Prognostic Impact of Chronic Kidney Disease in Patients with Heart Failure

Nektar Nikki Hakopian, PharmD[1]; Derenik Gharibian, PharmD[1]; Marlene M Nashed, PharmD, BCPS[1]

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ABSTRACT

Introduction: Heart failure (HF) and chronic kidney disease (CKD) share many risk factors, and cardiac and renal dysfunction often coexist. The close association between HF and CKD worsens patient prognosis.

Objective: To examine the association between progressing CKD with rates of hospitalization, 30-day readmission, and mortality in patients with HF.

Methods: A retrospective analysis was conducted from January 1, 2012, to December 31, 2016, in the Kaiser Permanente Southern California Region. All patients age 18 years or older with a diagnosis of comorbid CKD and HF were included. Patients were excluded if they were noncontinuous members of Kaiser Permanente. Those included in the study were stratified into 2 cohorts: Early-stage CKD (stages 1, 2, and 3) and late-stage CKD (stages 4 and 5) on the basis of their estimated glomerular filtration rate in accordance with the National Kidney Foundation.

Results: A total of 27,366 patients were identified with comorbid HF and CKD. At the first year of follow-up, patients with HF and late-stage CKD had higher all-cause hospitalization (rate ratio [RR] = 1.56, 95% confidence interval [CI] = 1.48-1.65, $p < 0.001$), HF-related hospitalization (RR = 1.25, 95% CI = 1.20-1.41, $p = 0.001$), and 30-day readmission rates (RR = 1.46, 95% CI = 1.31-1.63, $p < 0.001$) compared with patients with HF and early-stage CKD. In subsequent follow-up years, patients continued to have higher all-cause and HF-related hospitalization rates in late-stage CKD. The late-stage CKD cohort had a significantly higher risk of 5-year mortality (hazard ratio = 1.40, 95% CI = 1.35-1.45, $p < 0.001$).

Conclusion: Stage 4 and 5 CKD is a significant contributor to poor prognosis in patients with HF, leading to significantly higher rates of hospitalization, 30-day readmission, and mortality.

BACKGROUND

Heart failure (HF) constitutes a significant clinical and economic burden to the health care system because of the high rates of hospitalizations and 30-day readmissions associated with this diagnosis. HF is a clinical syndrome that is etiologically and pathophysiologically heterogeneous, resulting in inadequate systemic perfusion to meet the body's metabolic demands. The condition can result from structural and/or functional cardiovascular disorders or other systemic factors.[1] The American Heart Association has reported coronary artery disease (CAD), hypertension, prior myocardial infarction (MI), valvular heart disease, cardiomyopathies, congenital heart disease, anemia, hyperthyroidism, chronic arrhythmias, and obesity as common causes of HF. Patients with HF often have many comorbidities, such as hypertension, diabetes mellitus, anemia, and renal insufficiency. Renal dysfunction is especially common in patients with HF and is often potentiated by the presence of anemia, hyperkalemia, low serum albumin, and diuretics.[2,3]

Chronic kidney disease (CKD) is a heterogeneous group of disorders characterized by alterations in kidney structure and function. The Kidney Disease: Improving Global Outcomes and Kidney Disease Outcomes Quality Initiative define CKD by the presence of kidney damage or decreased kidney function for ≥ 3 months. Kidney damage is defined by pathologic kidney abnormalities, detected by imaging, or implied from markers of kidney damage, including sediment abnormalities, albuminuria, electrolyte abnormalities, and other abnormalities. Decreased kidney function refers to a decreased glomerular filtration rate (GFR) that is not associated with a transient, reversible condition, such as volume depletion. Kidney failure, also called end-stage renal disease, is defined as severely reduced kidney function that requires treatment with dialysis or transplantation.[3,4]

HF and CKD share many risk factors, including hypertension, diabetes, and CAD. Cardiac and renal dysfunction often coexist, and the association is referred to as cardiorenal syndrome (CRS). CRS is generally defined as disorders of the heart and kidneys in which acute or chronic dysfunction in 1 organ triggers acute or chronic dysfunction in the other. For example, heart disease as a primary disorder can experience reduced kidney function as a secondary disorder, and vice versa, or both can coexist based on shared risk factors or systemic disorders. In recent years, our understanding of the close interconnection between cardiac and renal function has evolved with better understanding of the pathophysiologic background.[5] The pathophysiologic mechanism of CRS encompasses a complex interaction among hemodynamic variations, including reduced renal perfusion, increased venous pressure, and activation of multiple neurohormonal systems.[5,6] The clinical management of patients with CRS includes the challenge of differentiating volume overload as caused by HF or CKD or the combination of the two. Furthermore, managing volume overload in patients with CRS may be mutually contradictory. For example, attempting to treat volume overload and congestion with aggressive use of diuretics may cause volume depletion and directly worsen renal function. Similarly, the use of renin-angiotensin system inhibitors, although cardiorenal protective, can lead

Author Affiliations
[1] Pharmacy Residency Program, Los Angeles Medical Center, CA

Corresponding Author
Nektar Nikki Hakopian, PharmD (nektar.n.hakopian@kp.org)

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to temporary worsening of renal function in the setting of acute kidney injury. [5,6,7]

The close association between HF and CKD worsens patient prognosis. The annual data report of the US Renal Data System in 2016 reported that the prevalence of congestive HF in patients with CKD who were age 66 years and older was 28%, compared with 6% among patients without CKD.[8] Furthermore, an estimated 35% to 70% of patients with HF have CKD, and the comorbidity of CKD is associated with increased HF-related hospitalizations and mortality.[4,8] Previous studies examined the short-term association of CKD stage on mortality and readmission rates 6 months after an HF-related hospitalization. The findings demonstrated increased postdischarge readmission and mortality with worsening renal function.[8,9,10] In this study, the analysis of HF in patients with different degrees of kidney dysfunction provides an opportunity to review short-term and long-term outcomes in a large population because it pertains to hospitalization, readmission, and mortality rates. This study further examines the extent to which different comorbidities and clinical characteristics contribute to patient outcomes. The findings of this study may identify a group of high-risk patients and suggest a pragmatic approach to improving the identification and care of patients with comorbid HF and CKD.

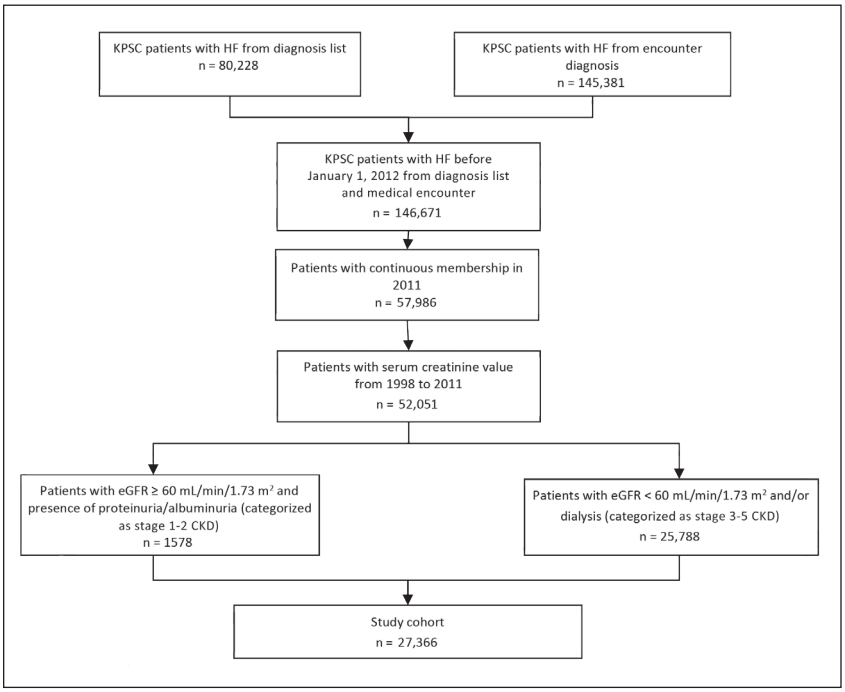

Figure 1. Flow chart of patient selection process.
CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; HF = heart failure; KPSC = Kaiser Permanente Southern California.

METHODS

Study Population, Selection Criteria, and Definitions

This study evaluated 27,366 patients from the Kaiser Permanente (KP) Southern California (KPSC) Region medical facilities from January 1, 2012, to December 31, 2016 (Figure 1). Study patients were included if they were age 18 years or older with a diagnosis of HF as noted by a physician and documented in the electronic medical record under diagnosis and/or discharge diagnosis for medical encounters. All diagnoses were classified using the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM).

To ensure adequate baseline characterization of the patient's clinical status, patients with < 12 months of continuous Health Plan membership before the index date were excluded from the study. Patients were also excluded if documented serum creatinine laboratory test values were missing between 1998 and 2011. The study was performed at the KP Los Angeles Medical Center. This study was reviewed and approved by the KPSC Region Institutional Review Board.

The presence of CKD was determined on the basis of kidney damage and level of kidney function. The estimated GFR (eGFR) was used to represent kidney function using the equation proposed in the Chronic Kidney Disease Epidemiology Collaboration in 2009, consistent with the National Kidney Foundation recommendations. We categorized CKD on the basis of eGFR as follows: ≥ 90 mL/min/1.73 m^2 (stage 1), 60 to 89 mL/min/1.73 m^2 (stage 2), 30 to 59 mL/min/1.73 m^2 (stage 3), 15 to 29 mL/min/1.73 m^2 (stage 4), < 15 mL/min/1.73 m^2 not undergoing dialysis (stage 5), and dialysis (stage 5). For stage 1 and 2 CKD, kidney damage was defined by the presence of albuminuria and proteinuria on the basis of the method of urine collection and sex: eGFR = 141 × minimum (serum creatinine/κ, 1)$^{\alpha}$ × maximum (serum creatinine/κ, 1)$^{-1.209}$ × 0.993 (age) × 1.018 (if female) × 1.159 (if black), with α = −0.329 (women) or −0.411 (men) and κ = 0.7 (women) or 0.9 (men). Tables 1 and 2 give the classification of CKD stage based on the presence of markers of kidney disease and eGFR.

Study patients (N = 27,366) were divided into 2 cohorts: 1) patients with HF and early-stage CKD, defined as stage 1, 2, and 3 CKD with eGFR ≥ 30mL/min/1.73 m^2 (n = 20,607) and 2) patients with HF and late-stage CKD, defined as stage 4 and 5 CKD with eGFR < 30 mL/min/1.73 m^2 or undergoing dialysis (n = 6759). Patients undergoing dialysis were not excluded from the primary and secondary outcomes.

Study Endpoints and Variables Analyzed

The primary outcomes of the study were rate of all-cause hospitalization and HF-related hospitalization. Secondary outcomes included 30-day readmission and mortality rates. To investigate the influence of the stages of CKD and HF, the primary and secondary endpoints were measured annually for 5 years starting at the prespecified index date of January 1, 2012. All

patients were followed-up until death, loss of Health Plan membership, or December 31, 2016, whichever event occurred first.

The following baseline covariates were collected and included in the hazard models: 1) demographic covariates, including age, sex, ethnicity, and body mass index; 2) pertinent laboratory test values, including serum creatinine, blood urea nitrogen, hemoglobin, and serum sodium; and 3) relevant comorbidities, identified by ICD-10-CM codes, including diabetes mellitus, hypertension, atrial fibrillation (AF), asthma, prior MI, angina, and CAD. MI, angina, and CAD were counted as separate covariates. All clinical data were collected in a retrospective manner throughout the study period.

Table 1. Chronic kidney disease stage classification based on estimated glomerular filtration rate

Stage	Description	eGFR, 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)

[a] Upward arrow indicate increased; downward arrow, decreased.
eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate.

Table 2. Kidney damage defined by the presence of albuminuria and proteinuria

Component	Urine collection method	Albuminuria/clinical proteinuria
Albumin	24-h microalbumin	>300 mg/L
	Microalbumin/creatinine	>250 µg/mg (men)
		>355 µg/mg (women)
Total protein	24-h excretion	>300 mg/L
	Protein, random	>30 mg/dL
	Protein-to-creatinine ratio	>200 mg/g

Table 3. Clinical characteristics stratified by chronic kidney disease stage[a]

Characteristic	Early-stage CKD (stage 1-3) (n = 20,607)	Late-stage CKD (stage 4-5) (n = 6759)	p value
Age, mean (SD), y	77.1 (10.90)	72.4 (13.18)	< 0.001
Female	10,384 (50.4)	3323 (49.2)	0.08
Ethnicity			< 0.001
White	12,939 (62.8)	2861 (42.3)	
Black	2732 (13.3)	1384 (20.5)	
Hispanic	3604 (17.5)	1873 (27.7)	
Asian	1164 (5.6)	556 (8.2)	
Other	168 (0.8)	85 (1.3)	
BMI > 30	12,275 (59.6)	4183 (61.9)	< 0.001
Creatinine, mean (SD), mg/dL	1.3 (0.30)	2.5 (0.94)	< 0.001
eGFR, mean (SD), mL/min/1.73 m^2	49.4 (12.84)	22.8 (5.58)	< 0.001
BUN, mean (SD), mg/dL	24.2 (10.60)	43.7 (21.23)	< 0.001
Hemoglobin, mean (SD), g/dL	12.6 (1.73)	11.3 (1.59)	< 0.001
Sodium, mean (SD), mEq/L	139.0 (3.04)	138.5 (3.38)	< 0.001
Diabetes mellitus	9980 (48.4)	4731 (70)	< 0.001
Hypertension	19,028 (92.3)	6617 (97.9)	< 0.001
Atrial fibrillation	7720 (37.5)	1855 (27.4)	< 0.001
Asthma	2759 (13.4)	731 (10.8)	< 0.001
Prior myocardial infarction	772 (3.7)	304 (4.5)	0.006
Angina	15,565 (75.5)	5070 (75)	0.388
Coronary artery disease	7547 (36.6)	2467 (36.5)	0.854

[a] Data are presented as number (percentage) of patients unless otherwise indicated.
BMI = body mass index; BUN = blood urea nitrogen; CKD = chronic kidney disease; eGFR = estimated glomerular infiltration rate; SD = standard deviation.

Statistical Analysis

The Wilcoxon rank-sum test was used for between-group comparisons for continuous variables, expressed as means (standard deviations). Categorical or dichotomous variables were expressed as percentages and compared using the χ^2 test. Multivariate negative binomial regression analysis was used to assess the association between different CKD stages and HF for hospitalization and readmission rates, expressed as incidence rate ratios (RRs) and 95% confidence intervals (CIs). To determine whether the effects of CKD stage on primary and secondary outcomes varied by patient clinical characteristics or baseline comorbidities, differences at baseline were adjusted using the multivariate negative binomial regression, and adjusted outcomes were expressed as RRs and 95% CIs. A Cox proportional hazards regression model was used to calculate 5-year mortality rates, with results reported as hazard ratios (HRs) and 95% CIs. Survival curves were produced using the Kaplan-Meier method for the patients in the 2 subgroups to determine the survival of patients with respect to the different eGFR quartiles. Given the large number of patients in this data set and to minimize the chance of a type I error, a 95% CI for the main analyses was chosen. Therefore, $p < 0.05$ was required to deem a result statistically significant.

All analyses were conducted using SAS statistical software, version 9.3 (SAS Institute, Inc, Cary, NC).

RESULTS

A total of 27,366 patients were retrospectively analyzed and included in the study. Table 3 gives the baseline clinical and demographic characteristics stratified by early-stage and late-stage CKD. Given the large sample size, some clinical and demographic characteristics with minimal difference demonstrated statistically

Table 4. Annual rate of adjusted and unadjusted all-cause hospitalization

Year	Incidence rate ratio (95% CI)		p value	Unadjusted rate ratio (95% CI)	p value	Adjusted rate ratio (95% CI)	p value
	Stage 1-3 CKD	Stage 4-5 CKD					
1	0.668 (0.650-0.686)	1.313 (1.258-1.371)	< 0.001	1.968 (1.870-2.070)	< 0.001	1.558 (1.475-1.645)	< 0.001
2	0.705 (0.689-0.721)	1.372 (1.322-1.424)	< 0.001	1.946 (1.863-2.033)	< 0.001	1.554 (1.483-1.628)	< 0.001
3	0.732 (0.717-0.748)	1.409 (1.361-1.459)	< 0.001	1.924 (1.848-2.004)	< 0.001	1.547 (1.481-1.615)	< 0.001
4	0.760 (0.744-0.775)	1.425 (1.378-1.474)	< 0.001	1.876 (1.805-1.951)	< 0.001	1.515 (1.453-1.579)	< 0.001
5	0.772 (0.757-0.787)	1.436 (1.390-1.484)	< 0.001	1.860 (1.791-1.932)	< 0.001	1.508 (1.448-1.570)	< 0.001

CI = confidence interval; CKD = chronic kidney disease.

Table 5. Annual rate of adjusted and unadjusted heart failure-related hospitalization

Year	Incidence rate ratio (95% CI)		p value	Unadjusted rate ratio (95% CI)	p value	Adjusted rate ratio (95% CI)	p value
	Stage 1-3 CKD	Stage 4-5 CKD					
1	0.088 (0.083-0.094)	0.141 (0.127-0.156)	< 0.001	1.596 (1.415-1.801)	< 0.001	1.245 (1.096-1.414)	0.001
2	0.097 (0.092-0.103)	0.141(0.129-0.154)	< 0.001	1.449 (1.306-1.608)	< 0.001	1.171 (1.051-1.306)	0.004
3	0.101(0.096-0.106)	0.138 (0.127-0.151)	< 0.001	1.367 (1.241-1.506)	< 0.001	1.121 (1.014-1.239)	0.026
4	0.107 (0.102-0.112)	0.137 (0.127-0.148)	< 0.001	1.285 (1.173-1.408)	< 0.001	1.066 (0.971-1.172)	0.181
5	0.108 (0.103-0.113)	0.135 (0.125-0.146)	< 0.001	1.253 (1.147-1.369)	< 0.001	1.036 (0.945-1.135)	0.453

CI = confidence interval; CKD = chronic kidney disease.

Table 6. Annual rate of adjusted and unadjusted 30-day readmission

Year	Incidence rate ratio (95% CI)		p value	Unadjusted rate ratio (95% CI)	p value	Adjusted rate ratio (95% CI)	p value
	Stage 1-3 CKD	Stage 4-5 CKD					
1	0.446 (0.420-0.474)	0.826 (0.764-0.892)	< 0.001	1.852 (1.678-2.044)	< 0.001	1.461 (1.310-1.629)	< 0.001
2	0.320 (0.305-0.336)	0.640 (0.599-0.685)	< 0.001	2.001 (1.843-2.172)	< 0.001	1.535 (1.403-1.680)	< 0.001
3	0.278 (0.266-0.291)	0.590 (0.554-0.629)	< 0.001	2.121 (1.966-2.290)	< 0.001	1.588 (1.461-1.726)	< 0.001
4	0.258 (0.248-0.269)	0.557 (0.525-0.592)	< 0.001	2.162 (2.011-2.324)	< 0.001	1.601 (1.480-1.733)	< 0.001
5	0.245 (0.235-0.254)	0.538 (0.507-0.570)	< 0.001	2.199 (2.050-2.358)	< 0.001	1.626 (1.507-1.754)	< 0.001

CI = confidence interval; CKD = chronic kidney disease.

significant differences. Patients with late-stage CKD were younger and had a higher comorbidity burden, including higher prevalence of diabetes, hypertension, and history of MI. In addition, given the spectrum of the disease activity, the late-stage CKD cohort had higher serum creatinine and lower eGFR values.

The short-term and long-term risks of all-cause hospitalization (Table 4), HF-related hospitalization (Table 5), and 30-day readmission (Table 6) were significantly higher in patients with HF and late-stage CKD compared with patients with HF and early-stage CKD. At the first year of follow-up, patients with late stage CKD had significantly higher hospitalization rates than patients with early-stage CKD. The crude or unadjusted hospitalization rate at the first year of follow-up for late-stage CKD was 97% higher than for early-stage CKD (RR = 1.97, 95% CI = 1.87-2.07, p < 0.001). After adjustment for baseline covariates, patients with late-stage CKD had 56% higher hospitalization rates (RR = 1.56, 95% CI = 1.48-1.65, p < 0.001). The long-term 5-year impact of late-stage CKD on the all-cause hospitalization rate continued to be significantly higher, with an unadjusted rate of 86% (RR = 1.86, 95% CI = 1.79-1.93, p < 0.001) and by an adjusted rate of 51% (RR = 1.51, 95% CI = 1.45-1.57, p < 0.001). The top baseline covariate predictors for increased hospitalization rates included history of AF, MI, asthma, diabetes, CAD, and angina (Figure 2).

The short-term and long-term HF-related hospitalization rates were also higher in late-stage CKD compared with early-stage CKD. HF-related hospitalization at the first year of follow-up was significantly higher by an unadjusted rate of 60% (RR = 1.60, 95% CI = 1.42-1.80, p < 0.001) and an adjusted rate of 25% (RR = 1.25, 95% CI = 1.20-1.41, p = 0.001) in late-stage CKD compared with early-stage CKD. At 5-year follow-up, patients continued to have higher HF-related hospitalization rates by an unadjusted rate of 25% (RR = 1.25, 95% CI = 1.15-1.37, p < 0.001). After adjustment for baseline covariates, patients with late-stage CKD did not have statistically significant HF-related hospitalization rates at 5 years (RR = 1.04, 95% CI = 0.95-1.14, p = 0.453). The top baseline covariate predictors for increased HF-related hospitalization included history of AF, MI, asthma, diabetes, CAD, angina, and patients of black decent (Figure 3).

Furthermore, 30-day readmission rates were significantly higher in patients with late-stage CKD throughout the 5-year study period by an unadjusted rate of 85% (RR = 1.85, 95% CI = 1.68-2.04, p < 0.001) and an adjusted rate of 46% (RR = 1.46, 95% CI = 1.31-1.63, p < 0.001) at year 1. At 5-year follow-up, patients with late-stage CKD continued to have statistically significantly higher 30-day readmission rates by an unadjusted

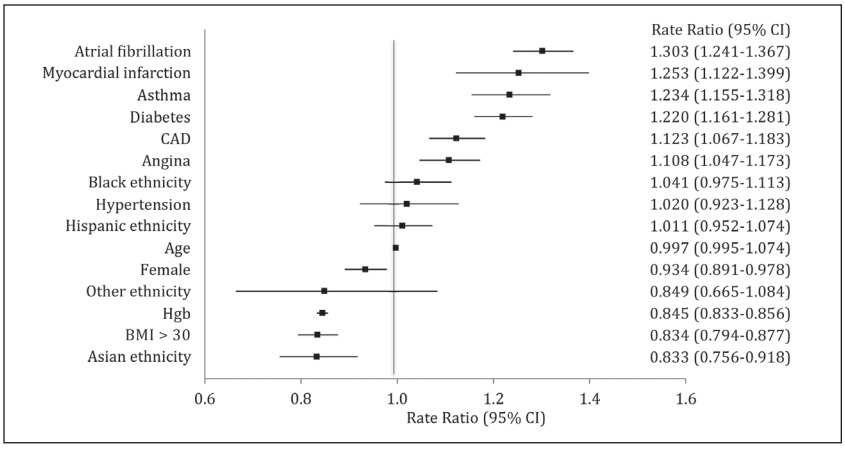

Figure 2. Baseline covariates predictive of increased all-cause hospitalization.
Forest plot graphically illustrating adjustment for baseline covariates.
BMI = body mass index; CAD = coronary artery disease; CI = confidence interval; Hgb = hemoglobin.

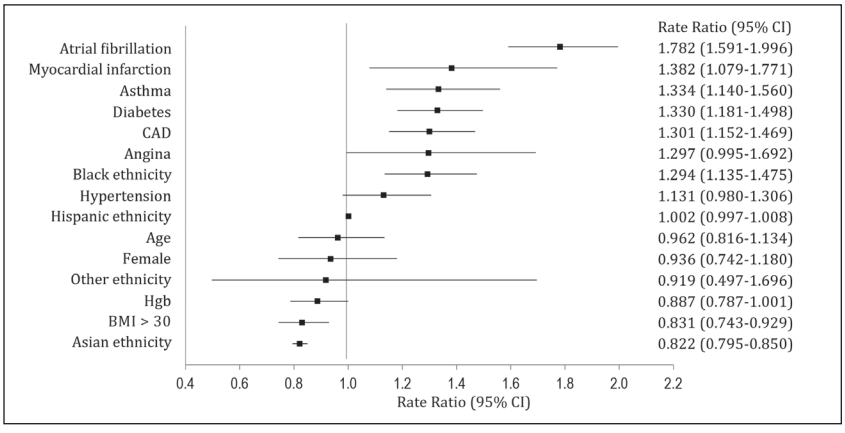

Figure 3. Baseline covariates predictive of increased heart failure-related hospitalization.
Forest plot graphically illustrating adjustment for baseline covariates.
BMI = body mass index; CAD = coronary artery disease; CI = confidence interval; Hgb = hemoglobin.

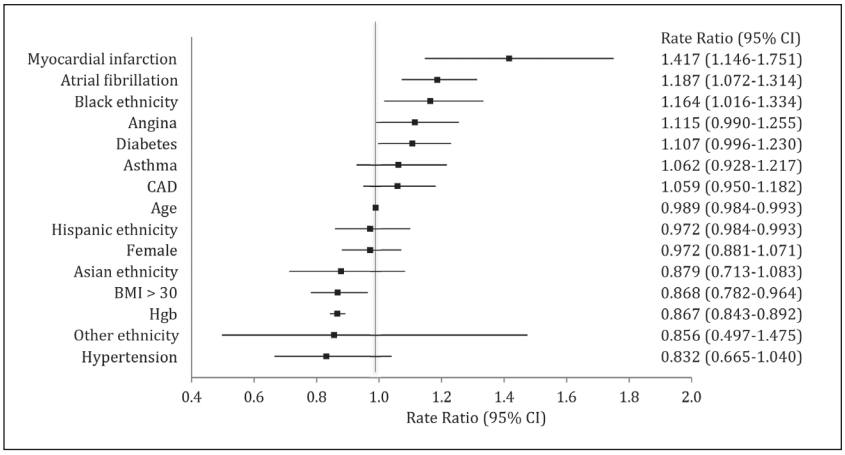

Figure 4. Baseline covariates predictive of increased 30-day readmission.
Forest plot graphically illustrating adjustment for baseline covariates.
BMI = body mass index; CAD = coronary artery disease; CI = confidence interval; Hgb = hemoglobin.

rate of 120% (RR = 2.20, 95% CI = 2.05-2.36, p < 0.001) and an adjusted rate of 63% (RR = 1.63, 95% CI = 1.51-1.75, p < 0.001). The top baseline covariate predictors for increased 30-day readmission included history of AF, MI, and patients of black decent (Figure 4).

The Cox proportional hazards regression model found that the late-stage CKD cohort had significantly higher risk of 5-year mortality (HR = 1.40, 95% CI = 1.35-1.45, p <0.001; Figure 5).

DISCUSSION

HF is a well-recognized condition and a major public health issue with high rates of hospitalization, readmission, and mortality. Despite improvements in care, HF morbidity and mortality remain high, with 1 in 9 deaths attributed to HF and an annual cost of $30.7 billion in the US.[11] An estimated 35% to 70% of patients with HF have abnormal renal function, which has been recognized as a major contributor to unfavorable cardiovascular outcomes in patients with HF.[12] It has also been reported that the presence of CKD increased the risk of mortality within the first year for patients with HF (odds ratio = 1.62, 90% CI = 1.15-2.30). Furthermore, the presence of CKD increased the risk of early readmission for CHF (odds ratio = 1.70, 90% CI = 1.18-2.44).[13]

This study examined the impact of different stages of CKD on the prognostic factors of patients with HF, in particular, hospitalization, readmission, and mortality. The study cohort consisted of patients age 18 years or older with HF, CKD, and a commercial health care plan. Laboratory-based CKD staging was used, and patients were stratified into 2 cohorts: Early-stage CKD (stages 1, 2, and 3) and late-stage CKD (stages 4 and 5). The subset with late-stage CKD had a higher comorbidity burden at baseline, including higher prevalence of diabetes, hypertension, and history of MI. To determine whether the effects of CKD stage on hospitalization varied by the patient clinical characteristics or baseline comorbidities, we adjusted for the imbalances. Even after adjusting for the baseline clinical characteristics, there was a significant trend noted with regard to patients with late-stage CKD and HF. Patients with advancing CKD stages had

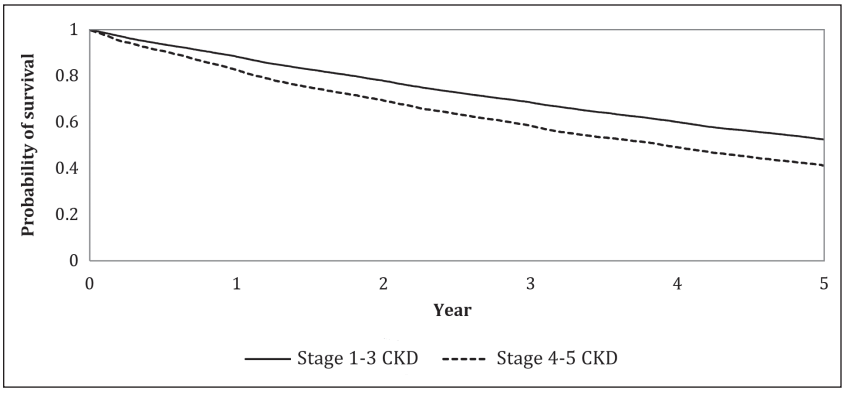

Figure 5. Cox proportional hazard regression models and Kaplan-Meier overall survival curve of the risk of mortality in patients with late-stage chronic kidney disease compared with patients with early-stage chronic kidney disease.
CKD = chronic kidney disease.

significantly higher risk of hospitalizations, readmissions, and mortality.

The observations of this study far exceeded what was expected on the basis of the available published data. For example, the 5-year impact of late-stage CKD on patients with HF was significantly higher 30-day readmission rates by an unadjusted rate of 120% (RR = 2.20, 95% CI = 2.05-2.36, $p < 0.001$) and an adjusted rate of 63% (RR = 1.63, 95% CI = 1.51-1.75, $p < 0.001$) when compared with patients with early-stage CKD. On the basis of the Kaplan-Meier probabilities, the late-stage CKD cohort had a significantly higher risk of 5-year mortality (HR = 1.40, 95% CI = 1.3-1.45, $p < 0.001$). As a result of high mortality rates, we saw a reduction in the study population with progressing years. Although it is not a true clinical implication, 52% of the study patients completed a 5-year follow-up (Figure 6). What was not accounted for in the study was the progression of kidney disease when measuring the 5-year outcomes. Although it is not unexpected that disease progresses, an estimated 13% of the patients progressed from early-stage CKD to late-stage CKD by year 5, which may underestimate the true association of late-stage CKD on study outcomes. Although the aim of the study was not to evaluate the pattern and rate of CKD progression, a follow-up study may consider evaluating the rate of progression in patients with stage 3 CKD with and without HF to confirm whether HF is a risk factor for CKD progression.

It is well recognized that studies report high mortality and hospitalization rates for individuals undergoing peritoneal dialysis and hemodialysis. This study did not make a distinction between individuals undergoing peritoneal dialysis and hemodialysis. A consideration can be made for future studies on what proportion of patients reaching end-stage renal disease began hemodialysis and how this would affect the prognostic factors. Additional limitations to this study include the inability to distinguish between the etiologic subtypes and severity of HF because of the inability to automate the extrapolation of ejection fraction data and additional measures of severity from electronic medical records. In addition, the study design was retrospective in nature; thus, the accuracy of the data was dependent on practitioner documentation. Lastly, albuminuria was used to assess kidney damage. However, its occurrence could be mitigated by the use of optimized medications, such as use of renin-angiotensin-system inhibitors, thereby inducing false-negative diagnoses. Albumin levels may also be transiently elevated, which may misclassify patients as having CKD and contribute to the large difference in outcomes between early- and late-stage CKD.

This study complements previous observations in patients with HF in that CKD imposes an unfavorable impact on the disease. More specifically, it demonstrates that stage 4 and 5 CKD is a significant contributor to poor prognosis in patients with HF. The cause of the overall findings of this study is likely multifactorial but suggests a need for a higher level of care in this population. A multidisciplinary team approach that consists of a cardiologist-nephrologist collaboration may be a novel way to synchronize goals of therapy given the complexity and bidirectional links between cardiac and renal function. Remaining challenges include identification of a subset of persons with CKD and HF who are likely to benefit from a multidisciplinary team approach and to determine the ideal components of the multidisciplinary team and renal/cardiac management. This important outcome should be assessed in future studies of multidisciplinary team care, as should mortality, hospitalization, readmission, and formal cost-effectiveness analyses.

In addition, AF was identified as a top baseline covariate predictor for increased all-cause hospitalization and HF-related hospitalization. AF frequently coexists with HF and may be explained by the presence of common risk factors, including hypertension, valvular heart disease, past MI, diabetes, and older age. The pathophysiologic association between AF and HF is a subject of great interest for research. It is believed that one of the mechanisms AF may be promoting (the development or progression of HF) is the result of shorter diastolic filling time attributable to the increase in resting heart rate and/or exaggerated heart rate. The rapid ventricular rate results in compromised ventricular filling, increased oxygen demand, and

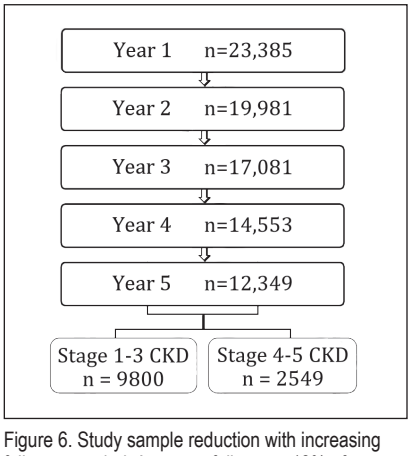

Figure 6. Study sample reduction with increasing follow-up period. At 5-year follow-up, 13% of patients with early-stage chronic kidney disease (CKD) progressed to late-stage CKD.

decreased coronary perfusion. The onset of AF is also believed to be associated with worsening HF functional class, peak oxygen consumption, and cardiac index. By restoring sinus rhythm, the cardiac output, exercise capacity, and maximal oxygen consumption are improved.[14,15] In our study, a time-dependent analysis was not conducted to assess for new-onset or chronic AF and whether patients were in sinus rhythm. Because the timing of AF in relation to HF may play a role in the prognosis of patients with HF, this methodologic limitation is important because it may leave uncertainties about the clinical implications of AF in HF.

CONCLUSION

This study found that stage 4 to 5 CKD was associated with increased risk of all-cause hospitalization, HF-related hospitalization, readmission, and mortality in patients with HF. With finite resources and the substantial cost burden imposed by HF, the findings of this study may have a number of implications for the management of this subset of patients. The findings of this study may help identify those at highest risk for hospitalizations, readmissions, and mortality. By implementing a multidisciplinary team approach to manage this high-risk subset of patients, we may potentially limit the economic and patient burden associated with HF. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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