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Chronic kidney disease: an independent risk factor of all-cause mortality for elderly Chinese patients with chronic heart failure

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Abstract

Objective To evaluate the prognostic value of chronic kidney disease (CKD) in elderly Chinese patients with chronic heart failure (CHF). **Methods** The study consisted of 327 elderly patients with CHF. All-cause mortality was chosen as an endpoint over the median follow-up period of 345 days. Cox regression analysis was used to identify the risk factors of mortality. **Results** The median age of the entire cohort was 85 years (60–100 years). The mortality for 168 elderly patients with CHF and CKD (51.4% of entire cohort) was 39.9% (67 deaths), which was higher than the mortality for CHF patients without CKD [25.2% (40/159 deaths)] and the mortality for entire cohort with CHF [32.7% (107/327 deaths)]. The Cox regression analysis showed that old age [hazard ratio (HR): 1.033; 95% confidence interval (95% CI): 1.004–1.064], CKD (HR: 1.705; 95% CI: 1.132–2.567), CHF New York Heart Association (NYHA) class IV (HR: 1.913; 95% CI: 1.284–2.851), acute myocardial infarction (AMI) (HR: 1.696; 95% CI: 1.036–2.777), elevated resting heart rate (HR: 1.021; 95% CI: 1.009–1.033), and decreased plasma albumin (HR: 0.883; 95% CI: 0.843–0.925) were independent risk factors of mortality for elderly patients with CHF. **Conclusions** CKD was an independent risk factor of mortality for elderly Chinese patients with CHF.

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Keywords: Chronic heart failure; Chronic kidney disease; Risk factor; The aged

1 Introduction

Due to a rapid growth in the size of the older population during recent decades, understanding the commonly encountered and critical diseases, such as chronic heart failure (CHF) and chronic kidney disease (CKD), in the elderly should be considered a high priority. It has been reported that CKD occurred in 20%–60% of the general population and the deterioration of kidney function was correlated with a higher mortality rate.[1,2] However, these studies did not aim directly at elderly patients with CHF, and had an under-representation of elderly and CHF patients. The heterogeneity resulting from aging and associated co-morbidities provides the need to reassess the prognostic value of CKD and other risk factors. Moreover, there is a close relationship between race and prognostic value of CKD. However, there has been little research regarding this problem in China. Therefore, the aim of the current study was to evaluate the prognostic value of CKD in elderly Chinese patients with CHF.

2 Methods

2.1 Study population

Patients > 60 years old with a diagnosis of CHF met the criteria for inclusion. The diagnosis of CHF was based on symptoms of long-term duration (dyspnea and/or fatigue), signs (edema and/or pulmonary rales), and abnormalities of cardiac structure or function, made by chief physicians according to ESC 2008 Guidelines.[3] Patients with severe aortic stenosis, anticipated cardiac transplantation, and a left ventricular assist device were excluded from the study. The study population consisted of 327 patients who fulfilled the study criteria. The Chinese People's Liberation Army (PLA) General Hospital was their designated hospital, and had the integrated long-term medical and final death records of patients, which made it easier for us to follow-up effectively and judge endpoints accurately.

2.2 Baseline variables

The baseline characteristics available for this study incl-

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uded demographics (age and gender), lifestyle (smoking), physical examination [height, weight, heart rate, systolic and diastolic blood pressure (SBP and DBP)], laboratory measurements [hemoglobin, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, and fasting plasma glucose (FCG)]. The New York Heart Association (NYHA) functional classifycation system was used to assess the stage of CHF and defined by asking patients, or their family members, to describe their symptoms. The NYHA system is comprised of the following four classes: Class I (no limitation of physical activity; ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea); Class II (slight limitation of physical activity; comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea); Class III (marked limitation of physical activity; comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea); and Class IV (unable to carry out any physical activity without discomfort; symptoms of cardiac insufficiency at rest, and if any physical activity is undertaken, discomfort is increased). Conventional echocardiograms were performed. In all patients, the estimated glomerular filtration rate (eGFR) was calculated using a modified version of the Modification of Diet in Renal Disease (MDRD) equation based on data from Chinese CKD patients as follows: $175 \times \text{serum creatinine (mg/dL)}^{-1.234} \times \text{age (year)}^{-0.179} \times 0.79$ (if female).[4] Smoking status was categorized as current, former, or never. Subjects were considered to be current smokers if they smoked more than one cigarette per day for the last year. Former smoking was defined as a history of cigarette use on a regular basis (more than one cigarette per day), but no current smoking. Body mass index (BMI) was defined as the weight in kilograms divided by the square of the height in meters. Reported SBP and DBP were the averages of five separate measurements.

2.3 Definition of diseases

We defined CKD as GFR < 60 mL/min per 1.73 m^2 based on the KDOQI working group definition.[5] Acute myocardial infarction (AMI) and atrial fibrillation (AF) were diagnosed by chief physicians according to the universal definition of MI[6] and the ACC/AHA/ESC 2006 guidelines for AF, respectively.[7] Patients with SBP > 140 mmHg, DBP > 90 mmHg, or receiving medication for the treatment of hypertension were defined as having hypertension. Diabetes mellitus (DM) was defined as a FCG > 7 mmol/L, or receiving an oral hypoglycemic agent, or insulin.

2.4 Follow-up

Given the priority of all-cause mortality in outcome studies as well as the high incidence of multiple organ failure in the elderly, we selected all-cause mortality as the endpoint. The study population had a median follow-up period of 345 days (75% range, 208–722 days). No patient was lost during the follow-up period. Death was ascertained from death records, a legal document with time, site, and other information.

2.5 Statistical methods

The proportion of patients who developed CKD and other co-morbidities in the study population were expressed as a prevalence rate with a 95% confidence interval (95% CI). Continuous variables were described as mean ± SD for data with a normal distribution, and the median and 75% range for non-normally distributed variables. The bivariate associations between CKD and variables in the Table 1 (exclusion of MDRD-eGFR) were assessed by Student's *t*-test for continuous variables (normal distribution), Mann–Whitney *U* test for continuous variables (abnormal distribution) and X^2 analysis for categorical variables.

For the purpose of identifying factors independently associated with CKD, we selected covariates with a $P < 0.10$ from the results of bivariate association analysis and entered the covariates into multivariable logistic regression with a backward stepwise (likelihood ratio test), which played a role in avoiding the interaction of variables. We then developed a multivariate logistic regression model (enter) with CKD as the dependent variable and variables from the backward stepwise ($P < 0.10$) as the independent variables. Variables were kept in the last model at a significance level of $P < 0.05$. To identify risk factors of mortality, we selected covariates with $P < 0.10$ from Cox regression univariate analysis and entered the covariates into a multivariate Cox regression model with death as the dependent variable, which was divided into two steps (stepwise and enter). The ability of the models to discriminate between patients with, and without, CKD and between survivor and deceased was estimated using the concordance index (c-statistic), which was identical to the area under the receiver operating characteristics (ROC) curve. The variables missing from > 10% of the study population were excluded, and the residual missing values were calculated by mutiple imputation to minimize bias.[8] All statistical analyses were performed with SPSS 17 (SPSS, Inc., Chicago, IL, USA).

3 Results

3.1 Prevalence of CKD in the elderly with CHF

The median age of the entire cohort was 85 years (60–100 years), with 74.3% (243 patients) of the participants > 80 years old. There were 168 patients with CKD (51.4%,

Table 1. Patient characteristics based on patients with, or without, chronic kidney disease.

Characteristics	Total	CKD absent	CKD present	*P*-value
Age (yr)*	85.0 (79.0–89.0)	85.0 (78.0–89.0)	85.0 (80.0–89.0)	0.434
Males (%)	256 (78.3)	123 (77.4)	133(79.2)	0.692
History of smoking (%)				
Current	19 (5.8)	8 (5.0)	11 (6.5)	0.558
Former	103 (31.5)	47 (29.6)	56 (33.3)	
Never	205 (62.7)	104 (65.4)	101 (60.1)	0.323
BMI (kg/m^2)*	23.3 (20.8–25.8)	22.7 (20.5–25.5)	23.8 (21.0–26.3)	0.063
Medical history				
AMI (%)	29 (8.9)	10 (6.3)	19 (11.3)	0.110
CHF (%)				
NYHA class II	98 (30.0)	63 (39.6)	35 (20.8)	< 0.001
NYHA class III	147 (45.0)	68 (42.8)	79 (47.0)	0.439
NYHA class IV	82 (25.1)	28 (17.6)	54 (32.1)	0.002
Hypertension (%)	271 (82.9)	119 (74.8)	152 (90.5)	< 0.001
DM (%)	144 (44.0)	69 (43.4)	75 (44.6)	0.820
AF (%)	101 (30.9)	51 (32.1)	50 (29.8)	0.651
Clinical presentation				
Heart rate (beats/min) *	73.0 (65.0–83.0)	74.0 (64.0–84.0)	72.0 (65.0–83.0)	0.611
MSBP (mmHg)*	131.2 (122.0–140.3)	131.2 (121.2–139.6)	131.5 (123.4–141.2)	0.381
MDBP (mmHg) *	67.6 (62.8–74.2)	68.4 (63.2–74.8)	67.2 (62.0–73.6)	0.299
EF (%)*	57.0 (50.0–61.0)	57.8 (51.8–62.0)	55.0 (46.1–60.0)	0.012
IVS (mm)*	11.0 (10.0–12.0)	11.0 (10.0–12.0)	11.0 (10.0–12.0)	0.331
LVPW (mm)*	10.0 (10.0–11.0)	10.0 (9.9–11.0)	10.0 (10.0–11.0)	0.752
LVEDD (mm)*	50.0 (46.0–54.0)	49.7 (46.0–52.0)	50.0 (47.0–55.4)	0.045
Laboratory results				
MDRD-eGFR (mL/min per 1.73 m^2)*	59.5 (44.1–76.6)	76.9 (68.4–85.1)	44.4 (34.2–53.6)	
Hemoglobin (g/L), mean(SD)	115.6 (22.2)	121.1 (21.2)	110.4 (21.8)	< 0.001
Plasma albumin (g/L), mean(SD)	36.8 (4.6)	37.4 (4.6)	36.2(4.6)	0.016
Glucose (mmol/L)*	5.5 (4.8–6.5)	5.5 (4.8–6.3)	5.5 (4.8–6.7)	0.543
Triglycerides (mmol/L) *	1.2 (0.9–1.9)	1.2 (0.8–1.6)	1.3 (0.9–2.1)	0.043
HDL (mmol/L)*	1.0 (0.8–1.2)	1.1 (0.9–1.3)	1.0 (0.7–1.2)	0.001
LDL (mmol/L)*	2.1 (1.6–2.6)	2.2 (1.7–2.7)	2.0 (1.6–2.5)	0.060

*Median (75% range); AF: atrial fibrillation; AMI: acute myocardial infarction; BMI: body mass index; CHF: chronic heart failure; CKD: chronic kidney disease; DM: diabetes mellitus; EF: ejection fraction; HDL: high-density lipoprotein; IVS: interventricular septum; LDL: low-density lipoprotein; LVEDD: left ventricular end-diastolic dimension; LVPW: left ventricular posterior wall; MDBP: mean diastolic blood pressure; MDRD-eGFR: estimated glomerular filtration rate calculated by a modifying Modification of Diet in Renal Disease equation; MSBP: mean systolic blood pressure; NYHA: New York Heart Association.

95% CI: 45.8%–56.9%) among all patients with CHF. CKD occurred in 35.7% (35/98, 95% CI: 26.3%–46.0%), 53.7% (79/147, 95% CI: 45.3%–62.0%), and 65.9% (54/82, 95% CI: 54.6%–76.0%) of patients with CHF NYHA classes II, III, and IV, respectively. There was a significant distinction in the prevalence of CKD between NYHA classes II and III (P = 0.006, HR: 2.091, 95% CI: 1.237–3.536), and a moderate, but not significant, distinction between NYHA classes III and IV (P = 0.075, HR: 1.660, 95% CI: 0.948–2.906). Among patients between 60–75 (47 patients), 75–90 (225 patients) or 90–105 (55 patients) years old, there was 19 (40.4%, 95% CI: 26.4%–55.7%), 118 (52.4%, 95% CI: 45.7%–59.1%) and 31 (56.4%, 95% CI: 42.3%–69.7%) patients with CKD, respectively.

3.2 The clinical features associated with CKD

Upon univariate analysis, CKD was associated with several factors, as shown in Table 1. Participants with CKD tended to have hypertension and CHF NYHA class IV. Those patients with CKD were more likely to have a lower ejection fraction (EF) and a larger left ventricular end-diastolic dimension. Lower levels of hemoglobin, serum albumin and HDL-C, and higher level of triglycerides were more commonly reported among those with CKD, than those without CKD. On multivariate analysis, CHF NYHA class IV, hypertension, hemoglobin concentration, and EF were independently associated with CKD (Table 2).

Table 2. Correlates of chronic kidney disease on multivariate analysis.

Characteristics*	Adjusted HR	95% CI	*P* value
CHF NYHA class IV	1.831	1.020–3.287	0.043
Hypertension	3.841	1.950–7.564	< 0.001
Hemoglobin (g/L)	0.979	0.968–0.990	< 0.001
EF (%)	0.966	0.943–0.990	< 0.001

*C-statistic for this model is 0.710. CHF: chronic heart failure; CI: confidence interval; EF: ejection fraction; HR: hazard ratio; NYHA: New York Heart Association.

3.3 The independent value of CKD in prognostic assessment

In 327 patients with CHF, 107 (32.7%) died during the follow-up period. CHF patients with CKD had a significantly higher mortality rate [39.9% (67/168 patients)] than those without CKD [25.2% (40/159 patients)] (P = 0.005, HR: 1.974, 95% CI: 1.230–3.167); as well as all patients with CHF (32.7%). There was a significant difference (P = 0.000) in survival between patients without CKD (median: 239 days; 75% range: 109–415 days) and patients with CKD (median: 190 days; 75% range: 74–314 days). The Kaplan-Meier estimate of survival for the patients with, or without, CKD was shown in Figure 1. The MDRD-eGFR differed markedly between the survivors and the non-survivors [62.8 (20.7) *vs*. 54.0 (26.9), P = 0.001]. Upon multivariate analysis, CKD was confirmed to be an independent risk factor of mortality for patients with CHF after adjusting for the factors in Table 1 (P = 0.011, HR: 1.705, 95% CI: 1.132–2.567). Other independent risk factors of mortality for all patients with CHF included: old age (P = 0.025, HR: 1.033, 95% CI: 1.004–1.064); CHF NYHA class IV (P = 0.001, HR: 1.913, 95% CI: 1.284–2.851); AMI (P = 0.036, HR: 1.696, 95% CI: 1.036–2.777); elevated resting heart rate (P = 0.001, HR: 1.021, 95% CI: 1.009–1.033); and decreased plasma albumin (P < 0.001, HR: 0.883, 95% CI: 0.843–0.925). The independent risk factors of mortality for patients with CHF and CKD included old age (P = 0.038, HR: 1.041, 95% CI: 1.002–1.081), CHF NYHA class IV (P = 0.003, HR: 2.093, 95% CI: 1.276–3.433), elevated resting heart rate (P < 0.001, HR: 1.029, 95% CI: 1.014–1.044) and decreeased plasma albumin (P < 0.001, HR: 0.853, 95% CI: 0.806–0.903) (Table 3).

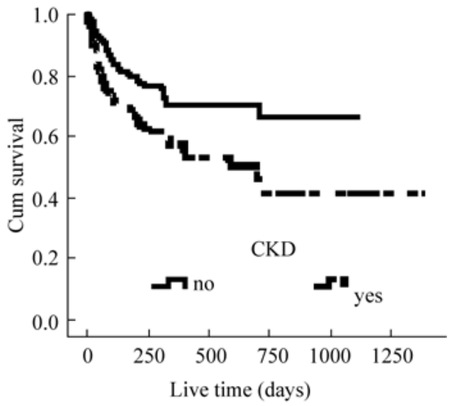

Figure 1. Older CHF patients with CKD had a significantly higher mortality rate than patients without CKD (P = 0.005). Results from Kaplan-Meier estimate of survival for these patients. CHF: chronic heart failure; CKD: chronic kidney disease.

4 Discussion

The major findings of this research were as follows: (1) elderly Chinese patients with CHF were at high risk for developing CKD (51.4%); (2) CKD was independently associated with several clinical factors; (3) CKD was an independent risk factor of mortality rate; and (4) there were several shared risk factors for general patients with CHF and patients with CHF and CKD.

Several studies have revealed that patients with CHF and CKD had significantly higher mortality than the entire population of patients with CHF.[2] However, these studies did not aim directly at elderly patients with CHF, and had an under-representation of the elderly people and CHF patients. The heterogeneity resulting from aging and co-morbidities provides the need to reassess the prognostic value of CKD and other risk factors. Moreover, race has a close relationship with the prognostic value of CKD. However, there has been little research regarding this problem in China. In the current study, CKD was an independent risk factor of mortality for elderly Chinese patients with CHF. We also demonstrated

Table 3. Risk factors of mortality on multivariate analysis.

Patients	Risk factors	Adjusted HR	95% CI	*P* value
CHF (327 patients) model A*	Age	1.033	1.004–1.064	0.025
	AMI	1.696	1.036–2.777	0.036
	CHF NYHA class IV	1.913	1.284–2.851	0.001
	CKD	1.705	1.132–2.567	0.011
	Heart rate (beats/min)	1.021	1.009–1.033	0.001
	Serum albumin (g/L)	0.883	0.843–0.925	< 0.001
CHF and CKD (168 patients) model B#	Age	1.041	1.002–1.081	0.038
	CHF NYHA class IV	2.093	1.276–3.433	0.003
	Heart rate (beats/min)	1.029	1.014–1.044	< 0.001
	Serum albumin(g/L)	0.853	0.806–0.903	< 0.001

*C-statistic for model A was 0.827; #C-statistic for model B was 0.839; AMI: acute myocardial infarction; CHF: chronic heart failure; CKD: chronic kidney disease; CI: confidence interval; HR: hazard ratio; NYHA: New York Heart Association.

that there were many significant distinctions between CHF patients with, and without, CKD. More significantly, CHF NYHA class IV, hypertension, hemoglobin concentration, and EF were independently related to CKD. All these factors were closely related to the generation and progression of CKD.

Moreover, the current study highlighted the shared risk factors for general patients with CHF and patients with CHF and CKD. As expected, the patients in the current study had increased mortality associated with old age and CHF NYHA class IV. Previous studies indicated the value of hypoalbuminemia in predicting mortality for patients with CHF.[9,10] Meanwhile, hypoalbuminemia was a risk factor of mortality, not only for patients with end-stage renal disease, but also patients with pre-dialysis CKD.[11] The current study also showed that a low serum albumin level was an independent risk factor for patients with CHF, whether the patients had CKD or not. Given the number of associated factors, the deleterious impact of hypoalbuminemia may reflect the influence of malnutrition, vascular injury, proteinuria, and/or fluid retention, illustrating that these medical problems should receive more attention by cardiologists in the daily treatment of elderly patients. In prior studies, an elevated resting heart rate received the recognition that it deserved as a predictor of mortality for patients with CHF.[12] Moreover, a relationship was observed between an elevated resting heart rate and mortality for patients with CKD.[13] The current study showed that patients with CHF and an elevated resting heart rate had a higher mortality, and the association was independent regardless of the presence of CKD. A higher resting heart rate might reflect increased sympathetic and/or reduced parasympathetic activity.

In conclusion, the current study demonstrated that CKD was an independent risk factor for mortality rate in elderly Chinese patients with CHF, implying that elderly Chinese patients with CHF and CKD were in desperate need of special attention and aggressive therapy.

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