Uric Acid Is Not An Independent Predictor of Cardiovascular Death in Patients with Angiographically Proven Coronary Artery Disease

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Background: The aim of this study is to investigate the impact of uric acid on clinical outcomes in patients with angiographically proven coronary artery disease.

Method: Six hundred and forty seven consecutive patients with angiographically proven significant coronary artery disease were enrolled in this retrospective study. Patients were assigned to serum uric acid level ≥ 6.4 mg/dL and < 6.4 mg/dL groups based on baseline fasting uric acid levels and determined by a receiver operating characteristic curve. The mean follow-up duration was 4.6 ± 1.1 years after coronary angiography. The primary endpoints were all-cause mortality and death from cardiovascular disease.

Results: The five-year survival rates for patients free from all-cause mortality with levels of uric acid ≥ 6.4 mg/dL and < 6.4 mg/dL were 82% and 92% respectively ($p < 0.0001$). Five-year survival rates for patients free from cardiovascular mortality with levels of uric acid uric acid ≥ 6.4 mg/dL and < 6.4 mg/dL were 91% and 97% respectively ($p = 0.003$). Multivariate Cox regression analysis showed that serum uric acid was an independent predictor of all-cause death ($p = 0.01$) but was not an independent predictor of cardiovascular mortality ($p = 0.063$) after adjusting for multi-vessel coronary artery disease, chronic renal insufficiency and a left ventricular ejection fraction < 40%.

Conclusions: After multivariate adjustment, the fasting serum uric acid level was an independent predictor of all-cause mortality, but probably not an independent predictor of cardiovascular mortality in patients with angiographically proven coronary artery disease.

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Key words: coronary artery disease, mortality, uric acid

The relationship between serum uric acid and cardiovascular disease has been known for nearly half a century.[1] Retrospective observational studies and prospective studies have reported this relation-

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ship.[2-6] In some epidemiological studies, serum uric acid was an independent risk factor for coronary artery disease and all-cause mortality.[4,7] It has also been found to be an independent risk factor for impaired prognosis in patients with moderate and severe heart failure, stroke, and cardiovascular events in patients with hypertension.[8-12] Despite the strength of these associations, uric acid has not been confirmed as a causal risk factor for coronary artery disease. In addition, uric acid seems inextricably linked to hypertension, dyslipidemia, and disordered glucose metabolism, each of which may play a causal role in the pathogenesis of coronary artery disease. Therefore, there is a debate whether hyperuricemia has an independent role in the pathogenesis of coronary artery disease, especially after controlling for other conventional atherosclerotic risk factors.[13,14] Although an elevated uric acid level is associated with angiographic evidence of coronary artery disease,[15] the impact of uric acid on clinical outcomes in patients with angiographically proven coronary artery disease remains unclear. Accordingly, this study investigated the impact of fasting serum uric acid on cardiovascular mortality and all-cause mortality in patients with angiographically proven coronary artery disease.

METHODS

Patient population

Between May 2000 and August 2001, 647 consecutive patients who were referred for elective coronary angiography for unstable angina pectoris or an abnormal stress test were included in this retrospective study. All patients had coronary artery disease confirmed by quantitative coronary angiography (any coronary stenosis > 50% in a major epicardial coronary artery). Patients with procedural complications, such as perforation, non-ST elevation myocardial infarction, acute stroke, no reflow phenomenon, ventricular tachyarrhythmia or procedure-related mortality, were excluded from this study.

Data collection

The following detailed baseline and follow-up data were obtained: age, gender, body mass index, coronary risk factors, number of diseased vessels, left ventricular ejection fraction, drug history, history of myocardial infarction, history of coronary artery bypass graft surgery, and cardiac or non-cardiac death. All baseline laboratory data, such as white blood cell count, blood total cholesterol, triglycerides, glucose, creatinine and uric acid levels were collected prior to coronary angiography. The starting point of observation was the date of coronary angiography. Causes of death from cardiovascular disease or other causes were obtained from medical records. Causes of death for patients outside of the hospital were obtained by telephone.

The primary endpoints were all-cause mortality and death from cardiovascular disease. Deaths from cardiovascular disease included fatal myocardial infarction, death from serious ventricular arrhythmia or refractory heart failure and sudden cardiac death.

Statistical analysis

Unless otherwise specified, data are presented as means ± standard deviation (SD) or percentages. Continuous variables were compared using the unpaired t-test and categorical variables were compared using the chi-square test. To compare different predictive values of the fasting serum uric acid at particular time points, areas under the receiver operating characteristic (ROC) curve for the sensitivity and specificity for predicting mortality were constructed. The best prognostic cutoff value for predicting mortality at the respective time was defined as that which yielded the highest product of sensitivity and specificity. The ROC curve determined the best cut-off value.[15] Rates of event-free survival were calculated using the Kaplan-Meier method and compared using the log-rank test. Multivariable Cox regression analysis was utilized to determine correlations between independent parameters and clinical events, including all-cause mortality and cardiovascular mortality; only parameters with a value of $p < 0.1$ in univariate analysis were evaluated. Statistical analysis were performed using a statistical software program (SPSS for Windows, version 13; SPSS Inc., IL, U.S.A.). Two-sided values of $p < 0.05$ were considered statistically significant.

RESULTS

Baseline characteristics of study patients

Table 1 lists the baseline characteristics for patients in this study. In total, 647 patients were enrolled. There were 464 men and 183 women, with

Table 1. Baseline Clinical Characteristics of Patients Studied

Variables	
Age (years)	67 ± 11
Male	464 (72%)
Body mass index (kg/m^2)	25.7 ± 3.6
Diabetes mellitus	213 (33%)
Hypertension	391 (60%)
Current smoker	310 (47.9%)
Previous coronary artery bypass surgery	20 (3%)
Prior myocardial infarction	119 (18%)
Unstable angina	363 (56%)
Multi-vessel disease	365 (56%)
Left ventricular ejection fraction < 40%	55 (8%)
Renal insufficiency (creatinine ≥ 1.4 mg/dL)	123 (19%)
Serum creatinine level (mg/dL)	1.5 ± 1.6
Serum uric acid level (mg/dL)	6.6 ± 2.0
Total plasma cholesterol (mg/dL)	197 ± 41
Blood triglycerides (mg/dL)	173 ± 121
Fasting blood glucose (mg/dL)	141 ± 65
WBC count (x 10^3/μL)	7193 ± 2295
β-blockers	442 (68%)
Aspirin	623 (96.3%)
Diuretics	96 (15%)
Statins	181 (28%)
Allopurinol	26 (4%)
Angiotensin-converting enzyme inhibitors	203 (31%)
Losartan	76 (12%)
Follow-up period (years)	4.6 ± 1.1

Data are expressed as mean ± SD or number (%) of patients.

a mean ± SD age of 67 ± 11 years (range 31 to 90). At a mean follow-up of 4.6 ± 1.1 years (range, 0.5–5.0 years) after coronary angiography, 81 (13%) patients had died from all causes and 37 (5.7%) patients had died from cardiovascular disease. The 37 cardiac disease-related deaths were due to fatal myocardial infarction (n = 8), death from serious ventricular arrhythmia (n = 5), refractory heart failure (n = 11), and sudden collapse (n = 13). The 44 non-cardiac disease-related deaths were due to cancer (n = 11), renal failure (n = 2), pneumonia (n = 9), sepsis with multiple organ failure (n = 8), cerebrovascular insult or bleeding (n = 10), accidents (n = 2), acute pancreatitis (n = 1) and gastrointestinal bleeding (n = 1). The sensitivity and specificity for predicting mortality using the best cut-off value for serum uric acid levels at 5 years (i.e. 6.4 mg/dL) were 57.9% and 58.4%, respectively. The area under the ROC curve (mean ± SEM) at 5 years was 0.659 ± 0.470 (95% confidence interval, 0.567–0.752). Therefore, patients were divided into two groups, according to baseline serum uric acid levels of ≥ 6.4 mg/dL and < 6.4 mg/dL (Table 2). There were more males, higher prevalences of hypertension, unstable angina, multi-vessel coronary artery disease and chronic renal insufficiency, and a higher body mass index in patients with serum uric levels ≥ 6.4 mg/dl than in patients with lower values. The plasma level of triglycerides and percentages of patients taking β-blockers, statins, diuretics, allopurinol and angiotensin-converting enzyme inhibitors were significantly higher in patients with serum uric levels ≥ 6.4 mg/dL than in the patients with lower serum uric levels. Furthermore, the prevalence of low left ventricular ejection fraction (< 40%) was also significantly higher in the patients with higher uric acid levels.

Predictors of all-cause mortality

Survival rates for patients free from all-cause mortality with uric acid levels ≥ 6.4 mg/dL and < 6.4 mg/dL were 82% and 92% at 5 years, respectively ($p < 0.0001$) (Fig. 1). Univariate analysis determined that the prevalence of hypertension, diabetes mellitus, poor left ventricular function and chronic renal insufficiency were significantly higher in patients with than those without all-cause mortality events (Table 3). Patients with all-cause mortality events were significantly older than the other patients. Multivariate Cox regression analysis demonstrated that serum uric acid was an independent predictor of all-cause mortality (Table 4). Three other variables, age, chronic renal insufficiency, and a left ventricular ejection fraction less than 40% were independently correlated with all-cause mortality (Table 4).

Predictors of cardiovascular mortality

Survival rates for patients free from death from cardiovascular disease with uric acid levels ≥ 6.4 mg/dL and < 6.4 mg/dL were 91% and 97% at 5 years, respectively ($p = 0.003$). Univariate analysis determined that the prevalence of multi-vessel coronary artery disease, poor left ventricular function and

Table 2. Univariate Analysis of Baseline Clinical Characteristics and Clinical Outcomes according to Uric Acid Level

	Serum uric acid level ≥ 6.4 mg/dL (N = 325)	Serum uric acid level < 6.4 mg/dL (N = 322)	*p* value
Age (years)	63 ± 11	63 ± 10	0.332
Male gender	261 (80%)	203 (63%)	< 0.0001
Body mass index (kg/m^2)	26.0 ± 3.6	25.4 ± 3.5	0.028
Hypertension	210 (64%)	181 (56%)	0.035
Diabetes mellitus	109 (33%)	104 (32%)	0.74
Current smoker	165 (50.8%)	145 (45.0%)	0.144
Previous coronar artery bypass surgery	9 (2.8%)	11 (3.4%)	0.64
Prior myocardial infarction	58 (18%)	61 (19%)	0.719
Unstable angina	195 (60%)	168 (52%)	0.045
Multi-vessel disease	208 (64%)	157 (48.8%)	0.001
Left ventricular ejection fraction < 40%	37 (11%)	18 (5%)	0.009
Total cholesterol (mg/dL)	199 ± 43	195 ± 39	0.257
Triglycerides (mg/dL)	187.9 ± 128.7	158.4 ± 129.2	0.004
Chronic renal insufficiency (creatinine ≧ 1.4 mg/dL)	80 (25%)	43 (13.4%)	< 0.0001
Serum creatinine level (mg/dL)	1.6 ± 1.7	1.3 ± 1.4	0.034
Fasting blood glucose (mg/dL)	139.5 ± 65.7	142.5 ± 64.2	0.562
Statins	105 (32.3%)	76 (23.6%)	0.014
Aspirin	319 (98%)	314 (97.5%)	0.577
Diuretics	68 (21%)	28 (8.7%)	< 0.0001
Allopurinol	23 (7%)	3 (0.9%)	0.001
Losartan	34 (10%)	42 (13%)	0.31
Angiotensin-converting enzyme inhibitors	117 (36%)	86 (26%)	0.01
β-blockers	238 (73%)	204 (63%)	0.007
Cardiovascular mortality	27 (8%)	10 (3%)	0.004
All-cause mortality	56 (17%)	25 (8%)	< 0.0001

Data are expressed as mean ± SD or number (%) of patients; Multi-vessel disease defined as ≧ 2-vessel disease.

chronic renal insufficiency was significantly higher in patients with than those without cardiovascular mortality events (Table 5). Multivariate Cox regression analysis demonstrated that serum uric acid was not an independent predictor of cardiovascular mortality (Table 6). However, multi-vessel coronary disease, chronic renal insufficiency and a left ventricular ejection fraction less than 40% were independent predictors of cardiovascular mortality (Table 6).

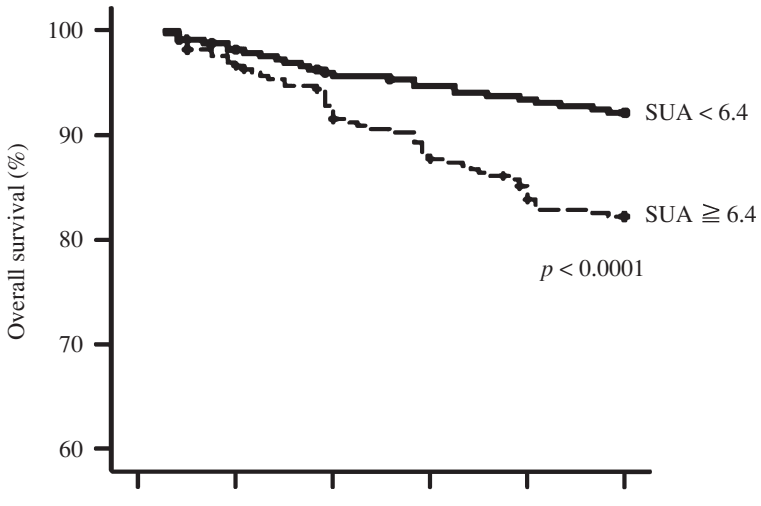
DISCUSSION

Potential mechanisms of association of uric acid with coronary artery disease

Several possible pathological mechanisms link serum uric acid to cardiovascular disease *in vitro*. The serum uric acid level may be an indicator of increased oxidative stress. Xanthine oxidase, a enzyme critical in purine degradation to uric acid, has been shown to be an important source of superoxide free radicals.[16] Uric acid also plays a role in formation of free radicals and oxidative stress, and has deleterious effects on endothelial function.[16,17] Uric acid has also been proven to stimulate smooth muscle proliferation and inflammation *in vitro*.[18] Urate crystals may promote platelet adhesiveness and aggregation.[19] These pro-atherosclerotic mechanisms of hyperuricemia may result in atherosclerosis and plaque progression, resulting in mortality and morbidity in patients with coronary artery disease. In addition, serum uric acid levels are frequently elevated in subjects with metabolic syndrome.[20] The World Health Organization recently deemed the serum uric acid level a significant component of metabolic syndrome and also speculated that an elevated serum uric acid may increase the risk of developing cardiovascular disease through its association with metabolic syndrome.[21] Evidence exists that serum uric acid may not only be a consequence of insulin resistance, but may also promote or worsen insulin resistance and, thus play an important role in the pathogenesis of metabolic syndrome, possibly through its ability to disturb endothelial function and thereby elucidate nitric oxide bioavailability.[22]

Hyperuricemia was an independent predictor of all-cause mortality but not cardiovascular mortality

Uric acid level, age, chronic renal failure and a



	0	12	24	36	48	60 Months
Uric acid < 6.4						
Patients at risk	322	313	303	299	295	291
Events free survival	100%	98.1%	95.6%	94.7%	93.4%	92.1%
Cumulated events	0	6	14	17	21	25
Uric acid ≥ 6.4						
Patients at risk	325	315	308	291	275	254
Events free survival	100%	98.5%	96.6%	91.9%	87.7%	82.2%
Cumulated events	0	5	11	26	39	56

Fig. 1 Kaplan-Meier estimates show that the overall survival rate at 5 years was significantly lower in patients with baseline serum uric acid levels ≧ 6.4 mg/dL than those with levels < 6.4 mg/dL (82% versus 92%, $p < 0.0001$). Abbreviation used: SUA: serum uric acid.

left ventricular ejection fraction less than 40% were all independent predictors of all-cause mortality in patients with angiographically proven coronary artery disease in this study. A recent study also showed that serum uric acid can predict long-term all-cause mortality in these patients.[23]

Bickel *et al*. found that serum uric acid is also an independent predictor of cardiac disease-related mortality.[23] However, we found that three parameters, multi-vessel coronary disease, chronic renal insufficiency, and a left ventricular ejection fraction less than 40%, but not the serum uric acid level, were independent predictors of cardiovascular mortality, after adjusting for those three parameters and other potential confounders in this study. The discrepancy could have occurred because several important parameters, including the three above, were not entered into multivariate Cox regression analysis in Bickel's study. In our study, the percentages of patients with these three parameters were significantly higher in patients with serum uric acid levels ≥ 6.4 mg/dL than in patients with lower levels. Previous studies have shown that left ventricular systolic function and impaired renal function are among the most important determinants of long-term outcome in patients with coronary artery disease.[24-26] Several studies have demonstrated that patients with systolic heart failure have high serum uric acid levels,[27,28] and the mechanisms may be overproduction of uric acid, impaired vascular function,[29] maximal oxygen uptake,[30] or impairment in urinary excretion of uric acid in patients with low cardiac output.[31] Persistent hyperuricemia is also found in patients with chronic renal insufficiency due to impairment of renal tubule secretion and glomerular filtration.[32] Thus, both renal failure and impaired left ventricular systolic function may be associated with higher serum uric acid levels. Accordingly, hyperuricemia may only be an indirect marker of adverse outcome by reflecting the association between uric acid and congestive heart failure and chronic renal insufficiency.

Table 3. Univariate Analysis of Baseline Clinical Characteristics between Patients with and without All-cause Mortality Events

	Patients with events all-cause mortality (N = 81)	Patients without events all-cause mortality (N = 566)	*p* value
Age (years)	68 ± 10	63 ± 10	0.001
Male gender	55 (68%)	409 (72%)	0.415
Body mass index (kg/m^2)	24.9 ± 4.0	26.2 ± 13	0.326
Hypertension	58 (72%)	333 (59%)	0.028
Diabetes mellitus	35 (43%)	178 (31%)	0.035
Current smoker	36 (44%)	274 (48%)	0.504
Previous coronary artery bypass surgery	2 (3%)	18 (3%)	0.729
Prior myocardial infarction	16 (20%)	103 (18%)	0.735
Unstable angina	49 (61%)	314 (56%)	0.395
Multi-vessel disease	49 (61%)	342 (60.4%)	0.58
Left ventricular ejection fraction < 40%	13 (16%)	42 (8%)	0.009
Total cholesterol (mg/dL)	201.6 ± 49.1	196.6 ± 40.3	0.351
Triglycerides (mg/dL)	179.0 ± 136.0	172.3 ± 128.7	0.668
Chronic renal insufficiency (creatinine ≧ 1.4 mg/dL)	29 (36%)	94 (17%)	< 0.0001
Serum creatinine level (mg/dL)	2.4 ± 3.1	1.3 ± 1.1	0.00001
Serum uric acid level (mg/dL)	7.4 ± 2.2	6.5 ± 1.9	0.0001
Fasting blood glucose (mg/dL)	154.2 ± 87.4	139.1 ± 61.0	0.051
Statins	19 (24%)	162 (29%)	0.333
Asprin	79 (97.5%)	554 (97.9%)	0.84
Diuretics	15 (19%)	81 (14%)	0.319
Allopurinol	6 (7%)	20 (4%)	0.097
Losartan	10 (12%)	66 (12%)	0.858
Angiotensin-converting enzyme inhibitors	28 (35%)	175 (31%)	0.508
β-blockers	48 (59%)	394 (69%)	0.061

Data are expressed as mean ± SD or number (%) of patients.

Table 4. Multivariate Cox Regression Analysis of Baseline Clinical Characteristics in Predicting All-cause Mortality (N = 647)

Variables	Hazard ratio	95% CI	*p* value
Age	1.047	1.021-1.073	< 0.0001
Serum uric acid level ≥ 6.4 mg/dL	1.90	1.166-3.109	0.010
Chronic renal insufficiency (creatinine ≧ 1.4 mg/dLl)	1.84	1.141-2.960	0.0012
Left ventricular ejection fraction < 40%	2.054	1.177-3.584	0.011

Abbreviation: CI: confidence interval.

Table 5. Univariate Analysis of Baseline Clinical Characteristics between Patients with and without Cardiovascular Mortality

	Patients with cardiovascular mortality (N = 37)	Patients without cardiovascular mortality (N = 610)	*p* value
Age (years)	67 ± 12	54 ± 37	0.06
Male gender	30 (81%)	434 (71%)	0.193
Body mass index (kg/m^2)	25.4 ± 4.1	25.7 ± 3.5	0.58
Hypertension	26 (70%)	365 (60%)	0.208
Diabetes mellitus	17 (46%)	192 (32%)	0.083
Current smoker	21 (57%)	289 (47%)	0.267
Previous coronary artery bypass surgery	2 (5%)	18 (3%)	0.402
Prior myocardial infarction	11 (30%)	111 (18%)	0.602
Unstable angina	25 (68%)	338 (55%)	0.148
Multi-vessel disease	30 (81%)	343 (56%)	0.003
Left ventricular ejection fraction < 40%	8 (22%)	47 (8%)	< 0.001
Total cholesterol (mg/dL)	206.0 ± 49.9	196.7 ± 40.8	0.16
Triglycerides (mg/dL)	174.2 ± 91.5	173.1 ± 131.76	0.96
Chronic renal insufficiency (creatinine ≧ 1.4 mg/dL)	16 (43%)	107 (18%)	< 0.0001
Serum creatinine level (mg/dL)	3.1 ± 4.1	1.4 ± 1.2	0.00001
Serum uric acid level (mg/dL)	7.7 ± 2.3	6.6 ± 1.9	0.0007
Fasting blood glucose (mg/dL)	151.8 ± 72.7	140.4 ± 6.4	0.3
Statins	11 (30%)	170 (28%)	0.807
Aspirin	36 (97.3%)	597 (97.9%)	0.817
Diuretics	9 (24%)	87 (14%)	0.095
Allopurinol	3 (8.1%)	23 (3.8%)	0.192
Losartan	5 (14%)	71 (12%)	0.731
Angiotensin-converting enzyme inhibitors	14 (38%)	189 (31%)	0.383
β-blockers	26 (70%)	416 (68%)	0.792

Data are expressed as mean ± SD or number (%) of patients.

Table 6. Multivariate Cox Regression Analysis of Baseline Clinical Characteristics in Predicting Cardiovascular Mortality (N = 647)

Variables	Hazard ratio	95% CI	*p* value
Chronic renal insufficiency (creatinine ≧ 1.4 mg/dL)	2.906	1.484-5.692	0.002
Left ventricular ejection fraction < 40%	3.236	1.511-6.932	0.004
Multi-vessel disease	2.431	1.06-5.575	0.036
Serum uric acid level ≥ 6.4 mg/dL	2.026	0.962-4.268	0.063

Abbreviation: CI: confidence interval.

Study limitations

First, this is a retrospective, cross-sectional study. The observational nature of this study does not allow for a conclusion regarding a causal relationship between serum uric acid levels and long-term all-cause mortality in patients with angiographically proven coronary artery disease. Thus, this causal relationship in patients with angiographically proven coronary artery disease warrants further validation with longitudinal, cohort, large-scale studies. Second, patients in the uric acid quartiles in this study were not normally distributed. Therefore, we dichotomized our patients and analyzed clinical outcomes according to baseline serum uric acid levels of ≥ 6.4 mg/dL and < 6.4 mg/dL, based on an ROC curve and this might have produced different analytic results.

Conclusions

In patients with angiographically proven coronary artery disease, the baseline fasting serum uric acid level is an independent predictor of all-cause mortality, but probably not an independent predictor of death from cardiovascular disease after multivariate adjustment.

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血清尿酸值對於血管攝影證明有冠狀動脈疾病的病人並不是一個預測因心血管疾病死亡的獨立因子

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背 景： 這個研究主要在探討血清尿酸對於血管攝影證明有冠狀動脈疾病病人的臨床預後影響。

方 法： 647 個血管攝影證明有冠狀動脈疾病的病人參與這個回顧性研究。藉由接收器運作指標曲線 (Receiver Operator Characteristic curve) 的測定，病人可以根據空腹後血清尿酸值 ≥ 6.4 mg/dL 及 < 6.4 mg/dL 分成兩組。在做完血管攝影後，病人平均追蹤的時間是 4.6 ± 1.1 年。主要試驗指標是探討總死亡率和因心血管疾病而造成死亡的死亡率。

結 果： 尿酸值 ≥ 6.4 mg/dL 和 < 6.4 mg/dL 的病人，其五年的存活率分別爲 82% 和 92% ($p < 0.0001$)。尿酸值 ≥ 6.4 mg/dL 和 < 6.4 mg/dL 的病人，其五年的非因心血管疾病而死亡的存活率分別爲 91% 和 97% ($p = 0.003$)。經由 Cox 多變項回歸分析再經調整多條冠狀動脈疾病、慢性腎衰竭及左心室衰竭 (心收縮率 < 40%) 後，發現尿酸是一個對總死亡是一個獨立預測因子，但對於因心血管疾病死亡卻不是一個獨立預測因子。

結 論： 空腹後血清尿酸值對於血管攝影證明有冠狀動脈疾病的病人是對總死亡的一個獨立預測因子，但對於因心血管疾病死亡卻不是一個獨立預測因子。

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關鍵詞： 冠狀動脈疾病，死亡率，尿酸

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