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Prognostic Importance of Chronic Kidney Disease in Japanese Patients With Chronic Heart Failure

—— Implications of the CHART Study ——

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Background Renal insufficiency is common in patients with chronic heart failure (CHF), so to improve the prognosis of patients with cardiovascular risks clinical guidelines recommend estimating the glomerular filtration rate (GFR), which detects chronic kidney disease more accurately than does the serum creatinine level alone. However, the clinical usefulness of the estimated GFR (eGFR) in Japanese CHF patients is still unclear.

Methods and Results Of 1,278 patients registered in a Japanese CHF registry, termed the Chronic Heart Failure Analysis and Registry in the Tohoku District study, the study population included 920 symptomatic patients with sufficient data. Baseline eGFR ($ml \cdot min^{-1} \cdot 1.73\,m^{-2}$) was calculated using the Cockcroft-Gault equation. Patients were divided into three groups based on eGFR: ≥60, 30–59, and <30 $ml \cdot min^{-1} \cdot 1.73\,m^{-2}$. Kaplan-Meier analysis revealed that the incidence of the combined event of all-cause death and admission because of CHF was significantly higher in patients with reduced eGFR and such patients were older and more frequently had an ischemic etiology of CHF, a higher prevalence of diabetes, lower hemoglobin level, and higher B-type natriuretic peptide level. Multivariate Cox regression analysis showed that reduced eGFR was significantly associated with the combined endpoint.

Conclusions GFR should be evaluated in all Japanese patients with CHF to improve risk stratification and treatment. (*Circ J* 2008; **72:** 173–178)

Key Words: Estimated glomerular filtration rate; Heart failure; Prognosis; Renal insufficiency; Risk stratification

Chronic heart failure (CHF) is the most frequent cause of mortality in many developed countries and the prevalence of patients with CHF will explosively increase in Japan, because of the rapid aging of the Japanese population.[1] Investigation of the risk factors for mortality and risk stratification of CHF patients is the first-line strategy to improve the prognosis and quality of life (QOL) of these patients.[2,3] Many Western investigators have reported that renal insufficiency is common in CHF patients and severe chronic kidney disease (CKD) is associated with mortality.[4,5] The serum creatinine level has been the commonly used marker for evaluating renal function in the clinical setting; however, this examination may not be sufficient for accurate diagnosis of CKD. The guidelines from the United States National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) recommend estimating the glomerular filtration rate (GFR) in all patients with risk factors for cardiovascular diseases to identify CKD earlier in order to slow disease progression. The estimated GFR (eGFR), calculated from the serum creatinine level using a prediction equation, detects CKD more accurately than does the serum creatinine level alone[6] and it is also used in disease staging. The purpose of the present study was to elucidate the prognostic importance of CKD evaluated by eGFR in Japanese patients with CHF using a heart failure cohort from the Chronic Heart Failure Analysis and Registry in the Tohoku District (CHART) study.

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Methods

Study Population

The rationale and details of the CHART study have been described previously.[2] Eligible subjects were stable patients with at least one of the following clinical findings: (1) certain organic heart disease and a documented history of clinical CHF defined by the Framingham criteria;[7] (2) organic heart disease and an echocardiographic ejection fraction (EF) ≤50%; or (3) organic heart disease and an echocardiographic left ventricular end-diastolic dimension ≥55 mm. We started the entry of patients on February 2000 and follow-up surveillance was performed annually. Of 1,278 patients who were included in the CHART registry, the present study population comprised 920 patients with sufficient data who had at least New York Heart Association (NYHA) class II symptoms. Patients on chronic hemodialysis at study entry were excluded.

Renal Function

We calculated the baseline eGFR using the Cockcroft-Gault (CG) equation (ml/min)[8] and the abbreviated Modification of Diet in Renal Disease (MDRD) Study equation ($ml \cdot min^{-1} \cdot 1.73\,m^{-2}$)[9] (Table 1). We adjusted the eGFR for body surface area (BSA: m^2) by multiplying by 1.73/BSA

Table 1 Formulas for Estimating Glomerular Filtration Rate

Cockcroft-Gault equation[8]
C_{Cr} (ml/min) = ((140 − age) × weight)/(72 × S_{Cr}) × (0.85, if female)
CG-eGFR (ml·min^{-1}·1.73 m^{-2}) = C_{Cr} × (1.73/BSA)
BSA (m^2) = (body weight)$^{0.425}$ × (height)$^{0.725}$ × 0.007184
Abbreviated MDRD Study equation[9]
MDRD-eGFR (ml·min^{-1}·1.73 m^{-2}) = 186 × (S_{Cr})$^{-1.154}$ × (age)$^{-0.203}$ × (0.742, if female) × (1.210, if black)

Age is in years and weight is in kilograms for each equation.
CG, Cockcroft-Gault equation; C_{Cr}, creatinine clearance; S_{Cr}, serum creatinine concentration (mg/dl); eGFR, estimated glomerular filtration rate; BSA, body surface area; MDRD, Modification of Diet in Renal Disease.

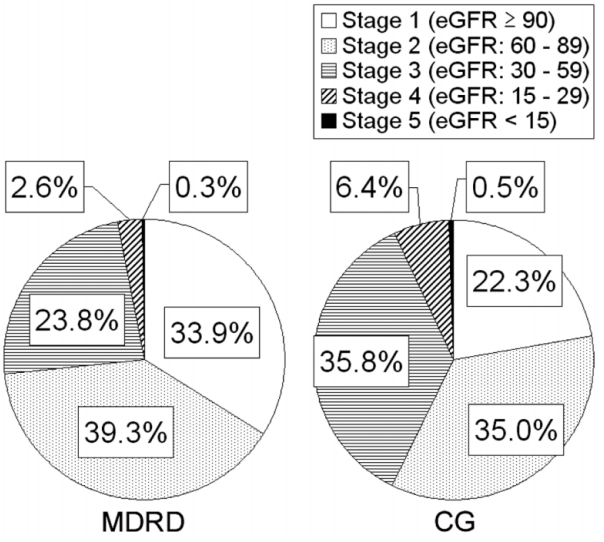

Fig 1. Distribution of the study population by stage of chronic kidney disease based on two equations for estimating of glomerular filtration rate. eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease Study equation; CG, Cockcroft-Gault equation.

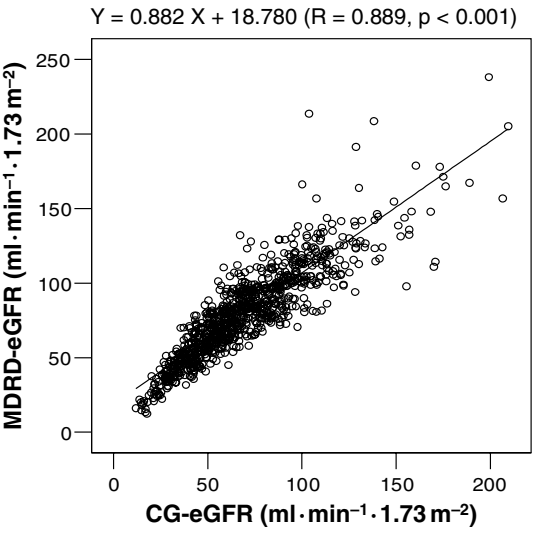

Fig 2. Correlation between estimated glomerular filtration rates using the MDRD or CG equation. GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease Study equation; CG, Cockcroft-Gault equation; eGFR, estimated glomerular filtration rate.

when using the CG equation. The eGFR was categorized into five stages as recommended by the KDOQI guidelines[6]

Statistical Analysis

The study population was divided into three groups based on the stage of CKD: (1) patients with normal or mildly reduced GFR (eGFR ≥60 ml·min^{-1}·1.73 m^{-2}), (2) those with moderately reduced GFR (eGFR: 30–59 ml·min^{-1}·1.73 m^{-2}), and (3) those with severely reduced GFR (eGFR <30 ml·min^{-1}·1.73 m^{-2}). The baseline characteristics of the patients in the three strata were compared by chi-square test for dichotomous variables and ANOVA tests for continuous variables. Data are expressed as means ± standard deviations (SD). Least-squares linear regression analysis and a correlation coefficient were used to describe the relationship between the eGFRs calculated by the MDRD and CG equations. A Bland-Altman plot was also used to assess the agreement between both eGFRs[10] Survival curves of patients with CKD were constructed using the Kaplan-Meier method and were compared with the log-rank test. Multivariate Cox proportional hazards analyses were also performed to determine the association of eGFR with a combination of all-cause mortality plus admission because of CHF, using the following covariates: age, gender, etiology of CHF, serum hemoglobin level, left ventricular EF, body mass index (BMI), NYHA functional class, medications for CHF, and comorbidities such as diabetes, dyslipidemia, or ventricular tachycardia. Prior to the multivariate analysis, the associations among all covariates were evaluated using the Spearman's rank correlation test. Statistical significance was defined as $p<0.05$. The Bland-Altman plot was constructed using MedCalc ver. 9.3.0 (available at: http://www.medcalc.be) and all other statistical analyses were performed using SPSS 15.0J for Windows (Chicago, IL, USA).

Results

The eGFR in Patients With CHF

The mean age of the study population was 68.3±13.6 years and males accounted for 65.1% of patients. The mean follow-up period was 3.45±1.75 years. The prevalence of patients with renal insufficiency, which was categorized based on the stages defined by the KDOQI guidelines using two equations, is shown in Fig 1. Patients with CKD, which was defined as eGFR <60 ml·min^{-1}·1.73 m^{-2}, accounted for 26.7% and 42.7% of the study population when using the MDRD equation and CG equation, respectively. Fig 2 shows the relationship between two eGFRs calculated using each equation. There was a significantly good correlation between them ($R=0.889$, $p<0.001$); however, the eGFR calculated using the MDRD equation tended to be greater than that calculated by the CG equation, especially in patients with reduced eGFR. The Bland-Altman plot

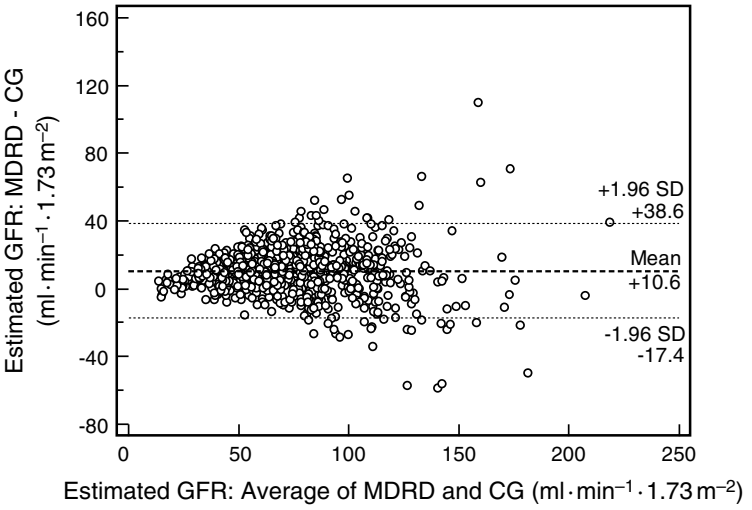

Fig 3. Bland-Altman plot of the two estimated glomerular filtration rates. MDRD, Modification of Diet in Renal Disease Study equation; CG, Cockcroft-Gault equation.

Table 2 Baseline Characteristics of the Study Population by Stage of Chronic Kidney Disease Evaluated by the CG-eGFR

	eGFR (ml·min⁻¹·1.73 m⁻²)			*p value*
	≥60	*30–59*	*<30*	
N	*527*	*329*	*64*	
Follow-up (years)	*3.7±1.7*	*3.2±1.8*	*2.7±1.7*	
Age (years)	*62.0±13.1*	*76.2±8.5*	*80.4±9.5*	*<0.001*
Male	*69.4%*	*60.5%*	*53.1%*	*0.03*
Body mass index	*23.9±3.7*	*22.1±3.5*	*21.2±2.8*	*<0.001*
NYHA III/IV	*14.60%*	*24.30%*	*39.10%*	*<0.001*
Kidney function				
eGFR (ml·min⁻¹·1.73 m⁻²)	*88.8±24.9*	*46.5±8.4*	*24.2±4.9*	
Serum creatinine (mg/dl)	*0.8±0.2*	*1.1±0.3*	*2.0±0.8*	*<0.001*
Ischemic etiology of CHF	*23.9%*	*36.5%*	*35.9%*	*<0.001*
Medical history				
HF admission	*30.0%*	*28.9%*	*26.6%*	*NS*
Hypertension	*45.5%*	*48.3%*	*64.1%*	*0.02*
Diabetes	*17.1%*	*21.9%*	*28.1%*	*<0.05*
Dyslipidemia	*18.2%*	*10.9%*	*17.2%*	*0.02*
Atrial fibrillation	*39.3%*	*47.1%*	*45.3%*	*0.07*
Ventricular tachycardia	*21.3%*	*21.6%*	*15.6%*	*NS*
Medications				
Diuretics	*77.0%*	*82.8%*	*87.3%*	*NS*
β-blocker	*34.3%*	*23.4%*	*20.3%*	*0.01*
ACEI/ARB	*74.4%*	*69.6%*	*54.7%*	*0.003*
Echocardiography				
LVDd (mm)	*57.2±9.6*	*54.1±10.1*	*53.2±8.4*	*<0.001*
LVEF (%)	*50.5±15.6*	*52.8±16.9*	*55.1±14.3*	*0.03*
Other factors				
BNP (pg/ml)	*196.1±297.4*	*329.6±347.5*	*432.4±394.8*	*<0.001*
Hemoglobin (g/dl)	*13.7±1.9*	*12.4±2.1*	*10.6±1.9*	*<0.001*
Anemia	*25.5%*	*52.6%*	*88.9%*	*<0.001*

NYHA, New York Heart Association; CHF, chronic heart failure; HF, heart failure; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; LV, left ventricular; Dd, end-diastolic dimension; EF, ejection fraction; BNP, B-type natriuretic peptide. Other abbreviations see in Table 1.

showed that the scatter of the differences between the two eGFRs increased as the eGFR increased and, importantly, the mean difference was 10.6 ml·min⁻¹·1.73 m⁻² (Fig 3).

Baseline Characteristics and Survival Analysis

Baseline characteristics of the patients stratified by eGFR calculated by the CG equation are summarized in Table 2. Reduced kidney function was associated with a variety of cardiovascular risks. Patients with lower eGFR were older and had lower BMI, more severe symptoms of CHF, higher level of B-type natriuretic peptide, lower level of hemoglobin, and a higher prevalence of hypertension and diabetes. Those patients were less likely to be taking β-blockers, angiotensin-converting-enzyme inhibitors, or angiotensin II receptor blockers. The Kaplan-Meier analyses included the following two endpoints: (1) combined event of all-cause death and admission because of congestive heart failure and (2) admission because of congestive heart failure (Fig 4). The event-free rates of patients with more severe CKD were significantly lower than those of patients with less severe CKD when eGFR was evaluated using the CG equation (Fig 4). The 1- and 3-year rates of the combined event of all-cause death and admission because of congestive heart failure in patients with eGFR <30 ml·min⁻¹·

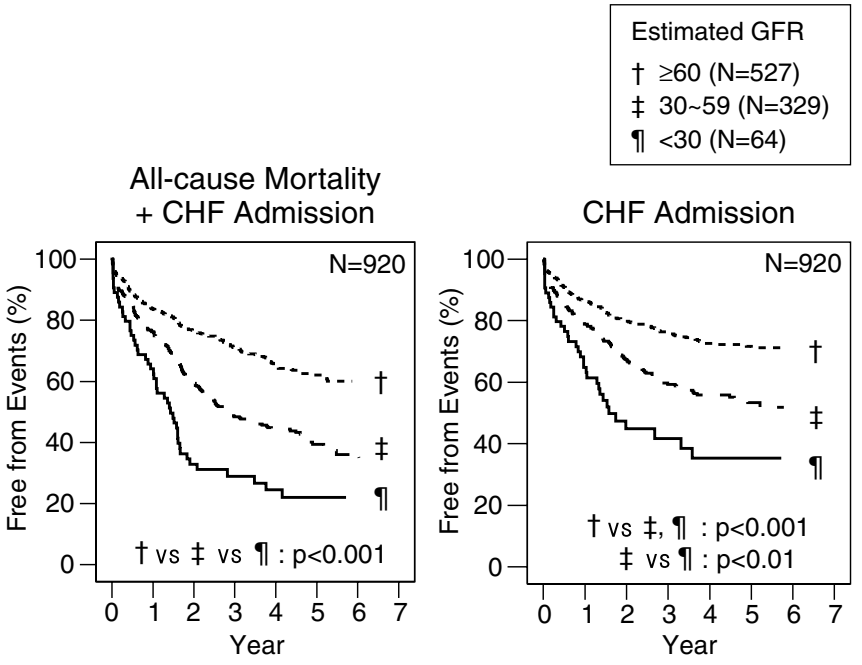

Fig 4. Kaplan-Meier curves of freedom from the two endpoints. (Left) Combined event of all-cause mortality and admission because of congestive heart failure. (Right) Admission because of congestive heart failure. CHF, congestive heart failure; GFR, glomerular filtration rate.

Table 3 Results of Multivariate Cox Analysis Using Two Methods of Calculating eGFR

Factors	*CG*				*MDRD*			
	N	*HR*	*95%CI*	*p value*	*N*	*HR*	*95%CI*	*p value*
Age (years)		*1.02*	*1.00–1.03*	*0.003*		*1.02*	*1.01–1.03*	*<0.001*
NYHA		*1.47*	*1.22–1.77*	*<0.001*		*1.45*	*1.20–1.74*	*<0.001*
Diabetes		*1.48*	*1.18–1.87*	*<0.001*		*1.47*	*1.12–1.85*	*0.001*
VT		*1.51*	*1.20–1.89*	*<0.001*		*1.50*	*1.20–1.89*	*<0.001*
Hemoglobin (g/dl)		*0.89*	*0.85–0.94*	*<0.001*		*0.89*	*0.85–0.94*	*<0.001*
EF (%)		*0.99*	*0.98–0.99*	*0.004*		*0.99*	*0.98–0.99*	*0.003*
eGFR (ml·min^{-1}·1.73 m^{-2})				*0.04*				*0.045*
≥60	*527*	*1.00*	*–*	*–*	*674*	*1.00*	*–*	*–*
30–59	*329*	*1.31*	*1.03–1.68*	*0.03*	*219*	*1.32*	*1.04–1.68*	*0.02*
<30	*64*	*1.56*	*1.05–2.32*	*0.03*	*27*	*1.51*	*0.91–2.50*	*0.12*

HR, heart rate; CI, confidence interval; VT, ventricular tachycardia. Other abbreviations see in Tables 1,2.

1.73 m^{-2} were 35.9% and 71.1%, respectively. The respective rates of admission because of congestive heart failure in those patients were 35.1% and 58.3%, respectively.

Multivariate Cox Regression Analysis

Results of the multivariate Cox regression analysis are shown in Table 3. The Spearman's rank correlation test did not show good or significant correlations between the severity of CKD and the covariates other than age, which was included in the equation of calculating GFR (Table 1). The eGFR was calculated using the CG and MDRD equations and a lower eGFR was significantly associated with the development of the combined event of all-cause death plus admission because of congestive heart failure, as were age, NYHA class, diabetes, ventricular tachycardia, lower hemoglobin level and lower left ventricular EF. When eGFR was calculated by the CG equation, hazard ratios of patients with moderate CKD (eGFR: 30–59 ml·min^{-1}·1.73 m^{-2}) and severe CKD (eGFR <30 ml·min^{-1}·1.73 m^{-2}) were 1.31 (95% confidence interval (CI) 1.03 to 1.68, p=0.03) and 1.56 (95% CI 1.05 to 2.32, p=0.03), respectively. However, when the eGFR was calculated using the MDRD equation, the significant relationship between reduced GFR and the combined endpoint was observed only in patients with moderate CKD, which showed a hazard ratio of 1.32 (95% CI 1.04 to 1.68, p=0.02) (Table 3).

Discussion

The major findings of the present study are as follows: (1) patients with CKD defined as eGFR <60 ml·min^{-1}·1.73 m^{-2} accounted for 26.7–42.7% of Japanese patients with symptomatic CHF; (2) GFR estimated using the abbreviated MDRD equation tended to be greater than that estimated by the CG equation; (3) patients with more severe CKD had more cardiovascular risks than those with less severe CKD and these patients also had a significantly increased risk of the combined event of the all-cause mortality and admission because of congestive heart failure. Therefore, risk stratification using eGFR is a first-line strategy to improve the survival and QOL of Japanese patients with symptomatic CHF.

Estimation of GFR

Significant kidney dysfunction may be present despite a normal serum creatinine level. The KDOQI guidelines define the stages of CKD based on an eGFR that is calculated

using the serum creatinine level. The two most commonly used formulas for GFR estimation are the abbreviated MDRD and CG equations (Table 1). We found a strong relationship between the two eGFRs (Fig 2), although the Bland-Altman plot did not reveal sufficient agreement between them (Fig 3). Furthermore, there was a considerable difference in the mean values of the two eGFRs, which might influence the diagnosis of CKD. Validation studies performed in middle-aged patients with CKD have shown that the MDRD equation is more accurate than the CG equation, which calculates creatinine clearance. However, we speculated that the CG equation might be more appropriate for our purposes because it can estimate GFR better than the MDRD equation in older patients[11] and the mean age of the population in the present study was 68.3 years, which was much older than that of the participants in the MDRD Study, whose mean age was 50.6 years.[9] Equations to estimate eGFR might need modification using Japanese coefficients. Imai et al reported that 0.881×MDRD might be a better estimation than the original MDRD equation; however, they also concluded that a new equation was needed for more accurate estimation of GFR in Japanese patients with CKD stage 3 or 4.[12]

Renal Dysfunction and Prognosis

Several investigators have explored the influence of renal impairment on the prognosis of patients with CHF. Multivariate analyses using populations of randomized treatment trials or population-based studies performed in Western countries showed that CKD is significantly associated with a poor prognosis of patients with CHF.[4,5,13] In the present study, Kaplan-Meier analysis showed that patients with a lower eGFR had an increased rate of the combined event of all-cause death and admission because of CHF. Furthermore, multivariate Cox regression analysis clearly showed that more severe CKD independently predicted a poor prognosis after adjustment for other cardiovascular risk factors (Table 3). When using the MDRD equation to calculate eGFR, the association between severe CKD (eGFR $<30\,ml\cdot min^{-1}\cdot 1.73\,m^{-2}$) and the combined endpoint did not reach the significant level. We speculate that this may be because of the limited number of patients who were categorized as severe CKD using the MDRD equation (n=27, Table 3).

Anemia and CKD

In the present study, patients with CKD were associated with many risk factors for cardiovascular disease (Table 2). Several researchers have shown that anemia and CKD are interrelated in patients with CHF.[4,5] Anemia can be caused by kidney dysfunction[14] and is reported to be an independent predictor of the prognosis of these patients.[5] Multivariate analysis in the present study revealed that a low hemoglobin level was independently and significantly associated with the development of events, as was the severity of CKD (Table 3).

Other Prognostic Risks and eGFR

GFR is considered to decrease as age increases and the eGFR is calculated by an equation including age as shown in Table 1.[8,9] The present study also showed that patients with more severe CKD were significantly older (Table 2). However, multivariate analysis including age as a covariate revealed that eGFR was one of the significant predictors for the prognosis in patients with CHF.

The present study also showed that other four covariates (ie, higher NYHA class, diabetes, ventricular tachycardia, and low EF) were significantly and independently associated with the prognosis of these patients, and those factors may be also associated with renal dysfunction. CKD is considered to be linked to increased incidence of atrial and ventricular arrhythmias.[15] Several structural and physiologic substrates, such as electrolyte abnormalities, volume overload, and adverse pharmacologic interactions, based on CKD may be potential mechanisms of such a relationship. Higher NYHA and low EF are frequently observed in patients with advanced CHF and the reduced cardiac output in these patients activates sympathetic nerve activity and the renin-angiotensin system, which results in further progression of CKD in CHF patients.[16] Chronic diabetes frequently results in diabetic nephropathy and it is one of the most common causes of CKD and end-stage renal disease. However, in the present study the Spearman's rank correlation test showed that there was not a good and significant relationship between the severity of CKD and the four covariates. Several researchers, including us, have already reported that these factors are significantly and independently associated with the prognosis of patients with CHF[2,3,5] and that they are still important prognostic factors for risk stratification as eGFR is.

Conclusions

CKD is also common in Japanese patients with CHF and its severity is inversely associated with survival and QOL, as several Western investigators have previously reported. GFR, which is easily calculated using a prediction equation, should be evaluated in all patients with CHF to improve risk stratification and treatment.

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