General Cardiology

Adding Hyperuricemia to Traditional Cardiac Risk Factors Does Not Improve Ability to Predict Cardiac or Total Death in the Asymptomatic Taiwanese General Population

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Background: Although hyperuricemia is associated with cardiovascular disease, such as coronary heart disease (CHD), stroke and hypertension, whether or not including it among traditional risk factors improves the ability to better predict cardiac mortality and total cause of death rates remains controversial.

Methods and Results: This was an observational study based on 57,100 participants without overt cardiovascular disease who were enrolled during routine health examinations at Taipei Veterans General Hospital. The participants' mean age was 52.3 ± 13.4 years. Researchers estimated their serum concentrations of uric acid, and the study used future cardiac and all-cause death as the primary endpoints. During an average follow-up period of 5.4 ± 3.0 years, there were 1,889 deaths, including 231 cardiac deaths among the study subjects. In a multivariable-adjusted analysis with traditional cardiovascular risk factors, the hazard ratio of cardiac death associated with hyperuricemia was 1.63 (95% confidence interval [CI]: 1.19-2.22) and 1.60 (95% CI: 0.95-2.71) respectively, for males and females. The hazard ratio for death from all causes associated with hyperuricemia was 1.12 (95% CI: 1.00-1.26) and 1.41 (95% CI: 1.17-1.70) for males and females, respectively. The addition of hyperuricemia to the roster of traditional risk factors for cardiac death increased the C statistic from 0.79 (95% CI, 0.76-0.82) to 0.80 (95% CI, 0.77-0.83) for males, and increased it from 0.89 (95% CI, 0.85-0.92) to 0.89 (95% CI, 0.85-0.92) for females; however, neither had statistical significance. Furthermore, adding hyperuricemia to known risk factors produced an integrated discrimination improvement of 0.009 and -0.0003 respectively, for males and females, with a 4.11% improvement according to net reclassification analysis ($p = 0.102$), and 0.13% improvement according to net reclassification improvement ($p = 0.484$).

Conclusion: Our results suggest that hyperuricemia is an independent risk factor for predicting cardiac or all-cause death, although it had borderline significance for females in cardiac death models. However, adding hyperuricemia to traditional cardiac risk prediction models did not significantly improve the ability of the model to predict the risk of cardiac or all-cause death, regardless of whether we used ROC analysis or reclassification methods. Therefore, hyperuricemia per se should not be designated as a treatment target for reducing cardiac or even all-cause death in the general Taiwanese population.

Key Words: Cardiovascular risk • Hyperuricemia • Prediction model

Received: August 13, 2011 Accepted: January 19, 2012

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INTRODUCTION

The association between high serum uric acid levels and gouty arthritis is well known. Uric acid levels are also linked to hypertension, dyslipidemia, kidney disease, metabolic syndrome and diabetes.[1-3] The increasing prevalence of hyperuricemia worldwide is closely related to the increasing incidence of obesity, metabolic

syndrome and the epidemic of diabetes.[4,5,32] The Taiwan Nutrition and Health Survey found that the prevalence of hyperuricemia was as high as 42.1% in men and 27.4% in women. The prevalence among Taiwan aborigines (90.5%) was even higher.[6] Comparing ethnic groups, hyperuricemia or mean serum uric acid levels were higher among ethnic Taiwanese than other groups.[10,11]

Although many epidemiological studies have shown an association between hyperuricemia and an increased incidence of cardiovascular disease, these results have been controversial.[7-9] The Framingham study failed to demonstrate a consistent independent association between serum uric acid levels and cardiovascular outcomes in a population-based study.[10] However, in the last ten years, many studies have concluded that increased serum uric acid is likely an independent risk factor for cardiovascular disease, especially among high-risk individuals. Moreover, a recent meta-analysis showed hyperuricemia may marginally increase the risk of coronary heart disease, independent of traditional coronary heart disease risk factors.[12] Two large population-based prospective studies done in Taiwan have revealed that hyperurciemia is indeed a significant risk factor for cardiovascular, and even all-cause mortality in the general Taiwan population, and potentially even in low-risk groups.[13,14] With considerable epidemiological evidence accumulating about cardiac and even all-cause mortality associated with hyperuricemia, it remains uncertain whether including hyperuricemia among traditional coronary heart disease risk factors can increase the ability to predict cardiac or all-cause mortality.

METHODS

Study subjects

We screened a prospective observational cohort of 59,089 subjects who received health examinations at Taipei Veterans General Hospital between November 17, 1997 and December 31, 2007. The basic demographic data and patient medical records were examined. Diabetes was defined as the presence of one of the following criteria: current use of anti-diabetic agents, diet modification because of diabetes, fasting glucose ≥ 126 mg/dl, or 2-h postprandial glucose ≥ 200 mg/dl. Metabolic syndrome (MS) was defined according to the modified NCEP ATP III as fulfillment of at least three of the following five criteria: (1) blood pressure > 130/85 mmHg, (2) fasting plasma glucose level > 110 mg/dL, (3) hypertriglyceridemia with triglyceride level > 150 mg/dL, (4) high-density lipoprotein-cholesterol (HDL-C) level < 40 mg/dL in men or < 50 mg/dL in women, and (5) central obesity with waist circumference > 90 cm in men, or > 80 cm in women. The definition of central obesity has been modified for the Asian population.[15] Brachial systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured manually by experienced clinicians using a mercury sphygmomanometer and a standard-sized cuff (13 × 50 cm). Two or more measurements separated by at least five minutes were taken from the right arm of participants after they had been seated for at least five minutes. Reported blood pressure values represent the average of at least two consecutive measurements. We excluded subjects with any symptoms of cardiovascular disease or history of coronary artery disease, stroke, peripheral artery disease and alcoholism. We also excluded those with valvular disease, idiopathic cardiomyopathy, resting electrocardiography (ECG) evidence of abnormalities such as atrial fibrillation and congestive heart failure New York Heart Association functional class II-VI.

Blood samples for biochemical analysis

We obtained blood samples from all patients after an overnight fast > 12 hours. We measured lipid profiles, including triglycerides, total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, serum uric acid, creatinine, fasting blood sugar and 2-h postprandial glucose using a Hitachi 7600 autoanalyzer (Hitachi Ltd., Tokyo, Japan).

Ascertainment of cardiac and all-cause death

The dates and causes of death were obtained by linking the subjects' data with the National Death Registry. The National Death Registry database registers all valid information identifying causes of death in Taiwan on the basis of the certified death certificates coded according to the International Classification of Disease (ICD), Ninth Revision. The ICD-9 codes used for cardiovascular death were 390 to 459. The accuracy of cause-of-death coding in Taiwan's National Death Registry database has been validated.[16,17]

Statistics

Data are expressed as the mean ± standard deviation for numeric variables and as the number (percent) for categorical variables. Baseline characteristics are represented by dividing serum uric acid levels into quartiles. Comparisons of continuous variables between groups were performed by ANOVA testing and trend testing. Subgroup comparisons of categorical variables were assessed by χ^2 or Fisher's exact test. Multivariate Cox regression analysis was performed to estimate the association between serum uric acid levels and the risk of cardiac death and all-cause death, after adjusting with models: Model 1 included age, hypertension, diabetes and metabolic syndrome; Model 2 included continuous variables for age, systolic and diastolic blood pressure, fasting glucose, and lipid profiles as well as HDL, LDL and body mass index.

To further investigate whether the inclusion of serum uric acid improved the models' ability to predict adverse outcomes, we used three methods. First we plotted receiver-operating-characteristic (ROC) curves for baseline covariates with or without serum uric acid values, to assess the ability of serum uric acid to more reliably predict the classification of mortality risk. The better understanding of incidences of cardiac or all-cause death were the primary outcomes of our study. The C statistic, a measure of the area under the ROC curve, was calculated with and without serum uric acid values. Additionally, we evaluated whether adding uric acid values to traditional cardiovascular risk factors could be used to reclassify risk, by calculating net reclassification improvement (NRI) and integrated discrimination improvement (IDI) for cardiac and all-cause death.[17,18] Subjects were classified into four risk categories of: 0-1%, 1-3%, 3-6%, and ≥ 6% derived from a probability distribution of 5-year risk for cardiac death, and then reclassified according to the predictive risks in regression models to include hyperuricemia. Similarly, subjects were grouped into four categories of 0-10%, 10-25%, 25-35%, and ≥ 35%, which were defined on the assumption that cardiac death was accountable for ~15% of all-cause death from the 2006 mortality statistics from the World Health Organization.[19] The NRI was the difference between the percentage of those with events who were reclassified into high-risk categories and those without events reclassified into lower risk categories (indicating successful improvement in the model's discrimination performance), and the percentage of those with events who were reclassified into low-risk categories and those without events reclassified into high risk categories (indicating a failure to improve discrimination performance). The calculation of IDI, on the other hand, is a clinically less intuitive method for assessing reclassification; it does not rely on pre-specified risk categories, but represents a continuous measure. We applied all these analyses to estimating the improvement in risk reclassification, after adding serum uric acid levels to the models. The analyses were performed with SPSS software, version 15.0, and the ROC curves and C statistics were generated using SAS 9.0.

RESULTS

A total of 57,100 subjects who obtained health examinations at Veterans General Hospital were enrolled, with 31,722 males (55.6%) and a mean age of 52.3 ± 13.4 years old. The deadline for the collection of the dates and causes of death was Dec. 31, 2007. The percentage of subjects being followed less than 1 year is 9.1% (5182/57,100). The range of follow-up period is a minimum 3 days, and a maximum 4014 days, with range around 4011 days. Table 1a shows the baseline characteristics of the female study population stratified by serum uric acid quartiles. The age, systolic and diastolic blood pressures, fasting blood glucose, 2 hours postprandial blood glucose, total cholesterol, LDL, and triglycerides all rose significantly with increasing quartiles of serum uric acid levels; but there was a decreasing trend in HDL levels. Besides, both the cardiac and all-cause death were highest in the 4th quartile of serum uric acid. On the other hand, the baseline characteristics of the study male population were noted in Table 1b. The systolic and diastolic blood pressure, cholesterol, LDL, and triglycerides were all significantly increased with serum uric acid quartiles with a decreasing trend in the HDL level. Interestingly, the aging and fasting blood glucose, and postprandial blood glucose trends were all non-significant in this male subgroup. The cardiac and all-cause death are both highest in the lowest quartile of serum uric acid.

Table 1a. Baseline characteristics of the female study population stratified by uric acid quartiles

Females	Total	Serum uric acid (mg/dL)				p value	p for trend
		Q1	Q2	Q3	Q4		
	5.3 ± 1.4	3.9 ± 0.5	4.8 ± 0.2	5.6 ± 0.3	7.1 ± 1.0		
n	25,378	6,692	5,843	6,414	6,429		
Age, years	51.4 ± 12.8	48.7 ± 12.2	49.9 ± 12.4	51.7 ± 12.7	55.4 ± 12.8	< 0.001	< 0.001
HTN, n (%)	5,393 (21.3)	836 (12.5)	960 (16.4)	1,343 (20.9)	2,254 (35.1)	< 0.001	< 0.001
MS, n (%)	10,263 (40.4)	2,513 (37.6)	2,404 (41.1)	2,738 (42.7)	2,608 (40.6)	< 0.001	< 0.001
Height, cm	156.5 ± 5.8	157.2 ± 5.9	156.9 ± 5.8	156.6 ± 5.8	155.6 ± 5.7	< 0.001	< 0.001
BMI	23.2 ± 3.6	21.9 ± 2.9	22.6 ± 3.2	23.5 ± 3.5	25.0 ± 4.0	< 0.001	< 0.001
SBP, mmHg	122.8 ± 20.3	118.0 ± 18.4	120.0 ± 19.0	123.3 ± 20.2	129.8 ± 21.4	< 0.001	< 0.001
DBP, mmHg	75.8 ± 15.0	73.6 ± 16.1	74.4 ± 13.9	76.4 ± 17.1	78.7 ± 11.7	< 0.001	< 0.001
FBS, mg/dL	98.2 ± 26.6	96.8 ± 29.4	96.0 ± 23.3	97.7 ± 24.6	102.2 ± 27.6	< 0.001	< 0.001
2 hr PC, mg/dL	124.5 ± 50.4	119.1 ± 53.9	119.6 ± 45.7	123.6 ± 46.8	135.6 ± 52.4	< 0.001	< 0.001
Cho, mg/dL	198.9 ± 37.6	191.1 ± 35.3	196.3 ± 36.5	201.3 ± 37.1	207.1 ± 39.5	< 0.001	< 0.001
LDL, mg/dL	121.9 ± 33.1	114.5 ± 30.8	119.7 ± 32.1	124.4 ± 33.0	129.2 ± 34.7	< 0.001	< 0.001
HDL, mg/dL	57.2 ± 14.4	60.4 ± 14.4	58.9 ± 14.5	56.7 ± 14.1	52.9 ± 13.5	< 0.001	< 0.001
Triglyceride, mg/dL	108.6 ± 63.2	88.8 ± 48.2	98.4 ± 58.0	111.7 ± 60.8	135.4 ± 73.3	< 0.001	< 0.001
Cardiac death, n (%)	62 (0.2)	10 (0.1)	7 (0.1)	16 (0.2)	29 (0.5)	0.001	< 0.001
All-cause death, n (%)	503 (2.0)	109 (1.6)	86 (1.5)	101 (1.6)	207 (3.2)	< 0.001	< 0.001

Table 1b. Baseline characteristics of the study male population stratified by uric acid quartiles

Males	Total	Serum uric acid (mg/dL)				p value	p for trend
		Q1	Q2	Q3	Q4		
	6.8 ± 1.5	5.1 ± 0.7	6.3 ± 0.3	7.2 ± 0.3	8.8 ± 1.0		
n	31,722	8,205	7,740	7,902	7,875		
Age, years	53.0 ± 13.9	56.0 ± 14.1	52.7 ± 13.7	52.0 ± 13.6	51.4 ± 13.7	< 0.001	< 0.001
HTN, n (%)	8,802 (27.7)	2,091 (25.5)	1,899 (24.5)	2,182 (27.6)	2,630 (33.4)	< 0.001	< 0.001
MS, n (%)	12,068 (38.0)	2,686 (32.7)	2,817 (36.4)	3,212 (40.6)	3,353 (42.6)	< 0.001	< 0.001
Height, cm	168.5 ± 6.4	167.8 ± 6.4	168.6 ± 6.3	168.7 ± 6.3	169.0 ± 6.3	< 0.001	< 0.001
BMI	24.6 ± 3.3	23.5 ± 3.1	24.2 ± 3.1	24.8 ± 3.1	25.7 ± 3.4	< 0.001	< 0.001
SBP, mmHg	126.4 ± 17.4	125.8 ± 17.7	125.4 ± 17.0	125.9 ± 17.0	128.4 ± 17.5	< 0.001	< 0.001
DBP, mmHg	78.9 ± 12.6	77.4 ± 12.6	78.3 ± 13.1	79.0 ± 11.2	80.9 ± 13.1	< 0.001	< 0.001
FBS, mg/dL	102.1 ± 29.7	108.0 ± 41.1	100.4 ± 26.2	99.9 ± 23.5	99.8 ± 22.8	< 0.001	0.208
2 hr PC, mg/dL	127.3 ± 58.9	139.2 ± 79.2	123.1 ± 52.8	122.4 ± 49.2	124.0 ± 45.5	< 0.001	0.832
Cho, mg/dL	196.1 ± 36.3	189.8 ± 34.6	194.3 ± 35.7	197.6 ± 36.1	203.0 ± 37.4	< 0.001	< 0.001
LDL, mg/dL	124.6 ± 32.1	119.6 ± 30.3	123.8 ± 31.8	125.9 ± 32.3	129.2 ± 33.3	< 0.001	< 0.001
HDL, mg/dL	46.4 ± 11.7	48.7 ± 12.6	47.0 ± 11.6	45.7 ± 11.2	44.2 ± 10.7	< 0.001	< 0.001
Triglyceride, mg/dL	138.7 ± 83.2	117.5 ± 70.9	129.6 ± 73.8	143.3 ± 81.0	165.3 ± 97.2	< 0.001	< 0.001
Cardiac death, n (%)	169 (0.5)	45 (0.5)	35 (0.5)	41 (0.5)	48 (0.6)	0.595	0.506
All-cause death, n (%)	1,386 (4.4)	508 (6.2)	305 (3.9)	271 (3.4)	302 (3.8)	< 0.001	< 0.001

BMI, body mass index; Cho, cholesterol; FBS, fasting blood sugar; HDL, high density lipoprotein; HTN, hypertension; LDL, low density lipoprotein; MS, metabolic syndrome defined by ATP III; SBP, DBP, systolic, diastolic blood pressure; 2-hr PC, post-prandial blood sugar.

During the follow-up period (mean, 5.4 ± 3.0 years), there were a total of 1,889 deaths, including 231 cardiac deaths. The incidences of cardiac death and all-cause death were positively correlated with increasing serum uric acid value quartiles (for counting both male and female subjects together). After adjusting for traditional

risk factors, including age, blood pressure, fasting blood sugar, and lipid profiles, as well as high serum uric acid levels (uric acid level ≥ 7.3 mg/dL in males and ≥ 6.3 mg/dl in females, the cut-off values used by the laboratory of Veterans General Hospital) in model 2. High serum uric acid level was positively associated with an increased risk of cardiac death (hazard ratio [HR]: 1.63, 95% confidence interval [CI], 1.19-2.22, in males, HR: 1.60, 95% CI, 0.95-2.71 in females) and all-cause death (HR: 1.12, 95% CI, 1.00-1.26, in males, HR: 1.41, 95% CI, 1.17-1.70, in females). Furthermore, after adjusting for potential confounders, increasing quartiles of serum uric acid levels were associated with a rising trend toward male cardiac death. The serum uric acid levels predicted cardiac death and death from all causes, if we took the high serum uric acid cut-off level into consideration except for borderline significance in female cardiac death (Table 2).

The survival curves for cardiac and all-cause mortality are shown in Figure 1, which reveals that hyperuricemia predicted higher cardiac and all-cause mortality among females. On the other hand, hyperuricemia predicted cardiac death but not all-cause mortality in males.

Comparison of discrimination and C-statistics for models with traditional risk factors and multivariate models before and after adding serum uric acid

Table 3 and Table 4 present a summary of the statistics for evaluation of model discrimination and reclassification performance. Using the traditional risk factors in a model incorporating uric acid (Table 4A) for male subjects, we found that 18 of 169 subjects who suffered cardiac death were reclassified into higher risk categories, and 12 subjects were classified into lower risk categories; however, among 31,553 subjects who did not experience cardiac death, 574 were designated as higher risk and 752 as lower risk categories. The NRI was 4.11% (p = 0.1023), IDI (0.09%), suggesting that the ability to predict the risk of cardiac death did not improve significantly after adding serum uric acid to the traditional risk factors. Likewise, for all-cause death, the NRI was -0.09% (p = 0.5823), IDI (-0.03%), indicating that adding serum uric acid did not improve the discriminative ability of this model. Furthermore, among female subjects who suffered cardiac death, the NRI was

Table 2. Multivariate-adjusted association between serum uric acid and cardiac and total mortality in males and females

		Quartiles				
	High uric acid HR (95% CI)	Q1 HR (95% CI)	Q2 HR (95% CI)	Q3 HR (95% CI)	Q4 HR (95% CI)	p for trend
Males						
Cardiac death						
Crude	1.39 (1.02-1.88)	Referent	0.88 (0.56-1.37)	1.09 (0.71-1.66)	1.34 (0.89-2.02)	0.110
Model 1	1.70 (1.25-2.31)	Referent	1.22 (0.78-1.90)	1.57 (1.02-2.40)	2.00 (1.33-3.02)	0.001
Model 2	1.63 (1.19-2.22)	Referent	1.17 (0.75-1.83)	1.53 (1.00-2.36)	1.87 (1.23-2.85)	0.002
All-cause death						
Crude	0.90 (0.80-1.00)	Referent	0.68 (0.59-0.78)	0.64 (0.55-0.74)	0.75 (0.65-0.86)	< .001
Model 1	1.10 (0.98-1.23)	Referent	0.91 (0.78-1.04)	0.89 (0.77-1.03)	1.09 (0.94-1.26)	0.532
Model 2	1.12 (1.00-1.26)	Referent	0.92 (0.79-1.06)	0.93 (0.80-1.08)	1.12 (0.97-1.30)	0.250
Females						
Cardiac death						
Crude	2.87 (1.74-4.73)	Referent	0.89 (0.34-2.33)	1.93 (0.88-4.26)	3.47 (1.69-7.14)	< .001
Model 1	1.50 (0.90-2.51)	Referent	0.78 (0.30-2.05)	1.27 (0.57-2.80)	1.49 (0.72-3.11)	0.143
Model 2	1.60 (0.95-2.71)	Referent	0.77 (0.29-2.05)	1.22 (0.54-2.74)	1.58 (0.74-3.36)	0.111
All-cause death						
Crude	2.30 (1.92-2.75)	Referent	0.99 (0.75-1.32)	1.11 (0.85-1.45)	2.26 (1.79-2.85)	< .001
Model 1	1.41 (1.17-1.70)	Referent	0.90 (0.68-1.20)	0.84 (0.64-1.11)	1.23 (0.97-1.56)	0.062
Model 2	1.41 (1.17-1.70)	Referent	0.88 (0.66-1.17)	0.79 (0.60-1.04)	1.18 (0.92-1.51)	0.148

Crude, only for serum uric acid; Model 1, adjusted for age, HTN, DM, MS; Model 2, adjusted for age, SBP, DBP, FBS, LDL, HDL, BMI.

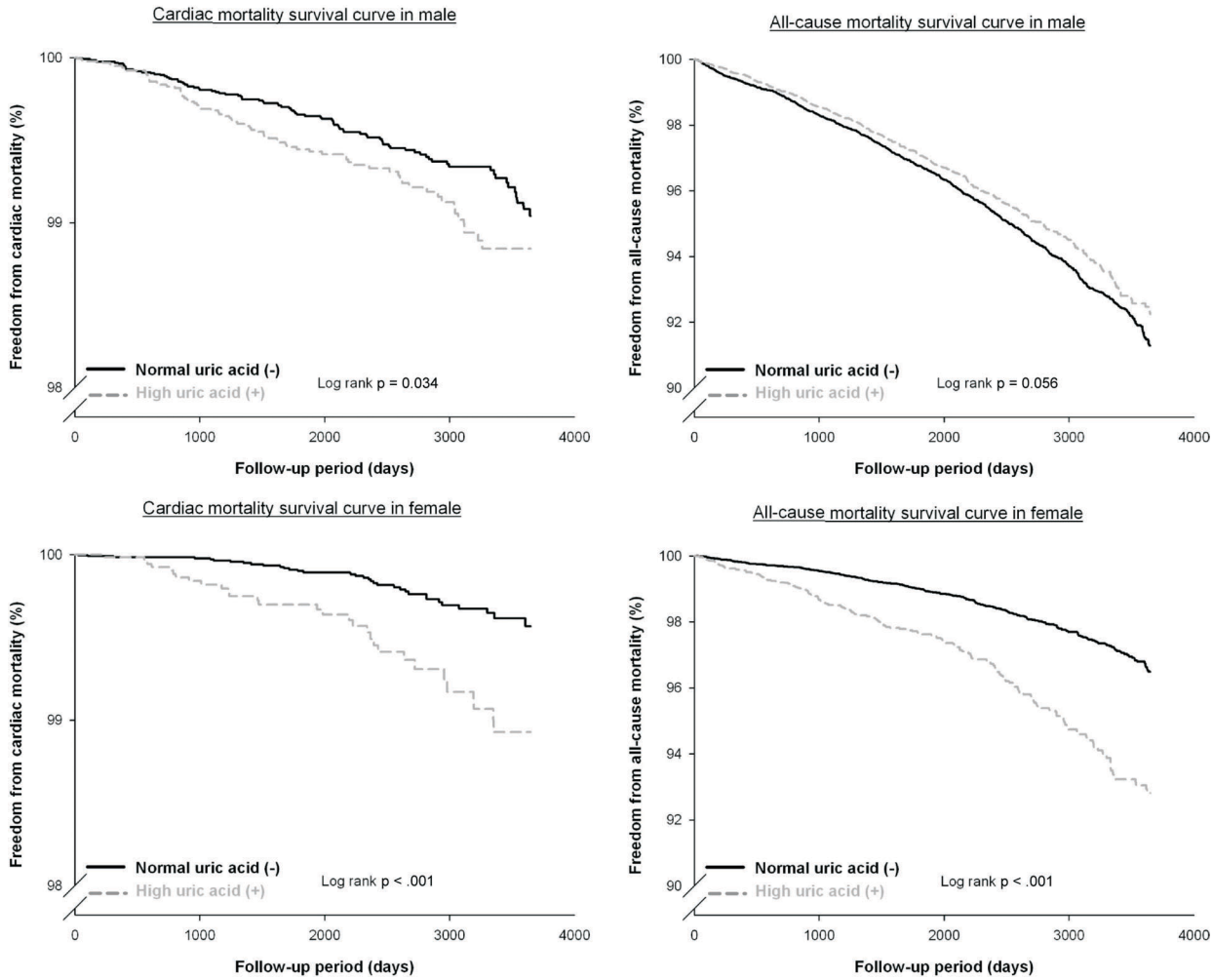

Figure 1. *Survival curves of cardiac mortality and all-cause mortality with high or normal serum uric acid level.*

Table 3. Improvement in discrimination performance and calibration for predicting risk of cardiac death and all-cause death with a multivariate-adjusted model including serum uric acid

	AUC	IDI (%)	NRI (%)	p value
Cardiac death				
Males				
Established risk factors	0.79 (0.76-0.82)		Referent	
Established risk factors + uric acid	0.80 (0.77-0.83)	0.09	4.11	0.1023
Females				
Established risk factors	0.89 (0.85-0.92)		Referent	
Established risk factors + uric acid	0.89 (0.85-0.92)	-0.03	0.13	0.4839
All-cause death				
Males				
Established risk factors	0.73 (0.72-0.75)		Referent	
Established risk factors + uric acid	0.73 (0.72-0.75)	0.03	-0.09	0.5823
Females				
Established risk factors	0.74 (0.72-0.76)		Referent	
Established risk factors + uric acid	0.74 (0.72-0.76)	-0.02	-0.73	0.8565

Established risk factors: age, obesity, hypertension, diabetes mellitus, LDL-c, HDL-c.

0.13% (p = 0.4839), IDI (0.03%), and the all-cause death NRI was -0.73% (p = 0.8565), IDI (-0.02%), all suggesting that serum uric acid did not improve the traditional risk prediction models for cardiac and all-cause mortality.

To further evaluate whether the serum uric acid level could improve the prediction of cardiac or all-cause death, we plotted receiver-operating-characteristic (ROC) curves for baseline covariates with or without uric acid levels to classify risk. In ROC analysis, the C statistic (AUC) showed insignificant improvement after the addition of serum uric acid to the traditional clinical risk factors model for predicting cardiac death, from 0.70 to 0.80 in males, 0.89 to 0.89 in females, and for predicting all-cause death from 0.73 to 0.73 in males, 0.74 to 0.74 in females (Table 3, all p valve > 0.05).

DISCUSSION

In this study, we attempted to investigate the independent and incremental utility of high serum uric acid

Table 4. Reclassification of risk of cardiac and all-cause death, after considering serum levels of uric acid

A. Cardiac death

Males

			With UA		
Without UA	< 1%	1-3%	3-6%	> 6%	Total
< 1%	80 (0.47)	6 (0.04)	0 (0.00)	0 (0.00)	86
1-3%	8 (0.05)	41 (0.24)	12 (0.07)	0 (0.00)	61
3-6%	0 (0.00)	4 (0.02)	11 (0.07)	0 (0.00)	15
> 6%	0 (0.00)	0 (0.00)	0 (0.00)	7 (0.04)	7
Total	88	51	23	7	169
			Participants who did not have events		
< 1%	26881 (0.85)	302 (0.01)	1 (0.00)	0 (0.00)	27184
1-3%	444 (0.01)	2,499 (0.08)	186 (0.01)	3 (0.00)	3132
3-6%	0 (0.00)	237 (0.01)	581 (0.02)	82 (0.00)	900
> 6%	0 (0.00)	1 (0.00)	70 (0.00)	266 (0.01)	337
Total	27325	3039	838	351	31553

The improvement in ability to predict cardiovascular death resulting from net reclassification is estimated at 4.11% (p = 0.1023).

A. Cardiac deaths

Females

			With UA		
Without UA	< 1%	1-3%	3-6%	> 6%	Total
< 1%	31 (0.18)	2 (0.01)	0 (0.00)	0 (0.00)	33
1-3%	1 (0.01)	16 (0.09)	0 (0.00)	0 (0.00)	17
3-6%	0 (0.00)	1 (0.01)	7 (0.04)	0 (0.00)	8
> 6%	0 (0.00)	0 (0.00)	0 (0.00)	4 (0.02)	4
Total	32	19	7	4	62
			Participants who did not have events		
< 1%	24005 (0.76)	42 (0.00)	0 (0.00)	0 (0.00)	24047
1-3%	75 (0.00)	806 (0.03)	36 (0.00)	0 (0.00)	917
3-6%	0 (0.00)	33 (0.00)	196 (0.01)	7 (0.00)	236
> 6%	0 (0.00)	0 (0.00)	10 (0.00)	106 (0.00)	116
Total	24080	881	242	113	25316

The improvement in ability to predict cardiovascular death resulting from net reclassification is estimated at 0.13% (p = 0.4839).

Table 4. Continued

B. Deaths from all causes deaths					
Males					
			With UA		
Without UA	< 10%	10-25%	25-35%	> 35%	Total
< 10%	908 (5.37)	7 (0.04)	0 (0.00)	0 (0.00)	915
10-25%	9 (0.05)	312 (1.85)	3 (0.02)	0 (0.00)	324
25-35%	0 (0.00)	6 (0.04)	57 (0.34)	6 (0.04)	69
> 35%	0 (0.00)	0 (0.00)	3 (0.02)	75 (0.44)	78
Total	917	325	63	81	1386
			Participants who did not have events		
< 10%	26846 (0.85)	80 (0.00)	0 (0.00)	0 (0.00)	26926
10-25%	108 (0.00)	2387 (0.08)	52 (0.00)	0 (0.00)	2547
25-35%	0 (0.00)	52 (0.00)	379 (0.01)	28 (0.00)	459
> 35%	0 (0.00)	0 (0.00)	17 (0.00)	387 (0.01)	404
Total	26954	2519	448	415	30336

The net improvement in ability to predict death from all causes resulting from reclassification is estimated at-0.09% (p = 0.5823).

B. Deaths from all causes deaths					
Females					
			With UA		
Without UA	< 10%	10-25%	25-35%	>35%	Total
< 10%	412 (2.44)	3 (0.02)	0 (0.00)	0 (0.00)	415
10-25%	5 (0.03)	63 (0.37)	0 (0.00)	0 (0.00)	68
25-35%	0 (0.00)	1 (0.01)	7 (0.04)	1 (0.01)	9
> 35%	0 (0.00)	0 (0.00)	2 (0.01)	9 (0.05)	11
Total	417	67	9	10	503
			Participants who did not have events		
< 10%	23902 (0.76)	37 (0.00)	0 (0.00)	0 (0.00)	23939
10-25%	57 (0.00)	720 (0.02)	14 (0.00)	0 (0.00)	791
25-35%	0 (0.00)	15 (0.00)	65 (0.00)	10 (0.00)	90
> 35%	0 (0.00)	0 (0.00)	4 (0.00)	51 (0.00)	55
Total	23959	772	83	61	24875

The improvement in ability to predict death from all causes resulting from net reclassification is estimated at -0.73% (p = 0.8565).

for predicting risk of cardiac and all-cause death in low-risk health examination subjects. Our results suggest that hyperuricemia is an independent risk predictor for cardiac or all-cause mortality in both males and females, except for cardiac death prediction in females (showing borderline significance in Cox models). However, adding hyperuricemia into traditional coronary heart disease risk prediction models did not improve the ability to predict the risk of cardiac or all-cause mortality, whether C statistics or reclassification methods were used.

The prevalence of hyperuricemia and gout in Taiwan is high, especially in mountainous areas and among aborigines, where prevalence rates may even reach as high as 90%.[6] This epidemic has stimulated many epidemiological and pathophysiological studies in Taiwan, and they all have suggested hyperuricemia may be a minor but significant risk factor for all-cause mortality and mortality from cardiovascular disease.[13,14]

The independent evidence for an association between hyperuricemia and cardiovascular or all-cause mortality remains controversial.[20,21] The Honolulu Heart Study and the Hypertension Detection Follow-up Program study showed a consistent independent relationship between serum uric acid levels and cardiovascular events.[22] Furthermore, the Chicago Heart Association

Detection Project and the early NHANES I study also found an independent relationship, but which was prominent only in women.[7,23] On the other hand, important previous studies such as the Framingham Heart Study have suggested that uric acid is not a risk factor for cardiovascular disease, and that clinicians should rely only on classic risk factors for patient assessment.[10] Moreover, the major hypertension or primary prevention guidelines do not consider it as a cardiovascular risk factor either.

In our study, serum uric acid levels increased with age in women but not in men, and this is frequently noted in other epidemiological studies.[7,13] The mean age is oldest in the lower quartile of serum uric acid and this aging effect maybe the predominant effect for cardiac or all cause death in the stratified data. However, cardiac deaths increase with uric acid quartiles and trend upwards as patients age, after confounder adjustments in multivariate model. Previous large epidemiological studies suggested that females had both higher cardiac death and all cause death hazard ratios for hyperuricemia, which is also reflected in our study. Although our HR for women is less significant, this maybe result from a lower cutoff level in women (serum uric acid ≥ 6.3 mg/dL) than other studies, which set the hyperuricemia cutoff level as 7.0 mg/dL in both men and women.[13]

It seems there must be a link between hyperuricemia and the risk for cardiovascular and even all-cause mortality. There are abundant animal, and even human experiments which have shown that lowering serum uric acid levels can lead to improvement in cardiovascular disease risk factors such as hypertension or kidney disease. Some longitudinal studies have also shown that an increased level of serum uric acid is associated with an increased risk of future hypertension.[24,25] Most recently, a study with a 6-year follow up of men 35-57 years of age without metabolic syndrome showed an 80% excess risk of incident hypertension.[26] Furthermore, detailed studies suggested that hyperuricemia related more to prehypertension, younger hypertension and isolated diastolic hypertension.[27] In animal models, in rats given a uricase inhibitor to promote mild hyperuricemia, systemic hypertension developed within 3 weeks. In human studies, a randomized trial has demonstrated improved blood pressure control associated with allopurinol use for lowering uric acid levels in 30 adolescents.[28] Besides, hyperuricemia correlates with both endothelial dysfunction and an increase in plasma renin activity, both of which over time may result in microvascular kidney disease.[29,30] However, there are also arguments against a causal relationship between hyperuricemia and cardiovascular disease risk. The most common arguments of this nature propose that the association is one of coincidence, reverse causation, and possible common-causal genetic variables.[20,21]

In clinical practice, it remains an important question whether, by adding hyperuricemia, we can improve our risk prediction models beyond traditional coronary heart disease risk factors. A delicate study using Cox proportional analysis and stratification methods by Wen et al. suggested that increased serum uric acid levels are more a risk marker than a target for treatment.[14] In this study, we re-examine the issue of adding hyperuricemia to the traditional risk factors model using ROC analysis and reclassification methods. Our results likewise suggest that hyperuricemia may be a cardiac and all-cause mortality marker, but not an appropriate target for treatment.

LIMITATIONS

There are several limitations in our study. Because study subjects first underwent routine health examinations, the medication profiles are not detailed and recorded. The medication effect for serum uric acid was not known. Second, there may be some recall bias regarding the subject's past history including other cardiovascular diseases such as valvular heart or cardiomyopathy, although these sorts of patients were less included in the routine healthy examination. Third, the possible misclassification for cardiovascular and all cause death should be considered during ascertainment of cardiac and all-cause death. However, these kinds of nondifferential biases could be overcome by a large sample size and long observation period.[31]

CONCLUSION

Our results suggest that hyperuricemia is an independent risk factor for predicting cardiac or all-cause death, although it had borderline significance for fe-

males in cardiac death models. However, adding hyperuricemia to traditional cardiac risk prediction models did not significantly improve the models' ability to predict the risk of cardiac or all-cause death, regardless of whether we used ROC analysis or reclassification methods. Hyperuricemia per se should not be designated as a treatment target for reducing cardiac or even all-cause death in the general Taiwanese population.

ACKNOWLEDGEMENTS

This study was supported by a grant from the Veterans General Hospital (V100B-031). We would like to thank Miss Hsiu-Wen Liao for her great assistance.

REFERENCES

1. Fam AG. Gout, diet, and the insulin resistance syndrome. *J Rheumatol* 2002;29:1350-5.
2. DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care* 1991;14:173-94.
3. Baker JF, Krishnan E, Chen L, Schumacher HR. Serum uric acid and cardiovascular disease: recent developments, and where do they leave us? *Am J Med* 2005;118:816-26.
4. Johnson RJ, Rideout BA. Uric acid and diet--insights into the epidemic of cardiovascular disease. *N Engl J Med* 2004;350:1071-3.
5. Conen D, Wietlisbach V, Bovet P, et al. Prevalence of hyperuricemia and relation of serum uric acid with cardiovascular risk factors in a developing country. *BMC Public Health* 2004;25;4-9.
6. Chang HY, Pan WH, Yeh WT, Tsai KS. Hyperuricemia and gout in Taiwan: results from the Nutritional and Health Survey in Taiwan (1993-96). *J Rheumatol* 2001;28:1640-6.
7. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971-1992. National Health and Nutrition Examination Survey. *JAMA* 2000; 283:2404-10.
8. Alderman MH, Cohen H, Madhavan S, Kivlighn S. Serum uric acid and cardiovascular events in successfully treated hypertensive patients. *Hypertension* 1999;34:144-50.
9. Niskanen L, Laaksonen DE, Lindström J, et al. Serum uric acid as a harbinger of metabolic outcome in subjects with impaired glucose tolerance: the Finnish Diabetes Prevention Study. *Diabetes Care* 2006;29:709-11.
10. Culleton BF, Larson MG, Kannel WB, Levy D. Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. *Ann Intern Med* 1999;131:7-13.
11. Klemp P, Stansfield SA, Castle B, Robertson MC. Gout is on the increase in New Zealand. *Ann Rheum Dis* 1997;56:22-6.
12. Kim SY, Guevara JP, Kim KM, et al. Hyperuricemia and coronary heart disease: a systematic review and meta-analysis. *Arthritis Care Res* 2010;62:170-80.
13. Chen JH, Chuang SY, Chen HJ, et al. Serum uric acid level as an independent risk factor for all-cause, cardiovascular, and ischemic stroke mortality: a Chinese cohort study. *Arthritis Rheum* 2009;61:225-32.
14. Wen CP, David Cheng TY, Chan HT, et al. Is high serum uric acid a risk marker or a target for treatment? Examination of its independent effect in a large cohort with low cardiovascular risk. *Am J Kidney Dis* 2010;56:273-88.
15. Tan CE, Ma S, Wai D, et al. Can we apply the National Cholesterol Education Program Adult Treatment Panel definition of the metabolic syndrome to Asians? *Diabetes Care* 2004;27:1182-6.
16. Wang KL, Cheng HM, Sung SH, et al. Wave reflection and arterial stiffness in the prediction of 15-year all-cause and cardiovascular mortalities: a community-based study. *Hypertension* 2010;55:799-805.
17. Lin HJ, Lee BC, Ho YL, et al. Postprandial glucose improves the risk prediction of cardiovascular death beyond the metabolic syndrome in the nondiabetic population. *Diabetes Care* 2009;32: 1721-6.
18. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med* 2008;27:157-72.
19. Pocock SJ, McCormack V, Gueyffier F, et al. A score for predicting risk of death from cardiovascular disease in adults with raised blood pressure, based on individual patient data from randomised controlled trials. *BMJ* 2001;323:75-81.
20. Krishnan E, Sokolove J. Uric acid in heart disease: a new C-reactive protein? *Curr Opin Rheumatol* 2011;23:174-7.
21. Tangri N, Weiner DE. Uric acid, CKD, and cardiovascular disease: confounders, culprits, and circles. *Am J Kidney Dis* 2010; 56:247-50.
22. Goldberg RJ, Burchfiel CM, Benfante R, et al. Lifestyle and biologic factors associated with atherosclerotic disease in middle-aged men. 20-year findings from the Honolulu Heart Program. *Arch Intern Med* 1995;155:686-94.
23. Levine W, Dyer AR, Shekelle RB, et al. Serum uric acid and 11.5-year mortality of middle-aged women: findings of the Chicago Heart Association Detection Project in Industry. *J Clin Epidemiol* 1989;42:257-67.
24. Shankar A, Klein R, Klein BE, Nieto FJ. The association between serum uric acid level and long-term incidence of hypertension: population-based cohort study. *J Hum Hypertens* 2006;20:937-45.
25. Perlstein TS, Gumieniak O, Williams GH, et al. Uric acid and the development of hypertension: the normative aging study. *Hypertension* 2006;48:1031-6.
26. Krishnan E, Kwoh CK, Schumacher HR, Kuller L. Hyper-

uricemia and incidence of hypertension among men without metabolic syndrome. *Hypertension* 2007;49:298-303.
27. Leite ML. Uric acid and fibrinogen: age-modulated relationships with blood pressure components. *J Hum Hypertens* 2011;25: 476-83.
28. Feig DI, Soletsky B, Johnson RJ. Effect of allopurinol on blood pressure of adolescents with newly diagnosed essential hypertension: a randomized trial. *JAMA* 2008;300:924-32.
29. Doehner W, Schoene N, Rauchhaus M, et al. Effects of xanthine oxidase inhibition with allopurinol on endothelial function and peripheral blood flow in hyperuricemic patients with chronic heart failure: results from 2 placebo-controlled studies. *Circulation* 2002;105:2619-24.
30. Mercuro G, Vitale C, Cerquetani E, et al. Effect of hyperuricemia upon endothelial function in patients at increased cardiovascular risk. *Am J Cardiol* 2004;94:932-5.
31. Lu TH, Chang HY, Hwu CM, et al. Comparison of official coders versus physician panel in assignment of underlying cause of death. *J Formos Med Assoc* 2001;100:365-9.
32. Su CH, Fang CY, Chen JS, et al. Prevalence of metabolic syndrome and its relationship with cardiovascular disease among hypertensive patients 55-80 years of age. *Acta Cardiol Sin* 2011; 27:229-37.