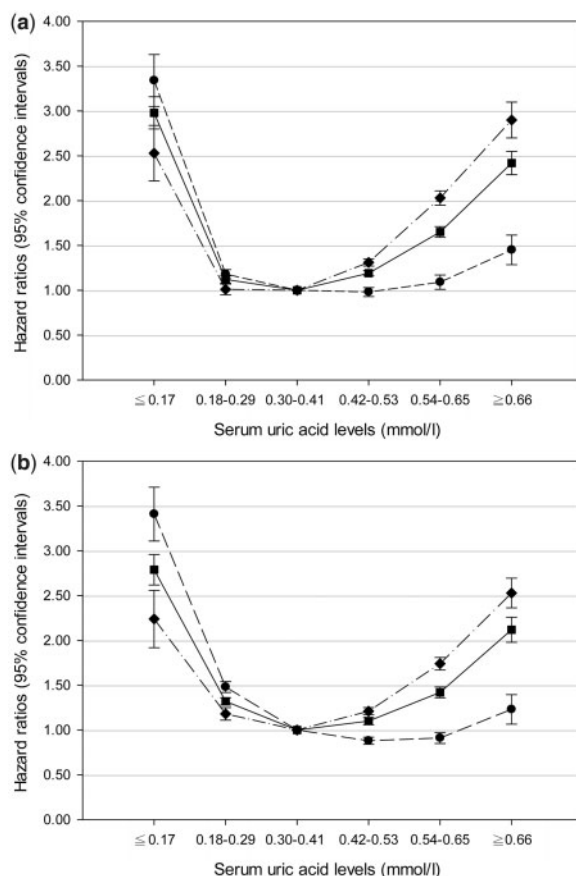
Fig. 2a shows the unadjusted HRs for mortality across the SUA strata, and Fig. 2b shows the age- and sex-adjusted HRs across the SUA strata. In general, the unadjusted HRs for all-cause mortality, cardiovascular mortality and cancer-related mortality showed a U-shaped association across the SUA strata. Using the SUA stratum 3 as a reference, the unadjusted HRs (95% CIs) for all-cause mortality were 2.98 (2.80, 3.16), 1.12 (1.08, 1.15), 1.00, 1.19 (1.16, 1.23), 1.65 (1.59, 1.71) and 2.42 (2.29, 2.54) across the SUA strata. Similarly, unadjusted HRs (95% CIs) for cardiovascular mortality were 2.53 (2.19, 2.93), 1.01 (0.94, 1.08), 1.00, 1.31 (1.23, 1.39), 2.03 (1.88, 2.20) and 2.90 (2.61, 3.22).

TABLE 1 Baseline characteristics of subjects

Characteristic	Male ($n = 193\,742$)	Female ($n = 160\,368$)	P-value
Age, mean (s.d.), years	49.3 (16.2)	50.4 (16.6)	<0.001
Follow-up, mean (s.d.), years	4.7 (2.6)	4.6 (2.5)	<0.001
Categorical variables (%; 95% CI)			
Hypertension	13.90 (13.74, 14.05)	15.64 (15.46, 15.82)	<0.001
DM	7.97 (7.85, 8.09)	8.95 (8.81, 9.09)	<0.001
CHD	5.67 (5.57, 5.78)	4.21 (4.12, 4.32)	<0.001
Stroke	4.73 (4.64, 4.83)	3.82 (3.73, 3.91)	<0.001
Heart failure	2.61 (2.54, 2.68)	2.60 (2.53, 2.68)	0.369
CKD	3.59 (3.51, 3.67)	3.81 (3.71, 3.90)	0.656
Any chronic disease	23.05 (22.87, 23.2)	23.23 (23.03, 23.44)	<0.001
Continuous variables, mean (s.d.)			
SUA (mmol/l)	0.42 (0.21)	0.33 (0.13)	<0.001
eGFR (ml/min/1.73 m ²)	76.0 (19.9) ($n = 182\,121$)	78.1 (22.7) ($n = 153\,006$)	<0.001
Fasting glucose (mmol/l)	5.94 (2.41) ($n = 156\,988$)	5.90 (2.43) ($n = 133\,737$)	<0.001
Cholesterol (mmol/l)	4.98 (1.10) ($n = 175\,853$)	5.04 (1.11) ($n = 148\,784$)	<0.001

Fig. 1 Distribution of subjects by SUA stratum.

Males, black; females, white.

Fig. 2 Unadjusted (a) and age- and sex-adjusted (b) HRs for mortality across the SUA strata.

Mortality: all-cause (squares), cardiovascular (diamonds) and cancer-related (circles).

However, low SUA strata were associated with greater risks for cancer-related mortality than were high SUA strata: the unadjusted HRs for cancer-related mortality were 3.34 (3.05, 3.65), 1.18 (1.13, 1.24), 1.00, 0.98 (0.93, 1.02), 1.09 (1.01, 1.17) and 1.45 (1.31, 1.61).

As shown in Fig. 2b, the age- and sex-adjusted HRs (95% CI) for all-cause and cardiovascular mortality also exhibited a U-shaped association across the SUA strata. The adjusted HRs (95% CI) for all-cause mortality were 2.79 (2.62, 2.96), 1.32 (1.28, 1.36), 1.00, 1.10 (1.07, 1.14), 1.42 (1.37, 1.48) and 2.12 (2.01, 2.23), and the adjusted HRs (95% CI) for cardiovascular mortality were 2.24 (1.93, 2.59), 1.18 (1.10, 1.27), 1.00, 1.21 (1.14, 1.29), 1.74 (1.60, 1.88) and 2.53 (2.28, 2.81). The risk for cancer-related mortality showed a reverse J-shaped trend across the SUA strata; age- and sex-adjusted HRs for cancer-related mortality were 3.41 (3.11, 3.73), 1.48 (1.42, 1.55), 1.00, 0.88 (0.84, 0.92), 0.91 (0.85, 0.98) and 1.23 (1.11, 1.36).

Relationship between specific cardiovascular disease-related mortality and SUA stratum

The mortality risk for patients with specific cardiovascular diseases, namely, hypertensive heart disease, CHD, ischaemic stroke, heart failure and other cardiovascular diseases, across the SUA strata was further investigated. Table 2 shows the adjusted HRs for different cardiovascular disease-related causes of mortality across the SUA strata. High SUA levels were associated with increased mortality due to hypertensive heart disease, CHD and heart failure. In contrast, low SUA levels were associated with increased risk of death from ischaemic stroke.

Risk for all-cause and cardiovascular mortality in subjects with specific cardiovascular risk factors

The influence of baseline cardiovascular risk factors, including history of DM, hypertension, CHD, stroke, heart failure or CKD, on mortality risks across the SUA strata was analysed. As shown in Table 3, a U-shaped association was evident, as the risk of mortality was higher in patients with high or very low SUA levels, regardless of the presence or absence of underlying cardiovascular risk factors.

Separate analyses were performed for each subgroup with different underlying risk factors. As shown in Table 4, a U-shaped association between SUA levels and all-cause mortality was evident in all subgroups, with the exception of individuals with heart failure. Table 4 shows the relationship between SUA levels and cardiovascular deaths in individuals with these underlying risk factors. In subjects with hypertension, the U-shaped association between SUA level and cardiovascular mortality was clear. The U-shaped trend was also found among patients with DM and CKD. However, in individuals who had experienced stroke, higher cardiovascular mortality was observed only in those with low SUA levels. Among individuals with

TABLE 2 Adjusted HRs for specific causes of cardiovascular mortality across SUA strata

SUA (mmol/l)	Adjusted HRs (95% CI)				
	Hypertensive heart disease (n = 381)	CHD (n = 1807)	Ischaemic stroke (n = 2412)	Heart failure (n = 454)	Other (n = 1981)
≤0.17	1.46 (0.71, 3.00)	1.27 (0.86, 1.88)	2.55 (2.09, 3.11)*	1.16 (0.54, 2.48)	1.48 (1.06, 2.05)*
0.18–0.29	0.88 (0.64, 1.20)	1.02 (0.88, 1.18)	1.33 (1.19, 1.48)*	0.96 (0.71, 1.29)	1.10 (0.96, 1.25)
0.30–0.41			Reference		
0.42–0.53	1.00 (0.77, 1.30)	1.23 (1.09, 1.38)*	0.96 (0.86, 1.07)	1.30 (1.02, 1.66)*	1.28 (1.14, 1.43)*
0.54–0.65	1.59 (1.15, 2.19)*	1.60 (1.38, 1.87)*	1.04 (0.89, 1.22)	2.24 (1.67, 2.99)*	1.74 (1.50, 2.01)*
≥0.66	1.78 (1.12, 2.82)*	2.56 (2.12, 3.10)*	1.22 (0.97, 1.54)	3.52 (2.47, 5.01)*	2.15 (1.76, 2.63)*

HRs were adjusted by age, sex, eGFR, fasting glucose, cholesterol and history of DM, CHD, stroke, heart failure or CKD. * $P < 0.05$.

TABLE 3 Adjusted HRs for all-cause and cardiovascular mortality in patients with and without underlying risk factors

SUA (mmol/l)	Adjusted HRs (95% CIs) for all-cause mortality		Adjusted HRs (95% CIs) for cardiovascular mortality	
	With risk factor (n = 81 928)	Without risk factor (n = 272 182)	With risk factor (n = 81 928)	Without risk factor (n = 272 182)
≤0.17	1.76 (1.57, 1.98)*	2.87 (2.67, 3.10)*	1.65 (1.32, 2.06)*	2.27 (1.87, 2.77)*
0.18–0.29	1.19 (1.13, 1.25)*	1.40 (1.35, 1.45)*	1.11 (1.01, 1.23)*	1.24 (1.13, 1.36)*
0.30–0.41			Reference	
0.42–0.53	1.04 (0.99, 1.09)	1.03 (0.99, 1.06)	1.04 (0.95, 1.14)	1.20 (1.10, 1.31)*
0.54–0.65	1.20 (1.13, 1.28)*	1.17 (1.11, 1.23)*	1.29 (1.15, 1.45)*	1.62 (1.44, 1.81)*
≥0.66	1.75 (1.62, 1.90)*	1.44 (1.34, 1.54)*	1.87 (1.60, 2.18)*	2.11 (1.82, 2.46)*

HRs were adjusted by age, sex, eGFR, fasting glucose, cholesterol and history of DM, CHD, stroke, heart failure or CKD. Baseline cardiovascular risk factors included DM, hypertension, CHD, stroke, heart failure and CKD. * $P < 0.05$.

TABLE 4 Adjusted HRs for all-cause and cardiovascular mortality in patients with specific cardiovascular risk factors

SUA (mmol/l)	DM (n = 29 787)	Hypertension (n = 52 005)	CHD (n = 17 756)	Stroke (n = 15 301)	Heart failure (n = 9231)	CKD (n = 13 059)
Adjusted HRs (95% CI) for all-cause mortality						
≤0.17	1.46 (1.24, 1.72)*	1.61 (1.37, 1.89)*	1.57 (1.13, 2.17)*	1.43 (1.20, 1.70)*	1.16 (0.54, 2.48)	1.55 (1.06, 2.26)*
0.18–0.29	1.19 (1.10, 1.28)*	1.16 (1.08, 1.24)*	1.07 (0.95, 1.22)	1.15 (1.05, 1.24)*	0.96 (0.71, 1.29)	1.07 (0.93, 1.22)
0.30–0.41			Reference			
0.42–0.53	1.07 (1.00, 1.15)*	1.03 (0.97, 1.09)	1.20 (1.98, 1.32)*	0.95 (0.87, 1.04)	1.30 (1.02, 1.66)*	1.07 (0.97, 1.17)
0.54–0.65	1.25 (1.13, 1.37)*	1.17 (1.08, 1.26)*	1.39 (1.22, 1.57)*	1.08 (0.95, 1.22)	2.24 (1.67, 2.99)*	1.22 (1.10, 1.37)*
≥0.66	1.64 (1.44, 1.87)*	1.57 (1.42, 1.75)*	2.16 (1.84, 2.53)*	1.53 (1.28, 1.83)*	3.52 (2.47, 5.01)*	1.58 (1.38, 1.81)*
Adjusted HRs (95% CI) for cardiovascular mortality						
≤0.17	1.33 (0.88, 2.02)	1.57 (1.16, 2.11)*	1.15 (0.59, 2.24)	1.87 (1.44, 2.45)*	0.95 (0.39, 2.30)	2.02 (0.89, 4.58)
0.18–0.29	1.20 (1.02, 1.43)*	1.14 (1.00, 1.29)*	0.89 (0.71, 1.11)	1.20 (1.05, 1.37)*	1.14 (0.89, 1.47)	1.02 (0.74, 1.41)
0.30–0.41			Reference			
0.42–0.53	1.11 (0.95, 1.31)	1.02 (0.91, 1.14)	1.22 (1.04, 1.43)*	0.87 (0.75, 1.00)	1.54 (1.28, 1.86)*	1.11 (0.88, 1.37)
0.54–0.65	1.39 (1.12, 1.72)*	1.15 (0.99, 1.33)	1.50 (1.22, 1.85)*	0.89 (0.71, 1.00)	2.00 (1.61, 1.86)*	1.42 (1.11, 1.81)*
≥0.66	1.72 (1.29, 2.29)*	1.45 (1.18, 1.79)*	2.38 (1.83, 3.09)*	1.37 (0.71, 1.10)	2.99 (2.32, 3.86)*	1.65 (1.22, 2.24)*

* $P < 0.05$.

CHD and heart failure, the risk of death was increased in those with high SUA levels.

Discussion

The present study examined the association between SUA levels and mortality. Our analysis involved a large cohort of 354 110 subjects and demonstrated a significant U-shaped association between SUA levels and both all-cause and cardiovascular mortality, with the lowest mortality occurring in individuals with SUA measurements ranging from 0.30 to 0.41 mmol/l. Importantly, this U-shaped association remained consistent, regardless of the presence or absence of underlying cardiovascular diseases. Our findings provide definitive evidence to describe the association between hyperuricaemia and mortality, a topic that has been presented as somewhat controversial in the published literature. Moreover, as low SUA levels were also associated with increased mortality, we propose that both high and low SUA levels are undesirable and warrant vigilant medical attention.

Traditionally, SUA levels were considered to be dichotomized, and normouricaemia in serum levels was assumed below predefined gender-specific cut-offs. However, our findings suggest that normouricaemic men and women include distinct subsets of individuals with mortality risks that may be lower than, equivalent to or higher than hyperuricaemic individuals. Therefore, the mortality risk associated with hyperuricaemia must be determined within the context of the relative composition of normouricaemic subjects, and this potentially explains the mixed and conflicting results presented in the previous published literature. Our study highlights that a dichotomous classification of SUA levels is not appropriate because the mortality risk posed by extremely low SUA levels may be masked by this classification. We suggest that normal or optimal SUA levels should fall between 0.30 and 0.41 mmol/l; this stratum included the greatest number of individuals (42.5% in our study) and had the lowest mortality rate of all strata analysed.

The mortality risk conferred by low SUA levels has been less frequently reported. Mazza *et al.* [8] found that the relative risk (RR) of CHD death in elderly subjects with DM was elevated in patients with the highest tertile (RR: 1.28) and lowest tertile (RR: 1.76) of SUA levels, when tertile 2 was the reference category. In individuals with ischaemic stroke, there was a 12% increase in the odds of having a good clinical outcome for each milligram per decilitre increase in SUA level [9]. Furthermore, both high (HR: 1.96) and low (HR: 1.42) SUA levels were associated with increased mortality in a cohort of individuals with CKD [11]. In the present study, increased mortality caused by hypertensive heart disease, CHD and heart failure was observed in hyperuricaemic individuals; in contrast, increased mortality caused by ischaemic stroke was found only in those with low SUA levels. Taking into consideration the underlying risk profile of individuals, we found that high SUA levels were associated with increased cardiovascular mortality in subjects with DM,

hypertension, CHD, heart failure or CKD, whereas low SUA levels were associated with increased cardiovascular mortality in subjects with DM, hypertension and those who experienced stroke. These findings were consistent with that of previous studies [10, 11, 21, 22]. Moreover, a U-shaped association was observed in individuals who did not have any of the aforementioned risk factors. This is suggestive of the two important opposing properties of uric acid, namely, its antioxidant properties and its role in endothelial dysfunction.

Although it is now largely accepted that uric acid can induce endothelial dysfunction [23], there has been considerable debate as to whether the role of uric acid as an antioxidant is clinically meaningful [24, 25]. Several experimental investigations have suggested that uric acid possesses important serum free radical-scavenging capacity [24, 26, 27]. Moreover, loss of free radical-scavenging capacity as a result of low SUA levels may increase damage caused by ischaemia, such as that seen in patients who have experienced ischaemic stroke [28]. The relative contributions of these two opposing properties may explain the U-shaped association between SUA levels and cardiovascular mortality observed in this study.

The sample population for this study was selected from individuals who had undergone SUA measurements, potentially leading to a bias. However, SUA measurement is part of a comprehensive biochemistry panel (sequential multiple analysis-12) used in our hospital and is often ordered as a routine test in general practice. The SUA measurement is also a routine laboratory test for all individuals who undergo health screening. Therefore, the cohort was a good representation of the general population, including individuals who needed blood tests and who received annual health screening.

The main limitation of this study was the lack of data on potentially important subject characteristics. We relied on a single test of SUA levels and were unable to take into account any variation that may have occurred over time. As medications may interfere with SUA levels, we excluded all individuals with gout, who were most likely to take such drugs. Another potential limitation of our study was the concern that the mortality classification obtained from the National Death Registry may be inaccurate. However, a previous study found satisfactory agreement between death certificates and mortality classification codes in the Taiwan National Death Registry files [17]. This study's strengths include its use of carefully standardized methods, the large size of the study cohort and the complete coverage of all death events in the National Death Registry of Taiwan, which essentially obviates the possibility of loss to follow-up.

In conclusion, the present study revealed that individuals with either high or low SUA levels are at high risk for all-cause and cardiovascular mortality. The lowest occurrence of all-cause and cardiovascular deaths was observed in individuals with SUA levels ranging from 0.30 to 0.41 mmol/l. This range should thus be regarded as optimal.

Rheumatology Key messages

- SUA levels at either extreme confer higher risk for all-cause and cardiovascular mortality.
- SUA levels between 0.30 and 0.41 mmol/l were associated with the lowest mortality.
- The association between SUA levels and mortality risk depends on underlying risk factors.

Acknowledgements

The authors thank Dr Weiya Zhang from Academic Rheumatology at the University of Nottingham for his assistance with editing the manuscript and his comments on this work. We would also like to thank the Ministry of Education of Taiwan and Chang Gung Memorial Hospital for their financial support of this research. This study is based on data from the National Death Registry provided by the Bureau of Health Promotion, Department of Health, Taiwan. The descriptions of conclusions herein do not represent the viewpoint of the Bureau. The authors also thank Hsiu-Feng Hsia for her excellent work during the whole process of data acquisition and draft preparation.

Funding: This work was supported by the Chang Gung Memorial Hospital and the Ministry of Education.

Disclosure statement: The authors have declared no conflicts of interest.

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