Journal of the American Heart Association

ORIGINAL RESEARCH

Prognostic Implications of Right Ventricular Dysfunction in Severe Degenerative Mitral Regurgitation

Yohann Bohbot, MD, PhD; Benjamin Essayagh, MD; Giovanni Benfari, MD; Jeroen J. Bax, MD, PhD; Thierry Le Tourneau, MD, PhD; Yan Topilsky, MD; Clemence Antoine, MD; Dan Rusinaru, MD, PhD; Francesco Grigioni, MD, PhD; Nina Ajmone Marsan, MD, PhD; Aniek van Wijngaarden, MD; Aviram Hochstadt, MD; Jean Christian Roussel, MD; Momar Diouf, PhD; Prabin Thapa, MSc; Hector I. Michelena, MD, PhD; Maurice Enriquez-Sarano, MD; Christophe Tribouilloy, MD, PhD

BACKGROUND: The prevalence and impact of right ventricular dysfunction (RVD) in degenerative mitral regurgitation (DMR) is unknown. We aimed to determine whether RVD assessed by echocardiography in routine clinical practice is independently associated with mortality in patients with DMR.

METHODS AND RESULTS: We used data from the MIDA-Q (Mitral Regurgitation International DAtabase-Quantitative) registry, which included patients with isolated DMR due to mitral valve prolapse from January 2003 to January 2020 from 5 tertiary centers across North America, Europe, and the Middle East. A cohort of 2917 (mean age: 66 years, 70.8% male patients, follow-up: 5.2 [3.3–8.3] years) consecutive patients with severe DMR was included and long-term mortality was analyzed. RVD, identified in 426 (14.6%) patients, was associated with reduced 8-year survival (55%±3% versus 77%±1%; P <0.001), overall and in all subgroups of patients, even after comprehensive adjustment including left ventricular dilatation and dysfunction, DMR severity, pulmonary pressures, and surgery (adjusted hazard ratio, 1.44 [95% CI, 1.17–1.77]; P <0.001). This excess mortality was observed under medical management (adjusted hazard ratio, 1.57 [95% CI, 1.20–2.05]; P=0.001) and after surgical correction of mitral regurgitation (adjusted hazard ratio, 1.45 [95% CI, 1.02–2.05]; P=0.039). Patients with RVD undergoing surgery within 3 months of diagnosis experienced a better 8-year survival (73%±4% versus 43%±4%; P <0.001), even after adjustment (adjusted hazard ratio, 0.44 [95% CI, 0.29–0.67]; P <0.001) despite an increase of 1-month postoperative mortality (7.1% versus 0.5% for patients without RVD; P <0.001).

CONCLUSIONS: RVD is observed in 14.6% of severe DMR and exhibits a powerful and independent association with excess mortality partially attenuated by mitral surgery. Therefore, assessment of right ventricular systolic function should be included in routine DMR evaluation and in the clinical decision-making process.

Key Words: degenerative mitral regurgitation ■ echocardiography ■ right ventricular dysfunction ■ surgery

See Editorial by Keen and Desai.

Right ventricular (RV) systolic dysfunction is a major determinant of survival in most cardiovascular diseases such as heart failure,[1] pulmonary hypertension (PH),[2] and myocardial infarction.[3] Conversely, in the field of left-sided valvular heart disease, considerable attention has been paid to left

Correspondence to: Maurice Enriquez-Sarano, MD, Department of Cardiovascular Diseases, Minneapolis Heart Institute, Abbott Northwestern Hospital, 800 E 28th St, Minneapolis, MN 55407. Email: sarano.maurice@gmail.com and Christophe Tribouilloy, MD, PhD, UR UPJV 7517, Jules Verne University, Amiens, France and Department of Cardiology, University Hospital Amiens, France, Avenue René Laënnec, 80054 Amiens Cedex 1, France. Email: tribouilloy.christophe@chu-amiens.fr

Preprint posted on MedRxiv November 12, 2023. doi: https://doi.org/10.1101/2023.11.10.23298404.

This manuscript was sent to Amgad Mentias, MD, Associate Editor, for review by expert referees, editorial decision, and final disposition.

For Sources of Funding and Disclosures, see page 10.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Right ventricular dysfunction (RVD) identifies individuals at increased risk of mortality in patients with severe degenerative mitral regurgitation, independent of pulmonary hypertension, left ventricular dysfunction, or presence of atrial fibrillation that can be reduced with mitral valve surgery.

What Are the Clinical Implications?

- RVD assessment should be included in routine degenerative mitral regurgitation evaluation.
- To avoid the excess mortality observed after mitral valve surgery related to RVD, surgery should be discussed before RVD occurs.
- Further studies are needed to understand the pathophysiological mechanisms linking RVD to prognosis in patients with severe degenerative mitral regurgitation.

Nonstandard Abbreviations and Acronyms

DMR	degenerative mitral regurgitation
LAVI	left atrial volume index
LVESD	left ventricular end-systolic diameter
PH	pulmonary hypertension
RVD	right ventricular dysfunction
SPAP	systolic pulmonary artery pressure
TAPSE	tricuspid annular plane systolic excursion

ventricular dysfunction, but RV function has been somewhat neglected. One possible explanation is that RV dysfunction (RVD) is often perceived as secondary to PH, which is a strong and recognized prognostic factor in left-sided valvular heart disease,[4–7] particularly in degenerative mitral regurgitation (DMR).[5,6] Indeed, the chronic increase in RV afterload induced by PH can lead to progressive RV failure with a negative correlation between RV function and pulmonary artery pressure.[8] Few studies of limited size have suggested that RVD is associated with poor outcome in patients with DMR[9–11] but without addressing the link with PH. Nevertheless, to date, assessment of RV function is not integrated into the clinical decision-making process in DMR[12,13] and no large-scale data are available regarding the impact of RV function assessed by echocardiography in these patients.

In this context, we sought to evaluate the prevalence of RVD diagnosed by transthoracic echocardiography in routine clinical practice using a large multicenter cohort of patients with severe mitral regurgitation (MR) of degenerative origin and to assess its independent impact on survival, under medical management and after surgical correction of MR.

METHODS

Study Design

The data that support the findings of this study are available from the corresponding author upon reasonable request. We used data from the Mitral Regurgitation International DAtabase-Quantitative registry, corresponding to the merging of electronic databases of patients with isolated DMR quantified prospectively in routine clinical practice of tertiary centers in Europe (University of Amiens, Amiens, France; University of Nantes, Nantes, France; Leiden University Medical Center, Leiden, the Netherlands), North America (Mayo Clinic, Rochester, MN), and the Middle East (Tel Aviv Medical Center, Tel Aviv, Israel). Patient recruitment ranged from January 2003 to January 2020, depending on each center's database.[14,15]

Consecutive adult patients (aged 18 years or older) with a diagnosis of mitral valve prolapse with or without a flail leaflet and a comprehensive clinical and echocardiographic evaluation at diagnosis were eligible for inclusion. We excluded patients (1) who declined research authorization; (2) without quantification of MR; (3) with functional or rheumatic MR, ≥moderate aortic valve disease or mitral stenosis, congenital heart disease, active endocarditis, dilated/hypertrophic/restrictive cardiomyopathies; and (4) with a history of valvular surgery. Patients were managed by the heart team in each tertiary center according to the guidelines prevailing at the time of diagnosis, considering their comorbidities, wishes, and operative risk. The present analysis was based on a study of patients with severe DMR and data on RV function. The study was approved by the Institutional Review Board of each center and conducted in accordance with institutional guidelines, national legal requirements, and the revised Declaration of Helsinki. Informed consent was waived due to the retrospective nature of the study.

Echocardiography

All patients underwent comprehensive Doppler-echocardiographic assessment using commercially available ultrasonography systems. All echocardiographic studies were analyzed by experienced investigators from each center. Left ventricular (LV) dimensions were assessed from parasternal long-axis views by 2-dimensional-guided M-mode, using the leading-edge methodology at end-diastole and end-systole. Left ventricular ejection fraction (LVEF) was calculated using Simpson's biplane method.[16,17] Left atrial volume

index (LAVI) was estimated using the biplane method from apical 4- and 2-chamber views and indexed for body surface area.[16] MR was graded according to current recommendations using a multiparametric and integrative approach, which included estimation of effective regurgitant orifice area (EROA) and regurgitant volume of MR using the proximal isovelocity surface area (PISA) technique.[18,19] Systolic pulmonary artery pressure (sPAP) was measured by applying the modified Bernoulli equation using the tricuspid regurgitation peak jet velocity and adding estimated right atrial pressure according to the inferior vena cava diameter and its respiratory variation. RV size and function was assessed as recommended per current guidelines using comprehensive imaging with multiple windows examining all segments of the complex RV anatomy and with the presence of RVD diagnosed based on a combination of qualitative and quantitative measures, including assessment of fractional area change (< or ≥35%), tissue-Doppler S′ (< or ≥9.5 cm/s), and tricuspid annular plane systolic excursion ([TAPSE] <or ≥17 mm).[16,17] The final diagnosis of RVD by the cardiologist responsible for the Doppler-echocardiographic examination final report was based on the integration of all information available in a categorical classification as per guidelines.[16,17]

Follow-Up and End Points

Median follow-up was 5.2 (interquartile range: 3.3–8.3) years. Events were ascertained by direct patient, family, or referent physician contact and by using institutional, private (Accurint in the United States), or public (social security mortality database or local equivalent) databases of vital status.[14] The primary end point was all-cause mortality, with medical and surgical treatment. Secondary end points were all-cause mortality under medical management in the overall population with censoring at mitral surgery (for patients operated on during follow-up), and postoperative mortality in patients who underwent mitral surgery.

Statistical Analysis

The study population was divided into 2 groups according to RV function. Categorical variables were reported as percentages and counts and continuous variables were expressed as mean ±1 SD or median (interquartile range). Factors associated with RVD were identified using multivariable binary logistic regression analysis. Crude survival distributions were estimated according to the Kaplan–Meier method and compared with 2-sided log-rank tests. Time-fixed survival rates were estimated from the Kaplan–Meier survival distributions. Multivariable analyses of all-cause mortality were performed using Cox proportional hazards models adjusted for age ≥65 years, sex, and recognized prognostic factors in DMR including atrial fibrillation (AF),[14,15,20] presence of symptoms, LV end systolic diameter (LVESD ≥40 mm),[14,21] LVEF ≤60%,[14,22] LAVI ≥60 mL/m^2,[14,15,23] sPAP ≥50 mm Hg,[5,14,15] and EROA ≥40 mm^2. To account for missing data in the adjustment factors, the Cox analyses were performed using multiple imputation with 3 replications. Proportional hazard assumptions were tested using the Shoenfeld residuals test. Given that the RVD variable and all other adjustment variables are binary, testing the linearity assumption was deemed unnecessary. Subgroup analyses were performed to determine the homogeneity of the association between RVD and mortality. The effect of RVD on the overall mortality risk was first estimated in each subgroup using a Cox univariate model and then formally tested for first-order interactions in Cox models by entering interaction terms separately for each subgroup. The limit of statistical significance was P <0.05. All tests were 2-tailed. SPSS version 26.0 software (IBM, Armonk, NY) was used for statistical analysis.

RESULTS

Baseline Characteristics

We included 2917 patients (mean age 66 years, 70.8% were male) with severe MR and available data on RV function. Among them, 1528 (52.4%) were from North America (United States) and 1389 patients (47.6%) were from Europe/Middle East. A bileaflet prolapse was observed in 1234 (42.3%), a posterior prolapse in 1505 (51.6%), and a flail leaflet in 1230 (45.2%) patients. Mean EROA was 51±17 mm^2, mean LVESD was 36±6 mm and mean LVEF was 64%±8% (Table 1).

Patients with RVD (n=426; 14.6%) were older, more often diagnosed with diabetes and coronary artery disease, had higher EuroSCORE II, and presented more frequently with symptoms and AF (all P <0.005). They had larger EROA and regurgitant volume, greater LVESD, LAVI and sPAP, and lower LVEF (47.9% had a LVEF ≤60%) than patients with normal RV function (all P <0.001) (Table 1).

On multivariable logistic regression, sPAP ≥50 mm Hg (Adjusted OR [AOR], 4.76 [95% CI, 3.73–6.07]) and LVEF ≤60% (AOR, 2.07 [95%CI, 1.61–2.67]) were the 2 factors most strongly associated with RVD, but age (AOR, 1.05 [95% CI, 1.04–1.06] per year increase), AF (AOR, 1.25 [95% CI, 1.02–1.62]), EROA (AOR, 1.12 [95% CI, 1.02–1.33] per 10 mm^2 increase), and LVESD ≥40 mm (AOR, 1.72 [95% CI, 1.32–2.22]) were also independently associated with RVD.

Long-Term Outcome Impact of RVD

Outcome in the Overall Population

There were 631 (21.6%) deaths recorded during follow-up. Eight-year estimated survival was

Table 1. Baseline Characteristics According to the Presence of Right Ventricular Dysfunction

Characteristics	Overall n=2917	Absence of RV dysfunction n=2491	Presence of RV dysfunction n=426	*P* value
Clinical characteristics				
Age, y	66±14	65±14	74±13	<0.001*
Female sex (%, n)	29.2 (853)	29.0 (723)	30.5 (130)	0.52
Body mass index, kg/m^2	25.7±4.6	25.7±4.6	25.7±4.6	0.81
Hypertension (%, n)	31.6 (921)	31.6 (786)	31.7 (135)	0.96
Diabetes (%, n)	7.1 (177)	5.4 (134)	10.1 (43)	<0.001*
Coronary artery disease (%, n)	21.9 (639)	21.0 (523)	27.2 (116)	0.005*
EuroSCORE II, %	1.2±0.9	1.1±0.8	1.8±1.2	<0.001*
Symptoms (%, n)	60.1 (1739)	57.5 (1421)	75.2 (318)	<0.001*
Atrial fibrillation (%, n)	25.6 (748)	23.3 (581)	39.2 (167)	<0.001*
Echocardiographic characteristics				
LV end-diastolic diameter, mm	58±7	58±7	58±8	0.58
Indexed LV end-diastolic diameter, mm/m^2	31±4	31±4	31±5	0.06
LV end-systolic diameter, mm	36±6	36±6	38±8	<0.001*
Indexed LV end-systolic diameter, mm/m^2	19±4	19±3	20±5	<0.001*
LV ejection fraction, %	64±8	65±7	60±10	<0.001*
LA volume index, mL/m^2	68±28	66±27	78±32	<0.001*
Mitral E-wave velocity (m/s)	1.6±0.4	1.5±0.4	2.0±0.4	0.21
E/e′ ratio	14±6	13±5	16±8	<0.001*
EROA, mm^2	51±17	50±16	54±19	<0.001*
MR regurgitant volume, mL	75±24	75±23	80±28	<0.001*
Bileaflet prolapse, (%, n)	42.3 (1234)	41.4 (1032)	47.4 (202)	0.022*
Posterior prolapse, (%, n)	51.6 (1505)	50.3 (1252)	59.4 (253)	0.001*
Flail leaflet, (%, n)	45.2 (1230/2720)	45.9 (1077/2346)	40.9 (153/374)	0.07
≥Moderate to severe TR	14.9 (426/2860)	12.8 (313/2436)	26.7 (113/424)	<0.001*
PA systolic pressure, mm Hg	42±16	39±13	55±17	<0.001*

Continuous variables are expressed as mean ±1 SD and categorical variables are expressed as percentages and numbers. EROA indicates effective regurgitant orifice; LA, left atrial; LV, left ventricular; MR, mitral regurgitation; PA, pulmonary artery; RV, left ventricular; and TR, tricuspid regurgitation.
**P*-value indicates $P<0.05$.

55%±3% for patients with RVD versus 77%±1% for patients with normal RV function (log- rank *P* <0.001) (Figure 1A).

On Cox multivariable analysis, after adjustment for age, sex, presence of symptoms, AF, LVESD, LVEF, LAVI, sPAP, and EROA, the impact of RVD on mortality was partially attenuated but persisted (adjusted hazard ratio [HR],1.57 [95% CI, 1.26–1.96]; *P* <0.001) (Table 2, Figure 1B). Results remained unchanged after further adjustment for mitral valve surgery treated as a time-dependent variable (adjusted HR, 1.44 [95% CI, 1.17–1.77]; *P* <0.001) or after adjustment for ≥moderate to severe tricuspid regurgitation (adjusted HR, 1.43 [95% CI, 1.16–1.77]; *P* <0.001). Using the Schoenfeld residuals test, the proportional hazard assumptions were rejected in the 3 imputed data sets with *P*=0.025, *P*=0.034, and *P*=0.028, respectively; thus, the variation in the RVD effect across time is significant. Therefore, a time interaction term was added to the model for all variables that violated the proportional hazards assumption (RVD, age, AF, and sPAP).

RVD remained independently associated with a poor survival in patients with sPAP <50 mm Hg (adjusted HR, 1.27 [95% CI, 1.03–1.90]; *P*=0.031) or ≥50 mm Hg (adjusted HR, 1.84 [95% CI, 1.36–2.50]; *P* <0.001). Results were comparable for patients included before 2010 and after 2010 without interaction between the inclusion period and RVD (p for interaction=0.46).

When the population was stratified according to stored TAPSE ≥ or <17 mm (available in 1473 patients), the results in term of outcome were not different from the categorical RV function classification with an estimated 8-year survival of 72%±2% for patients with TAPSE ≥17 mm versus 51%±5% for patients with TAPSE <17 mm (*P* <0.001) and an adjusted HR of 1.46 [95% CI, 1.03–2.09]; *P*=0.035.

To verify the association of RVD with mortality in different population subsets, forest plot analysis was

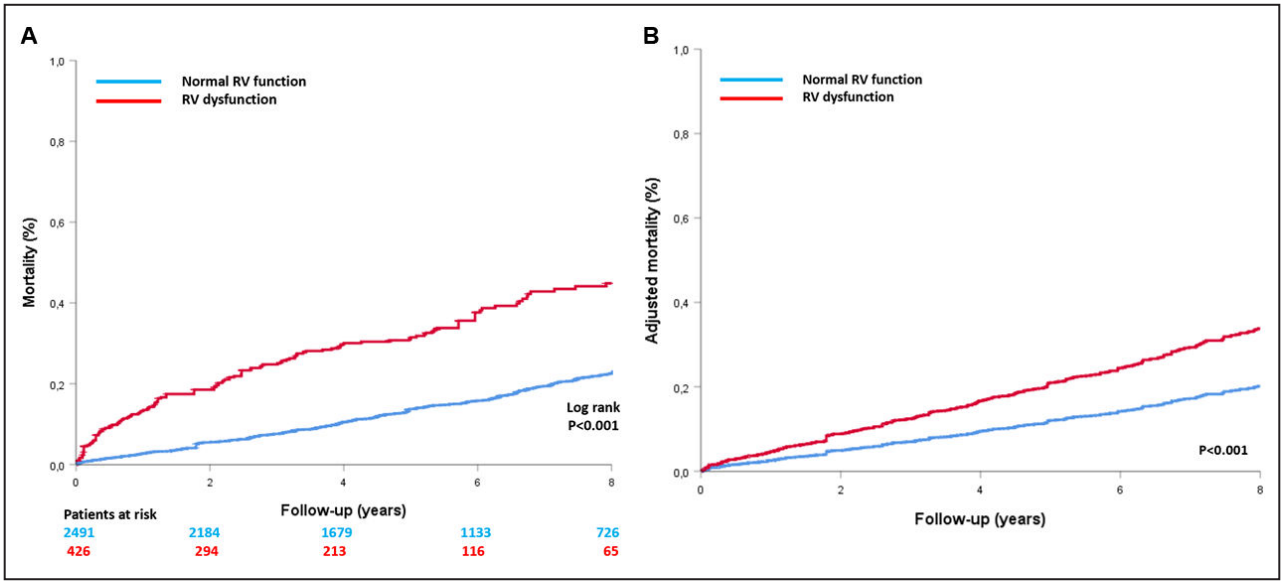

Figure 1. Mortality curves in the overall population.
Kaplan–Meier (**A**) and Cox adjusted (**B**) 8-year mortality curves according to right ventricular function in the overall population. RV indicates right ventricular.

performed. Hazard ratios for mortality associated with RVD are presented in Figure 2 for multiple subgroups based on clinical and echocardiographic variables. The association between RVD and risk of death was consistent in subgroups of patients with no interactions between RVD and any of the subgroups (all *P* for interaction ≥0.12) (Figure 2).

Outcome Under Medical Management

Under medical management, 332 deaths (42.7% of nonoperated patients) were recorded. Eight-year estimated survival under medical management was 45%±5% for patients with RVD versus 60%±2% for patients with normal RV function (log-rank *P* <0.001) (Figure 3A). On Cox multivariable analysis, RVD remained independently associated with increased mortality (adjusted HR, 1.57 [95% CI, 1.20–2.05]; *P*=0.001) (Figure 3B), even after adjustment for ≥moderate-to-severe tricuspid regurgitation (adjusted HR, 1.45 [95% CI, 1.11–1.91]; *P* <0.001).

Table 2. Univariable and Multivariable Hazard Ratio for Mortality for Right Ventricular Dysfunction

Model	Overall population	
	HR (CI [95%]) for RVD	*P* value
Univariable	2.63 (2.20–3.15)	<0.001*
Adjusted for age, male sex, atrial fibrillation, symptoms, and EROA	2.16 (1.78–2.62)	<0.001*
Further adjustment for LVESD, LVEF, LAVI, and sPAP	1.57 (1.26–1.96)	<0.001*
Further adjustment for mitral valve surgery (time-dependent)	1.44 (1.17–1.77)	<0.001*

EROA indicates effective regurgitant orifice area; HR, hazard ratio; LAVI, left atrial volume index; LVESD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; RVD, right ventricular dysfunction; and sPAP, systolic pulmonary artery pressure.
**P*-value indicates *P*<0.05.

Post–Mitral Valve Surgery Outcome

Mitral valve surgery was performed in 2140 patients (73.4%), of which 299 (14.0%) died during follow-up. One-month postoperative mortality was 2.6% in patients with normal RV function versus 11.4% in patients with RVD (*P* <0.001). On multivariable logistic regression, RVD remained associated with increased 1-month postoperative mortality after adjustment for age, sPAP, EuroSCORE II, and time from baseline echocardiography to surgery (adjusted OR, 3.76 [95% CI, 2.11–7.70]; *P* <0.001).

Eight-year estimated postoperative mortality was 71%±4% for patients with RVD versus 86%±1% for patients with normal RV function (log-rank *P* <0.001) (Figure 4A). On Cox multivariable analysis, RVD remained independently associated with increased long-term postoperative mortality (adjusted HR, 1.45 [95% CI, 1.02–2.05]; *P*=0.039) (Figure 4B), even after adjustment for ≥moderate-to-severe tricuspid regurgitation (adjusted HR, 1.49 [95% CI, 1.01–2.21]; *P*=0.048).

Impact of Mitral Valve Surgery in Patients With RVD

Among the 426 patients with RVD, 245 (57.5%) underwent mitral valve surgery during follow-up, including

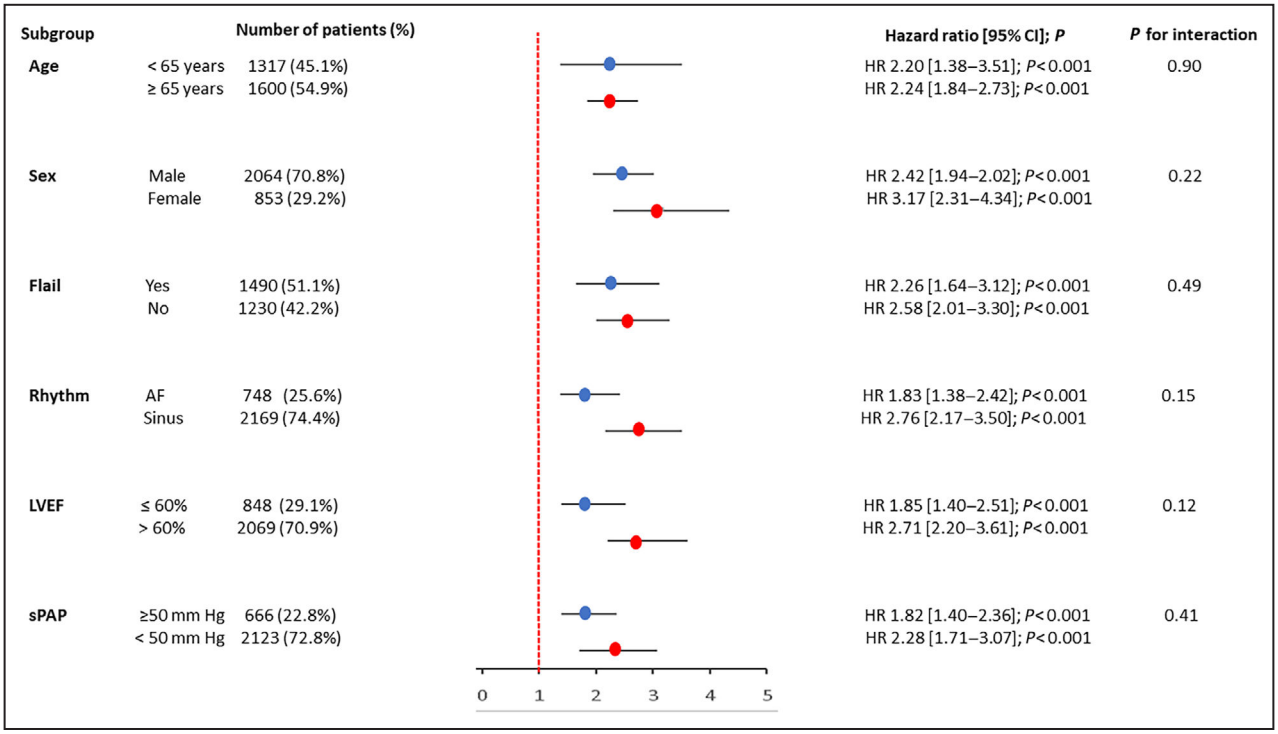

Figure 2. Subgroup analysis.
Forest plot for the risk of all-cause mortality associated with right ventricular dysfunction in subgroups of patients with degenerative mitral regurgitation. AF indicates atrial fibrillation; HR, hazard ratio; LVEF, left ventricular ejection fraction; and sPAP, systolic pulmonary artery pressure.

168 within 3 months of diagnosis (1-month postoperative mortality of 7.1% versus 0.5% in patients without RVD; *P* <0.001). Patients who underwent surgery within 3 months of diagnosis were younger and had a lower EuroSCORE II (both *P* <0.001). They tended to be more symptomatic (*P*=0.085) with more severe MR

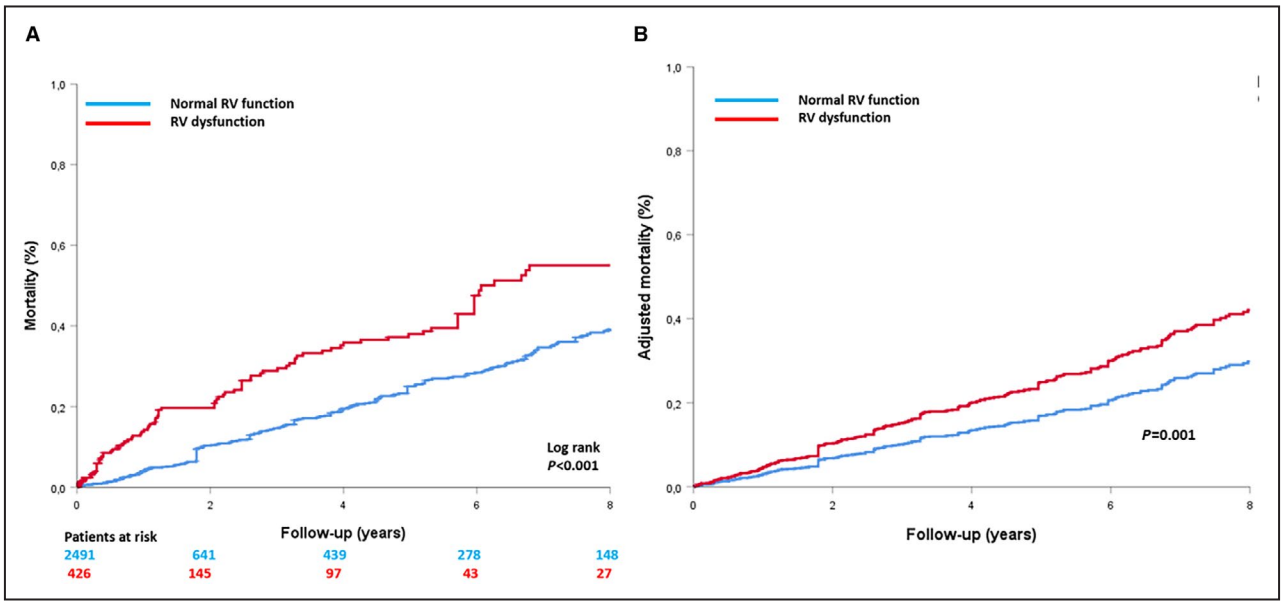

Figure 3. Mortality curves under medical management.
Kaplan–Meier **(A)** and Cox adjusted **(B)** 8-year mortality curves according to right ventricular function in patients under conservative management. RV indicates right ventricular.

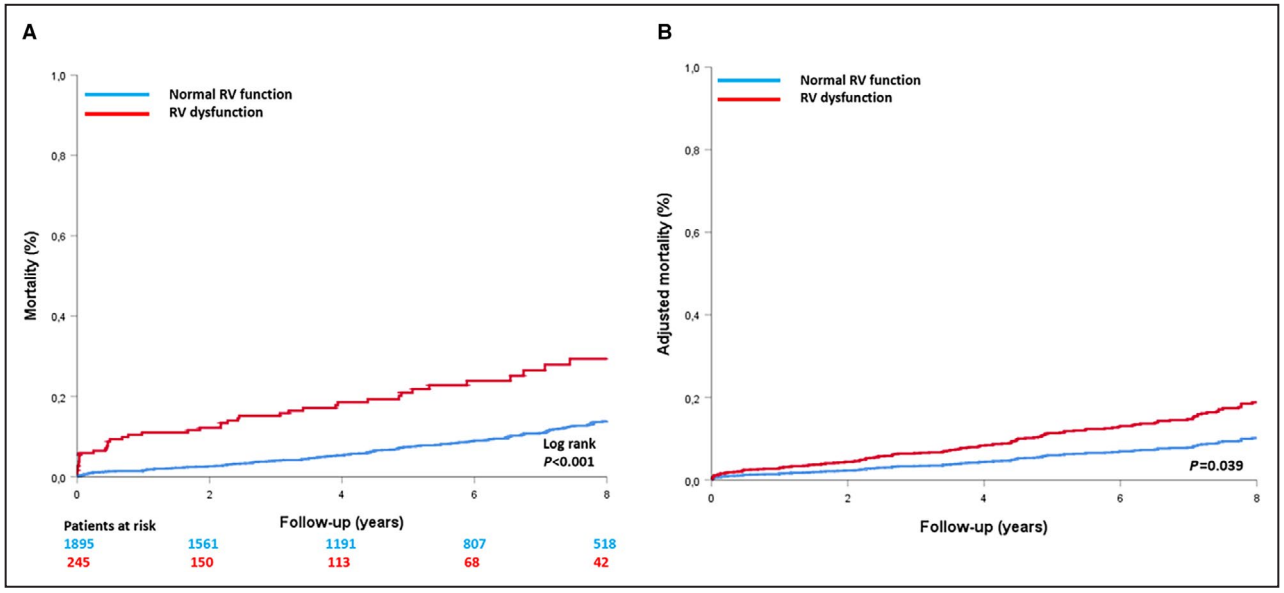

Figure 4. Postoperative mortality curves.
Kaplan–Meier (**A**) and Cox adjusted (**B**) 8-year postoperative mortality curves according to right ventricular function. RV indicates right ventricular.

and more likely to have a flail leaflet than patients not operated on within 3 months of baseline echocardiography (all P <0.05) (Table 3).

Eight-year estimated survival was 73%±4% for patients with RVD who underwent surgery within 3 months of diagnosis versus 43%±4% for patients with RVD not operated within 3 months (log-rank P <0.001) (Figure 5A). On Cox multivariable analysis, age ≥65 years (adjusted HR, 9.39 [95% CI, 4.65–18.96]; P <0.001) and sPAP ≥50 mm Hg (adjusted HR, 2.28 [95% CI, 1.50–3.44]; P <0.001) were independently associated with mortality whereas surgery ≤3 months was associated with a better outcome (adjusted HR, 0.44 [95% CI, 0.29–0.67]; P <0.001) in patients with RVD (Figure 5B).

DISCUSSION

The present study, based on a multicenter large cohort of patients with severe MR managed in routine clinical practice, demonstrates that RVD assessed by transthoracic echocardiography is a major and independent determinant of long-term survival in response to conservative or surgical management. Indeed, RVD (observed in 14.6% of patients) has a strong impact on mortality, persisting after adjustment for covariates known to be major determinants of outcome in DMR, such as age, comorbidity, AF, LV dilatation and dysfunction, left atrial volume, and pulmonary pressures. Importantly, the current results demonstrate that RVD is not simply predictive of greater mortality under medical management, but is also associated with worse survival after MR surgical correction, despite the substantial mortality reduction associated with surgery. Therefore, mitral valve surgery should be discussed before the onset of RVD.

Prevalence of RVD

RV function has not been extensively studied in MR and only small series have been published so far,[9,24,25] complicating the estimation of the prevalence of RVD in patients with severe DMR. Recent data on transcatheter mitral valve repair report a high prevalence of RVD assessed by echocardiography in primary MR, ranging from 30% to 39% of patients, but this is a selected population of older patients with severe symptomatic MR.[26] Le Tourneau et al[11] also reported a high RVD prevalence of 30% in a population of 208 patients with severe organic MR undergoing radionuclide angiography before mitral valve surgery. Thus, the reported prevalence of RVD in DMR depends on the method used for its identification and on the studied population. No large study has yet reported the prevalence of RVD assessed by routine clinical echocardiography in a population of consecutive patients with DMR. We identified RVD in 14.6% of patients with severe DMR. Interestingly, LVEF was reported as normal in half of these patients and RVD was identified in all patient subgroups, illustrating that it should be routinely investigated.

Mechanisms and Determinants of RVD in DMR

The thin RV wall is very sensitive to changes in loading conditions, especially for pressure overload, explaining

Table 3. Baseline Characteristics of Patients With Right Ventricular Dysfunction According to Initial Management

Characteristics	Surgery ≤ 3 months (n=168)	Medical management or surgery >3 months (n=258)	*P* value
Clinical characteristics			
Age, y	70±10	77±13	<0.001*
Female sex (%, n)	31.0 (52)	30.2 (78)	0.91
Body mass index, kg/m^2	26.4±4.1	25.3±4.9	0.018*
Hypertension (%, n)	30.4 (51)	32.6 (84)	0.67
Diabetes (%, n)	10.1 (17)	10.1 (26)	1.00
Coronary artery disease (%, n)	30.4 (51)	25.2 (65)	0.27
EuroSCORE II, %	1.4±0.8	2.1±1.5	<0.001*
Symptoms (%, n)	79.8 (134)	72.2 (184)	0.085
Atrial fibrillation (%, n)	37.5 (63)	40.3 (104)	0.61
Echocardiographic characteristics			
LV end-diastolic diameter, mm	57±7	58±8	0.77
Indexed LV end-diastolic diameter, mm/m^2	31±5	32±5	0.023*
LV end-systolic diameter, mm	37±8	38±9	0.42
Indexed LV end-systolic diameter, mm/m^2	20±4	21±5	0.033*
LV ejection fraction, %	61±10	59±11	0.08
LA volume index, mL/m^2	78±29	79±34	0.63
Mitral E-wave velocity, m/s	1.9±0.5	2.1±0.4	0.67
E/e′ ratio	16±6	17±9	0.69
EROA, mm^2	59±20	53±18	0.046*
MR regurgitant volume, mL	82±27	79±29	0.24
Bileaflet prolapse, (%, n)	37.5 (63)	53.9 (139)	0.001*
Posterior prolapse, (%, n)	50.0 (84)	65.5 (169)	0.002*
Flail leaflet, (%, n)	49.3 (73)	35.4 (80)	0.010*
PA systolic pressure, mm Hg	55±18	55±17	0.97

Continuous variables are expressed as mean ±1 SD and categorical variables are expressed as percentages and numbers. EROA indicates effective regurgitant orifice area; LA, left atrial; LV, left ventricular; MR, mitral regurgitation; and PA, pulmonary artery.

**P*-value indicates $P<0.05$.

RV systolic performance alteration in case of primary[3] or secondary PH.[1,2] In MR, the increase in left atrial pressure results in a backward elevation of pulmonary venous pressure, pulmonary capillary wedge, and sPAP. In addition, pulmonary vascular remodeling with abnormal vasoconstriction contributes to the rise in pulmonary pressures.[11,27] Nevertheless, if there is a clear relationship between sPAP and RV function, sPAP is not the only factor associated with RVD.[11,28] Indeed, as identified in the present study, increased sPAP was the factor most strongly associated with RVD but other parameters including age, MR severity, LAVI, and LV systolic dysfunction were also independently associated with RVD in patients with DMR. In addition, RVD predicted mortality after adjustment to PH and was also associated with poor survival in patients with sPAP <50 mm Hg.

Severe MR leads to LV remodeling to compensate for chronic volume overload by eccentric hypertrophy, resulting in a more spherical shape of the left ventricle. This remodeling will alter the RV performance through a double mechanism: (1) the interventricular septum will curve, resulting in altered RV free wall contraction with increasing ventricular interdependence, while (2) the spherical shape of the left ventricle will also generate increased intrapericardial constraint, transmitted through ventricular interdependence into the RV.[29,30] It is also important to point out that in severe MR, LV dysfunction is often masked by an apparently preserved LVEF but this contractile dysfunction will affect RV systolic function, notably through the interventricular septum. Importantly, a LVEF ≤60% is found in 54% of patients with altered RV ejection fraction, suggesting that RVD may reflect chronic LV systolic impairment, which is the consequence of long-standing MR.[11,29] Accordingly, in our study, 47.9% of patients with RVD had a LVEF ≤60%.

Outcome of RVD in DMR

Over the past few years, the prognostic importance of RVD has been increasingly emphasized in many cardiovascular diseases.[1–5] Nevertheless, regarding DMR,

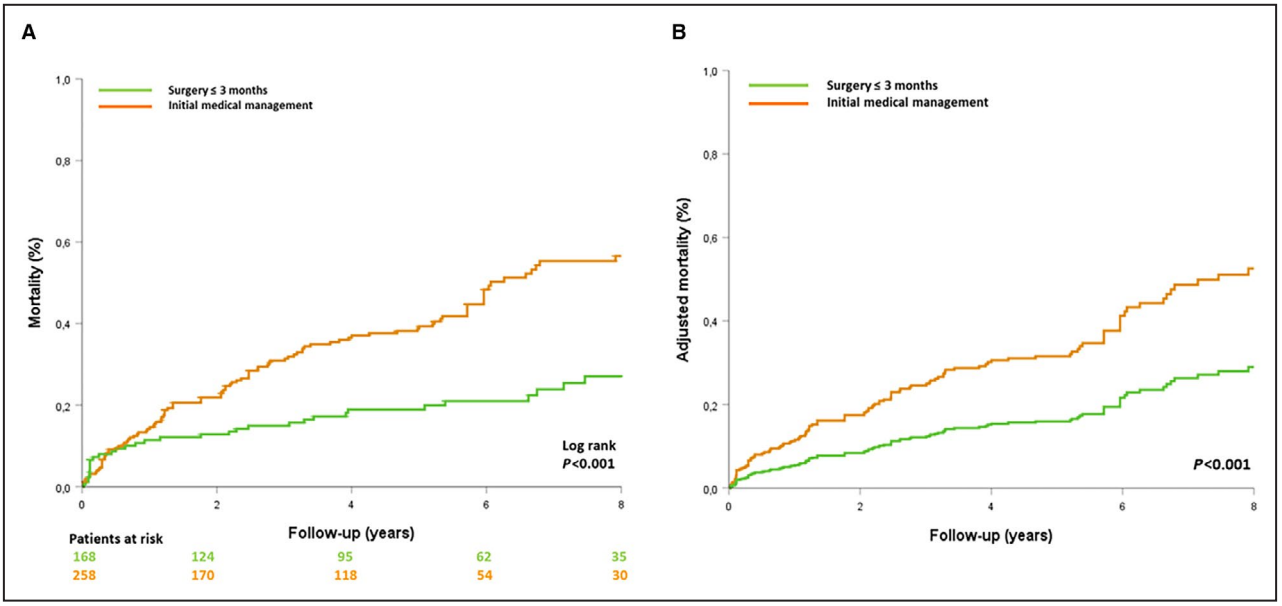

Figure 5. Mortality curves according to management in RVD.
Kaplan–Meier **(A)** and Cox adjusted **(B)** 8-year mortality curves in patients with right ventricular dysfunction according to initial management. RVD indicates right ventricular dysfunction.

data on RVD are scarce. Doldi et al[26] recently reported that RVD assessed by echocardiography was associated with a reduced survival in patients undergoing transcatheter mitral valve repair for primary MR. Older studies also reported that patients with severe DMR and LV dysfunction undergoing mitral valve surgery had reduced survival in patients with associated RVD.[11,31,32] However, the present study is the first to report the prognostic impact of RVD assessed by echocardiography in clinical routine in a population of consecutive patients with severe DMR. The current study shows that RVD has a strong impact on mortality, partially attenuated but persisting after adjustment for covariates known to be major determinants of outcome in DMR including LV dysfunction, AF, and PH, under medical or surgical management. The adverse effect of RVD was consistently observed in subgroups of patients with MR even in patients without apparent LV dysfunction or PH, suggesting that RV function should be systematically assessed in case of severe primary MR.

Although mitral valve surgery was associated with reduced mortality in patients with RVD compared with conservative management, excess mortality persisted after surgery in these patients, and 1-month postoperative mortality was more than 3-fold higher than in patients without RVD. Therefore, surgery should be considered before impairment of RV systolic performance occurs. Indeed, while early surgery is often considered as the ideal treatment for patients with severe DMR, it is rarely performed, especially in elderly patients with comorbidities, and we need to identify all the potential risk markers in order to reduce under-treatment of this disease. Finally, our results strongly suggest that assessment of RV function by echocardiography should be performed systematically for risk stratification of patients with DMR.

Limitations

The current study is subject to the limitations inherent in observational registries with retrospective follow-up data. However, echocardiographic data were collected prospectively at each center by multiple operators, which allowed us to constitute the largest international cohort of patients with DMR quantified in clinical routine. Transthoracic echocardiography is limited in the assessment of RV function, due to the asymmetrical and crescentic shape of the RV. Nevertheless, it remains the first-line imaging technique and the cornerstone for diagnosis of RVD in clinical practice. While all centers applied the guidelines available for the comprehensive determination of RV function based on qualitative and quantitative data, the databases available at time of patient diagnosis in most cases did not have fields available for recording all quantitative measures that form part of the basis of the classification as RVD. Thus, the TAPSE was the most frequently stored quantitative variable recorded (n=1473). When the population was stratified according to stored TAPSE ≥17 mm or <17 mm, the results in term of outcome were not different from the categorical RV function classification. Thus, the quantitative or integrative assessment of RV function are linked to outcome in a very similar manner and do not affect the results of the study, underscoring

for the first time the importance of RVD, incrementally to PH and all baseline characteristics, in defining the prognosis of patients with DMR. Coronary artery disease involving the right coronary artery may have contributed to RVD in some patients. Because coronary angiography is generally considered only a preoperative testing in patients with DMR, and not all patients underwent surgery immediately after diagnosis, gathering coronary data and affirming noncollinearity of RVD, coronary artery disease, and age was impossible despite the size of our cohort. Postoperative echocardiogram results were not recorded in our database, preventing us from assessing the evolution of RV function after surgery and its association with prognosis, but future prospective studies with predetermined echocardiographic planning should be conducted to address this important question. Patients were included over an extended period (2003–2020), during which the echocardiography machines and probes, as well as the diagnostic criteria for RVD, evolved. Our results are only applicable to patients with DMR due to mitral valve prolapse, and further studies are needed for other subsets of patients with organic MR. In our study, there is no reproducibility assessment. Indeed, because the measurements of RV function are performed for clinical use, there is no ongoing "reproducibility" assessment routinely performed in a clinical laboratory. Contrary to a validation study for a new measure in a pilot study, studies performed in routine practice, such as ours, do not entail "reproducibility" measures. In fact, because our study aimed to respond to the question "as measured in routine practice based on clinical guidelines," is the classification of RV function as normal or dysfunctional associated with prognostic significance and is it therefore usable in routine practice to prognosticate the outcome of the patients? Finally, future prospective studies with core laboratory-driven designs should be conducted to test the prognostic impact of new parameters, such as RV free-wall strain.

CONCLUSIONS

This study is the first to demonstrate in a large cohort that RVD assessed by echocardiography is a powerful predictor of survival in patients with severe DMR due to mitral valve prolapse. Although patients with RVD (14.6%) exhibited increased mortality under medical and surgical management, they should still be considered for surgery to improve their outcomes. To avoid the excess mortality observed after mitral valve surgery related to RVD, surgery should be discussed before RVD occurs.

ARTICLE INFORMATION

Received April 25, 2024; accepted September 30, 2024.

Affiliations

Department of Cardiology, Amiens University Hospital, Amiens, France (Y.B., D.R., C.T.); UR UPJV 7517, Jules Verne University of Picardie, Amiens, France (Y.B., D.R., C.T.); Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN (B.E., G.B., C.A., P.T., H.I.M., M.E.); Department of Echocardiography, Cardio X Clinic, Cannes, France (B.E.); Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands (J.J.B., N.A.M., A.v.W.); Department of Cardiology, University of Nantes, Nantes, France (T.L.T., J.C.R.); Department of Cardiology, Tel Aviv Medical Center and Sackler Faculty of Medicine, Tel Aviv, Israel (Y.T., A.H.); Department of Cardiology, University Campus Bio-Medico, Rome, Italy (F.G.); Department of Clinical Research, Amiens University Hospital, Amiens, France (M.D.); and Abbott Northwestern Hospital, Minneapolis, MN (M.E.).

Sources of Funding

This work was supported by the Mayo Foundation, French Ministry of Health "PHRC-I 2012" (to Dr T. Le Tourneau, API12/N/019, Paris, France), Fédération Française de Cardiologie (to Dr T. Le Tourneau, 2015, Paris, France), and Fondation Cœur et Recherche (to Dr T. Le Tourneau, 2015, Paris, France).

Disclosures

The Department of Cardiology of the Leiden University Medical Center received research grants from Abbott Vascular, Alnylam, Bayer, Bioventrix, Medtronic, Biotronik, Boston Scientific, GE Healthcare, and Edwards Lifesciences. Dr J. J. Bax has received speaking fees from Abbott and Edwards Lifesciences. Dr A. Marsan has received speaking fees from Abbott Vascular, Philips Ultrasound, and GE Healthcare, and has served on the Medical Advisory Board of Philips Ultrasound and Trimensio/Pie and as a consultant on the board of the EACVI. Dr J. C. Roussel has received consulting fees from Edwards Lifesciences. Dr T. Le Tourneau received payments/honoraria from Bayer and GE Healthcare. Dr M. Enriquez-Sarano received consulting fees from Edwards LLC, Cryolife Inc, ChemImage, and HighLife Inc. The remaining authors have no disclosures to report.

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