Relationship between Stage of Kidney Disease and Incident Heart Failure in Older Adults

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Key Words

Chronic kidney disease • Heart failure

Abstract

Background: The relationship between stage of chronic kidney disease (CKD) and incident heart failure (HF) remains unclear. **Methods:** Of the 5,795 community-dwelling adults ≥ 65 years in the Cardiovascular Health Study, 5,450 were free of prevalent HF and had baseline estimated glomerular filtration rate (eGFR: ml/min/1.73 m²) data. Of these, 898 (16%) had CKD 3A (eGFR 45–59 ml/min/1.73 m²) and 242 (4%) had CKD stage $\geq 3B$ (eGFR <45 ml/min/1.73 m²). Data on baseline proteinuria were not available and 4,310 (79%) individuals with eGFR ≥ 60 ml/min/1.73 m² were considered to have no CKD. Propensity scores estimated separately for CKD 3A and $\geq 3B$ were used to assemble two cohorts of 1,714 (857 pairs with CKD 3A and no CKD) and 557 participants (148 CKD $\geq 3B$ and 409 no CKD), respectively, balanced on 50 baseline characteristics. **Results:** During 13 years of follow-up, centrally-adjudicated incident HF occurred in 19, 24 and 38% of pre-match participants without CKD (reference), with CKD 3A [unadjusted hazard ratio (HR) 1.40; 95% confidence interval (CI) 1.20–1.63; $p < 0.001$] and with CKD $\geq 3B$ (HR 3.37; 95%

CI 2.71–4.18; $p < 0.001$), respectively. In contrast, among matched participants, incident HF occurred in 23 and 23% of those with CKD 3A and no CKD, respectively (HR 1.03; 95% CI 0.85–1.26; $p = 0.746$), and 36 and 28% of those with CKD $\geq 3B$ and no CKD, respectively (HR 1.44; 95% CI 1.04–2.00; $p = 0.027$). **Conclusions:** Among community-dwelling older adults, CKD is a marker of incident HF regardless of stage; however, CKD $\geq 3B$, not CKD 3A, has a modest independent association with incident HF.

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Elevated serum creatinine is associated with an increased risk of incident heart failure (HF) [1, 2]. However, serum creatinine is a poor marker of kidney function, especially among older adults [3]. Although estimated glomerular filtration rate (eGFR) has emerged as a more reliable marker of kidney function, and low eGFR has been shown to be associated with poor outcomes in those with HF [4], little is known about the true association between kidney function, as determined by eGFR and incident HF. The aim of this study was to determine the association between CKD stage and incident HF in propensity-matched cohorts of community-dwelling older adults.

Fig. 1. Kaplan-Meier plots for incident HF by CKD stages: CKD 3A (a) and CKD ≥3B (b).

Methods

Study Design and Participants

The Cardiovascular Health Study (CHS) is a population-based prospective study of cardiovascular disease in older adults funded by the National Heart, Lung, and Blood Institute (NHLBI). Details of background, design and recruitment process for CHS have been previously reported [1, 2, 5–9]. Briefly, an original cohort of 5,201 community-dwelling older adults (age ≥65 years) was recruited during 1989–1990, and a second cohort of 687 African-American participants was recruited during 1992–1993. For this study, we used a de-identified public-use copy of the CHS data, which was obtained from the CHS Coordinating Center through the NHLBI and which is identical to the original CHS data except that 93 participants did not consent to be included in it. Of the 5,795 participants, 78 with missing baseline eGFR data and 267 with baseline HF were excluded, leaving 5,450 participants for the current analysis.

Baseline CKD and Other Measurements

Of the 5,450 patients, 898 (16%) had CKD stage 3A, defined as eGFR 45–59 ml/min/1.73 m², and estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [10]. Because the deleterious effects of CKD are not often observed until CKD is more advanced [11, 12], we also identified 242 (4%) participants who had stage ≥3B CKD (eGFR <45 ml/min/1.73 m²). Structural or functional kidney damage for ≥3 months as evidenced by pathological abnormalities in the composition of the blood or urine or in an imaging test is required to define CKD in individuals with eGFR ≥60 ml/min/1.73 m² [13]. However, baseline data on kidney damage were not available from CHS participants. Because the prevalence of albuminuria among those with eGFR 60–89 ml/min/1.73 m² is low [14], and the vast

majority of these individuals likely have no kidney damage, for the purpose of the current analysis, we considered eGFR ≥60 ml/min/1.73 m² as having no CKD.

Assembly of the Balanced Cohorts

Propensity score matching was used to assemble a cohort of participants with and without CKD who would be balanced in all measured baseline characteristics. Propensity scores for CKD stage 3A were estimated for each of the 5,208 participants using a non-parsimonious multivariable logistic regression model [4, 15–20]. In the model, CKD stage 3A was used as the dependent variable and the 50 baseline characteristics displayed in figure 1 were entered as covariates. We then used a 1-to-1 matching protocol to assemble a cohort of 857 pairs of participants with CKD stage 3A and no CKD who had similar propensity scores.

Propensity score models are sample-specific adjusters and are not intended to be used for out-of-sample prediction or estimation of coefficients. Therefore, absolute standardized differences, rather than measures of fitness and discrimination, are more appropriate for the assessment of the model's effectiveness [4, 5, 8, 15–20]. Absolute standardized differences directly quantify the bias in the means (or proportions) of covariates across the groups, expressed as a percentage of the pooled standard deviations. Therefore, we calculated pre- and post-match absolute standardized differences and presented those findings as Love plots [21–26]. An absolute standardized difference of 0% indicates no residual bias and <10% is considered of inconsequential bias.

Then we repeated the above process to assemble a cohort of participants with CKD stage ≥3B and no CKD (eGFR ≥60 ml/min/1.73 m²). Because of the small number of participants with CKD stage ≥3B (n = 242), we used a greedy matching protocol in which 1 participant with CKD stage ≥3B could be matched with up to 3 participants without CKD. In the end, we were able to

match 148 participants with CKD stage $\geq 3B$ and 409 participants without CKD, who had similar propensity scores, thus assembling a cohort of 557 participants. Absolute standardized differences for all 50 covariates were estimated and presented as Love plots [4, 15–20, 27].

Incident HF and Other Outcomes

The primary outcome for this study was new-onset HF during a median follow-up of over 13 years. Data on incident HF was collected annually and was centrally adjudicated in CHS, the process of which has been well described in the literature [2, 5, 28, 29]. Briefly, a central Events Committee adjudicated the diagnosis of HF based on a constellation of symptoms, physical signs, and other supporting findings suggestive of HF, including the use of medications commonly used for HF, and follow-up surveillances. The CHS criteria for diagnosis of HF has been reported to be more conservative than the criteria used in the Framingham Heart Study, and HF patients diagnosed using either criteria have been reported to have similar all-cause mortality rates [30]. Secondary outcomes include all-cause mortality and other incident cardiovascular events.

Statistical Analysis

Descriptive analyses included Pearson's χ^2 test, Student's *t* test, the Wilcoxon rank-sum test, and paired sample *t* test used as appropriate for between-group comparisons. We then used Kaplan-Meier and Cox proportional hazard analyses to estimate the associations between baseline CKD and outcomes. Proportional hazards assumptions were checked using log-minus-log scale survival plots. We examined the association of baseline CKD stage 3A and incident HF among 5,208 participants and baseline CKD stage $\geq 3B$ and incident HF among 4,552 participants using unadjusted and multivariable-adjusted models adjusting for all baseline characteristics used in the propensity model. A multivariable adjustment model using the propensity score was also performed. Associations of baseline CKD stage 3A with incident HF in the propensity-matched cohorts were assessed using Cox regression. A similar analysis was also completed comparing CKD stage $\geq 3B$ to those with no CKD. A formal sensitivity analysis was conducted to quantify the degree of a hidden bias that would need to be present to invalidate our conclusions based on the propensity-matched cohort [31]. All statistical tests were two-tailed with 95% confidence levels and a *p* value < 0.05 was considered significant. SPSS for Windows (Release 18, 2009; SPSS Inc., Chicago, Ill., USA) was used for all data analyses.

Results

Baseline Characteristics

Before matching, compared to participants without CKD, those with CKD stage 3A were more likely to be older and of Caucasian descent. They were also more likely to have coronary artery disease, hypertension, and higher systolic blood pressure (online suppl. table 1, for all online supplementary material see, www.karger.com/doi/10.1159/000328905). These and other

baseline characteristics were well balanced after matching (online suppl. fig. 1). Pre-match imbalances and post-match balances in baseline characteristics between patients with CKD stage $\geq 3B$ and no CKD are displayed in online supplementary table 2 and online supplementary figure 2.

Association of Baseline CKD with Incident HF

In the pre-match cohort, incident HF occurred in 24 and 19% of patients with CKD stage 3A and no CKD, respectively [unadjusted hazard ratio (HR) when CKD 3A was compared with no CKD, 95% confidence intervals (CI) 1.40; 95% CI 1.20–1.63; *p* < 0.001] (table 1). Multivariable-adjusted and propensity-adjusted associations of CKD with incident HF are displayed in table 1. Among the propensity-matched cohort, incident HF occurred in 23 and 23% of those with CKD stage 3A and without CKD (HR 1.03; 95% CI 0.85–1.26; *p* = 0.746) (table 1; fig. 1). No formal sensitivity analysis was conducted due to lack of any significant association between CKD and incident HF.

When we repeated our analysis comparing CKD stage $\geq 3B$ (eGFR < 45 ml/min/1.73 m²) with no CKD, incident HF occurred in 38% of those with CKD stage $\geq 3B$ and 19% of those with no CKD (unadjusted HR when CKD stage $\geq 3B$ is compared with no CKD, 3.37; 95% CI 2.71–4.18; *p* < 0.001) (table 1). Multivariable-adjusted and propensity-adjusted associations of CKD with incident HF are displayed in table 1. In the propensity-matched cohort, incident HF occurred in 36% of participants with CKD stage $\geq 3B$ and 28% of those with no CKD (HR 1.44; 95% CI 1.04–2.00; *p* = 0.027) (table 1). Findings from the Kaplan-Meier survival analysis suggest that the increased incidence of HF among those with CKD stage $\geq 3B$ compared to the no CKD group did not occur until after 5 years of follow-up (fig. 1). In the absence of a hidden bias, a sign-score test for matched data with censoring provides evidence (*p* = 0.117) that the incidence of HF did not significantly vary between older adults with CKD stage $\geq 3B$ and those with no CKD.

Association of Baseline CKD with Other Outcomes

Compared to the no CKD group, both CKD stage 3A and stage $\geq 3B$ were associated with an increased risk of all-cause mortality, both before and after matching (table 2). Associations of baseline CKD stages 3A and $\geq 3B$ with other outcomes are displayed in table 2.

Table 1. Association of CKD stage with incident HF

	Events, n (%)		Absolute risk difference ¹ , %	Hazard ratio (95% CI)	p value
	no CKD	CKD 3A			
Before matching (n = 5,208)	4,310	898			
Unadjusted	824 (19)	213 (24)	+5	1.40 (1.20–1.63)	<0.001
Multivariable-adjusted				1.00 (0.85–1.18)	0.967
Propensity-adjusted				1.01 (0.86–1.19)	0.870
After matching (n = 1,714)	857	857			
Propensity-matched	200 (23)	200 (23)	0	1.03 (0.85–1.26)	0.746
	no CKD	CKD ≥3B			
Before matching (n = 4,552)	4,310	242			
Unadjusted	824 (19)	92 (38)	+8	3.37 (2.71–4.18)	<0.001
Multivariable-adjusted				1.59 (1.24–2.05)	<0.001
Propensity-adjusted				1.48 (1.10–2.00)	0.009
After matching (n = 557)	409	148			
Propensity-matched	115 (28)	53 (36)	+8	1.44 (1.04–2.00)	0.027

¹ Absolute risk differences were calculated by subtracting the percentage of events in the no CKD group from those in the CKD 3A and CKD ≥3B groups before rounding, respectively.

Table 2. Hazard ratios (95% CI) for other outcomes by CKD

	Before matching		After matching	
	hazard ratio (95% CI)	p value	hazard ratio (95% CI)	p value
CKD 3A				
All-cause mortality	1.61 (1.46–1.78)	<0.001	1.20 (1.05–1.36)	0.008
Acute myocardial infarction	1.26 (1.02–1.56)	0.032	1.10 (0.83–1.46)	0.505
Stroke	1.37 (1.13–1.66)	0.002	1.27 (0.98–1.65)	0.066
Transient ischemic attack	1.27 (0.86–1.87)	0.227	0.98 (0.60–1.62)	0.946
Peripheral artery disease	1.97 (1.42–2.72)	<0.001	1.43 (0.93–2.21)	0.100
CKD ≥3B				
All-cause mortality	3.30 (2.84–3.84)	<0.001	1.33 (1.05–1.67)	0.018
Acute myocardial infarction	1.74 (1.18–2.57)	0.005	0.84 (0.46–1.52)	0.569
Stroke	2.26 (1.63–3.13)	<0.001	1.36 (0.87–2.11)	0.177
Transient ischemic attack	2.79 (1.61–4.85)	<0.001	1.47 (0.63–3.43)	0.375
Peripheral artery disease	3.66 (2.26–5.93)	<0.001	1.55 (0.75–3.19)	0.237

Discussion

The findings of the current study suggest that although CKD stage 3A (eGFR 45–59 ml/min/1.73 m²) was a predictor of incident HF among community-dwelling older adults, this association lacked independence. In contrast, a more advanced CKD stage ≥3B was a stronger predictor of incident HF, which also had a modest inde-

pendent association. We also observed that both CKD stages were associated with increased mortality. To the best of our knowledge, this is the first report of the relationship between various baseline CKD stages and incident HF from a prospective cohort study of community-dwelling older adults. These findings are important as they suggest that although CKD is an important predictor of incident HF, it may not be a risk factor for incident

HF until it reaches an advanced stage, and even when CKD is more advanced, it may be only a modest risk factor with a late effect.

The disappearance of the significant unadjusted association between CKD stage 3A and incident HF after risk adjustments using various methods including propensity score matching suggest that the association was likely not intrinsic in nature and was the result of confounding by imbalances in baseline risk factors. Although the baseline prevalence of hypertension was similar between those with CKD stage $\geq 3B$ (vs. those with no CKD), those with CKD stage $\geq 3B$ may have developed hypertension at a higher rate and hypertension in those individuals may have been more difficult to control, thus explaining the independent increased risk of HF. It is also possible that a more severe impairment of sodium and fluid balance in CKD stage $\geq 3B$ may have expedited the development of clinical HF in those patients. An activated renin-angiotensin-aldosterone system and sympathetic nervous system in advanced CKD may also have increased their risk for new-onset HF [32, 33]. Finally, oxidative stress, inflammation, hypercoagulability, and endothelial dysfunction associated with advanced CKD may have played a role in increasing the risk of incident HF [34–37].

Although findings from our sensitivity analysis suggest that the association of CKD stage $\geq 3B$ with incident HF may be sensitive to an unmeasured confounder, sensitivity analysis cannot determine whether such an unmeasured confounder actually exists or not. To be a confounder, an unmeasured covariate, in addition to being associated with CKD, would also need to have a near-perfect association with incident HF and not have a strong association with any of the 50 measured baseline covariates used in our study, a possibility which seems highly unlikely. Further, because the sign-score test used in the sensitivity analysis is based on ranks of the data rather than their actual values, it is considerably less powerful than the matched Cox survival analysis, which may also in part explain the non-significant sensitivity analysis. Therefore, while the association between CKD stage $\geq 3B$ and incident HF based on our matched Cox survival analysis results are statistically significant, the conclusions may not be robust, and need to be viewed as preliminary and replicated in future studies.

The association between serum creatinine and incident HF is well recognized [1, 2]. However, serum creatinine concentration is affected by factors other than GFR [11]. Several other studies have also examined the association between CKD and incident HF [38, 39]. However, our study is distinguished by the use of CKD-EPI for-

mula to estimate GFR, use of various CKD stages, central adjudication of HF, longer follow-up, and a host of other outcomes. Major HF guidelines either do not mention CKD as an etiologic risk factor or mention 'end-stage renal failure' as a risk factor for HF [40, 41]. Findings from our study confirm that CKD stage 3A is not an independent risk factor, stage $\geq 3B$ may be, and the risk of HF among those with CKD stage $\geq 3B$ was not immediate. These observations would suggest that there might be a window of opportunity to prevent HF in those with CKD. However, whether more aggressive management of risk factors would be more effective in reducing the risk of incident HF is currently unknown and will need to be determined in future prospective studies.

There were several limitations to our study. Because CHS participants are community-dwelling older adults and many had no CKD, we used CKD-EPI to estimate eGFR and define CKD. Unlike the commonly used Modification of Diet in Renal Disease formula to estimate GFR [11], the CKD-EPI is more reliable in those with eGFR >60 ml/min/1.73 m². However, the CKD-EPI has not been validated in older adults and misclassification is possible. It is also possible that participants without CKD developed CKD during follow-up, and it is possible that the resultant regression dilution may in part explain the non-significant findings of our study.

In conclusion, among community-dwelling older adults, CKD is a predictor of incident HF regardless of stage and CKD stage $\geq 3B$ may have an independent modest association with incident HF.

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Disclosure Statement

This article was prepared using a limited access dataset obtained by the NHLBI and does not necessarily reflect the opinions or views of the CHS or the NHLBI.

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