Mitral Regurgitation and Mortality Risk in Medicare Beneficiaries With Heart Failure and Preserved Ejection Fraction

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The association of mitral regurgitation (MR) severity and mortality in heart failure with preserved ejection fraction (HFpEF) is uncertain. We sought to evaluate the relation between MR severity on transthoracic echocardiography (TTE) and subsequent all-cause mortality in Medicare beneficiaries with HFpEF. We linked 57,608 patients referred for TTE at Beth Israel Deaconess Medical Center to Medicare inpatient claims from 2003 to 2017. In those with a history of HF and a physician-reported left ventricular ejection fraction ≥50%, we evaluated the relation of MR severity and time to the primary end point of all-cause mortality using Kaplan-Meier methods. A total of 7,778 individuals (14.5%) met inclusion criteria (mean age 75.5 years ± 11.9, 55.9% female). Over a median follow-up of 8.1 years, 2,016 (25.9%) died at a median (interquartile range) of 1.7 (0.3 to 4.1) years. At 1 year, 15.8% with 3 to 4+ MR had died versus 10.5% with 0 to 2+ MR (hazard ratio 1.54, 95% confidence interval 1.22 to 1.95, p <0.001). After multivariable adjustment, 3 to 4+ MR continued to be associated with increased all-cause mortality (hazard ratio 1.48, 95% confidence interval 1.14 to 1.94, p = 0.004) except in the subset with atrial fibrillation (interaction p = 0.03) or recent (<3 months) HF hospitalization (p = 0.54). In conclusion, in this large, single-institution retrospective study of Medicare beneficiaries with HFpEF who underwent TTE, moderate-to-severe and severe MR were significantly associated with an increased risk of all-cause mortality after multivariable adjustment, except in those with atrial fibrillation or recent HF. Prospective studies are needed to assess the role of MR reduction in mitigating this risk. **(Am J Cardiol 2022;183:40−47)**

The role of mitral regurgitation (MR) in the prognosis of older adults with heart failure (HF) with preserved ejection fraction (HFpEF) is not well understood, despite the increasing prevalence of significant MR with age.[1,2] Numerous echocardiographic and cardiac catheterization studies have demonstrated that the presence and degree of MR are associated with poor outcomes in HF with reduced ejection fraction (HFrEF).[3−8] Furthermore, recent trials have demonstrated that reducing MR through transcatheter mitral valve repair decreases mortality in patients with MR and HFrEF.[9,10] Despite these encouraging results, it remains uncertain whether MR severity is similarly associated with mortality in the case of HFpEF.[11,12] In several studies, even mild MR was associated with increased mortality risk and HF readmission in HFpEF.[11,13] In contrast, other studies have suggested that MR severity may have negative prognostic implications in HFrEF alone.[12] Thus, it remains uncertain if MR is independently associated with adverse outcomes in older adults with HFpEF and, by extension, whether structural interventions targeted toward the mitral valve would effectively mitigate any presumed risk. As such, we sought to investigate the independent relation between MR severity and all-cause mortality in older adults with HFpEF in a large echocardiographic cohort study linked to Medicare inpatient claims.

Methods

We retrospectively evaluated echocardiographic report data from 57,608 Medicare Fee-for-service beneficiaries referred for transthoracic echocardiography (TTE) at the Beth Israel Deaconess Medical Center (BIDMC) from January 1, 2003, to December 31, 2017. As part of routine clinical care at BIDMC, echocardiographic data were entered at the time of clinical interpretation into a reporting software that stores structured echocardiographic findings and measurements in a large electronic dataset (the "ENCOR" database).

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The ENCOR database was previously directly linked to the United States Centers for Medicare and Medicaid Services (CMS) Medicare Provider Analysis and Review dataset as part of the Echocardiography and Health Services Outcomes study, which seeks to evaluate the outcomes of individuals with structural and functional abnormalities identified by echocardiography. The specific Medicare Provider Analysis and Review database used consists of a 100% sample of inpatient (i.e., part A) discharge claims for Medicare Fee-for-service beneficiaries from January 1, 2000, to December 31, 2017.

For the present study, only the first sequential TTE of an individual at BIDMC was considered. As individuals may be eligible for Medicare because of disability rather than age, we excluded those Medicare beneficiaries <65 years old at the time of their TTE. Individuals were additionally excluded if they lacked information on MR severity, had evidence of presumed infective endocarditis on TTE (i.e., presence of a probable or definite vegetation, ascertained by way of structured fields in the ENCOR dataset), moderate or greater mitral stenosis (mitral valve mean gradient ≥5 mm Hg), aortic stenosis with transaortic peak velocity ≥2.5 m/s, moderate or greater aortic regurgitation, or any valve replacement or repair on TTE. Additionally, individuals with a left ventricular ejection fraction (LVEF) <50% (physician reported) or missing LVEF information were excluded. Only patients with a history of HF preceding their baseline TTE were included. HF history was determined using chronic condition indicators published by the CMS Chronic Conditions Data Warehouse (Supplementary Table 1).[14] These indicators use validated claims algorithms using claims for inpatient and outpatient visits to ascertain the presence or absence of previous HF. Cell values <11 are omitted from tables per Medicare data use policy.[15] The study was approved by the BIDMC institutional review board with a waiver of informed consent.

Demographic, physiologic, and echocardiographic variables were obtained directly from the baseline TTE reports. These included age, gender, height, weight, blood pressure, heart rate (at the time of image acquisition), image quality, presence of mitral valve prolapse (MVP; identified by query of structured data fields on the baseline TTE), LVEF (physician reported), left atrial volume index, aortic valve peak velocity, peak tricuspid regurgitant velocity (as a proxy for pulmonary artery systolic pressure), pulmonary vein S-wave and D-wave velocities and their ratio, presence, and degree of MR, presence and degree of tricuspid regurgitation (TR), and presence of an eccentric MR regurgitant jet.[16] The severity of MR and TR were graded using an integrative approach as recommended by the American Society of Echocardiography guidelines.[17] To highlight differences between significant and nonsignificant MR, MR severity was categorized as 0 to 2+ or 3 to 4+ MR in the current analysis. MR jet eccentricity was recorded as a binary indicator variable in the ENCOR dataset. Over the study period, TTEs were interpreted by 29 individuals with an intraclass correlation coefficient for MR severity of 0.72. The indication for obtaining each echocardiogram was determined using natural language processing techniques (Supplementary Table 2). All echocardiographic images were acquired using E-95, Vivid 7, Vivid Q, Vivid 9, Vivid Q, Vivid I, and Vivid S70 echocardiographs and analyzed using EchoPAC software (GE Healthcare, Waukesha, Wisconsin).

Non-HF clinical covariates were obtained using chronic condition indicators using validated algorithms from the CMS Chronic Conditions Data Warehouse for identifying co-morbidities using claims data (Supplementary Table 1) and included a history of atrial fibrillation, dementia, cancer, hypothyroidism, depression, asthma, anemia, diabetes mellitus, ischemic heart disease, hypertension, hyperlipidemia, chronic obstructive pulmonary disease, chronic kidney disease, and history of ischemic stroke or transient ischemic attack.[14]

The primary end point was time to all-cause mortality after the baseline TTE. Mortality and date of death were defined using vital statistics available in the linked Medicare Beneficiary Summary File. The secondary end point was time to mitral valve annuloplasty, replacement, or repair (MVR) after the baseline TTE. The dataset was linked to the cardiac surgical dataset of the institution to obtain the date of MVR. The earlier one of this date or the first TTE after baseline demonstrating an MVR was used as the date of MVR for analyses. As death was ascertained through administrative data, follow-up information was complete for all included individuals. Time to HF hospitalization was not evaluated, as codes for HF after the initial TTE may represent a history of HF rather than new HF exacerbation.[18]

Continuous baseline variables were recorded using means and SDs or medians and interquartile ranges (IQRs) and compared across categories of MR using analysis of variance and Kruskal-Wallis tests, respectively. Categorical variables were recorded using counts and percentages and compared using chi-square tests. The proportion of patients hospitalized with acute decompensated HF at the time of TTE was determined as the percentage with HF codes in the first or second coding position for the hospitalization of record. Time to the primary end point of all-cause mortality was plotted using Kaplan-Meier curves and compared across categories of MR severity using the log-rank test. Multivariable Cox proportional hazards regression was used to model the independent relation of MR severity as a categorical predictor and the primary end point. Clinical variables were included in multivariable models if they were significantly related to the primary outcome on univariate testing. Subsequently, this process was repeated for the secondary end point evaluating time to MVR, using Fine-Gray methods to account for the competing risk of death. For survival analyses, patients were censored at the end of the study or the date of the first TTE demonstrating MVR. All analyses were performed in JMP v15.0 and SAS v9.4 (SAS Institute, Cary, North Carolina), using a 2-tailed $p \leq 0.05$ to define statistical significance.

As jet eccentricity could impact the observed results, the analysis was repeated, excluding those with an eccentric MR jet. Moreover, the analysis was repeated in the subgroup with primary MR (e.g., MVP) and a history of atrial fibrillation. Furthermore, as time duration from the onset of HF and the date of the TTE could influence prognosis, we evaluated the unadjusted risk of all-cause mortality in the subset with HF codes present in the 3 months preceding the date of the TTE using Cox proportional hazards models.

Moreover, we evaluated the interactions of obesity (body mass index [BMI] ≥30 kg/m^2) and BMI and MR severity on the risk of mortality.

Results

Of 53,608 individuals in the ENCOR-CMS linked dataset during the study period, 29,900 (55.8%) were excluded because of the absence of preceding HF hospitalization, 7,586 (14.2%) because of EF <50% or missing LVEF data, 3,923 (7.3%) because of aortic stenosis with peak velocity ≥2.5 m/s, 2,541 (4.7%) because of missing MR severity, 1,455 (2.7%) because of the presence of a valve replacement or repair, 252 (0.5%) because of moderate or greater mitral stenosis, 117 (0.2%) because of evidence of endocarditis, and 56 (0.1%) because of moderate or greater aortic regurgitation (Figure 1).

A total of 7,778 individuals (14.5%) were included, of which 6,329 (81.4%) had zero to mild (0 to 1+) MR, 1,261 (16.2%) had moderate (2+) MR, 188 (2.4%) had moderate-to-severe (3+) or severe (4+) MR. The median (IQR) follow-up time was 8.1 years (3.8 to 11.3 years). On baseline TTE, 149 (1.9%) had MVP, and 299 (3.8%) had an eccentric MR jet. The mean age was 75.7 ± 11.9 years, and 4,348 (55.9%) were female. Image quality was adequate or good in 73.2%. Of those hospitalized at the time of their TTE (n = 5,604 [72.0%]), a total of 1,103 (19.7%) had acute decompensated HF at the time of TTE. The mean LVEF was 67.8 ± 10.9% (Supplementary Figure 1). Baseline clinical and echocardiographic characteristics of individuals according to MR severity are listed in Table 1. Individuals with 3 to 4+ MR were older, had larger left atrial sizes, lower S/D ratios, and more frequently had MVP or an eccentric MR jet than individuals with 0 to 2+ MR (p <0.05 for all).

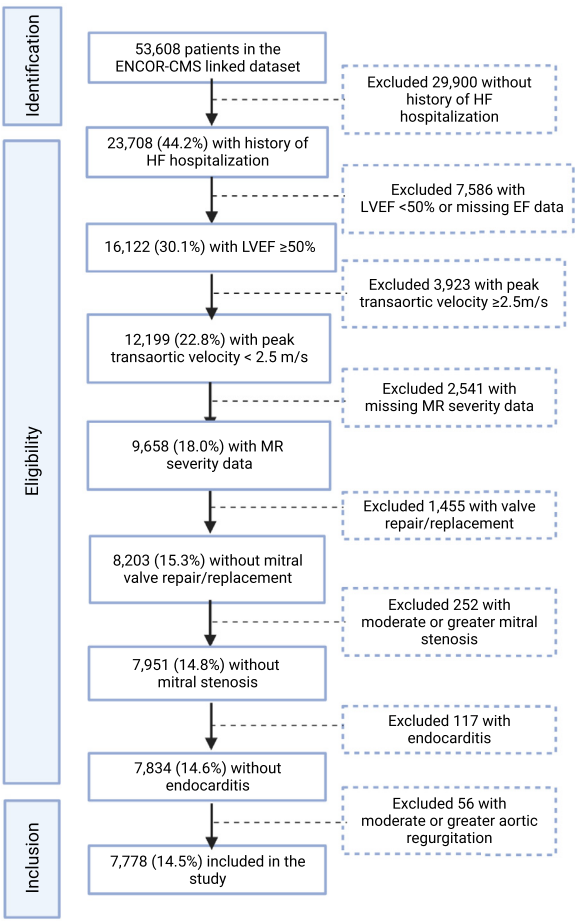

Figure 1. Flow diagram of included patients. ENCOR-CMS refers to the institutional echocardiographic database at BIDMC, which has been previously linked to Medicare inpatient claims.

A total of 2,017 individuals (25.9%) experienced the primary end point of all-cause death at a median (IQR) of 1.7 (0.3 to 4.1) years. On unadjusted analysis, 37.8% with 3 to 4+ MR died versus 25.6% with 0 to 2+ MR over the total study period (p <0.001). At 1 year, 15.8% with 3 to 4+ MR had died versus 10.5% with 0 to 2+ MR; a similar trend was persistent at 5 and 10 years (Table 2). Integrating across all time points, 3 to 4+ MR was significantly related to increased risk of all-cause mortality compared with 0 to 2+ MR (hazard ratio [HR] 1.54, 95% confidence interval [CI] 1.22 to 1.95, p <0.001) (Table 2). With increasing MR severity, there was an earlier occurrence of death (time to 25th percentile of mortality, 3 to 4+ MR versus 0 to 2+ MR, 2.7 vs 5.6 years, log-rank p <0.001) (Figure 2). After multivariable adjustment for age, gender, LVEF, systolic blood pressure (at the time of echocardiogram), depression, anemia, diabetes mellitus, ischemic heart disease, cancer, atrial fibrillation, chronic obstructive pulmonary disease, dementia, MVP, eccentric MR, TR severity, peak systolic tricuspid velocity, 3 to 4+ MR remained significantly associated with death (HR 1.48, 95% CI 1.14 to 1.94, p = 0.004).

On unadjusted analysis, 72 individuals (0.9%) underwent MVR (24 annuloplasties, 15 mitral valve repairs, 33 mitral valve replacements) at a median (IQR) of 19 days (3 to 130) after TTE. Individuals who underwent MVR were older, were more likely to have ischemic heart disease and atrial fibrillation, more frequently had MVP, eccentric MR jet, 2+ or greater TR, and more likely had studies performed for the indication of preoperative evaluation (p <0.05 for all; Supplementary Table 3). Integrating across all time points, 3 to 4+ MR was associated with an increased incidence of MVR (p for Gray's test <0.001) (Supplementary Figure 2).

Given that individuals with 3 to 4+ MR were more likely to have eccentric MR, we separately evaluated the effect of eccentric MR on the primary outcome. There were 299 patients with eccentric MR of which 40 (13.4%) have MVP versus 86 (1.2%) without eccentric MR (p <0.001). Of those with eccentric MR, 146 (48.8%) had a history of atrial fibrillation versus 2,605 (34.8%) without eccentric MR (p <0.001). After excluding those with eccentric MR, 3 to 4+ MR remained significantly associated with increased risk of all-cause mortality compared with 0 to 2+ MR on both univariate (HR 1.58, 95% CI 1.20 to 2.09, p = 0.0013) and multivariable (HR 1.48, 95% CI 1.10 to 2.00, p = 0.009) analyses.

Individuals with 3 to 4+ MR were also more likely to have atrial fibrillation. A total of 2,751 individuals with atrial fibrillation were included, of which 2,625 (95.4%) had 0 to 2+ MR and 126 (4.6%) had 3 to 4+ MR. Both on a univariate (HR 1.21, 95% CI 0.89 to 1.63, p = 0.22) and

Table 1
Baseline clinical and echocardiographic characteristics by degree of mitral regurgitation

Variable	N obs	3-4+ MR(N = 188)	0-2+ MR(N = 7590)	P Value
Age (years)	7778	81.0 ± 10.0	76.0 ± 11.9	< 0.001
Female	7777	115 (61.2%)	4233 (55.8%)	0.16
Inpatient status	7778	137 (72.9%)	5467 (72.0%)	0.87
Suboptimal image quality	7777	35 (18.6%)	2051 (27.0%)	0.03
Height (cm)	7776	164 ± 10	166 ± 11	0.009
Weight (kg)	7777	69 ± 17	80 ± 23	< 0.001
Body mass index (kg/m^2)	7775	25.6 ± 5.3	29.1 ± 7.9	< 0.001
Systolic blood pressure (mmHg)	7724	133 ± 61	131 ± 34	0.48
Diastolic blood pressure (mmHg)	7716	73 ± 46	70 ± 39	0.30
Heart rate (bpm)	7778	77 ± 18	76 ± 17	0.45
Study indication	7778			
LV function		74 (39.4%)	3336 (44.0%)	< 0.001
Heart failure		59 (31.4%)	2004 (26.4%)	0.54
AF/AFL		32 (17.0%)	811 (10.7%)	0.06
Preoperative		12 (6.4%)	262 (3.5%)	0.09
Other		11 (5.9%)	1177 (15.5%)	< 0.001
Dementia	7778	56 (29.8%)	1777 (23.4%)	0.045
Cancer	7778	29 (15.4%)	997 (13.1%)	0.38
Hypothyroidism	7778	38 (20.2%)	16784 (22.1%)	0.59
Depression	7778	56 (29.8%)	3034 (40.0%)	0.005
Asthma	7778	20 (10.6%)	1194 (15.7%)	0.07
Anemia	7778	115 (61.2%)	5210 (68.6%)	0.03
Diabetes mellitus	7778	69 (36.7%)	3577 (47.1%)	0.005
Ischemic heart disease	7778	153 (81.4%)	5374 (70.8%)	0.001
Hypertension	7778	166 (88.3%)	6811 (89.7%)	0.54
Hyperlipidemia	7778	116 (61.7%)	4967 (65.4%)	0.31
Atrial fibrillation	7778	126 (67.0%)	2625 (34.6%)	< 0.001
Chronic obstructive pulmonary disease	7778	48 (25.5%)	2640 (34.8%)	0.008
Chronic kidney disease	7778	96 (51.1%)	4223 (55.6%)	0.23
History of ischemic stroke or TIA	7778	28 (14.9%)	1294 (17.1%)	0.49
Pacemaker or implantable cardioverter defibrillator	7778	< 11	378 (5.0%)	0.61
Left ventricular ejection fraction (%)	7778	64.6 ± 11.2	67.8 ± 10.9	< 0.001
Mitral valve prolapse	7778	25 (13.3%)	101 (1.3%)	< 0.001
Eccentric mitral regurgitation jet	7778	59 (31.4%)	240 (3.2%)	< 0.001
Left atrial volume index (mL)	677	48 ± 12	33 ± 11	< 0.001
Left ventricular mass index (g/m^2)	7076	108 ± 35	95 ± 27	< 0.001
Pulmonary vein S/D ratio	1857	0.9 ± 0.5	1.3 ± 0.6	< 0.001
2+ or greater TR	7021	89 (50.3%)	1020 (14.9%)	< 0.001
AR severity	6132			< 0.001
0+		44 (23.4%)	3198 (42.1%)	
1+		92 (48.9%)	2495 (32.9%)	
2+		20 (10.6%)	283 (3.7%)	
Peak TR velocity (m/s)	5928	3.2 ± 0.5	2.8 ± 0.5	< 0.001

Values are listed as means ± standard deviations unless otherwise indicated. Cell values that included <11 individuals were omitted per CMS data use policy.

N obs = number observed; MR = mitral regurgitation; N = number; SD = standard deviation; cm = centimeter; kg = kilogram; mmHg = millimeter of mercury; bpm = beats per minute; mL = milliliter; TR = tricuspid regurgitation; AR = aortic regurgitation.

multivariable (HR 1.12, 95% CI 0.80 to 1.58, p = 0.51) basis, MR severity in this subgroup was not associated at risk of mortality. There was a significant interaction between atrial fibrillation status and MR severity on the risk of mortality (interaction p = 0.03; Supplementary Table 4). MR severity was only associated with mortality in the subset without MVP (Supplementary Table 5).

A total of 1,526 (19.6%) individuals had an HF hospitalization in the 3 months preceding the date of TTE. In this cohort, no significant increased risk of all-cause mortality with increasing MR severity was identified (3 to 4+ MR vs 0 to 2+ MR, unadjusted HR 1.15, 95% CI 0.74 to 1.80, p = 0.54).

Although those with obesity less frequently had 3 to 4+ MR (1.3% vs 3.1%, p <0.001), they also more frequently had suboptimal image quality (36.9% vs 20.9%, p <0.001). Nonetheless, there were no significant interactions between either obesity (interaction p = 0.46) or BMI (interaction p = 0.75) on the risk of all-cause mortality.

Discussion

In this large, single-institutional, retrospective cohort study of Medicare beneficiaries with HFpEF who underwent TTE, moderate-to-severe, and severe MR were independently associated with an increased risk of all-cause

Table 2
Cumulative incidence of adverse events at each time point from transthoracic echocardiography

	1-Year	5-Years	10-Years	Univariate HR (95% CI)	Multivariable HR (95% CI)
Combined, % (N = 7,778)					
All-cause death	827 (10.6%)	1,872 (24.1%)	2,498 (32.1%)		
MVR	11 (0.1%)	25 (0.3%)	72 (0.9%)		
0-2+ Mitral regurgitation, % (N = 7,590)					
All-cause death	797 (10.5%)	1806 (23.8%)	2414 (31.8%)	Ref	Ref
MVR	< 11	15 (0.2%)	41 (0.5%)	Ref	Ref
3-4+ Mitral regurgitation, % (N = 188)					
All-cause death	30 (15.8%)	66 (35.2%)	84 (44.8%)	1.54 (1.22-1.95)	1.48 (1.14-1.94)
MVR	< 11	< 11	31 (16.4%)	29.65 (18.64-47.17)	N/A

Listed are actual 1-year, 5-year, and 10-year mortality rates both overall and stratified by MR severity, and the univariate and multivariable HRs and 95% CIs for risk of all-cause death by MR severity. Multivariable models are adjusted for age, gender, LVEF, systolic blood pressure (at the time of echocardiogram), depression, anemia, diabetes mellitus, ischemic heart disease, cancer, atrial fibrillation, chronic obstructive pulmonary disease, dementia, MVP, eccentric MR, TR severity, and peak systolic tricuspid velocity. Also presented are rates of mitral valve annuloplasty, replacement, or repair at 1 year, 5 years, and 10 years after the index echocardiogram and univariate and multivariable HRs and 95% CI by MR severity. All comparisons are significant at a $p < 0.001$ level except for the relation between MR severity and all-cause death ($p = 0.004$). Cell values <11 are omitted per the data use agreement with the Centers for Medicare and Medicaid Services. Because of the low number of mitral valve surgeries, multivariable adjustment was not performed when assessing the relation between MR severity and subsequent mitral valve surgery.

CI = confidence interval; HR = hazard ratio; MR = mitral regurgitation; MVR = mitral valve annuloplasty, replacement, or repair; N = number; N/A = not applicable; ref = reference group.

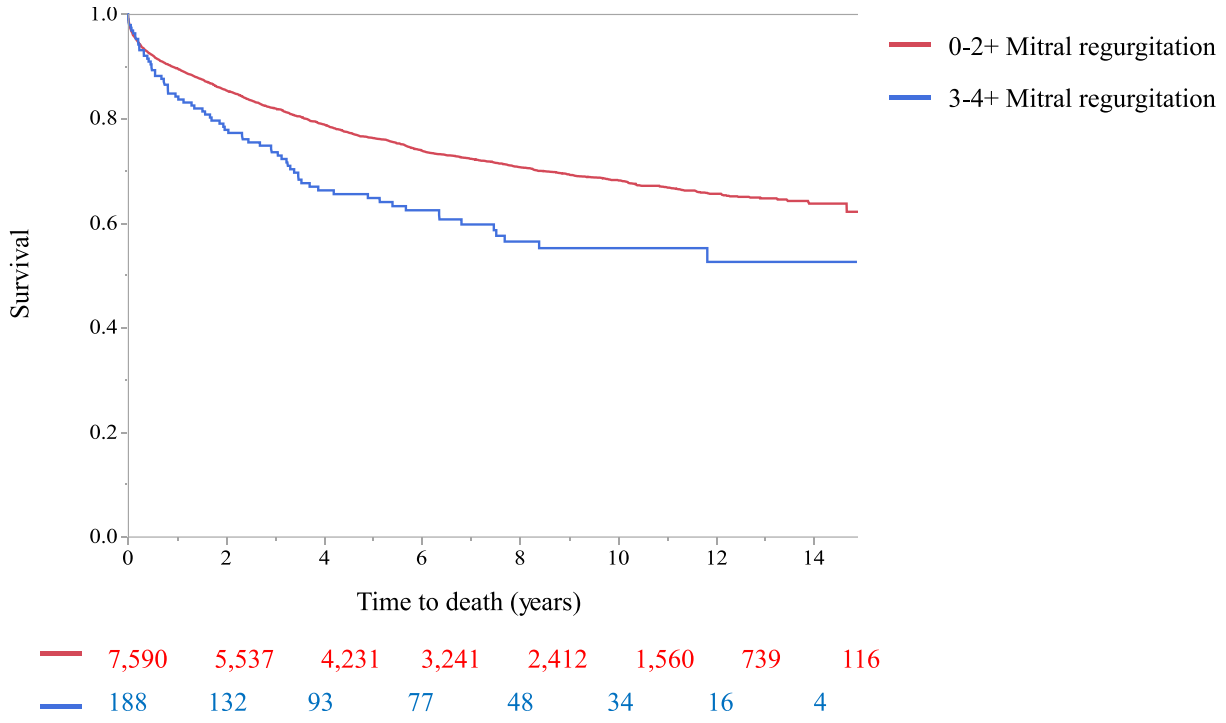

Figure 2. Kaplan-Meier curve for all-cause mortality by MR severity after baseline transthoracic echocardiography. Kaplan-Meier estimates of the primary end point of all-cause mortality as stratified by MR severity (red curve = 0−2+ MR; blue curve = 3−4+ MR). Shaded areas indicate the 95% confidence interval for effect estimates. Numbers in the risk set at each time point are provided later. Log-rank $p < 0.001$.

death after multivariable adjustment. This increased risk was only present in individuals without a history of atrial fibrillation or HF hospitalization >3 months before the date of TTE. Rates of mitral valve surgery were overall low. Further studies are needed to assess the role of MR reduction in mitigating the risk of mortality.

MR is a frequent echocardiographic finding in HFpEF, occurring in 30% to 72% of individuals and increasing in prevalence with age.[1,11,19–21] Despite being common, the prognostic impact of MR in HFpEF remains uncertain. Several authors have identified a potential increased risk of mortality with increasing MR severity in clinical trial populations.[12,22] However, because of the selection of healthier participants into clinical trials, these findings may not generalize to individuals encountered in routine clinical practice.[23] Moreover, at least 1 study by Pecini et al[12] found that MR severity was only associated with an increased risk of mortality in patients with an LVEF <25%. Shah et al[22] demonstrated an association between MR severity and a composite end point of HF hospitalization and

cardiovascular death in a cohort of patients with HFpEF. However, the association with cardiovascular death alone did not persist after multivariable adjustment. Previous cohort studies evaluating this question have predominantly enrolled patients with coexisting atrial fibrillation or ascertained outcomes using data from a single center.[11,13,24–26] In contrast, in the present study, we ascertained outcomes using Medicare claims which allows for a complete assessment of deaths occurring outside the initial site of performance of echocardiography.

In this study, moderate-to-severe and severe MR were significantly associated with the primary end point of all-cause mortality after multivariable adjustment. Reasons for the apparent discrepancy between studies indicating an absence of a significant relation between MR severity and mortality and the present study remain unclear at present and should be explored in future investigation.[11,12] However, the predominant inclusion of an older, multimorbid Medicare population and complete long-term follow-up over 10 years may have allowed ascertainment of deaths not reported to the primary site of enrollment. Although it is not possible to determine the proportion of deaths that are cardiovascular or attributable to the presence of significant MR, our findings nevertheless indicate that significant MR in older individuals with HFpEF is independently prognostic and adds to the existing body of knowledge suggesting MR is associated with excess mortality in HFpEF.[13,26] Interestingly, individuals with recent (<3 months) HF hospitalization did not have an excess risk of mortality. Although this may reflect that the association between MR severity and risk of mortality is present only over long-term follow-up, it may also reflect the comparatively lower sample size in this subset and power to detect an effect if present.

In the present study, whereas MVP was identified in 13.3% of those with 3 to 4+ MR versus 1.3% of those with 0 to 2+ MR, most individuals with 3 to 4+ MR did not have MVP, suggesting the prevalence of atrial functional MR may be significant. Indeed, in those with 3 to 4+ MR, a history of atrial fibrillation was present in 67.0% versus 34.6% with 0 to 2+ MR. Moreover, in the subset of patients with atrial fibrillation, MR severity was not related to mortality, with a statistically significant interaction between MR severity and atrial fibrillation status on risk of death. Reasons for the lack of prognostic significance of atrial functional MR in this setting are uncertain. They may reflect differences in the adaptation of the left atrium to volume loading that may be prognostically important. However, future studies should confirm and explore this hypothesis further.

Given the uncertainty about the association of MR with outcomes in HFpEF, the potential benefit of MR-reducing therapies in this setting remains unclear.[27–31] Although mitral valve annuloplasty for severe ischemic MR in HFrEF is limited by recurrence rates of up to 32.6%, this high relapse rate may be related to persistent leaflet tethering from LV dilation,[32,33] and more durable outcomes might be expected mechanistically in HFpEF. Indeed, several small case series have highlighted favorable outcomes after mitral annuloplasty in patients with preserved EF, although more long-term studies are needed.[34,35] The efficacy of mitral valve interventions in HFpEF in the absence of LV dilation is not clear. Further studies are needed to clarify the prognostic role of MR reduction in HFpEF.[9,10,27,36] In the present study, only 16.4% of those with 3 to 4+ MR and HFpEF underwent mitral valve surgery over 10 years of follow-up, reflecting this uncertainty about the benefit of MVR in this population.

Although large, our study had several limitations. First, as a single-center study, results may not generalize to other institutions, although the use of claims to ascertain outcomes allows death to be well captured regardless of the site of occurrence. Second, because all patients were referred for TTE, they may differ in unmeasured ways from patients not referred. Third, despite controlling for multiple clinical and echocardiographic factors, residual confounding may exist that may explain the observed relations, and causality should not be inferred with the current methods. Fourth, detailed quantitative information (e.g., effective regurgitation orifice, regurgitant volume, and so on) was used to determine MR severity using the integrative method. Still, this information was not stored for analysis and may better reflect risk because of MR.[37] Fifth, as individuals could have undergone MVR and follow-up TTE at other sites, the numbers of MVRs may be underestimated. Sixth, the association between MR severity and other outcomes such as HF hospitalization was not evaluated because of concerns about the validity of coding for HF in follow-up. Further investigations are needed to identify the association between MR severity and other relevant cardiovascular end points. Seventh, it is possible that some included patients may have HF with improved EF rather than HFpEF, and the associations observed may differ in this subset. Eighth, cause-specific mortality information was not available, and thus it is not possible to determine if deaths were cardiovascular-related.

In this large, single-center retrospective cohort study of Medicare beneficiaries referred for TTE, moderate-to-severe and severe MR were associated with an increased risk of all-cause death in patients with HFpEF after multivariable adjustment for clinical and echocardiographic variables. This increased risk was only present in individuals without a history of atrial fibrillation and those with HF hospitalization more than 3 months preceding the date of TTE. Rates of mitral valve surgery were overall low. Further longitudinal studies are needed to clarify the role of MR reduction in this population in mitigating risk mortality.

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Supplementary materials

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