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The Association of Ejection Fraction With Hospital-Associated Cardiac Arrest and Heart Failure Hospitalization Differs According to Baseline Estimated GFR

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Introduction: Chronic kidney disease (CKD) and left ventricular (LV) dysfunction are risk factors for cardiovascular events. We explore whether the association of LV ejection fraction (LVEF) with cardiac arrest, heart failure hospitalization, and all-cause mortality differs across stages of kidney impairment.

Methods: We performed an observational cohort study of 19,032 patients from 2004 to 2014 with estimated glomerular filtration rate (eGFR) ≤90 ml/min per 1.73 m^2 and without end-stage kidney disease (ESKD). Cox regression models, incorporating an interaction term for eGFR and LVEF, were fit and adjusted for relevant covariates.

Results: Mean age of the patients was 67 ± 14 years, and 51% were male. The mean eGFR was 64 ± 19 ml/min per 1.73 m^2 and LVEF was 54 ± 13%. Over a median follow-up of 3.0 (0.7–6.0) years there were 504 cardiac arrests, 4181 heart failure hospitalizations, and 6989 deaths. The association of LVEF with cardiac arrest and heart failure hospitalization differed according to continuous eGFR (*P*-interaction <0.01 for both outcomes). The association of LVEF with cardiac arrest in the lowest quartile was attenuated (adjusted hazard ration [aHR] per 5% higher LVEF 0.92; 95% confidence interval [CI] 0.88–0.96) compared to the highest eGFR quartile (aHR per 5% higher LVEF 0.85; 95% CI 0.78–0.91). The association of LVEF with heart failure hospitalization was similarly attenuated in the lowest eGFR quartile. There was no effect modification of LVEF by continuous eGFR for all-cause mortality (*P*-interaction 0.26).

Conclusion: Among non-ESKD patients with eGFR ≤90 ml/min per 1.73 m^2, the association of LVEF with cardiac arrest and heart failure hospitalization is attenuated at lower levels of kidney function. Further research is required to elucidate what factors beyond LVEF drive these observations.

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CKD is a potent risk factor for cardiovascular complications, such as sudden cardiac death (SCD) and coronary artery disease (CAD),[1] independent of LV systolic dysfunction, which is also a risk factor for cardiovascular events.[2] Heart failure and CKD commonly coexist, in part due to common risk factors (e.g., hypertension and diabetes), and may have similar pathogenic mechanisms (e.g., excess renin-angiotensin-aldosterone system activation, heightened sympathetic tone, and oxidative stress).[3]

SCD is a common mode of death among those with ischemic cardiomyopathy with reduced EF.[4,5] CKD presents an additional risk factor for SCD, as well as for heart failure and all-cause mortality among patients with cardiovascular disease.[3,6] However, the degree to which the combined presence of CKD and LV systolic dysfunction modify the risk of adverse cardiac events and mortality remains to be fully explored. Here, we investigate whether the association of LVEF with hospital-associated cardiac arrest, heart failure hospitalization, and all-cause mortality differs by eGFR across stages of kidney impairment.

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METHODS

Study Design and Population

The present study uses the Research Patient Data Registry, a centralized registry of clinical data from the 5 Mass General Brigham teaching hospitals. Patients of age ≥18 years who had transthoracic echocardiography with tissue doppler imaging between January 1, 2004 and January 6, 2014 were included in this retrospective cohort study. Patients with history of heart or kidney transplants were excluded. Information regarding comorbidities prior to the index echocardiogram was collected using International Classification of Diseases (ICD-9) codes. Baseline laboratory values were considered as the most proximal value (between 365 days before and 90 days after) of the index echocardiogram (median time between echocardiogram and baseline laboratory values: 0 [−24 to +7] days). Medications prescribed before the date of the index echocardiogram were considered to be medications used at baseline.

Exposures

LVEF was determined using the American Society of Echocardiography scanning protocol. This study is based on a data set which was created and used for prior studies.[7,8] To be included in the data set, patients needed at least 1 creatinine level during the 365 days preceding and 1 in the 90 days following the echocardiogram. To be included in the present analyses, eGFR was restricted to ≤90 ml/min per 1.73 m^2 based on the CKD 2009 Epidemiology Collaboration equation[9]; patients whose charts included the ICD-9 code, 585.6, for ESKD were excluded; and a baseline LVEF was required (see CONSORT diagram of inclusion, Supplementary Figure S1).

In exploratory analyses, we explored whether the association of LV mass index (LVMi) with our outcomes was modified by eGFR.

Study Outcomes

The primary outcome of this study was cardiac arrest. Secondary outcomes were heart failure hospitalization and death. Outcomes were identified using their respective ICD-9 codes (Supplementary Table S1). Cardiac arrest was only captured if it occurred and was documented at the hospital. To capture mortality, the Research Patient Data Registry was continuously matched to the social security death index, a comprehensive nationwide database encompassing all fatalities within the United States. Patients were censored at their last clinic encounter date, last medication refill date, or the date of their last laboratory result.

Statistical Analysis

Continuous variables were described as mean ± SD if normally distributed or medians (25th–75th percentiles) if nonnormally distributed. Categorical variables were described as proportions (percentages). Baseline characteristics, according to eGFR quartiles, were compared with tests for trend based on linear regression, chi-square trend test, and the Cuzick nonparametric trend test.[10] Cox proportional hazards models were fit for time-to-event analyses. We tested for the presence of effect modification according to baseline eGFR via inclusion of a cross-product term for continuous eGFR and LVEF in all models. Our primary model adjusted for age, sex, Black race, hypertension, diabetes, CAD, and the setting of echocardiography (inpatient vs. outpatient). An exploratory model additionally adjusted for the baseline use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β-blockers, statin medications, loop diuretics, spironolactone, aspirin, and warfarin. An additional exploratory model adjusted for LVMi (available in $n = 5141$ patients; Supplementary Table S2). These variables were chosen based on prior studies using the data set and biological plausibility.[7] The proportional hazards assumption was checked in all models using global tests for the assumption. Where variables violated proportional hazards, the relevant variables were included as time varying covariates. All analyses were performed at an alpha level of 0.05 without correction for multiple hypothesis testing. The reported *P*-values reflect 2-sided tests. Missing data was not imputed. Analyses were completed using STATA 16.1 (College Station, TX).

Ethics

The Mass General Brigham Institutional Review Board approved this study (#2014P002016). The investigation conforms with the principles outlined in the Declaration of Helsinki.[11]

RESULTS

Baseline Characteristics

LVEF was reported in baseline echocardiograms in 19,032 individuals who had eGFR ≤90 ml/min per 1.73 m^2 and who did not have ESKD. Of those patients, the mean age was 67 ± 14 years and 51% were male. The mean baseline eGFR was 64 ± 19 ml/min per 1.73 m^2 and the mean LVEF was 54 ± 13%. Individuals with lower eGFR were more likely to be older, female, and to have hypertension, diabetes mellitus, and CAD. They were more likely to be prescribed angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β-blockers, statin medications, loop diuretics, spironolactone, aspirin, and warfarin. They had lower hemoglobin, albumin, and LVEF. Baseline

Table 1. Baseline characteristics according to eGFR quartile

Characteristic	Total population	Categories of eGFR (CKD-EPI, ml/min per 1.73 m^2)				
	N = 19,032	Quartile 1 *n* = 4758	Quartile 2 *n* = 4758	Quartile 3 *n* = 4758	Quartile 4 *n* = 4758	*P*-trend
eGFR (ml/min per 1.73 m^2) mean ± SD	64 ± 19	37 ± 10	59 ± 5	73 ± 4	85 ± 3	
Age (yrs)	67 ± 14	73 ± 13	70 ± 12	65 ± 13	62 ± 14	<0.001
Male sex, *n* (%)	9674 (51%)	2328 (49%)	2411 (51%)	2500 (53%)	2435 (51%)	0.01
African American Ethnicity, *n* (%)	1514 (8%)	395 (8%)	381 (8%)	384 (8%)	354 (7%)	0.15
Hypertension	10,896 (57%)	2880 (61%)	2957 (62%)	2620 (55%)	2439 (51%)	<0.001
Diabetes mellitus	4346 (23%)	1480 (31%)	1208 (25%)	863 (18%)	795 (17%)	<0.001
Coronary artery disease	9702 (51%)	2781 (58%)	2532 (53%)	2265 (48%)	2124 (45%)	<0.001
ACEI or ARB use	6921 (39%)	2070 (46%)	1883 (43%)	1587 (36%)	1381 (32%)	<0.001
β-blockers use	10,152 (58%)	2966 (66%)	2553 (58%)	2323 (53%)	2310 (53%)	<0.001
Statin use	8470 (48%)	2459 (55%)	2207 (50%)	2021 (46%)	1782 (41%)	<0.001
Loop diuretic use	5995 (34%)	2339 (52%)	1525 (35%)	1150 (26%)	981 (23%)	<0.001
Spironolactone use	697 (4%)	269 (6%)	203 (5%)	128 (3%)	97 (2%)	<0.001
Aspirin use	8736 (50%)	2522 (57%)	2247 (51%)	2021 (46%)	1946 (45%)	<0.001
Warfarin use	2888 (16%)	844 (19%)	729 (17%)	693 (16%)	622 (14%)	<0.001
Hemoglobin, g/dl	12.3 ± 2.1	11.4 ± 2.0	12.3 ± 2.1	12.8 ± 2.1	12.8 ± 2.1	<0.001
Albumin, g/dl	3.8 ± 0.6	3.6 ± 0.7	3.8 ± 0.6	3.9 ± 0.6	3.9 ± 0.6	<0.001
LVEF, %	54 ± 13	51 ± 15	53 ± 13	55 ± 12	56 ± 11	<0.001
LVMi, g/m^2	102 ± 35	110 ± 38	104 ± 36	97 ± 33	96 ± 32	<0.001

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD-EPI, chronic kidney disease epidemiology collaboration; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction.
Continuous variables presented as mean ± SD if normally distributed or median (25th–75th percentile) if non-normally distributed; categorical variables presented as count (%).
Baseline characteristics, according to quartiles of LVEF group, were compared with tests for trend based on linear regression, chi-square trend test, and the Cuzick nonparametric trend test.

characteristics for the study population by eGFR quartile are shown in Table 1. Baseline characteristics of those excluded for not having recorded LVEF (n = 1517) are shown in Supplementary Table S3.

Risk of Cardiac Arrest, Heart Failure Hospitalization, and Death According to LVEF

Over a median follow-up time of 2.9 (0.6–6.0) years, a cardiac arrest event occurred in 504 (3%) patients. In the primary model and adjusting for eGFR (without interaction term), each 5% higher LVEF was associated with a 12% lower risk of cardiac arrest (aHR 0.88, 95% CI 0.86–0.91; $P < 0.001$).

Over a median follow-up time of 2.0 (0.3–5.2) years, heart failure hospitalization occurred in 4181 (25%) patients. In the main model and adjusting for eGFR (without interaction term), each 5% higher LVEF was associated with a 17% lower risk of heart failure hospitalization (aHR 0.83, 95% CI 0.82–0.84; $P < 0.001$).

Over a median follow-up time of 3.0 [0.7–6.0] years, death occurred in 6989 (37%) patients. In the main model and adjusting for eGFR (without interaction term), each 5% higher LVEF was associated with a 5% lower risk of death (aHR 0.95, 95% CI 0.94–0.96; $P <$ 0.001).

Risk of Cardiac Arrest With Lower LVEF in the Setting of Variable eGFR: Effect Modification

The association of LVEF with cardiac arrest differed according to eGFR in the main adjusted model (P-interaction 0.01). The association of LVEF with cardiac arrest in the lowest quartile of eGFR was less potent (aHR per 5% higher LVEF 0.92; 95% CI 0.88–0.96) than the association in the highest quartile of eGFR (aHR per 5% higher LVEF 0.85; 95% CI 0.78–0.91; Figure 1) in the main adjusted model. Similar results were seen in the exploratory model (Table 2).

Risk of Heart Failure Hospitalization With Lower LVEF in the Setting of Variable eGFR: Effect Modification

The association of LVEF with heart failure hospitalization differed according to eGFR in the main adjusted model (P-interaction < 0.001). The association of LVEF with heart failure hospitalization in the lowest quartile of eGFR was less potent (aHR per 5% higher LVEF 0.87; 95% CI 0.85-0–88) than the association in the highest quartile of eGFR (aHR per 5% higher LVEF 0.78; 95% CI 0.76–0.80); Figure 2) in the main adjusted model. Similar results were seen in the exploratory model (Table 3).

Risk of Death With Lower LVEF in the Setting of Variable eGFR: Effect Modification

There was no evidence for effect modification of the association of LVEF with mortality according to eGFR in the main adjusted model (P-interaction 0.26; aHR per 5% higher LVEF 0.96; 95% CI 0.95–0.97 in the lowest eGFR quartile; aHR per 5% higher LVEF 0.92; 95% CI 0.90–0.95 in the highest eGFR quartile, in the main adjusted model) (Table 4).

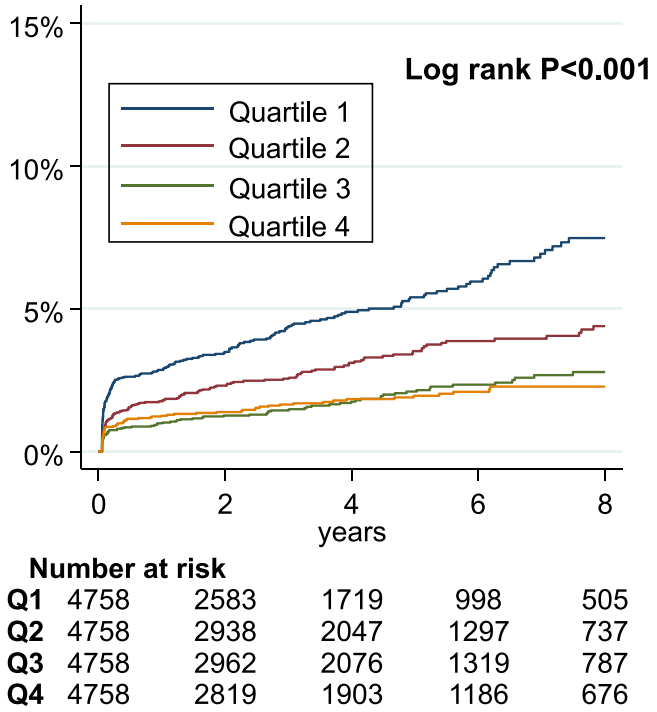

Figure 1. Cumulative incidence of cardiac arrest according to baseline eGFR quartile (quartile 1 eGFR mean ± SD: 37 ± 10 ml/min per 1.73 m^2; quartile 2 eGFR mean ± SD: 59 ± 5 ml/min per 1.73 m^2; quartile 3 eGFR mean ± SD: 73 ± 4 ml/min per 1.73 m^2; quartile 4 eGFR mean ± SD: 85 ± 3 ml/min per 1.73 m^2).

Exploratory Analyses Adjusting for LVMi

In additional exploratory analyses, we further adjusted for LVMi (available in $n = 5141$ patients in whom we also have LVEF). Similar patterns of association were noted, that is, the association of LVEF with cardiac arrest and heart failure hospitalization was attenuated at lower levels of eGFR (for cardiac arrest, *P*-interaction 0.02; for heart failure hospitalization, *P*-interaction 0.03), whereas the association of mortality with LVEF was not different according to eGFR (*P*-interaction 0.11) (Supplementary Table S2).

Exploratory Analyses for Effect Modification by eGFR of the Association With LVMi With Cardiac Arrest, Heart Failure Hospitalization, and Death

LVMi was available for 5141 patients. Among these individuals, cardiac arrest occurred in 134 individuals (median follow-up 1.7 [0.4–3.5] years), heart failure hospitalization occurred in 1081 individuals (median follow-up 1.2 [0.2–3.0] years), and death occurred among 1614 individuals (median follow-up 1.8 [0.4–3.5] years). In the primary model and adjusting for eGFR (without interaction term), each 10% g/m^2 higher LVMi was not associated with a higher risk of cardiac arrest (aHR 1.04, 95% CI 0.99–1.09; $P = 0.10$) or death (aHR 1.01, 95% CI 1.00–1.03; $P = 0.12$); however, it was associated with a 10% higher risk of heart failure hospitalization (aHR 1.10, 95% CI 1.08–1.11; $P < 0.001$). The association of LVMi with cardiac arrest, heart failure hospitalization, and death did not differ according to eGFR in the main adjusted model (*P*-interaction 0.46, 0.12, and 0.22, respectively). (Supplementary Table S4).

DISCUSSION

We examined the association of LVEF with cardiac arrest, heart failure hospitalization, and death across various levels of kidney function among 19,032 patients at 5 Mass General Brigham hospitals from 2004 to 2014. We found that lower LVEF is strongly associated with cardiac arrest at higher levels of kidney function and that this association is attenuated in the setting of more advanced CKD. This is consistent with prior findings that the mechanisms of SCD are different in CKD patients compared to the general population.[12-14] Reasons for the differences in mechanisms of SCD in patients with CKD are, to date, not well understood. Our findings similarly demonstrate that the association of LVEF with heart failure hospitalization is attenuated at lower levels of kidney disease, suggesting that other

Table 2. Risk of cardiac arrest per 5% higher LVEF according to eGFR quartiles

	No. events/no. at risk hazard ratio (95% CI) per 5% higher LVEF			
Outcome	Quartile 1 eGFR 37 ± 10 ml/min per 1.73 m^2	Quartile 2 eGFR 59 ± 5 ml/min per 1.73 m^2	Quartile 3 eGFR 73 ± 4 ml/min per 1.73 m^2	Quartile 4 eGFR 85 ± 3 ml/min per 1.73 m^2
Unadjusted	208/4758 0.88 (0.84–0.91) $P < 0.001$	135/4758 0.86 (0.82–0.91) $P < 0.001$	85/4758 0.79 (0.74–0.84) $P < 0.001$	76/4758 0.80 (0.74–0.86) $P < 0.001$
Main adjusted model	206/4714 0.92 (0.88–0.96) $P < 0.001$	134/4708 0.90 (0.85–0.96) $P = 0.001$	84/4708 0.80 (0.75–0.86) $P < 0.001$	76/4725 0.85 (0.78–0.91) $P < 0.001$
Exploratory model	192/4420 0.92 (0.88–0.97) $P = 0.001$	131/4361 0.90 (0.85–0.96) $P = 0.002$	79/4312 0.80 (0.74–0.87) $P < 0.001$	72/4318 0.84 (0.77–0.91) $P < 0.001$

CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LVEF, left ventricular ejection fraction.
Main adjusted model adjusted for age, gender, Black race, hypertension, diabetes mellitus, coronary artery disease, and location of echocardiogram (inpatient vs. outpatient).
Exploratory model adjusted for all parameters of the main adjusted model and additionally for the use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β-blockers, statin medications, and spironolactone.

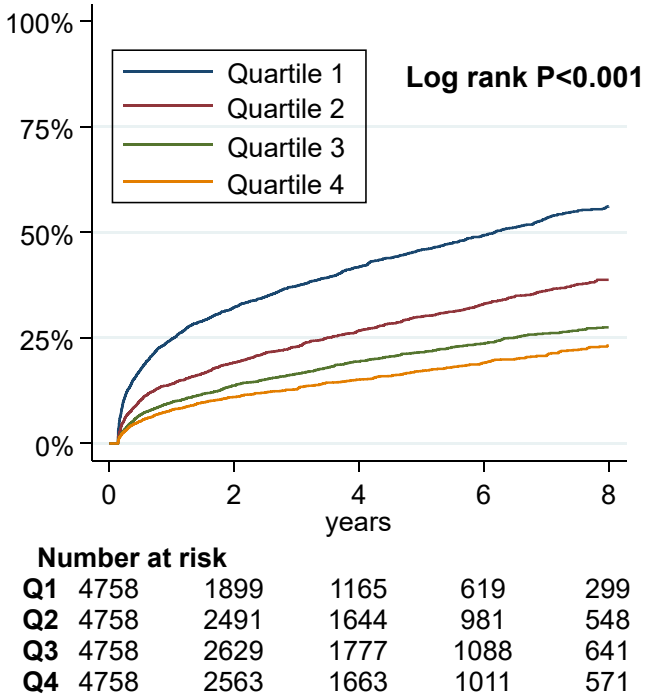

Figure 2. Cumulative incidence of heart failure hospitalization according to baseline eGFR quartile (quartile 1 eGFR mean ± SD: 37 ± 10 ml/min per 1.73 m^2; quartile 2 eGFR mean ± SD: 59 ± 5 ml/min per 1.73 m^2; quartile 3 eGFR mean ± SD: 73 ± 4 ml/min per 1.73 m^2; quartile 4 eGFR mean ± SD: 85 ± 3 ml/min per 1.73 m^2).

factors are at play when patients with lower kidney function are admitted with heart failure exacerbation.

LV mass increases with advancing CKD, and LV hypertrophy is seen in 70% to 80% of patients with CKD 4 to 5.[15] This is partially explained by increased arterial stiffness, hypertension, and volume expansion, which can all result in increased afterload.[16] One potential explanation for the higher observed rates of cardiac arrest in CKD may be that higher LV mass is arrhythmogenic, independent of change in LVEF.[17] To address this, we performed an exploratory assessment of the association of LVMi with cardiac arrest across levels of CKD, but did not find evidence of differential associations. However, these results are limited by available LVMi, introducing selection bias to the associated results, and by the relative paucity of events among this subset of patients. Our analyses must therefore be interpreted with caution. It has also been hypothesized that CKD mimics accelerated aging, in that it causes a proinflammatory state.[1] This results in myocardial remodeling, vascular calcification, and myocardial fibrosis, which may also predispose to cardiac arrhythmia regardless of ejection fraction. Further, advancing CKD portends a higher risk for electrolyte disturbances (e.g., hyperkalemia), which could contribute to the etiology of SCD.[18] Whereas patients with advanced CKD have more CAD, rates of SCD are disproportionately high with regard to the prevalence of CAD, compared to the general population.[1] Therefore, our finding that lower LVEF, which is in part driven by CAD, is less predictive of cardiac arrest in patients with advancing CKD may be less surprising.

It is interesting to consider what factors aside from LVEF may be at play when patients with more advanced CKD are admitted for heart failure. Prior studies have demonstrated that heart failure hospitalization is more frequent in patients with eGFR <30 ml/min per 1.73 m^2 compared to those with higher eGFR. However, in those with more advanced kidney disease, the rate of first heart failure hospitalization with preserved EF was higher than the rate of first heart failure hospitalization in those with reduced EF.[19] Our observed attenuation of the association of LVEF with heart failure hospitalization at lower eGFRs may thus, in part, derive from a larger proportion of admissions for heart failure in those with preserved, rather than reduced, LVEF. Consistent with this notion, prior research has demonstrated that CKD is associated with admission for heart failure with preserved EF despite the fact that rates of change in other echocardiographic parameters (LVEF, LV diameter, pulmonary artery pressure, and LVMi) did not differ in patients with CKD (eGFR <60 ml/min per 1.73 m^2) compared to those

Table 3. Risk of heart failure hospitalization per 5% higher LVEF according to eGFR quartiles

	No. events/no. at risk hazard ratio (95% CI) per 5% higher LVEF			
Outcome	Quartile 1 eGFR 37 ± 10 ml/min per 1.73 m^2	Quartile 2 eGFR 59 ± 5 ml/min per 1.73 m^2	Quartile 3 eGFR 73 ± 4 ml/min per 1.73 m^2	Quartile 4 eGFR 85 ± 3 ml/min per 1.73 m^2
Unadjusted	1601/4758 0.86 (0.85–0.88) $P < 0.001$	1141/4758 0.82 (0.81–0.84) $P < 0.001$	815/4758 0.80 (0.79–0.82) $P < 0.001$	624/4758 0.78 (0.75–0.80) $P < 0.001$
Main adjusted model	1575/4714 0.87 (0.85–0.88) $P < 0.001$	1132/4708 0.84 (0.82–0.85) $P < 0.001$	805/4708 0.80 (0.78–0.82) $P < 0.001$	615/4725 0.78 (0.76–0.80) $P < 0.001$
Exploratory model	1461/4420 0.89 (0.87–0.91) $P < 0.001$	1044/4361 0.88 (0.86–0.90) $P < 0.001$	733/4312 0.86 (0.83–0.88) $P < 0.001$	552/4318 0.81 (0.78–0.83) $P < 0.001$

CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction.
Main adjusted model adjusted for age, gender, Black race, hypertension, diabetes mellitus, coronary artery disease, and location of echocardiogram (inpatient vs. outpatient).
Exploratory model adjusted for all parameters of the main adjusted model and additionally for the use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β-blockers, statin medications, and spironolactone.

Table 4. Risk of death per 5% higher LVEF according to eGFR quartiles

	No. events/no. at risk hazard ratio (95% CI) per 5% higher LVEF			
Outcome	Quartile 1 eGFR 37 ± 10 ml/min per 1.73 m^2	Quartile 2 eGFR 59 ± 5 ml/min per 1.73 m^2	Quartile 3 eGFR 73 ± 4 ml/min per 1.73 m^2	Quartile 4 eGFR 85 ± 3 ml/min per 1.73 m^2
Unadjusted	2719/4758 0.95 (0.94–0.96) $P < 0.001$	1799/4758 0.94 (0.93–0.96) $P < 0.001$	1268/4758 0.95 (0.93–0.97) $P < 0.001$	1203/4758 0.92 (0.90–0.94) $P < 0.001$
Main adjusted model	2697/4714 0.96 (0.95–0.97) $P < 0.001$	1786/4708 0.95 (0.94–0.97) $P < 0.001$	1258/4708 0.95 (0.93–0.98) $P < 0.001$	1194/4725 0.92 (0.90–0.95) $P < 0.001$
Exploratory model	2541/4420 0.96 (0.95–0.98) $P < 0.001$	1689/4361 0.97 (0.95–0.99) $P = 0.01$	1186/4312 0.97 (0.95–1.00) $P = 0.04$	1137/4318 0.94 (0.91–0.96) $P < 0.001$

CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction.
Main adjusted model adjusted for age, gender, Black race, hypertension, diabetes mellitus, coronary artery disease, and location of echocardiogram (inpatient vs. outpatient).
Exploratory model adjusted for all parameters of the main adjusted model and additionally for the use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β-blockers, statin medications, and spironolactone.

without CKD (eGFR ≥90 ml/min per 1.73 m^2).[20] Further research on the association of hospitalization with variable types of heart failure (preserved vs. reduced EF) in the setting of variable eGFR may help to further elucidate the mechanisms underlying these observations.

Our study has several strengths. Our data came from a large cohort, and we were able to adjust for several potential confounding variables across ranges of kidney dysfunction. As with all observational studies, however, several limitations exist. First, despite the use of adjusted models, the potential for residual confounding remains and owing to data limitations, we only examined patients with eGFR ≤90 ml/min per 1.73 m^2. Further, longitudinal studies have the potential for ascertainment bias (e.g., patients with lower eGFR may have other comorbidities that require closer follow-up and therefore, their outcomes may be more likely to be captured). In addition, we were only able to capture hospital-associated cardiac arrest, while many patients may have died from this complication outside the hospital. Given the use of ICD-9 codes to identify cardiac arrest events, details regarding whether patients were in the hospital versus out of the hospital at the time of their cardiac arrest could not be elucidated. It should be noted that out of hospital cardiac arrests may differ in characteristics and etiology compared to those that occur in the hospital or in those cases that presented to the hospital following their occurrence. In addition, with regard to this point, cardiac arrest and heart failure hospitalization events were only captured if patients presented at one of the 5 Mass General Brigham teaching hospitals from which data was captured for the Research Patient Data Registry data set; therefore, events which occurred within other hospital systems were not included. It should be noted that our study population is a select group of patients who underwent echocardiogram for clinical indication, thus predisposing to potential indication bias, and this may limit generalizability. In addition, patients with progressive CKD typically accumulate comorbid diseases, raising the possibility that some of these could be preferentially recorded as a cause of death (over sudden death or arrest for example). Our analyses exclude patients with ESKD based on the presence of the ICD-9 code for this status. However, due to the potential for miscoding, we cannot be sure of the absence of misclassification and some patients with ESKD may have remained in our analysis. LVEF was not recorded in 1517 individuals in the cohort; given concerns that such patients may differ, we have provided data regarding some of their baseline differences to the rest of the cohort (Supplementary Table S3). Furthermore, repeated measures of LVEF, which would have given greater clarity about how the progression of heart failure may affect outcomes over time, were not available. Our analysis may lack generalizability, given that only 8% of participants were Black. Further, the data set does not provide any further information regarding ethnic minorities. Lastly, the data for this study were collected from 2004 to 2014, and therefore preceded the use of several medications which are now common, including angiotensin receptor/neprilysin inhibitors, sodium-glucose cotransporter-2 inhibitors, and finerenone; it therefore remains unknown how the use of these medications in a more contemporary cohort may affect the associations explored in this study.

Overall, our results show that among patients with eGFR ≤90 ml/min per 1.73 m^2 but without ESKD, the association of LVEF with cardiac arrest and heart failure hospitalization are attenuated at lower (vs. higher) levels of kidney function. Further research is required to elucidate what factors beyond LVEF drive cardiac arrest and heart failure hospitalization in the setting of more advanced kidney disease.

DISCLOSURE

TAM received speaker honoraria from Daiichi Sankyo, BMS Canada, Janssen, and Pfizer; and has served on

advisory boards for Boehringer Ingelheim, Bayer, and Servier outside the submitted work. DMC reports consultancy from Eli Lilly/Boehringer Ingelheim, Janssen (steering committee), PLC medical (clinical events committee), Astra Zeneca, Allena Pharmaceuticals (DSMB), Fresenius, Amgen, Gilead, Novo Nordisk, GSK, Medtronic, Merck, Amgen, CSL Behring, Zogenix, Renalytix, and Nitto Biopharmarceuticals; research funding: Medtronic-clinical trial support, Bioporto-clinical trial support, Gilead, NovoNordisk, Amgen, and expert witness fees related to proton pump inhibitors. FRMC reports research support from NIH, Satellite Healthcare, Fifth Eye, Novartis, and Lexicon that is paid directly to his institution; he reports consulting fees from GSK and Zydus Therapeutics. KSR has declares no conflicting interests.

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The Mass General Brigham Institutional Review Board approved this study (#2014P002016).

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. CONSORT diagram of inclusion.

Table S1. Condition specific diagnostic codes (International Classification of Diseases, 9th revision).

Table S2. Association of left ventricular ejection fraction with outcomes by category of baseline eGFR (exploratory model and additional adjustment for left ventricular mass index).

Table S3. Baseline characteristics in study population compared to patients excluded for not having reported left ventricular ejection fraction.

Table S4. Association of left ventricular mass index with outcomes by category of baseline eGFR.

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