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Original research

Mortality associated with moderate and severe mitral regurgitation in 608 570 men and women undergoing echocardiography

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ABSTRACT

Background Although the prognostic implications of severe mitral regurgitation (MR) are well recognised, they are less clear in moderate MR. We therefore explored the prognostic impact of both moderate and severe MR within the large National Echocardiography Database Australia cohort.

Methods Echocardiography reports from 608 570 individuals were examined using natural language processing to identify MR severity and leaflet pathology. Atrial (aFMR) or ventricular (vFMR) functional MR was assessed in those without reported leaflet pathology. Using individual data linkage over median 1541 (IQR 820 to 2629) days, we examined the association between MR severity and all-cause (153 612/25.2% events) and cardiovascular-related mortality (47 840/7.9% events).

Results There were 319 808 men and 288 762 women aged 62.1±18.5 years, of whom 456 989 (75.1%), 102 950 (16.9%), 38 504 (6.3%) and 10 127 (1.7%) individuals had no/trivial, mild, moderate and severe MR, respectively, reported on their last echo. Compared with those with no/trivial MR (26.5% had leaflet pathology, 19.2% died), leaflet pathology (51.8% and 78.9%, respectively) and actual 5-year all-cause mortality (54.6% and 67.5%, respectively) increased with MR severity. On an adjusted basis (age, sex and leaflet pathology), long-term mortality was 1.67-fold (95% CI 1.65 to 1.70) and 2.36-fold (95% CI 2.30 to 2.42) higher in moderate and severe MR cases (p<0.001) compared with no/trivial MR. The prognostic pattern for moderate and severe MR persisted for cardiovascular-related mortality and within prespecified subgroups (leaflet pathology, vFMR or aFMR, and age<65 years).

Conclusions Within a large real-world clinical cohort, we confirm that conservatively managed severe MR is associated with a poor prognosis. We further reveal that moderate MR is associated with increased mortality, irrespective of underlying aetiology.

Trial registration Australian New Zealand Clinical Trials Registry (ACTRN12617001387314)

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The prognostic implications of severe mitral regurgitation (MR) are well recognised, but are less clear in respect to moderate MR.
⇒ There is a broad clinical consensus that less-than-severe MR, although routinely reported following an echocardiogram, is a benign condition not requiring MR severity quantitation.

WHAT THIS STUDY ADDS

⇒ This study confirms poor outcomes associated with untreated severe MR.
⇒ It further reveals that moderate MR is common and not a benign condition, given it is also associated with increased mortality.
⇒ This association is independent of age, sex, atrial fibrillation, left ventricular function and mechanism of MR.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ There is a need for proactive follow-up of patients with moderate MR as well as further clinical research to establish whether existing and new therapeutic strategies can be applied to improve poor outcomes in such individuals.

INTRODUCTION

Chronic mitral regurgitation (MR) is a common valvular heart disease requiring clinical management.[1 2] Despite becoming more prevalent[1 2] and an array of therapeutic options for severe MR,[3–5] the prognostic importance of moderate MR remains poorly understood. Typical cardiac adaptive changes to chronic MR include increasing left ventricular (LV) dilatation and hypertrophy, impaired diastolic function, atrial dilatation, and pulmonary hypertension.[6] These adaptive responses are associated with heart failure (HF) and higher mortality, irrespective of the underlying aetiology.[7] Primary MR is a mechanical problem due to mitral leaflet pathology resulting in mal-coaptation, prolapse or flail. Secondary MR is broadly categorised into two groups: (1) Ventricular functional MR (vFMR) primarily due to ventricular dilatation (with papillary muscle displacement) and/or ventricular systolic dysfunction and (2) Atrial functional MR (aFMR) due predominantly to mitral annular dilatation in the setting of persistent atrial fibrillation (AF) or HF with preserved ejection fraction.

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In severe symptomatic primary MR, valve intervention is considered.[8] However, there is less clarity in managing moderate MR, and/or secondary MR.[8] This, perhaps, reflects a broad clinical consensus that less-than-severe MR, although routinely reported following an echocardiogram, is a benign condition not requiring MR severity quantitation. Even if there is clinical concern, choosing the optimal timing for intervention can be problematic as LV systolic function may remain relatively preserved until late in the trajectory of MR and associated symptoms difficult to characterise objectively.

Study hypotheses and aims

By analysing data derived from a large real-world, clinical cohort with individual data linkage to mortality, we identified all reported MR cases captured by the National Echocardiography Database Australia (NEDA).[9] We then aimed to examine the echocardiographic characteristics and mortality pattern associated with MR severity. We hypothesised that independent of age, sex and underlying cause of MR, both moderate and severe MR reported on echocardiography are prognostically significant when compared with those with less severe or no reported MR.

METHODS

Study setting and design

As described in previous reports,[10–12] NEDA is a multicentre, observational registry that captures standardised echocardiographic data of adults referred for routine cardiac investigation. This report is generated from more than 600 000 cases investigated within community-based echocardiography services to tertiary referral centres, and represents city, regional and remote services Australia-wide. The study conforms to the Declaration of Helsinki[13] and reporting conforms to the RECORD (REporting of studies Conducted using Observational Routinely-collected Data) guidelines for observational studies.[14]

Study data

NEDA applies an automated process (agnostic to vendor) to extract all demographic profiling and echo reporting data from each site to create a uniform, master NEDA database. This process also captures the text contained within the cardiologist-finalised report. These data have specific relevance to the routine clinical reporting of MR even if MR quantitation measurements were not performed and/or reported. Expert guidelines recommend specific quantification of the effective orifice area (ERO) to classify MR.[8] However, in reality, we observed that ERO was only reported in ~1.1% of echocardiograms. Reporting this information alone introduces strong reporting biases with no meaningful comparator group identified. Thus, our analyses focused on the MR grade specifically reported by the reviewing cardiologist considering all factors including MR quantitation. We extracted all text outputs via natural language processing (NLP, see online supplemental method S1 and online supplemental figure S1) to capture all relevant comments on MR, its cause and severity, the presence of ventricular remodelling and systolic dysfunction, atrial and/or mitral annular dilatation and the presence of leaflet pathology. Where available, comprehensive mitral quantification data including mitral jet area, jet width, vena contracta width, regurgitant volume, regurgitant orifice area and regurgitant fraction were extracted to enhance determination of MR severity.

For this report, we analysed individuals investigated from 1 January 2000 to 21 May 2019 with data linkage to the National Death Index.[15] The primary cause of death was classified according to International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10AM) coding, with those in the range of I00-I99 categorised as a cardiovascular-related death.

Study cohort

We included men and women aged ≥18 years with ≥1 echocardiographic investigation (the *last* recorded investigation used if multiple investigations documented) and no evidence of prior MVR or replacement, or transcatheter edge-to-edge repair (TEER) (figure 1).

Study outcomes

The text reports from 608 570 individuals were scrutinised with NLP. The primary NLP output was the presence/absence and extent of MR according to the following four (mutually exclusive) groups:

- **Group 1:** No text indicating the presence of MR ('No/trivial MR', allocated to this group if 'No/trivial/trace' or 'Grade 0' MR was reported or if no MR comment was made—noting that the '*absence of MR*' is not routinely reported, while healthy individuals may have a trace of MR).[16]
- **Group 2:** Text description of 'mild MR' (with 'trivial-to-mild' or 'Grade I' MR classified as 'mild').
- **Group 3:** Text description of 'moderate MR' (with 'mild-to-moderate' or 'Grade II' MR classified as 'moderate').
- **Group 4:** Text description of 'severe MR' (with 'moderate-to-severe', 'moderately severe', 'Grade III' or 'Grade IV' MR classified as 'severe').

For this study, we specifically focused on groups 3 and 4 (moderate and severe MR). We also categorised each echocardiogram according to the presence/absence of leaflet pathology and/or functional mitral valve disease using a combination of NLP and routine measurement data. For leaflet pathology screening, we applied the Euro Heart Survey definition of leaflet pathology[7] while also identifying mitral stenosis (calcific and/or rheumatic leaflet pathology, and a diastolic transvalvular mitral gradient >5 mm Hg at any heart rate). Degenerative leaflet pathology (intended to identify primary MR) was defined as *any* leaflet abnormality extracted using NLP from the text (online supplemental method S1 and online supplemental figure S1). If no leaflet pathology was reported, it was assumed to be absent and two further mutually exclusive groups were created:

1. aFMR was defined (using echocardiographic measurement data[17] as severe left atrial (LA) dilatation in the setting of no/mild LV dilatation and preserved left ventricular ejection fraction (LVEF). The full definition of aFMR is shown in online supplemental method S2.
2. vFMR was defined by the presence of moderate/severe LV dilatation and/or LVEF <50%. The full definition is shown in online supplemental method S2.

A total of 153 612 (47 840 cardiovascular-related) deaths were identified during median 1541 (IQR 820–2629) follow-up days. We explored the relationship between mortality and reported MR (from no/trivial to severe) overall and then among those identified with leaflet pathology. Sensitivity analyses confirmed equivalent mortality outcomes for those identified with 'no MR' and 'trivial MR' and these groups were therefore merged (data on request).

Statistical analyses

No study power calculations were performed given our analyses were based on >150 000 deaths during 2.5 million person-years follow-up. No imputation was performed for

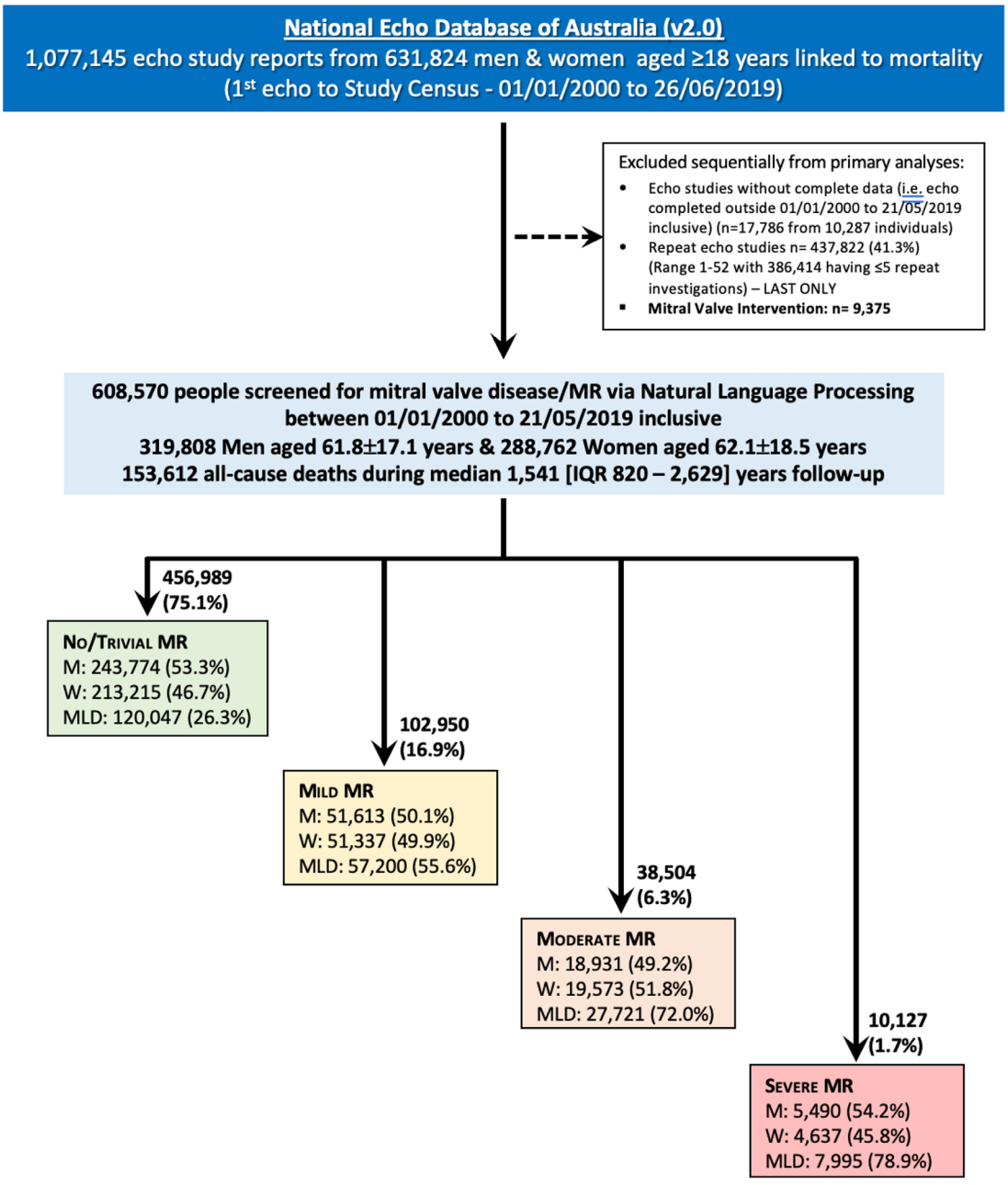

Figure 1 Study schema. The National Echocardiography Database Australia (NEDA) V.2.0 used to extract all individuals ≥18 years of age between 1 January 2000 and the census date in May 2019. To ensure the most recent investigation was used, only the last echo was chosen for analysis, and all patients with prior mitral valve intervention (repair or replacement) were excluded. Natural language processing (NLP) was applied to echocardiographic report data and the reported mitral regurgitation (MR) severity was extracted.

missing data or missing echocardiographic variables. Discrete variables were summarised by frequencies and percentages (with 95% CIs where appropriate). Continuous variables were summarised by standard measures of central tendency and dispersion. No/trivial MR cases (group 1) were the reference group for all analyses. Binary logistic regression was used to derive actual 1-year and 5-year ORs calculated from the 591 638 and 340 558 individuals according to MR severity. Cox proportional hazards models (entry model with proportional hazards confirmed by visual inspection) generated HRs for long-term all-cause and cardiovascular-related mortality (with censored events) during entire follow-up, with models first adjusting for age and sex (reference female) plus leaflet pathology (where appropriate, reference group being the absence of pathology) and then a combination of age, sex, leaflet pathology, aFMR, vFMR, AF or other atrial arrhythmia, LVEF, TR velocity and timing of echo (to adjust changes in clinical practice over time, first vs last 3 years of the study timeframe) to derive adjusted HR with 95% CI. These same models were applied to mortality outcomes for those with or without leaflet pathology and aged <65 years. All analyses were performed with SPSS V.29.0 and statistical significance accepted at a two-sided alpha of 0.05.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Table 1 Baseline characteristics of the study cohort (n=608 570)

	Men (n=319 808)				Women (n=288 762)			
	No MR (n=243 774)	Mild MR (n=51 613)	Moderate MR (n=18 931)	Severe MR (n=5490)	No MR (n=213 215)	Mild MR (n=51 337)	Moderate MR (n=19 573)	Severe MR (n=4637)
Demographic profile								
Age at echo, years	59.0±17.0	69.5±14.2	73.5±13.4	72.9±14.3	58.7±18.3	70.3±15.5	75.3±14.3	75.9±15.3
Anthropometric profile								
Body mass index, kg/m²	28.4±5.7	28.0±5.6	27.0±5.3	26.0±5.2	28.3±7.2	27.9±6.9	26.6±6.4	25.4±6.2
Mitral valve profile/function								
Mean gradient, mm Hg	2.0 (1.0–3.5)	2.4 (1.4–4.0)	2.9 (1.7–4.4)	3.0 (1.8–4.5)	3.0 (1.6–4.4)	3.0 (2.0–5.0)	3.7 (2.2–5.5)	4.0 (2.5–6.5)
Mitral thickening, *n (%)*	44 948 (18.4%)	21 549 (41.8%)	10 344 (54.6%)	3238 (59.0%)	42 106 (19.7%)	22 395 (43.6%)	11 109 (56.8%)	2944 (63.5%)
Mitral calcification, *n(%)*	16 289 (6.7%)	9879 (19.1%)	4879 (25.8%)	1312 (23.9%)	17 890 (8.4%)	12 438 (24.2%)	6694 (34.2%)	1731 (37.3%)
Mitral prolapse, *n (%)*	7029 (2.9%)	1724 (3.3%)	1806 (9.5%)	1236 (22.5%)	6212 (2.9%)	2010 (3.9%)	1729 (8.8%)	872 (18.8%)
Mitral endocarditis, *n (%)*	812 (0.3%)	295 (0.6%)	197 (1.0%)	188 (3.4%)	495 (0.2%)	261 (0.5%)	188 (1.0%)	118 (2.5%)
Rheumatic MS, *n (%)*	705 (0.3%)	272 (0.5%)	257 (1.4%)	122 (2.2%)	1316 (0.6%)	668 (1.3%)	756 (3.9%)	329 (7.1%)
Any form of leaflet pathology, n (%)	61 558 (25.3%)	27 481 (53.2%)	13 169 (69.6%)	4194 (76.4%)	58 489 (27.4%)	29 719 (57.9%)	14 552 (74.4%)	3801 (82.0%)
Ventricular FMR, *n (%)*	4903 (2.7%)	1616 (6.7%)	952 (16.5%)	294 (22.7%)	3828 (2.5%)	752 (3.5%)	455 (9.1%)	151 (18.1%)
Atrial FMR, *n (%)*	5018 (2.8%)	6676 (29.7%)	844 (17.6%)	66 (6.6%)	4652 (3.1%)	5921 (28.4%)	982 (21.5%)	72 (10.5%)
Left ventricular dimensions and function								
LVDD, *cm*	4.8±0.7	5.1±0.8	5.3±0.9	5.8±1.0	4.4±0.6	4.5±0.7	4.6±0.8	4.9±0.9
LVSD, *cm*	3.2±0.7	3.4±0.9	3.9±1.1	4.4±1.3	2.8±0.6	2.8±0.7	3.1±0.9	3.5±1.1
LVMi, *g/m²*	91.9±25.6	114.0±34.8	122.0±36.8	132.2±37.3	78.5±22.4	98.3±33.7	105.3±35.0	116.0±36.8
LVEF, *%*	61.2±11.1	58.6±15.4	49.1±17.4	44.0±19.1	65.1±9.5	64.6±12.7	58.1±15.4	51.8±18.0
LVEF <50%, *n (%)*	20 065 (8.2 %)	9944 (19.2%)	7117 (37.6%)	2553 (46.5%)	7827 (3.7%)	4171 (8.1%)	3812 (19.5%)	1494 (32.2%)
LVOT SVi, *ml/m²*	41.1±11.7	41.2±12.1	39.1±13.4	34.9±14.7	39.6±11.3	40.7±12.1	39.7±13.9	35.5±13.6
LV septal e' velocity, *cm/s*	8.4±2.9	6.9±2.4	6.6±2.4	6.4±2.5	8.8±3.1	7.2±2.7	6.7±2.5	6.3±2.5
Mitral E/e' ratio	9.3±3.8	12.5±5.1	15.1±7.0	18.1±8.9	9.7±4.1	12.7±5.6	15.7±7.3	19.5±9.1
LAVi, *ml/m²*	33.5±16.2	69.6±37.5	79.8±48.7	84.9±54.2	31.6±15.3	61.0±32.5	73.51±42.4	88.6±55.6
Right heart parameters								
Moderate–severe TR, *n (%)*	4105 (1.68%)	4614 (8.9%)	5134 (27.1%)	1865 (34.0%)	5553 (2.6%)	6241 (12.2%)	6199 (31.7%)	1929 (41.6%)
Estimated RVSP, *mm Hg*	35.2±10.6	39.8±11.6	43.6±13.2	48.3±14.9	35.0±10.8	39.4±11.9	43.5±13.5	49.4±15.4

Values are presented as mean±SD, n (%) or median (IQR). Body mass index (385 547 cases); MV mean gradient (25 179 cases); FMR in the absence of leaflet pathology (ventricular: 395 607 cases and atrial: 382 656 cases); LVDD (446 684 cases); LVSD (355 783 cases); LVMi (298 417 cases); LVEF (456 378 cases), SVi (138 107 cases); LV septal e' velocity (241 068 cases); mitral E/e' (218 061 cases); LAVi (183 202 cases); TR (133 071 cases); RVSP (assuming right atrial pressure =5 mm Hg) (303 595 cases); rheumatic MS, postrheumatic fever induced MS (4425 cases).
E/e', Ratio of the mitral E wave to septal e prime velocity; FMR, functional mitral regurgitation; LAVi, Left Atrial Volume Index; LV, left ventricular; LVDD, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; LVMi, Left Ventricular Mass Index; LVOT, left ventricualr outflow tract; LVSD, left ventricular systolic diameter; MR, mitral regurgitation; MS, mitral stenosis; MV, mitral valve; RVSP, right ventricular systolic pressure; SVi, Stroke Volume Index; TR, tricuspid regurgitation.

RESULTS

Overall, 456 989 (75.1%), 102 950 (16.9%), 38 504 (6.3%) and 10 127 (1.7%) individuals had no/trivial, mild, moderate and severe MR, respectively, reported on their last echo (figure 1). Despite numerical differences (more men investigated), a similar proportion of men (1.7%) and women (1.6%) had severe MR. However, proportionally more women than men had moderate (6.8% *vs* 5.9%) or mild MR (17.8% *vs* 16.1%); all p<0.001. Leaflet pathology was reported in 26.3% of individuals with no/trivial MR, and in most individuals with mild, moderate or severe MR (55.6%, 72.0% and 78.9%, respectively).

Table 1 profiles the study cohort according to reported MR severity. Those with no/trivial MR were younger, with predominantly normal LV dimensions, mass and LVEF with 11.6% of men and 4.9% of women having impaired systolic function. Measures of diastolic function and pulmonary artery pressure were also predominantly normal. Moderate and severe MR was associated with increasing age overall and a decline in body mass index. The aFMR phenotype was seen in a small proportion of men (2.8%) and women (3.1%) without MR. Conversely, the vFMR phenotype became more common with worsening MR. vFMR, in the absence of any leaflet disease, was observed in 16.5% and 9.1% of men and women with moderate MR, and 22.7% and 18.1% in severe MR, respectively. The equivalent proportions for aFMR, in the absence of leaflet disease, was 29.7% and 17.6% for men and women with moderate MR, and 21.5% and 10.5%, for severe MR, respectively. Mitral stenosis occurred in <0.5% of cases (mostly in severe MR). Overall, typical volume-loaded cardiac changes (ventricular and atrial dilatation and impaired systolic and diastolic function) were positively associated with moderate and severe MR across all commonly reported LV function/structure and pulmonary artery pressure parameters. While directionally similar, the degree of LV dilatation was less marked in women than in men, and LVEF was 4%–6% higher in women across all MR categories. Online supplemental table S1 provides the same data for 212 963

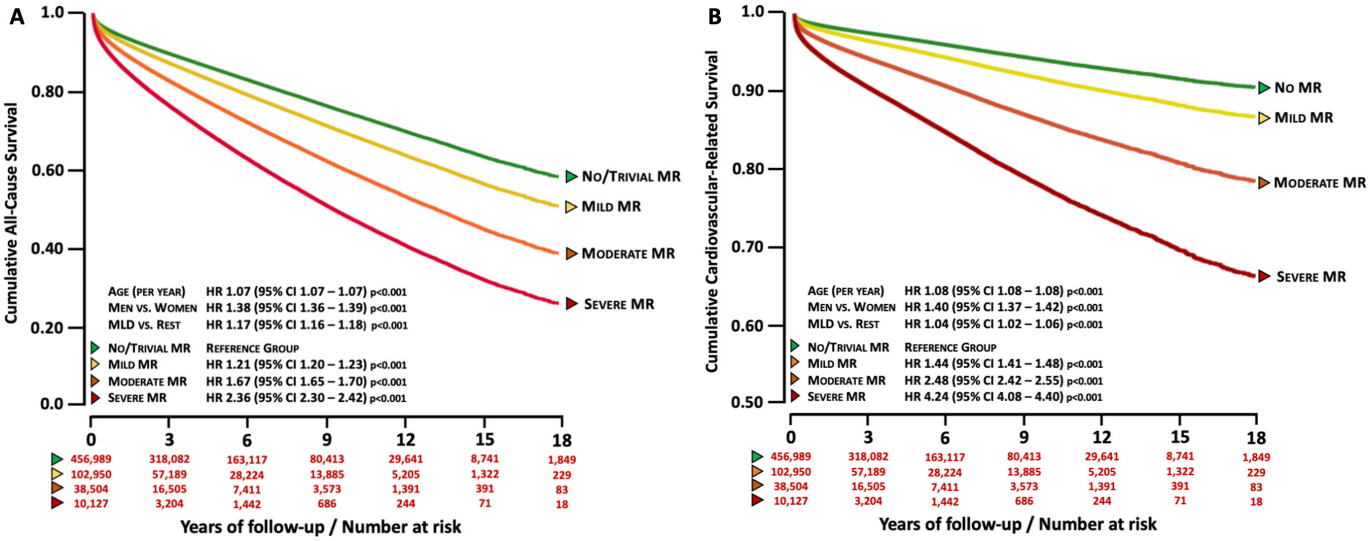

Figure 2 Adjusted long-term all-cause (Panel A) and cardiovascular-related (Panel B) survival according to severity of mitral regurgitation for all cases (n=608 570). The green lines represent no or trivial MR, yellow lines represent mild MR, orange lines represent moderate MR, and red lines represent severe MR. Panel A: Adjusted risk for all-cause mortality. Panel B: Adjusted risk for cardiovascular-related mortality. Clinical severity of mitral regurgitation (MR) adjusted for age, sex (reference female) and presence of mitral leaflet pathology (MLD, reference no disease). Cox proportional hazards model plots of all-cause survival in all patients with MR severity values. All associations significant at p<0.001. The numbers at risk are shown in red under the corresponding follow-up year for each MR severity group.

individuals with leaflet pathology, showing similar trends associated with increasing MR. Mitral leaflet thickening, calcification and prolapse accounted for the majority (>90%) of mitral leaflet pathology observed in both men and women, with mitral valve prolapse more frequently associated with severe MR than with moderate MR.

Overall, compared with those with no/trivial MR (19.8% and 5.2%) both all-cause mortality and cardiovascular-related mortality was higher in moderate (51.6% and 22.1%) and severe (62.3% and 32.6%) MR, with an early (1-year and 5-year) mortality signal evident (online supplemental table S2). Those with mild MR also have significantly higher mortality than no/trivial MR cases (35.7% vs 11.8%). Among those with cardiovascular-related mortality, the death certificate-attributed contribution of coronary heart disease and HF were proportionally similar between moderate and severe MR (45.8% and 9.1%, respectively, for moderate MR, and 46.3% and 9.3% for severe MR). Online supplemental tables S3–S10 summarise the outcomes according to men and women, with or without leaflet pathology and for the 505 620 cases with no/trivial, moderate or severe MR only.

Figure 2 presents the adjusted (age, sex and leaflet pathology), all-cause and cardiovascular-related survival curves according to MR severity (n=608 570). The adjusted HRs for all-cause mortality associated with mild, moderate and severe MR were 1.21 (95% CI 1.20 to 1.23), 1.67 (95% CI 1.65 to 1.70) and 2.36 (95% CI 2.30 to 2.42), respectively; all p<0.001. Although mortality rates were higher among the 212 963 cases with leaflet pathology (figure 3, as well as the adjusted HRs shown in figure 2), a similar pattern associated with increasing MR severity was observed among the 395 607 cases without leaflet pathology (figure 4). On a fully adjusted basis (including age, sex, LVEF, AF, aFMR and vFMR, and timing of echo), initially observed gradients of increasing all-cause and cardiovascular-related mortality with increasing MR persisted regardless of underlying aetiology (for the overall group and the presence or absence of mitral leaflet disease, see online supplemental figures S2–S7). These observations also persisted when excluding those reported to have mild MR (online supplemental figures S8–S13).

Sensitivity analyses performed on those aged <65 years (n=305 866), reaffirmed an increasing risk of long-term cardiovascular-related mortality in those with moderate (HR 1.81, 95% CI 1.58 to 2.07) and severe MR (HR 2.35, 95% CI 1.99 to 2.77), while confirming that increasing mortality associated with MR severity persisted in the presence of aortic stenosis.

Online supplemental table S11 shows the 4960 cases where MR severity was reported and at least one guideline-recommended[8] quantitative measurement of MR severity was performed. A total of 1072/10 127 (10.6%) cases with severe MR and 1618/38 504 (4.2%) cases with moderate MR had ERO available. Substantial discrepancies between physician-reported MR severity and quantitative values were identified and shown in online supplemental table S12, and the corresponding long-term all-cause mortality for physician-reported and quantitatively derived MR severity is demonstrated in online supplemental figure S14.

DISCUSSION

To our knowledge, this is the largest study of (reported) MR severity and its prognostic significance undertaken to date. Within a cohort of >600 000 individuals without prior mitral valve intervention, 5.9%–6.8% and 1.6%–1.7% of men and women, had moderate and severe MR. Like severe MR, at the time of investigation, moderate MR was not benign and had typical cardiac phenotypical responses reflecting worsening cardiac function[8] and a poor prognosis thereafter.

The prevalence of MR (around one in four individuals) found in NEDA is broadly consistent with previous reports suggesting that around one in five individuals undergoing echocardiography are found to have MR.[18] The OxValve Study that enrolled 2500 UK individuals aged ≥65 years from primary care without known valvular heart disease found mild-to-severe MR in 22% of individuals, with moderate or severe MR present in 2.3%.[19] As in our cohort, a steep age gradient has been consistently

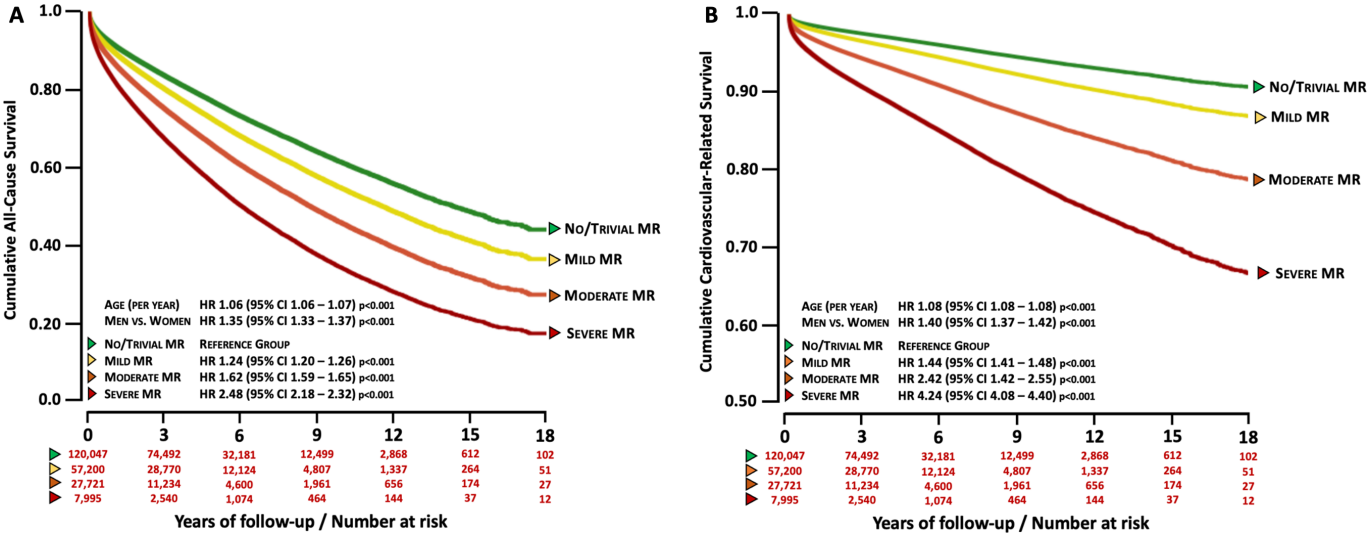

Figure 3 Adjusted long-term all-cause (Panel A) and cardiovascular-related (Panel B) survival according to severity of mitral regurgitation (mitral leaflet pathology cases, n=212 963). The green line represents no or trivial MR, yellow line represents mild MR, orange line represents moderate MR, and red line represents severe MR. Panel A: Adjusted risk for all-cause mortality. Panel B: Adjusted risk for cardiovascular-related mortality. Clinical severity of mitral regurgitation (MR) adjusted for age and sex (reference female). All associations significant at p<0.001. The numbers at risk are shown in red under the corresponding follow-up year for each MR severity group.

identified across populations studied[1] and, importantly, symptoms were not strongly associated with MR severity.[19] Within the NHLBI: National Heart, Lung and Blood Institute USA (NHLBI) population study of moderate-to-severe MR, its prevalence rose from 6.4% to 9.3% among those aged 65–74 years to >75 years; their estimated population prevalence of MR being 1.7%.[1] The high frequency (24.8%) of moderate-to-severe MR cases in the EuroHeart Survey reflects the inherent bias in recruitment from hospital outpatient settings.[2] Consistent with our findings, the EuroHeart Study showed that degenerative leaflet was the dominant cause (61.3%) of MR.[2] We also demonstrated low/inconsistent use of guideline-recommended MR quantitation, and when performed, was frequently discrepant with reported MR severity. Previous reports with MR quantitation have either included specific subgroups,[20] or did not report the degree of quantitation and/or discrepancy with physician reports.[21]

When left untreated, severe MR is consistently associated with a very poor prognosis.[1 7] A Mayo Clinic study, limited to those with moderate-to-severe MR (predominantly leaflet pathology), reported an HR of 2.23 for all-cause mortality compared with the general population.[21] Critically, only 15% of this cohort underwent mitral valve intervention. The national French MR outcomes study[22] showed similarly low intervention rates in severe MR (8% at 1 year), with conservative

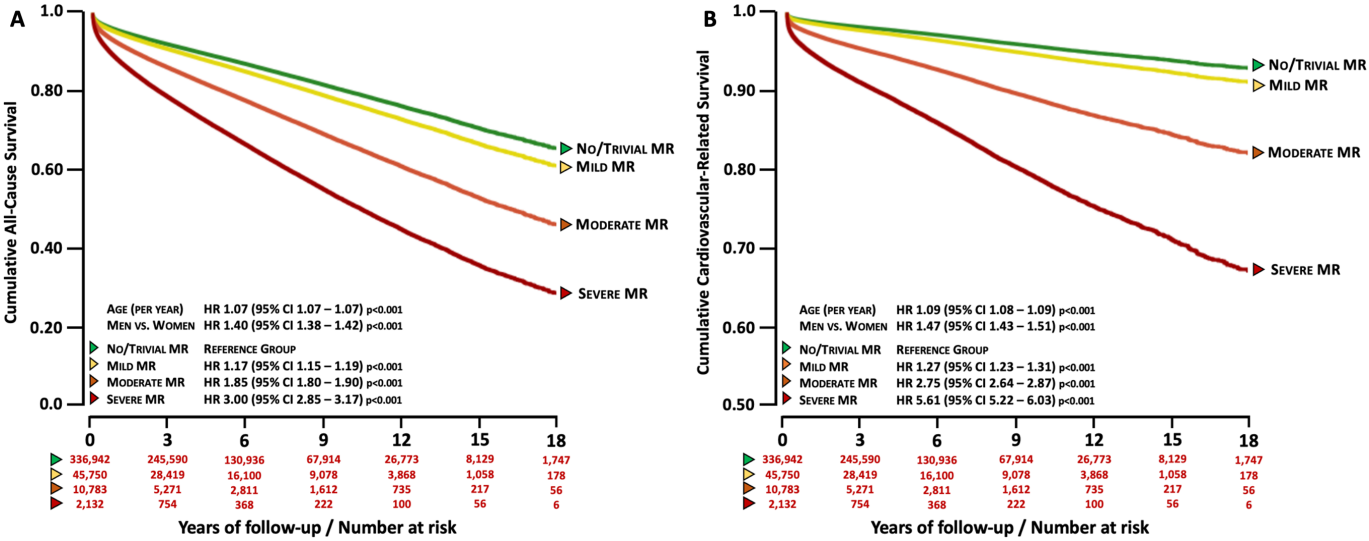

Figure 4 Adjusted long-term all-cause (Panel A) and cardiovascular-related (Panel B) survival according to severity of mitral regurgitation (cases without mitral leaflet pathology). The green line represents no or trivial MR, yellow line represents mild MR, orange line represents moderate MR, and red line represents severe MR. Panel A: Adjusted risk for all-cause mortality, graph axis is shown from 0.0 to 1.0. Panel B: Adjusted risk for cardiovascular-related mortality, graph axis is shown from 0.50 to 1.0. Clinical severity of mitral regurgitation (MR) adjusted for age and sex (reference female). All associations are statistically significant at p<0.001. The numbers at risk are shown in red under the corresponding follow-up year for each MR severity group.

management resulting in HF hospitalisations and very high event rates in both leaflet MR and functional MR categories. Similarly, a Mitral Regurgitation International Database[23] report of MR due to mitral flail showed that conservative management resulted in substantially worse HF, AF and mortality outcomes over a 10-year follow-up. Alternatively, surgical repair markedly improved these outcomes (especially if performed early in the disease trajectory).[24]

While confirming the clinical importance of severe MR, our findings are highly relevant to the substantive number of individuals who present with what is generally considered a benign condition—moderate MR. However, one retrospective study of mitral valve prolapse with less-than-severe MR at their index echo, demonstrated more than half of patients experienced MR progression and/or development of LV dysfunction despite ongoing optimal follow-up.[25] Consistent with these observations, we have shown that moderate MR (like severe MR) is also associated with significantly increased mortality. To address expected variations in MR reporting, we have been intentionally conservative in our severity allocation, by 'upgrading' mild-to-moderate or grade 2 MR into the moderate MR category. Additionally, we found a small mortality increase associated with mild MR, however, we are unable to exclude all potential confounders and comorbidities, and these require further investigation. Nevertheless, although similar confounders may have had an effect on moderate MR, our findings in this category are more substantial and robust—particularly when considering the consistency of findings within prespecified subgroups (eg, presence/absence of leaflet pathology) and the striking signal found in relation to cardiovascular-related mortality.

There are multiple mechanisms whereby any haemodynamically significant MR, irrespective of cause, may result in higher mortality.[7] When added to the forward stroke volume, the regurgitant volume results in progressive LV and LA dilatation,[1] although the degree of LV dilatation we observed was relatively mild (particularly in women). Chronic exposure to LV volume loading conditions results in LV hypertrophy, LV fibrosis and subendothelial ischaemia, which are independently associated with an increased mortality risk. Due to decreased afterload from MR despite increased peripheral resistance, impaired LV contractile reserve has been shown to be impaired when LVEF falls below 60%.[26 27] The LA volume loading from MR raises atrial pressure, resulting in atrial dilatation and an increased prevalence of AF and its clinical consequences (and secondarily, aFMR), along with group 2 pulmonary hypertension. The self-sustaining vicious cycle produced by these mechanisms tends to worsen MR over time, thereby provoking HF hospitalisations and premature mortality.[28] In specific diseases such as mitral valve endocarditis or mitral valve disjunction, the leaflet pathology itself is associated with higher risk, or conversely in aFMR and vFMR, the underlying risk mirrors the severity of the atrial dilatation or ventricular dysfunction, respectively.[7] In our definition of functional MR, we excluded any leaflet pathology. The prevalence of aFMR and vFMR we observed may be seen as the minimum indicative prevalence, since some patients may have the coexistence of functional MR and leaflet disease.

Despite the low rates of mitral valve intervention currently applied to severe MR cases[21] and the capacity constraints that may explain them, our data also highlight the need to proactively follow moderate MR cases in routine clinical practice and re-evaluate (via clinical trials) strategies to improve mortality outcomes. The growing armamentarium of mitral valve therapies including transcatheter techniques such as the TEER and MVR,[3 4 29] and mitral annular reduction[5] systems means that at-risk patients previously not considered suitable surgical candidates, may now be considered for catheter-based valve therapy.[7]

Limitations

Beyond the reliance on 2D-echocardiography, the inherent limitations of using the big data approach of NEDA have been previously described.[10 11] NEDA does not currently capture detailed socioeconomic variables or other key determinants of outcome (eg, clinical symptoms, pharmacotherapy, comorbidities common to MR and hospital care). Furthermore, this real-world clinical cohort typically comprises subjects being investigated for known or suspected heart disease. We relied on NLP extraction to detect MR (as reported by the treating cardiologist), which may have included subjective determination of MR severity, although comprehensive guideline-recommended quantitation of MR severity[8] may also have been performed but not documented. However, this reflects current real-world echocardiography practice, and the method determining severity that prompts referral for consideration of valve therapy. Similarly, blood pressure and dynamic loading conditions were not routinely reported. A small number of cases may have had acute MR, and we cannot discount the overestimated or underestimated MR severity that is mitigated by the size of reports analysed. In this respect, we found that 'trivial MR' showed the same characteristics and outcomes as 'no MR'. Lastly, we only broadly classified MR into leaflet pathology and two categories of functional MR. In clinical practice, classification of MR is more complex and includes the many different forms of leaflet pathology as originally described in Carpentier's surgical classification.[30]

CONCLUSIONS

In summary we confirm that when left untreated, severe MR is associated with a very poor prognosis. Furthermore, we reveal that moderate MR is also not benign. Instead, it is associated with an increased risk of mortality irrespective of a person's age or the underlying cause of MR. As with severe MR, some individuals with moderate MR also have comorbidities that may independently affect their mortality trajectory. Nevertheless, these new findings have important clinical implications given the frequency of moderate MR. Strategies are needed to improve proactive clinical surveillance of these cases. Moreover, in this rapidly developing era of improved mitral valve therapies, our findings provide a strong rationale for more research to determine whether there is a role for interventions to minimise clinical deterioration, hospitalisation for HF, AF and premature death, among those presenting with moderate MR. Further studies are needed to examine the independence of moderate MR from comorbidities and other potential clinical confounders. Finally, the persistently poor prognosis associated with severe MR renews calls for active clinical review of these individuals, for more informed patient-centred discussions and consideration of timely intervention where appropriate.

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