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Epidemiology and survival of the five stages of chronic kidney disease in a systolic heart failure population

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Aims The epidemiology of the five stages of chronic kidney disease (CKD) in systolic heart failure (HF) patients has predominantly been described in hospitalized White patients, with little known about the prevalence in outpatient Blacks and Hispanics. The purpose of this study was to compare the prevalence of the five stages of CKD by race, ethnicity (Whites, Blacks, and Hispanics), and gender in an outpatient systolic HF population and also to evaluate the impact of CKD on mortality.

Methods and results We conducted a prospective study of 1301 patients recruited from two hospital facilities in Louisiana and Florida, USA. All patients were enrolled in a systolic HF disease management programme (HFDMP), which enrolled patients with an ejection fraction of $\leq$40% by echocardiography. The estimated glomerular filtration rate was calculated using the abbreviated Modification of Diet in Renal Disease Study equation. Patients were classified into five stages of CKD according to the National Kidney Foundation classification system. A total of 338 patients (26%) were found to have CKD. Patients with CKD were older, more likely to be Hispanics, to have less education, New York Heart Association class III, elevated systolic blood pressure, and diabetes. There was no statistical difference in prevalence by gender. Survival was reduced in patients with CKD.

Conclusion The prevalence of CKD in an outpatient systolic HFDMP is high, with over one in four patients affected. CKD patients had significantly lower survival rates compared with patients without CKD.

Keywords Chronic kidney disease • Heart failure • Ethnicity • Race • Gender • Mortality

Introduction

In 2002, the National Kidney Foundation Disease Outcomes Quality Initiative (KDOQI) published guidelines to establish a new nomenclature system, in which all patients with persistent proteinuria or a glomerular filtration rate (GFR) $<$60 mL/min/1.73 m^2 for at least 3 months independent of the underlying pathology are classified as having chronic kidney disease (CKD).[1] The National Kidney Foundation classification system stratifies patients with CKD into five stages according to the level of GFR. Using this staging classification, the Third National Health and Nutrition Examination Survey (NHANES III) reported that CKD affects 19.2 million of the US adult population (16.8%). By stages, an estimated 5.9 million individuals have Stage 1 CKD; 5.3 million have Stage 2; 7.6 million have Stage 3; 400 000 individuals have Stage 4, and 300 000 individuals have Stage 5 CKD which is an end-stage renal disease (ESRD).

Chronic kidney disease and HF share several risk factors and pathogenic pathways such as hypertension, diabetes, and the activation of the renin–angiotensin–aldosterone system.[2] Chronic kidney disease is becoming a highly prevalent condition among patients with HF, with a significant number of patients progressing

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to ESRD.[3] According to the American Heart Association 2009 Statistics, the 2006 prevalence of HF in the USA was 5.7 million with 3.2 million men and 2.5 million women affected by this disease.[4]

The prevalence of CKD in HF populations has been described mainly in an inpatient setting, and there seems to be a paucity of data about the prevalence of CKD in HF outpatients. Therefore, the purpose of this study was to examine the prevalence of CKD by ethnicity, race, and gender in an outpatient heart failure disease management programme (HFDMP), and also to evaluate the impact of CKD on mortality within this population.

Methods

Patients

We conducted a prospective cohort study that included patients from two outpatient health care facilities in Louisiana and Florida, USA. All patients were enrolled in a HFDMP, and all had an ejection fraction (EF) of $\leq$40% by echocardiography.

The Louisiana site was at the Leonard J. Chabert Medical Center (LJCMC), which is a rural safety-net hospital located in south Louisiana providing care primarily to uninsured and underinsured patients with a severely depressed socioeconomic (SES) background (more than 55% of patients were 200% below the federal poverty level). Recruitment of study participants took place from August 1999 to December 2007.

At the Florida site, patient enrolment took place from September 2007 to January 2009 at Jackson Memorial Hospital which is a large, urban 1600-bed safety-net hospital located in Miami, Florida. The patient population served at this hospital is largely indigent; 43% of patients in this study were classified as indigent and did not have any type of insurance, 38% had either Medicare or Medicaid, and the remaining 19% had private insurance. In addition, the patient population at this facility was largely comprised of immigrants, with 98% born outside the U.S. Institutional Review board approval was obtained from the University of Miami-Miller School of Medicine and the Louisiana State University Health Sciences Center. All patients gave written informed consent to have their data included in an electronic data registry.

Definitions and outcomes

Patients identified as having eGFR $<$60 mL/min/1.73 m^2 were classified as having CKD (CKD group), whereas patients identified as having eGFR $\geq$ 60 mL/min/1.73 m^2 were classified as not having CKD or non-CKD group.

The KDOQI working group defined CKD in adults as evidence of structural or functional kidney abnormalities (abnormal urinalysis, imaging studies, or histology) that persist for at least 3 months, with or without a decreased GFR (as defined by a GFR of $<$60 mL/min/1.73 m^2).[5] Laboratory tests performed closest to the date of enrolment into the clinic were used to stratify patients. Two blood samples taken at least 3 months apart were used to define CKD.

The most common manifestation of kidney damage is persistent albuminuria, including microalbuminuria.[6] The normal rate of albumin excretion is $<$20 mg/day (15 μg/min). Persistent albumin excretion between 30 and 300 mg/day (20–200 μg/min) is called microalbuminuria. Urinalysis performed closest to the date of enrolment was used to assess the presence of proteinuria.

The eGFR was calculated using the abbreviated Modification of Diet in Renal Disease Study equation:[5,7] eGFR (mL/min/1.73 m^2) = 186 $\times$ (serum creatinine in mg/dL)$^{-1.154}$ $\times$ (age in years)$^{-0.203}$ $\times$ 0.742 in female subjects $\times$ 1.210 in black subjects.

Patients were classified into five stages of CKD in accordance with the classification of the National Kidney Foundation (*Table 1*).

The online Social Security Death Index was used in order to obtain all-cause mortality data. Mortality was assessed up to 31 December 2009.

Statistical analysis

The overall CKD prevalence and prevalence by ethnic/race and gender were calculated. Ethnic/race and gender differences in CKD prevalence were analysed using the χ^2 test. Demographic and other clinical characteristics were compared between patients with CKD and those without CKD. For categorical variables, a χ^2 test was used to evaluate group differences. For continuous variables, analysis of variance was used to evaluate between-group differences. Survival was estimated by the Kaplan–Meier curves product–limit method and was compared between the two groups (patients with CKD and patients without CKD) with the χ^2 test. Careful consideration was taken to avoid pitfalls in the survival plots of time to event data.[8] The number of cases at risk was calculated as the number of cases that entered the respective interval alive minus half of the number of cases lost or censored in the respective interval. Unadjusted survival rates are presented and compared with *P* for trend and χ^2. For the adjusted analysis, we used two methods. First, we calculated the hazard ratio (HR) of death for subjects with CKD adjusting for EF, type of cardiomyopathy, use of angiotensin-converting enzyme (ACE) inhibitors and beta-blockers, and diabetes using Cox proportional models. We did not include demographic variables in our multivariate model because they were accounted for in the eGFR calculation. The second method was a Cox proportional model that included CKD stages as a dummy variable, for this analysis we used Stage 1 CKD as the reference value. All analyses were conducted using SAS 9.1, all tests were two-tailed, and a *P*-value of $<$0.05 was considered statistically significant.

Results

The study population consisted of 1301 patients. A total of 338 patients (26%) with HF were found to have CKD. Demographic and clinical characteristics according to the presence or absence of CKD are presented in *Table 2*. CKD patients were more likely to be older, to be of Hispanic ethnicity, to have less education, to have a higher NYHA class, to have diabetes, and higher systolic

Table 1 Staging of chronic kidney disease according to the National Kidney Foundation classification system

Stage	Description	GFR, mL/min/1.73 m^2
1	Kidney damage with normal or ↑ GFR	≥90
2	Kidney damage with mild ↓ GFR	60–89
3	Moderate ↓ GFR	30–59
4	Severe ↓ GFR	15–29
5	Kidney failure	<15 (or dialysis)

GFR glomerular filtration rate.

Table 2 Demographic characteristics of chronic kidney disease compared to non-chronic kidney disease patients

Variable	CKD (n = 338)	Non CKD (n = 963)	P-value
Age, years (SD)	62 (12)	54 (11)	<0.001
Gender			
Female, n (%)	109 (32%)	347 (36%)	$X^2 = 1.57$; $P = 0.210$
Male, n (%)	229 (68%)	616 (64%)	
Race			
White, n (%)	132 (39%)	408 (42%)	$X^2 = 9.38$; $P = 0.009$
Hispanic, n (%)	86 (25%)	171 (18%)	
Black, n (%)	120 (36%)	384 (40%)	
Education level			
Elementary school (0–5 years)	57 (19%)	111 (12%)	$X^2 = 8.51$; $P = 0.014$
High school (6–12 years)	205 (68%)	675 (75%)	
Post high school (more than 12 years)	38 (13%)	111 (12%)	
NYHA, n (%)			
Class 1	66 (20%)	260 (28%)	$X^2 = 8.69$; $P = 0.034$
Class 2	113 (35%)	317 (34%)	
Class 3	114 (35%)	267 (29%)	
Class 4	32 (10%)	92 (10%)	
Systolic blood pressure, mmHg (SD)	135 (29)	130 (25)	0.002
Diastolic blood pressure, mmHg (SD)	79 (18)	79 (17)	0.775
Ischaemic cardiomyopathy, n (%)	278 (82%)	774 (80%)	$X^2 = 0.5$; $P = 0.451$
Diabetes, n (%)	143 (42%)	291 (30%)	$X^2 = 16.4$; $P = <0.001$
Mean EF, % (SD)	28 (10)	29 (11)	0.250
Mean eGFR, mL/min per 1.73 m^2 (SD)	42 (15)	94 (31)	<0.001
Beta blocker, n (%)	326 (96%)	929 (97%)	$X^2 = 0.08$; $P = 0.777$
ACE/ARB, n (%)	291 (91%)	898 (95%)	$X^2 = 6.73$; $P = 0.009$
Spironolactone, n (%)	56 (17%)	200 (21%)	$X^2 = 2.79$; $P = 0.095$
Digoxin, n (%)	71 (21%)	245 (25%)	$X^2 = 2.67$; $P = 0.102$

Table 3 Prevalence of chronic kidney disease and survival according to chronic kidney disease stage

CKD stage	Prevalence of stage, n (%)	% survival
1	449 (34.5)	93.3
2	514 (39.5)	91.8
3	267 (20.5)	90.6
4	47 (3.6)	87.2
5	24 (1.5)	87.5

P-value χ^2 (4 dof) = 0.23; P-value trend (4 dof) = 0.059.

blood pressure (SBP) in comparison with non-CKD patients. Chronic kidney disease patients were also less likely to be prescribed ACE inhibitors.

Chronic kidney disease was more prevalent in men than in women although this difference was not statistically significant.

Table 3 shows the prevalence of CKD and survival percentage by CKD stage during the period of the study. Patients in Stage 1 CKD had the highest survival rate. The lowest survival rate was found in patients in Stage 4 and 5 CKDs, which was marginally significant compared with Stage 1 CKD ($P = 0.075$). Although mortality consistently increases at each stage of CKD, this trend was not statistically significant ($P = 0.059$).

One hundred and six patients died after enrolment into the HFDMP. The survival curve (*Figure 1*) shows that CKD patients had significantly lower survival rates compared with patients without CKD (χ^2 for 1 dof $P = 0.04$). The survival of heart failure patients worsened with worsening CKD stage.

The adjusted HR of death for patients with CKD was 1.29 (95% CI 0.81–2.05), $P = 0.27$. When each stage of CKD was evaluated individually in the multivariate model, we found a graded increase in the risk of death and that Stage 4 had an HR of 2.4 (95% CI 1.01–6.11), $P = 0.04$.

Discussion

This study examined the prevalence of CKD across three race/ethnic groups of HF patients as well as by gender. We found that the prevalence of CKD was high with over one in four HF patients affected.

In contrast to previous studies, we found that the prevalence of CKD was higher among Hispanics in our sample. In the literature,

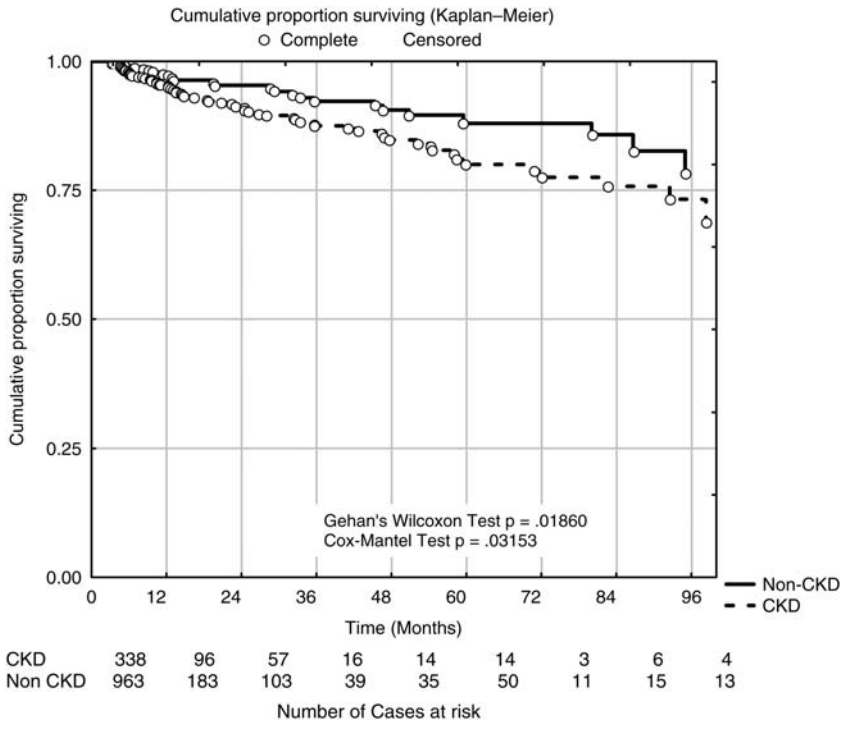

Figure 1 Kaplan–Meier cumulative survival curve by chronic kidney disease.

the prevalence of CKD among non-Hispanic blacks and Mexican Americans is higher in comparison with non-Hispanic Whites.[9]

The lack of concordance between our results and reports from previous studies may be attributed to differences in the study populations and associated risk factors. The Hispanic group in our sample was composed mainly of Cuban descendents and very few Mexican Americans, who represents the majority of Hispanics in the USA, were enrolled.

Past studies have reported a higher prevalence of CKD in males in comparison with females. Our results are in concordance with these reports;[10] however, in our sample, this difference was not statistically significant.

Our results further support an association between diabetes and CKD since the prevalence of CKD was clearly higher among our diabetic patients. As a matter fact diabetes mellitus, types 1 and 2, is the leading cause of incident and prevalent CKD, accounting for ~30–40% of CKD and up to 45% of ESRD.[11]

In this study, SBP was higher among CKD patients. Hypertension is one of the leading causes of ESRD in Europe and in the United States. Previous research has identified hypertension as an independent risk factor in the development and progression of CKD.[11–13] Furthermore, in a study by Young *et al.*,[13] SBP was identified as a strong predictor of a decline in kidney function among patients aged ≥70 years. Moreover, the risk of kidney dysfunction was strongly associated with SBP, when compared with diastolic blood pressure and mean arterial pressure. However, in contrast to previous studies,[9] we did not find statistically significant differences in the prevalence of ischaemic cardiomyopathy.

Regarding medications, the use of ACE inhibitor and angiotensin-receptor blocker was more prevalent among non-CKD patients, which is not surprising since the use of these drugs is sometimes prohibited in patients with a decreased GFR.[14,15]

In our study, CKD was more prevalent among those with lesser educational attainment. Several other authors[16–19] have previously described an association between lower SES and educational achievement and progressive CKD.

In agreement with the findings from the majority of previous studies, we found that patients with more severe kidney dysfunction have higher mortality than patients with less severe kidney impairment[10] as shown by decreased survival among patients in CKD Stages 4 and 5.

Our study has some limitations. The study population was mainly from a low SES background and were either uninsured or underinsured; therefore, it is unclear whether the results from this study could be generalized to Whites, Blacks, and Hispanics with a higher SES background or with private insurance.

The Hispanic patients in this study were primarily Cuban in origin. Although Cubans represent a majority in Miami, Mexican Americans represent the majority of Hispanics in the USA so again; these results may not be applicable to Hispanics in the USA in general.

Understanding the role of renal impairment in HF could provide more precise risk stratification, prognostication and, ultimately, the development of optimal therapeutic strategies. The precise magnitude of these risk factors are not known, however, given the

growing incidences of HF and CKD, both exceptionally costly and morbid conditions, it is important to acknowledge the magnitude of this problem.

Conclusion

Chronic kidney disease affects more than one in four patients from an outpatient systolic HF population, which is higher than the prevalence of CKD in the general population. Chronic kidney disease patients have significantly lower survival rates compared with patients without CKD. It is vital to understand the best method of estimating and characterizing renal impairment among HF patients as well as defining effective management strategies since this can have an impact on their survival.

Conflict of interest: none declared.

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