Potentials of Cystatin C and Uric Acid for Predicting Prognosis of Heart Failure

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Few studies have explored the clinical potentials of combined Cystatin C (Cys) and uric acid (UA) in heart failure (HF). The authors evaluated Cys and UA as predictors of clinical outcomes compared with conventional renal biomarkers. This prospective cohort study included 587 HF patients presenting with dyspnea. At admission, Cys, UA, and other renal measures including serum urea nitrogen (BUN), creatinine (Cr), and glomerular filtration rate (GFR) were obtained. The primary endpoint was the composite of cardiac death and rehospitalization for worsening HF. During a 25-month median follow-up period, 68 patients experienced clinical outcomes: 9 cardiac deaths and 59 HFs. They showed higher BUN and Cr values and lower GFR. Within these parameters, Cys and UA had the most favorable area under the curves, and patients with Cys $\geq$0.8 mg/L and UA $\geq$6.6 mg/dL showed more frequent events. The net reclassification improvement analysis showed the combination of Cys and UA had a greater incremental effect for cardiac prognosis. On multivariate Cox hazard analysis, Cys and UA were independent predictive markers for clinical outcomes. In HF patients presenting with dyspnea, Cys and UA appear to be more useful predictors of clinical events than other renal measures. ©2012 Wiley Periodicals, Inc.

Patients with acute heart failure (HF) usually have concomitant diseases, such as hypertension, diabetes, or peripheral vascular disorders. Among these diseases, renal dysfunction has played an important role in predicting future adverse cardiac events. Importantly, ''cardiorenal syndrome,'' which is the interaction between the heart and renal function, has clarified the risk-stratification and prognosis of cardiac patients.[1,2] Indeed, the presence of even subtle or mild renal dysfunction is usually associated with a higher risk for adverse cardiac outcomes.[3,4]

Serum urea nitrogen (BUN), creatinine (Cr), and glomerular filtration rate (GFR) are classic biomarkers that have been widely used to evaluate renal function. Similarly, uric acid (UA) and cystatin C (Cys) have been studied for use in evaluating renal dysfunction. UA has been considered a metabolic marker, while Cys has been considered an early marker for acute kidney injury.[5–8] Based on these characteristics, UA and Cys may be used for the prognosis of HF or ischemic heart disease (IHD).[9–12]

The potential value that Cys and UA may offer for prognosis has been unclear; however, it is unknown how they could improve the evaluation of cardiac events in acute HF patients with mild to moderate renal dysfunction. With regard to the interaction between the heart and renal function, we hypothesized that admission Cys and UA would be related to long-term prognosis. Therefore, the aim of this study was to assess the clinical impact of using UA and Cys to predict adverse clinical outcomes and compare their performance to conventional renal biomarkers.

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METHODS

Study Population

From June 2008 to May 2010, patients in this prospective cohort study were recruited at a single university hospital center after they had been admitted for the treatment or evaluation of HF. The diagnosis of HF was defined according to the criteria of the European Society of Cardiology[13] and made by a physician based on a review of patient history, symptoms, physical examination, and a chest radiography performed on admission. The patients' inclusion criteria were: (1) age older than 18 years, (2) an HF diagnosis, and (3) Cys, UA, BUN, and Cr measured at baseline.

The exclusion criteria were: (1) severe renal dysfunction (GFR of $<$30 mL/min/1.73 m^2) or renal replacement therapy, (2) moderate or severe valvular heart diseases, (3) chronic obstructive pulmonary diseases, or (4) an acute coronary syndrome requiring revascularization or myocardial infarction within the previous 6 weeks. Finally, after the initial inclusion screening and exclusion criteria were applied, 587 patients were analyzed in this study. Our institutional review board approved this study. The study complies with the Declaration of Helsinki and written informed consent was obtained from all patients.

Laboratory Studies

BUN, Cr, UA, and Cys were measured at admission. UA was measured using uroxidase/peroxidase method (Siemens Healthcare Diagnostics, Marburg, Germany). The lower detection limit was 0.2 mg/dL (range 0.2 to 25.0 mg/dL). Cys was measured with the use of nephelometry method (Siemens Healthcare Diagnostics). GFR was estimated using the simplified Modification of Diet in Renal Disease equation as follows: $186.3 \times (\text{serum creatinine})^{-1.154} \times \text{age}^{-0.203} \times (0.742$ for women), which has been developed and validated as an accurate estimate of GFR. We measured the level of N-terminal Pro–B-type natriuretic peptide (NT-ProBNP) to evaluate the severity of HF.

Follow-Up

Patients were followed up for a median of 25 months after being discharged from the hospital. The clinical outcomes of this study were cardiac death and worsening HF requiring hospitalization.

Statistical Analyses

Data were analyzed using the Statistical Package for Social Science Software for Windows version 12.0 (SPSS Inc, Chicago, IL). Results are presented as mean±standard deviation for continuous variables and as percentage for categorical variables. Differences between the two groups were determined using chi-square test or unpaired *t* test. Receiver-operating characteristic (ROC) curves and area under the curves (AUC) were used to evaluate the ability of renal parameters to predict the primary endpoint. Furthermore, to improve risk prediction and to investigate whether Cys and UA add incremental values for prediction of clinical events beyond the established risk factors and conventional renal measures, we performed the net reclassification improvement (NRI) and integrated discrimination improvement (IDI) compared with AUC or C statistic (Harrell's C index). Kaplan-Meier curves were constructed using the overall Mantel-Cox log-rank statistic and Cox proportional hazards regression analysis was performed. All tests were two-sided, and a P value $<.05$ was considered statistically significant.

TABLE I. Baseline Characteristics of Study Population According to Clinical Outcomes

Variables	Events (–) (n=519)	Events (+) (n=68)	*P* Value
Age, y	65.4±11.8	68.8±12.1	.026
Women, %	41.0	42.6	NS
Systolic BP, mm Hg	125±18	120±20	.046
Diastolic BP, mm Hg	75±11	73±15	NS
Heart rate, beats per min	74±12	78±16	.022
Ejection fraction, %	58.6±12.3	48.5±16.4	<.001
NYHA class III/IV, %	48.7	83.8	<.001
Medical history			
Admission for HF, %	15.7	46.7	<.001
IHD, %	40.5	56.0	.014
Diabetes, %	29.6	33.2	NS
Hypertension, %	42.4	39.1	NS
Atrial fibrillation, %	28.9	32.1	NS
Laboratory values			
BUN, mg/dL	17.4±6.2	20.4±8.2	.005
Creatinine, mg/dL	1.1±0.3	1.2±0.4	.001
GFR, mL/min/1.73 m^2	71.5±22.9	63.4±28.0	.008
Cystatin C, mg/L	0.78±0.25	1.12±0.56	<.001
Uric acid, mg/dL	5.6±1.8	7.0±2.3	<.001
NT-ProBNP, pg/mL	1.029±3.739	4.998±8.101	<.001
Medications			
ACE inhibitor or ARB, %	58.0	47.1	NS
BB, %	59.9	55.9	NS
CCB, %	23.3	25.0	NS
Diuretics, %	30.2	35.3	NS
Aldosterone antagonist, %	5.2	2.9	NS
Amiodarone, %	3.7	5.9	NS
Aspirin, %	73.6	76.5	NS
Coumadin, %	28.9	25.0	NS

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BB, β-blocker; BP, blood pressure; BUN, serum urea nitrogen; CCB, calcium channel blocker; GFR, glomerular filtration rate; HF, heart failure; IHD, ischemic heart disease; NT-ProBNP, N-terminal Pro–B-type natriuretic peptide; NS, not significant; NYHA, New York Heart Association.

RESULTS

A total of 587 patients were enrolled in this study, and during a median follow-up period of 25 months, 68 patients (11.5%) experienced the clinical outcomes of 9 cardiac deaths and 59 HFs. The baseline clinical and laboratory characteristics of the study population are presented in Table I. Patients with cardiac events were older and more often had experienced prior HF and IHD compared with patients without events. They had lower systolic blood pressure, lower EF, and worse New York Heart Association (NYHA) functional class. The prevalence of diabetes, hypertension, atrial fibrillation, and types of prescribed medication taken were similar between the two groups. Based on conventional renal measures, including BUN, Cr, and GFR, renal function was more deteriorated in the cardiac events group. In addition, that group showed higher levels of Cys, UA, and NT-ProBNP.

By ROC curve analyses, BUN ≥18 mg/dL, Cr ≥1.1 mg/dL, GFR ≤57.8 mL/min/1.73 m^2, UA ≥6.6 mg/dL, and Cys ≥0.8 mg/L were the best cut-off values for predicting clinical outcomes (Figure 1, left). Although the differences of areas under the ROC of each UA and Cys were not significant, both AUCs were significantly greater than that of BUN, Cr, and GFR. With regard to the validity of model-

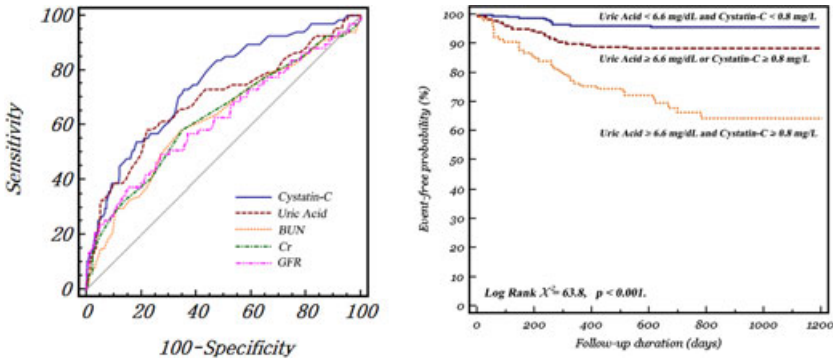

FIGURE 1. Receiver-operating characteristic curve analysis of renal measures to identify clinical adverse outcomes (left). Kaplan-Meier survival curves presenting both uric acid and cystatin C level (right).

ing, C indices between each model were not significantly different, but the Cys- or UA-based modeling in both NRI and IDI could provide the addictive prediction probability more over 10% than those of conventional renal measures (Table II, Figure 2). Clinical outcomes were compared by Kaplan-Meier analysis according to the cutoff values of UA and Cys: UA <6.6 mg/dL and Cys <0.8 mg/L, UA ≥6.6 mg/dL or Cys ≥0.8 mg/L, and UA ≥6.6 mg/dL and Cys ≥0.8 mg/L (Figure 1, right). Serum UA and Cys levels independently and significantly predicted unfavorable prognosis; thus, combining the best UA and Cys cutoff values could improve the prediction of adverse clinical outcomes.

Univariate and multivariate analyses were performed to identify independent predictors of each measure (Table III). All 5 measures for renal function were significantly associated with increased clinical outcomes in the univariate analysis (data not shown). In the multivariate analysis, however, UA and Cys remained the significant prognostic factors, after adjusting for NYHA class and previous history of HF and IHD. Furthermore, we used UA and Cys to evaluate the impact that both parameters had on clinical events. Pooled estimates of adjusted hazard ratios for clinical outcomes (using categories for both UA and Cys) are shown in Figure 3. Throughout the full range of hazard ratios, UA and Cys were associated strongly and positively with clinical events and appeared to follow a log-linear model. The risk of clinical events was substantially higher for patients with a UA level of ≥7.0 mg/dL than for patients with UA concentrations of 3.0 to 6.5 mg/dL. We noted similar findings for Cys. Events were strongly clustered in Cys levels >0.8 mg/L, increasing more than 3-fold over the full range.

DISCUSSION

The important finding of the current study is that in acute HF, Cys and UA could provide the incremental prognostic benefits over the conventional classic renal measures: BUN, Cr, and GFR. Despite the small but significantly different impacts of BUN and Cr, the renal dysfunction could signal worsening HF. Together with direct hemodynamic impact, the decreased renal function might accelerate the progression of atherosclerosis or IHD. Cys has been regarded as a useful marker for renal dysfuction and could also be a

TABLE II. Comparison of Cox Regression Models in Prediction of the Occurrence of Cardiovascular Adverse Events

Prognostic Model[a] With Risk Factors at Presentation	Harrell's C Index	Net Reclassification Improvement	*P* Value	Integrated Discrimination Improvement	*P* Value
Prognostic model	0.79	Reference	–	Reference	–
Prognostic model+BUN	0.79	0.000	1.000	0.000	.511
Prognostic model+Cr	0.78	0.082	.035	0.017	.020
Prognostic model+GFR	0.78	0.060	.028	0.006	.062
Prognostic model+UA	0.79	0.124	.016	0.023	.004
Prognostic model+Cys	0.79	0.120	.001	0.018	.101
Prognostic model+UA+Cys	0.79	0.113	.036	0.030	.003

Abbreviations: BUN, serum urea nitrogen; Cr, creatinine; Cys, Cystatin C; GFR, glomerular filtration rate; UA, uric acid. [a]Prognostic modeling includes a previous history of heart failure and ischemic heart disease, New York Heart Association functional class III or IV, and N-terminal Pro–B-type natriuretic peptide level.

Established Prognostic Model		Prognostic Model plus Cystatin C and Uric Acid			
		< 8% Risk	8 - 16 % Risk	> 16 % Risk	Total No.
Patients with Events	< 8% Risk	11	7	1	19
	8 - 16 % Risk	1	9	0	10
	> 16 % Risk	0	3	36	39
	Total No.	12	19	37	68
Patients without Events	< 8% Risk	323	23	0	346
	8 - 16 % Risk	9	47	2	58
	> 16 % Risk	0	44	71	115
	Total No.	332	114	73	519

FIGURE 2. Net reclassification improvement of patients with or without events. In the event group, 8 (21%) patients were correctly reclassified as at lower risk for events (green) and 4 (10%) patients incorrectly moved downward (pink). In the event-free group, 53 (10%) patients were reclassified in a desirable direction (green) and 25 (5%) patients incorrectly moved upward with a higher risk (pink). The Established Prognostic Model includes a previous history of heart failure and ischemic heart disease, New York Heart Association functional class III or IV, and N-terminal Pro–B-type natriuretic peptide level.

TABLE III. Cox's Proportional Hazards Analysis for Prediction of the Occurrence of Cardiovascular Adverse Events

	Univariate			Multivariate		
Variables	HR	95% CI	*P* Value	HR	95% CI	*P* Value
HF	7.09	3.866–12.99	<.001	2.97	1.523–5.789	.001
IHD	2.38	1.370–4.093	.001	1.18	0.683–2.034	.555
NYHA III/IV	5.01	2.627–9.554	<.001	3.11	1.501–6.433	.002
EF ≥50%	0.96	0.943–0.971	<.001	1.09	0.626–1.905	.757
UA	1.31	1.204–1.427	<.001	1.10	1.000–1.206	.049
Cystatin C	3.10	2.350–4.080	<.001	1.69	1.067–2.664	.025
NT-ProBNP	2.61	1.356–1.696	<.001	1.18	1.026–1.359	.021

Abbreviations: CI, confidence interval; EF, ejection fraction; HF, heart failure; HR, hazard ratio; IHD, ischemic heart disease; NYHA, New York Heart Association; NT-ProBNP, N-terminal Pro–B-type natriuretic peptide; UA, uric acid.

valuable tool for predicting cariovascular clinical outcomes.[7,12–15] Apart from renal dysfunction, high Cys level may increase the risk for cardiac events in patients with peripheral arterial disesase or IHD.[16,17] On the contrary, Cys levels may be increased by arterisoclerosis lesion or aging, although these factors have not been conclusively proven.[18] In addition, Cys seems to reflect hemodynamic changes or myocardial damage.[11,19] In the present study, we found a clear correlation between Cys level and cardiac events in patients with a history of HF admission.

The mechanism that allows UA and Cys to predict future cardiovascular events has been recently evaluated. Although the exact mechanism that causes Cys to be linked with the cardiovascular system was not suggested, cardiorenal hemodynamic interaction is primarily responsible for the relationship between Cys and the adverse outcomes.[1,2,8,20] The level of Cys is elevated in proportion to the level of renal dysfunction. Cys levels also increase during cardiac injury, such as ischemic conditioning.[11,21] Like Cys, UA is also associated with cardiovascular risk factors.[5,9] This is because the xanthine oxidase system is stimulated by cardiac disorders. It remains unknown, however, whether UA and Cys at admission might be the active markers reflecting acute HF or only the result of the renal dysfunction. UA has been associated with inflammatory marker or oxidative products. Similarly, Cys level could show a significant correlation of the inflammatory markers suggesting that Cys generation might be accelerated by inflammatory cytokines.[22,23] Indeed, from these findings, UA and Cys may provide the comprehensive information across a broad spectrum that could be observed with conventional renal measures.

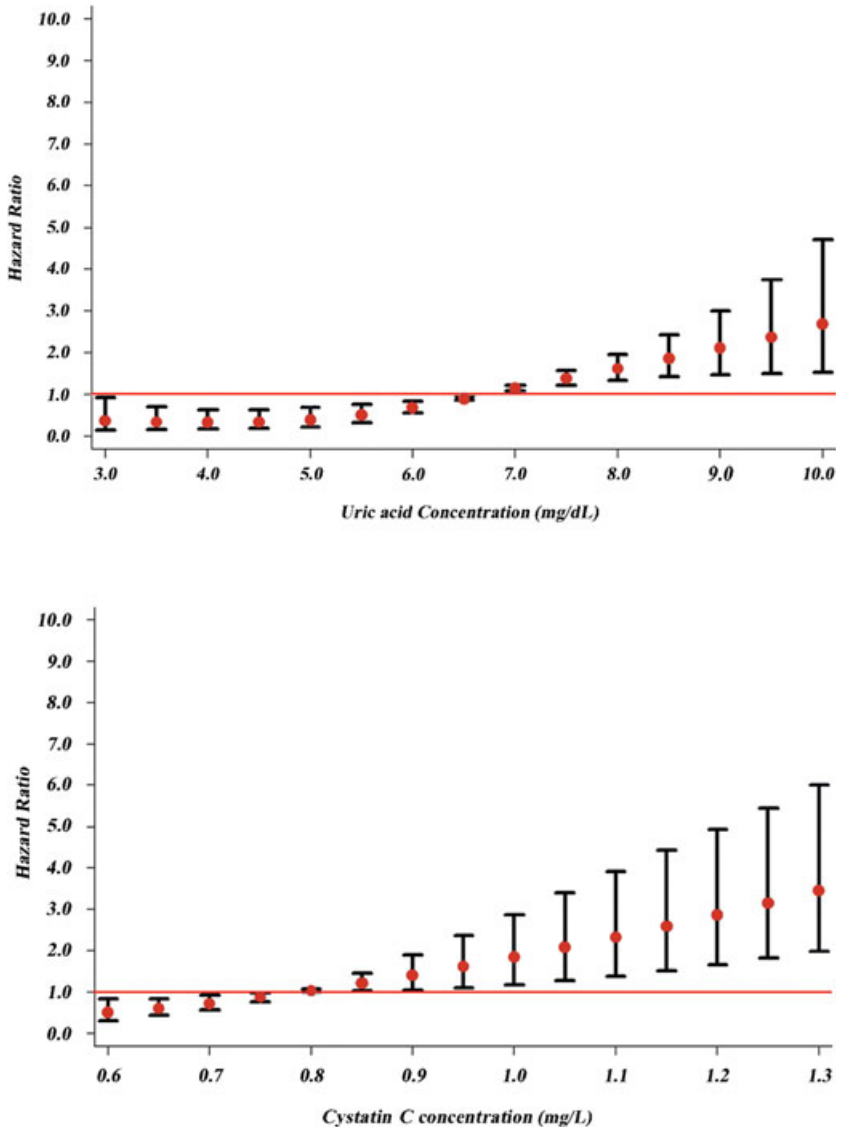

FIGURE 3. Hazard ratio of clinical outcomes by category of uric acid (upper) and cystatin C (lower) level. Data are adjusted for New York Heart Association (NYHA) class and previous history of heart failure and ischemic heart disease. Error bars represent 95% confidence intervals.

With regard to renal measures, we demonstrated that only UA and Cys showed a strong prediction for outcomes. In fact, renal estimation by BUN, Cr, or GFR is usually reliable on stable conditions, but it is less useful when sudden renal function changes develop. However, UA and Cys could provide a more stable evaluation of renal function in patients with acute HF.[10,24–26] Cys is a marker of renal function evaluation, but it has been a more sensitive tool for reflecting renal dysfunction, particularly even at the atmosphere of normal or mild elevation of Cr.[27] Likewise, the role of UA as a predictior of outcome has been examined in previous many studies.[5,9,28] In the current study, we included UA and Cys and compared them with conventional renal measures; their ability to determine adverse outcomes may vary slightly. Therefore, for a full comparision of their usefulness, further studies are needed.

While past studies have shown that the highest quartile of Cys was associated with clinical outcome more than the lowest quartile, the best cutoff point is still under debate.[12,14,29] The current study showed the cutoff level of 0.8 mg/L of Cys, which is lower compared with levels determined by previous studies.[12,25,30] One possible explanation is that the baseline characteristics of our study population showed the relatively normal or mildly decreased mean Cr and GFR levels, respectively. However, these findings may imply that cardiac events could increase steadily from low Cys and UA levels. Despite the cutoff value of

6.7 mg/dL of UA, the hazard ratio increased in proportion to the UA level. When it comes to exploration of the individual potential effect, we could not find individual exact values indicating the steep increasing hazard ratio, possibly due to the fact that clinical outcomes seem to occur even within normal ranges or at the low levels of UA and Cys. Thus, it may be desirable that we should consider both parameters for early identification of a subgroup of patients at risk for outcomes.

Regarding predicting prognosis, we found that combining UA and Cys would provide more useful information than each one alone. This is partially explained by the good correlation between two parameters. Cys showed the favorable correlation with UA (r=0.457, P<.001), which is as significant as those of GFR or Cr. Thus, the role of Cys could be comparable to those of UA. Particularly, when we graphically explored the impact of Cys and UA for the whole patients on Kaplan-Meier analysis, the clinical outcomes occurred more significantly than when using each parameter, even after more than 1.5 years of follow-up. Therefore, we found that the combination of both UA and Cys may allow long-term prognostic information, while each parameter could provide relatively short-term prognosis <1 year.

STUDY LIMITATIONS

Our study had some limitations. We could not follow the course of renal dysfunction in the hospital because we did not obtain follow-up data for each parameter. Another limitation was that the patients in this study showed relatively low incidence of clinical outcomes. These findings could be explained by the fact that this study was performed with consecutive patients presenting with dyspnea who were admitted to the hospital and they had some preserved ejection fraction. Therefore, there might be a substantial number of patients with a varying degree of HF. Accordingly, the level of NT-ProBNP in our study may be relatively low for acute HF, although the expert physicians including cardiologists finally evaluated and confirmed the HF patients in this study. Furthermore, we could not assess nonpharmacologic treatment. The design of our study did not allow us to analyze the possible influence of implantable cardioverter-defibrillator or biventricular pacemaker to the results. Therefore, large long-term follow-up studies ascertaining the ability of these devices to affect outcomes are necessary. Nevertheless, the results of the current study may suggest that UA and Cys were significantly associated with increased risk for clinical outcomes.

CONCLUSIONS

Cys correlated well with the UA level and showed the cardiac risk-stratification early and easily. Thus, the combined index of UA and Cys levels at admission appears to be a more useful predictor of clinical events than other renal measures in HF patients presenting with dyspnea.

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