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ORIGINAL RESEARCH

Reappraisal of the Concept and Implications of Pulmonary Hypertension in Degenerative Mitral Regurgitation

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ABSTRACT

BACKGROUND European and U.S. clinical guidelines diverge regarding pulmonary hypertension (PHTN) in degenerative mitral regurgitation (DMR). Gaps in knowledge underpinning these divergences affect risk assessment and management recommendations attached to systolic pulmonary pressure (SPAP) in DMR.

OBJECTIVES This study sought to define PHTN links to DMR severity, prognostic thresholds, and independent outcome impact in a large quantitative DMR registry.

METHODS This study gathered a large multicentric registry of consecutive patients with isolated moderate-to-severe DMR, with DMR and SPAP quantified prospectively at diagnosis.

RESULTS In 3,712 patients (67 ± 15 years, 36% women) with ≥ moderate-to-severe DMR, effective regurgitant orifice (ERO) was 0.42 ± 0.19 cm^2, regurgitant volume 66 ± 327 mL/beat and SPAP 41 ± 16 mm Hg. Spline-curve analysis showed excess mortality under medical management emerging around SPAP 35 mm Hg and doubling around SPAP 50 mm Hg. Accordingly, severe pulmonary hypertension (sPHTN) (SPAP ≥50 mm Hg) was detected in 916 patients, moderate pulmonary hypertension (mPHTN) (SPAP 35-49 mm Hg) in 1,128, and no-PHTN (SPAP <35 mm Hg) in 1,668. Whereas SPAP was strongly associated with DMR-ERO, nevertheless excess mortality with sPHTN (adjusted HR: 1.65; 95% CI: 1.24-2.20) and mPHTN (adjusted HR: 1.44; 95% CI: 1.11-1.85; both $P \leq 0.005$) was observed independently of ERO and all baseline characteristics and in all patient subsets. Nested models demonstrated incremental prognostic value of mPHTN and sPHTN (all $P < 0.0001$). Despite higher operative risk with mPHTN and sPHTN, DMR surgical correction was followed by higher survival in all PHTN ranges with strong survival benefit of early surgery (<3 months). Postoperatively, excess mortality was abolished ($P \geq 0.30$) in mPHTN, but only abated in sPHTN.

CONCLUSIONS This large international registry, with prospectively quantified DMR and SPAP, demonstrates a Doppler-defined PHTN impact on mortality, independent of DMR severity. Crucially, it defines objectively the new and frequent mPHTN range, independently linked to excess mortality under medical management, which is abolished by DMR correction. Thus, at DMR diagnosis, Doppler-SPAP measurement defining these new PHTN ranges, is crucial to guiding DMR management. (J Am Coll Cardiol Img 2024;■:■-■) © 2024 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

DMR = degenerative mitral regurgitation

ERO = effective regurgitant orifice

FTR = functional tricuspid regurgitation

LAVI = left atrial volume index

LVEF = left ventricular ejection fraction

LVESD = left ventricular end-systolic diameter

mPHTN = moderate pulmonary hypertension

PHTN = pulmonary hypertension

RVol = regurgitant volume

SPAP = systolic pulmonary artery pressure

sPHTN = severe pulmonary hypertension

TR = tricuspid regurgitation

Degenerative mitral regurgitation (DMR) is the most common type of organic mitral regurgitation in developed countries[1,2] and with increasing severity is associated with serious outcome consequences.[3,4] These serious consequences have led clinical guidelines to recommend prompt consideration of surgical treatment.[5,6] However, DMR remains pervasively undertreated worldwide,[1,2] contrasting with proven benefits of early repair,[7] or transcatheter repair[8] for patients deemed inoperable.[9] Undertreatment may stem from overestimation of operative risks in older subjects,[10] unbalanced by suitable risk assessment under medical management. Clinical guidelines recommend few Class I surgical triggers, based mainly on left ventricular DMR consequences, that are coherent in U.S. and European guidelines.[5,6] Conversely, for Class II triggers, specifically pulmonary hypertension (PHTN), guidelines display notable divergence,[5,6] reflecting significant gaps in knowledge and representing a clinical conundrum.

Indeed, PHTN by Doppler echocardiography, a Class II trigger for surgery in European guidelines,[5] is not mentioned in U.S. guidelines.[6] Such divergence may stem from initial studies suggesting that PHTN may be associated with poor outcome,[11] based on a priori definition as systolic pulmonary artery pressure (SPAP) ≥50 mm Hg without objectively defining thresholds of risk throughout the SPAP range. Thus, whether different SPAP levels, particularly below those previously arbitrarily defined, affect clinical outcomes, is unknown. Furthermore, PHTN analysis was confined to patients affected by DMR that was probably severe but was nonquantified.[11] Hence, it is uncertain whether PHTN is not just a surrogate for DMR severity, and little is known about its outcome affect when DMR quantified severity is fully defined.[3,4] Moreover, most evidence linking PHTN to poor outcomes regards postoperative[12-16] or post-intervention[17-20] follow-up. Such data may not encourage treating DMR with PHTN if the balance of medical and postoperative outcomes is not carefully weighted. Finally, with downgraded credibility of Doppler-defined PHTN,[21] it is unclear whether this measure remains important in DMR management[5] and whether new thresholds should be defined, warranting a new multicenter registry of patients diagnosed with DMR.

Therefore, we gathered a large international cohort from multiple continents, of patients with isolated DMR, moderate or severe, all with quantified regurgitation and SPAP, prospectively measured at diagnosis by Doppler echocardiography. In this new cohort, our aim was to verify the following: 1) the link between SPAP and DMR quantitatively defined; 2) the association SPAP outcome, independently of all baseline characteristics, particularly DMR quantitative assessment; 3) rigorously defined PHTN thresholds associated with poor outcome; and 4) potential benefit of early surgery at various ranges of PHTN. These data should allow reconciling current clinical guidelines, thereby potentially reducing undertreatment, and considering enhanced monitoring/therapeutic approaches for DMR.

METHODS

PATIENTS. This new multicentric registry merged series of consecutive patients with prospective DMR quantification in routine practice of tertiary care centers from North America (Mayo Clinic), Europe (Amiens, France; Nantes, France; Leiden, the Netherlands), and the Middle-East (Tel Aviv, Israel).

Eligibility criteria involved all consecutive patients who met the following: 1) age ≥18 years; 2) with isolated mitral valve prolapse or flail leaflet; 3) with DMR prospectively quantified by Doppler echocardiography with measurement of effective regurgitant orifice (ERO) and regurgitant volume (RVol), of at least moderate severity (ERO ≥0.20 cm^2); 4) with SPAP calculated prospectively at diagnosis by Doppler echocardiography per guidelines[22]; 5) with first diagnosis between 2003 and 2020; 6) with comprehensive echocardiographic and clinical assessment of symptoms, vital signs, clinical history, comorbidities, and cardiac rhythm at diagnosis; and 7) without significant associated cardiac condition. We excluded patients: 1) without MR and SPAP quantification; 2) with moderate-to-severe aortic regurgitation/stenosis, moderate-to-severe mitral stenosis, congenital heart

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disease (patent foramen ovale not excluded), identified dilated or hypertrophic or restrictive cardiomyopathies, previous valvular surgery, significant pericardial disease; 3) with diagnosed overt causes of PHTN[21] other than DMR (eg, severe pulmonary disease, pulmonary thromboembolic disease); or 4) who denied research authorization. The study was conducted in accordance with Institutional Review Boards' approval, national legal requirements, and the revised Declaration of Helsinki. As a low-risk study, written consent requirement was waived for follow-up by survey centers with maintenance of anonymized datasets.

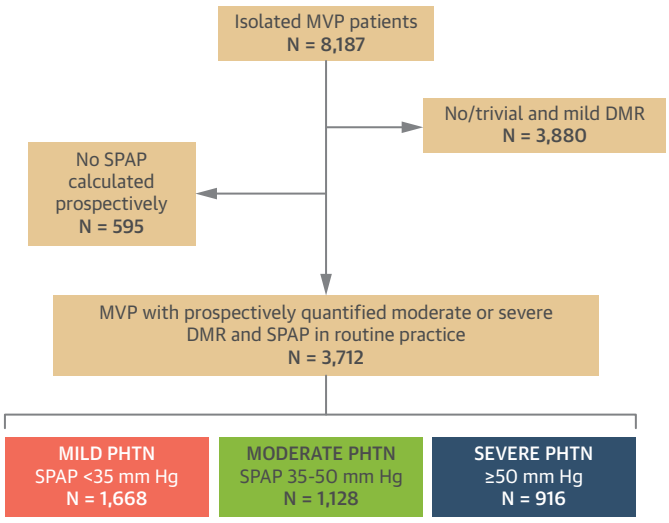
ECHOCARDIOGRAPHIC EVALUATION. Echocardiographic examination was performed in routine clinical practice as recommended[23] and is described in the Supplemental Methods.

As main independent variable of interest, SPAP was measured in routine practice with standard continuous-wave Doppler without contrast and used as a continuous variable and also as a categorical variable with subgroups defined by the spline curve analysis as part of survival analysis. Accordingly, moderate PHTN (mPHTN) was defined as SPAP ≤35 to <50 mm Hg, and severe PHTN (sPHTN) as SPAP ≥50 mm Hg at rest, whereas patients with SPAP <35 mm Hg were considered as having no PHTN.

CLINICAL EVALUATION. Patients' history, symptoms, comorbidities, and all testing performed were recorded at diagnosis by patients' personal physicians in routine practice and electronically retrieved from medical records without alteration. EuroSCORE (European System for Cardiac Operative Risk Evaluation) II was calculated at DMR diagnosis as a measure of surgical risk and combined comorbidities.[24] Vital signs were measured at index echocardiography.

OUTCOME. The outcome examined was overall mortality after diagnosis, with events collected using direct patient/family/physician contact and using institutional, private (Accurint in the United States) or public (social security mortality database or local equivalent) databases of vital status. Due to inconsistent legalities of certificate of death availability and to vagaries of their interpretation, cardiac mortality was not considered a reliable endpoint,[25] in contrast to robust overall mortality. The primary endpoint was long-term survival under medical management. Secondary endpoint was postoperative survival. Surgical procedures were collected and dated using institutional surgical registries and clinical notes for patients operated outside their respective institutions. Outcomes were ascertained by investigators blinded to baseline characteristics.

FIGURE 1 Study Population Flowchart



Sequence of eligibility yielding a cohort of 3,712 patients with moderate or severe degenerative mitral regurgitation (DMR) and systolic pulmonary artery pressure (SPAP) prospectively quantified. MVP = mitral valve prolapse; PHTN = pulmonary hypertension.

STATISTICAL ANALYSIS. Continuous variables expressed as mean ± SD and categorical variables as percentages were compared using analysis of variance, Wilcoxon test, or chi-square test as appropriate. The subgroups of SPAP were defined based on the link between SPAP and excess mortality, after diagnosis under medical treatment, analyzed using spline curves.

The main endpoint was survival under medical management to which all patients contributed with time at risk measured between initial diagnosis on one end and death, mitral surgery (if performed), or end of follow-up on the other end. Postoperative survival was a secondary endpoint. Statistical approach is further detailed in the Supplemental Methods.

RESULTS

BASELINE CHARACTERISTICS. All consecutive eligible cases encompassed 3,712 patients (36% women, age 67 ± 15 years) (**Figure 1**) from the centers detailed in the Supplemental Methods. Baseline demographic/clinical characteristics (**Table 1**) are typical for moderate-to-severe DMR, with bileaflet prolapse in 1,073 patients (36%), posterior prolapse in 1,589

TABLE 1 Baseline Characteristics

	Overall Population (N = 3,712)	SPAP <35 mm Hg (n = 1,668)	SPAP 35-50 mm Hg (n = 1,128)	SPAP ≥50 mm Hg (n = 916)	*P* Value
Clinical characteristics					
Age, y	67 ± 15	60 ± 15	69 ± 13	75 ± 12	<0.0001
Female	1,328 (36)	515 (31)	432 (38)	381 (42)	<0.0001
Heart rate, beats/min	72 ± 15	69 ± 13	73 ± 16	77 ± 17	<0.0001
Systolic BP, mm Hg	122 ± 18	122 ± 17	123 ± 18	124 ± 19	0.0003
Diastolic BP, mm Hg	70 ± 11	70 ± 10	70 ± 11	70 ± 12	0.20
Atrial fibrillation, %	825 (22)	189 (11)	325 (29)	311 (34)	<0.0001
Previous CABG, %	121 (3)	37 (2)	44 (4)	40 (5)	0.003
Hypertension, %	928 (37)	394 (31)	299 (41)	235 (45)	0.01
Dyspnea, %	1742 (50)	664 (42)	548 (52)	530 (63)	<0.0001
EuroSCORE II, %	1.4 ± 1.4	0.9 ± 0.7	1.5 ± 1.2	2.2 ± 2.0	<0.0001
LV and hemodynamic characteristics					
LVEDD, mm	56 ± 7	56 ± 7	56 ± 8	55 ± 8	0.60
LVESD, mm	34.9 ± 6.6	34.6 ± 5.9	35.2 ± 6.8	35.1 ± 7.5	0.04
LVEF, %	63 ± 8	64 ± 7	62 ± 9	62 ± 10	<0.0001
LAVI, mL/m^2	61 ± 26	53 ± 21	65 ± 27	72 ± 31	<0.0001
E/e′	13 ± 6	12 ± 4	14 ± 6	19 ± 8	<0.0001
Degenerative MR characteristics					
MR severity					<0.0001
Moderate	1,881 (51)	928 (56)	565 (50)	388 (42)	
Severe	1,831 (49)	740 (44)	563 (50)	528 (58)	
ERO, cm^2	0.42 ± 0.19	0.40 ± 0.17	0.43 ± 0.19	0.46 ± 0.22	<0.0001
RVol, mL	66 ± 27	62 ± 26	68 ± 27	70 ± 27	<0.0001
Flail leaflet, %	249 (7)	94 (6)	76 (7)	79 (9)	0.02
Bileaflet, %	1,073 (36)	647 (44)	277 (31)	149 (24)	<0.0001
Posterior, %	1,589 (53)	706 (48)	499 (56)	384 (61)	<0.0001
Right-sided characteristics					
SPAP, mm Hg	41 ± 16	28 ± 5	41 ± 4	63 ± 12	<0.0001
FTR severity					<0.0001
No/trivial	1,194 (33)	813 (50)	271 (24)	110 (12)	
Mild	1,502 (41)	634 (39)	535 (48)	333 (37)	
Moderate	608 (17)	132 (8)	210 (19)	266 (29)	
Severe	353 (10)	60 (4)	96 (9)	197 (22)	

Values are mean ± SD or n (%).

BP = blood pressure; CABG = coronary artery bypass graft; EDD = end-diastolic diameter; EF = ejection fraction; ERO = effective regurgitant orifice; ESD = end-systolic diameter; EuroSCORE = European System for Cardiac Operative Risk Evaluation; FTR = functional tricuspid regurgitation; LAVI = left atrial volume index; LV = left ventricle; MR = mitral regurgitation; RVol = regurgitant volume; SPAP = systolic pulmonary artery pressure.

(53%) and flail leaflet in 249 (7%). Clinically, 50% had dyspnea, 37% hypertension, 22% atrial fibrillation, 3% previous coronary artery bypass graft, and EuroSCORE II was 1.4% ± 1.4%. By echocardiography, left ventricular ejection fraction (LVEF) was 63% ± 8%, left ventricular end-systolic diameter (LVESD) 35 ± 7 mm, left atrial volume index (LAVI) 61 ± 26 mL/m^2, and E/e′ ratio 13 ± 6. By DMR quantitation, ERO was 0.42 ± 0.19 cm^2 and RVol 66 ± 27 mL, stratified as 1,881 patients (51%) with ERO 0.20-0.39 cm^2, 1,202 (32%) with ERO 0.40-0.59 cm^2, and ERO in the "very-severe" range ≥0.60 cm^2 in 629 (17%). SPAP averaged 41 ± 16 mm Hg, with most frequently no PHTN (SPAP <35 mm Hg, 28 ± 5 mm Hg) in 1,668 (45%), mPHTN (SPAP 35-49 mm Hg, 41 ± 4 mm Hg) in 1,128 (30%), and sPHTN (SPAP ≥50 mm Hg, 63 ± 12 mm Hg) in 916 (25%).

Baseline characteristics stratified by SPAP categories are presented in Table 1 (right). Almost all variables were statistically different due to the cohort considerable size, with wide variation of SPAP response across DMR severity. However, most clinically relevant differences showed patients with higher SPAP being older, more often female, more symptomatic, with more frequent atrial fibrillation, and higher surgical risk score (all $P < 0.0001$). Echocardiographically, patients with elevated SPAP had worse systolic and diastolic LV function, larger LA,

more severe MR and tricuspid regurgitation (TR) (all $P \leq 0.0001$), whereas differences in LV dimensions were of little clinical relevance. However, these associations with presence/severity of PHTN were relatively loose with wide overlap between categories; for example, symptomatic patients had higher distribution of PHTN ranges (sPHTN in 30% and mPHTN in 32%; $P < 0.0001$ vs asymptomatic), but asymptomatic patients nevertheless often presented with PHTN (sPHTN in 18% and mPHTN in 29%). Echocardiographic characteristics stratified by MR severity are presented in the Supplemental Table 1.

Baseline characteristics independently associated with PHTN were several (multivariable odds ratios displayed in Table 2), particularly strong for age ≥65 years, E/e′ ≥14, and DMR severity measured by ERO. Of note, E/e′ showed very weak correlation to DMR ERO ($R^2 = 0.03$) and both were independent determinants of SPAP (Table 2). Less strongly associated to PHTN was female sex and EF <60% with overall area under the curve of 0.78 and 0.80, respectively, for mPHTN and sPHTN (Table 2). Thus, SPAP is not just determined by DMR severity, emphasizing its potential independent link to outcome.

TABLE 2 Multivariable PHTN Determinants

Determinants of PHTN	OR (95% CI) of Moderate PHTN	*P* Value	OR (95% CI) of Severe PHTN	*P* Value
AUC	0.78		0.80	
Age ≥65 y	3.82 (3.04-4.80)	<0.0001	4.14 (2.92-5.88)	<0.0001
Female	1.34 (1.06-1.70)	0.01	1.32 (0.98-1.78)	0.07
LVEF <60%	1.38 (1.06-1.80)	0.02	1.13 (0.8-1.58)	0.50
E/e′ ≥14	2.71 (2.15-3.40)	<0.0001	3.79 (2.82-5.10)	<0.0001
MR ERO (vs <0.39), cm^2				
0.40-0.59	1.52 (1.18-1.94)	0.001	1.81 (1.30-2.53)	<0.0001
≥0.60	2.70 (1.96-3.70)	<0.0001	4.06 (2.79-5.92)	<0.0001

AUC = area under the curve; PHTN = pulmonary hypertension; other abbreviations as in Table 1.

LONG-TERM OUTCOME UNDER MEDICAL MANAGEMENT. Total follow-up was 5.2 ± 3.4 years, during which 2,214 patients underwent mitral valve surgery (92% repair, 8% replacement) and 910 died, mostly under medical management (n = 625) and more seldomly after mitral valve surgery (n = 285).

Survival under medical management. Survival under medical management was overall 67% ± 1% at 5 years and 45% ± 2% at 10 years. As a continuous variable, SPAP elevation was strongly linked to long-term survival under medical management in univariable analysis (per 10-mm Hg increments, HR: 1.43; 95% CI: 1.38-1.49; $P < 0.0001$) (Table 3, left). Furthermore, adjusting for age, sex, EuroSCORE II, DMR severity. and guideline-based Class I surgical indications (LVEF <60%, LVESD >40 mm, and symptoms), SPAP elevation remained strongly associated to subsequent survival (per 10-mm Hg increments, adjusted HR: 1.22; 95% CI: 1.15-1.29; $P < 0.0001$). Further adjustment for Class II surgical indications (LAVI ≥60 mL/m^2, atrial fibrillation [AF], and functional tricuspid regurgitation [FTR] severity) did not affect SPAP link with excess mortality (per 10-mm Hg SPAP increments, adjusted HR: 1.37; 95% CI: 1.11-1.71; $P = 0.007$). HRs for all covariates of the comprehensive model are further detailed in the Supplemental Results.

Spline curve analysis. Spline curve analysis showed excess mortality under medical management crossing the line of the HR of 1.00 (representing average cohort mortality under medical management), around SPAP 35 mm Hg (Figure 2). With higher SPAP risk linearly and steeply increased, there is approximately a doubling of mortality risk around SPAP 50 mm Hg. On this basis, the subset mPHTN involved SPAP 35-49 mm Hg, and the sPHTN involved the classical SPAP ≥50 mm Hg threshold.

Stratified by PHTN subsets. Stratified by PHTN subsets, outcome was considerably different, with 10-year survival under medical management of 63% ± 3% with no PHTN, 35% ± 4% with mPHTN, and 22 ± 3% with sPHTN ($P < 0.0001$) (Figure 3, left). Univariable HRs attached to PHTN subsets were 2.98 (95% CI: 2.40-3.71) for mPHTN and 5.65 (95% CI: 4.57-6.98) for sPHTN vs no PHTN, both $P < 0.0001$ (Table 3). Because PHTN is linked to older age, thereby amplifying absolute survival differences, several approaches were used to assess the independent association of PHTN survival: First, stratification by age (<65 and ≥65 years) showed that while attenuated, survival differences related to PHTN subsets remained highly significant in young and older patients (Figure 4). Second, comprehensive adjustment, including for age, did not suppress but attenuated HRs attached to mPHTN (1.67; 95% CI: 1.32-2.12) and to sPHTN (2.18; 95% CI: 1.69-2.81 vs no PHTN; both $P < 0.0001$) (Table 3). Third, adjusted survival curves showed attenuated but markedly persistent survival differences by PHTN grades (Figure 3). Thus, sPHTN and mPHTN, irrespective of age differences, are undeniably associated with excess mortality under medical management.

To verify that excess mortality with PHTN is not spuriously linked to models/variables used, alternative models were examined: Replacing ERO by RVol left adjusted HRs unaffected (adjusted HR: 1.65 [95% CI: 1.27-2.15] for mPHTN and 2.18 [95% CI: 1.63-2.93] for sPHTN). Similarly, in models with MR

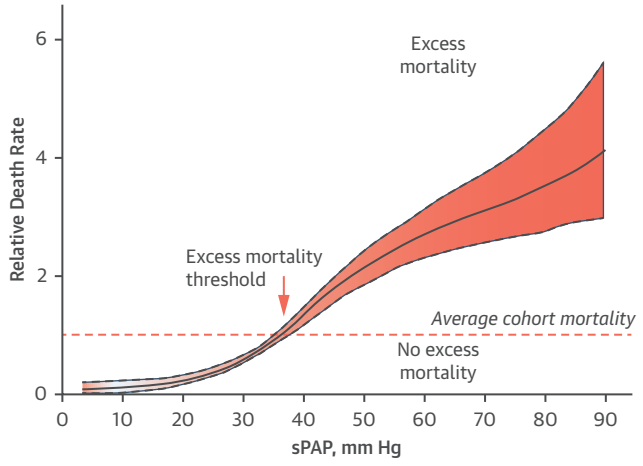
TABLE 3 Univariable and Multivariable Hazard Ratio (HR) of Mortality

		Mortality Under Medical Treatment		Post Mitral Surgery Mortality	
	SPAP (mm Hg)	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Univariable	Per 10	1.43 (1.38-1.49)	<0.0001	1.30 (1.23-1.30)	<0.0001
	35-50[a]	2.98 (2.40-3.71)	<0.0001	1.64 (1.20-2.23)	0.002
	≥50[a]	5.65 (4.57-6.98)	<0.0001	3.41 (2.57-4.52)	<0.0001
Adjusted for age, sex, ERO, EuroSCORE II, symptoms, EF, LVESD	Per 10	1.22 (1.15-1.29)	<0.0001	1.12 (1.03-1.21)	0.005
	35-50[a]	1.65 (1.30-2.10)	<0.0001	1.05 (0.76-1.45)	0.80
	≥50[a]	2.10 (1.61-2.71)	<0.0001	1.57 (1.14-2.16)	0.006
Further adjustment for LAVI, AF, and FTR grade	Per 10	1.37 (1.11-1.71)	0.005	1.15 (1.04-1.26)	0.006
	35-50[a]	1.44 (1.11-1.85)	0.005	1.09 (0.71-1.68)	0.70
	≥50[a]	1.65 (1.24-2.20)	0.0007	1.88 (1.21-2.92)	0.005

[a]vs SPAP <35 mm Hg.
AF = atrial fibrillation; other abbreviations as in Table 1.

integrative grading, HRs for mPHTN (1.67; 95% CI: 1.32-2.12) or sPHTN (2.18; 95% CI: 1.69-2.81; all $P < 0.0001$) were unaffected. With additional adjustment for LAVI, AF, and FTR grade (Table 3), HRs of mortality remained highly significant (1.44 [95% CI: 1.11-1.85] for mPHTN and 1.65 [95% CI: 1.24-2.20] for sPHTN; both $P < 0.0001$). Similarly, adjunct models adjusting for additional individual characteristics did not affect PHTN strong association with mortality and HRs of mortality linked to PHTN remained unaffected (Supplemental Results).

FIGURE 2 Spline Curve of Mortality Risk According to SPAP



Mortality risk under medical management (HR = 1.00 represents average cohort mortality and excess mortality is defined by HR >1.00) with systolic pulmonary artery pressure (SPAP) on the x-axis. Around 35 mm Hg, excess mortality emerges, with risk rapidly and steeply increasing with SPAP increment and doubling of mortality around SPAP 50 mm Hg.

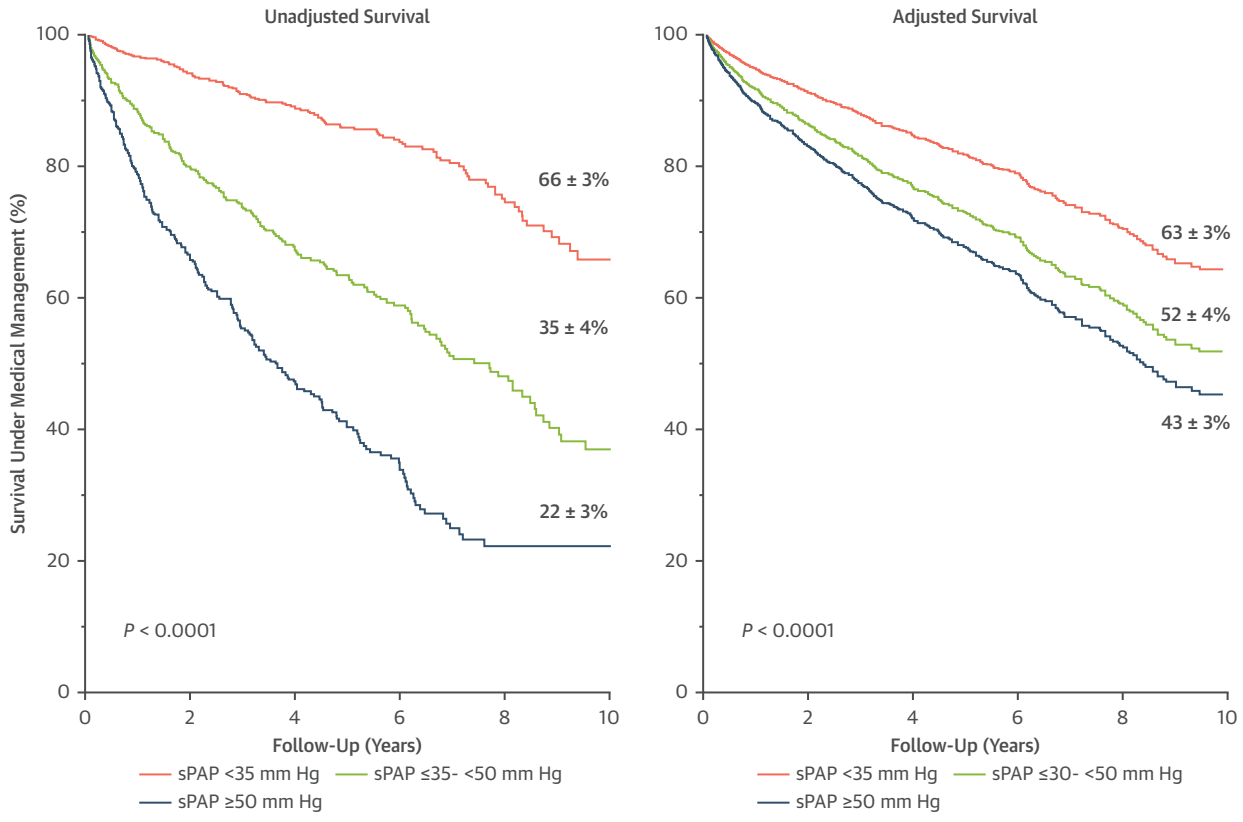
Nested models demonstrated PHTN incremental value in predicting long-term mortality: addition of SPAP as continuous or categorical variables on top of any model, provided consistently incremental power (all $P < 0.0003$).

To assess whether conclusions were valid in all patient subsets, Forrest plot analysis (Figure 5) showed that in all possible subsets, both mPHTN and sPHTN were associated with excess mortality (Figure 5) representing the stratification variable (eg, male and female sex), with in each stratification row (eg, male patients) 2 subrows with 2 HRs (1 in each subrow) for the subset (ie, 1 for mPHTN vs no PHTN and 1 for sPHTN vs no PHTN). Particularly, stratification by MR severity (moderate and severe) similarly shows that mPHTN and sPHTN both strongly affect adjusted survival irrespective of DMR grade, and Kaplan-Meier analysis stratified by MR severity shows wide separation of adjusted survival by PHTN subsets (Figure 6). Finally, when restricted to severe DMR, implications for survival under medical management of SPAP and PHTN remained unaffected (Supplemental Table 2).

Thus, under all circumstances, all subsets and all adjustments, SPAP and PHTN grades, particularly the new mPHTN range, are strong determinants of survival under medical management, incremental to all other known determinants of survival.

POST MITRAL SURGERY SURVIVAL AND THE IMPACT OF EARLY SURGERY. Survival after mitral surgery was 91% ± 1% at 5 years and 83 ± 1% at 10 years, which is higher than under medical management but remained linked to PHTN presence/severity. Indeed, operative mortality (at 1 month) was 0.4% without PHTN, 1.0% with mPHTN, and 3.3% with sPHTN ($P < 0.001$), a difference persistent after adjustment

FIGURE 3 **Survival Stratified by SPAP Categories**

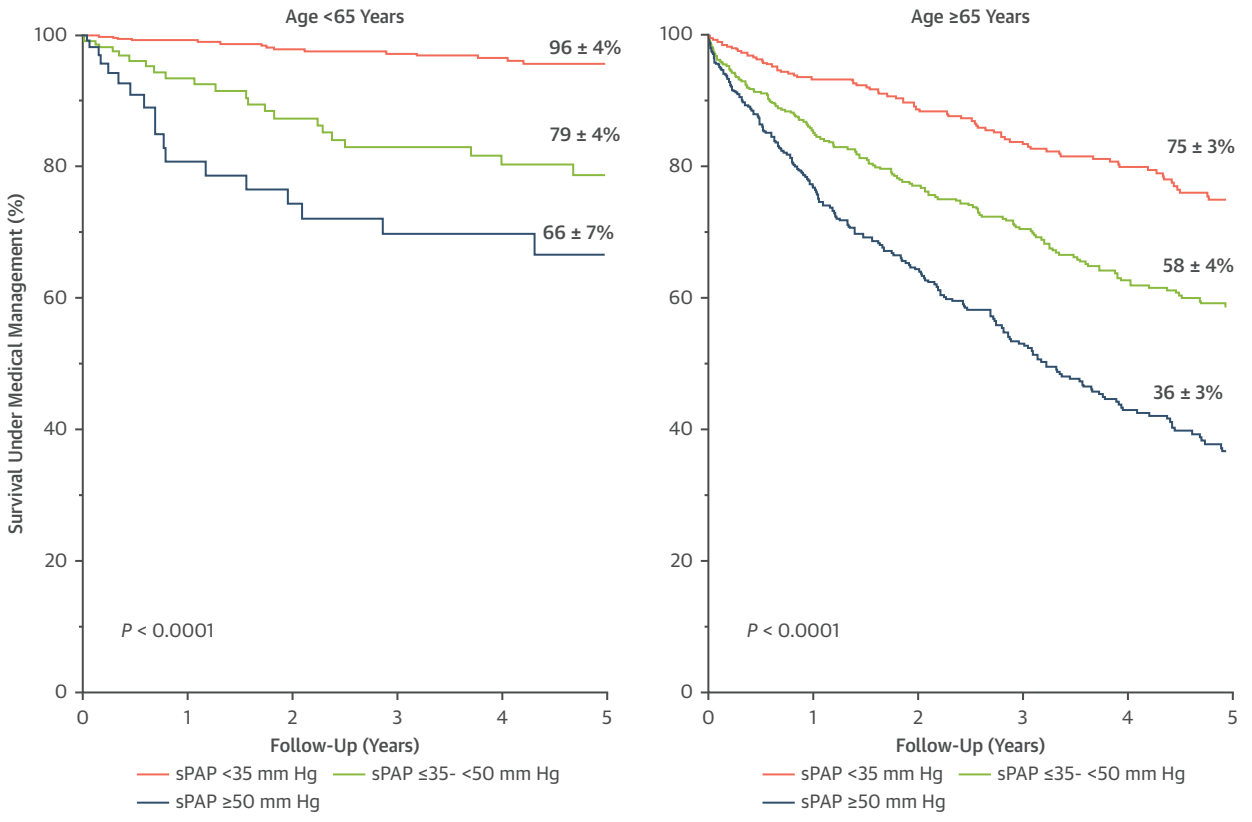


Kaplan-Meier curves for systolic pulmonary artery pressure (SPAP) subsets under medical management, unadjusted (left) and adjusted for age, sex, mitral regurgitation severity by effective regurgitant orifice, symptoms, EuroSCORE (European System for Cardiac Operative Risk Evaluation) II, left ventricular ejection fraction ≤60%, ventricular end-systolic diameter ≥40 mm (right). Note marked separation between curves in both panels, maintained throughout follow-up with considerable mortality with higher SPAP (≥50 mm Hg) but also moderate SPAP (35-49 mm Hg). Note also that adjustment, particularly for age, results in more dampened survival differences intrinsically related to pulmonary hypertension.

for age, sex, and EuroSCORE II ($P = 0.005$). Furthermore, 10-year postoperative survival by SPAP categories was 86% ± 2% for no PHTN, 80% ± 2% for mPHTN, and 67% ± 3% for sPHTN; $P < 0.0001$ (Supplemental Figure 1). As shown **Table 3**, SPAP as a continuous variable was persistently associated with postoperative long-term mortality, as well as mPHTN and sPHTN vs no PHTN. In multivariable analysis, postoperative excess mortality associated with SPAP elevation persisted, but whereas this link remained highly significant for sPHTN, it became insignificant for patients with mPHTN ($P \geq 0.30$), emphasizing the strong benefit of mitral repair in this PHTN subset (**Table 3**). Outcome implications post mitral surgery of SPAP and PHTN, restricted to severe MR, were unaffected (Supplemental Table 1).

To assess early surgery (<3 months after diagnosis) affects on survival in moderate/severe MR by PHTN ranges, the entire follow-up was analyzed. In multivariable models (excluding patients who died within 3 months under medical management), early surgery was associated with higher survival, adjusting for core (age, sex, ERO, EuroSCORE II, symptoms, LVEF, LVESD) model (adjusted HR: 0.47; 95% CI: 0.40-0.55; $P < 0.0001$) and comprehensive (further adjusted for LAVI, AF, and FTR grade) model (adjusted HR: 0.35; 95% CI: 0.29-0.44; $P < 0.0001$). Early surgery was beneficial in each PHTN category (adjusted HR: 0.45 [95% CI: 0.35-0.57] in sPHTN, 0.33 [95% CI: 0.24-0.44] in mPHTN, and 0.52 [95% CI: 0.37-0.71] in no PHTN; all $P < 0.0001$) similarly ($P_{interaction} = 0.19$). However, Kaplan-Meier landmark analysis provides additional insights by demonstrating absolute survival benefit in each category of PHTN. Indeed, whereas survival is highest with early surgery in the no-PHTN subset, absolute survival "improvement" (vs medical

FIGURE 4 Survival Associated With PHTN Ranges Stratified by Age



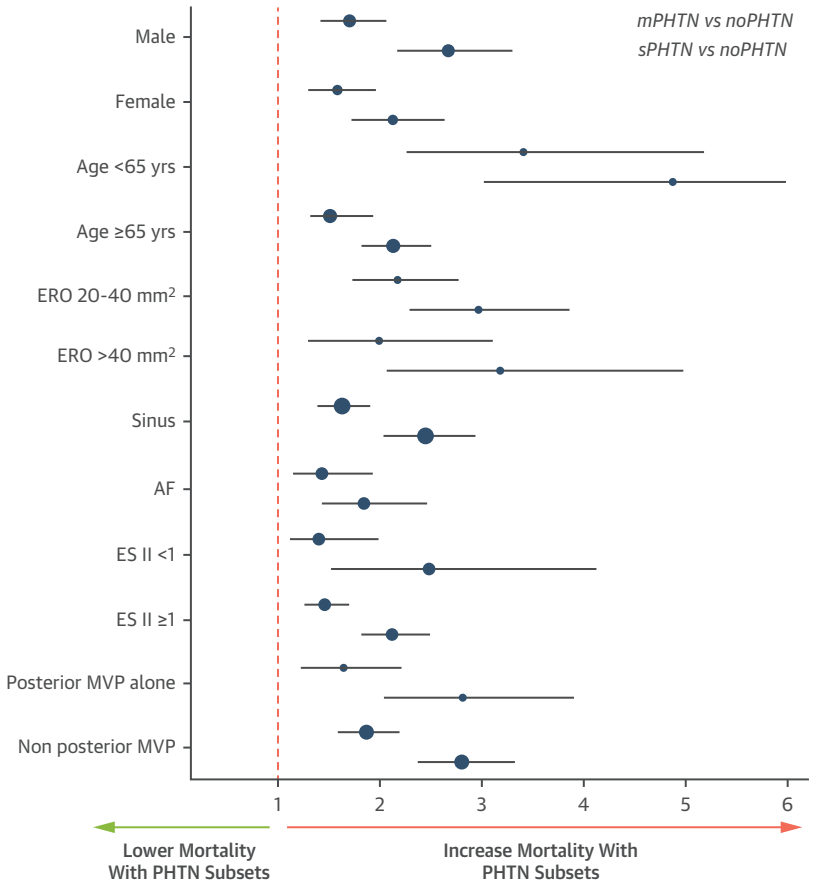
Kaplan-Meier survival curves according to SPAP by age (<65 years [left]; ≥65 years [right]). Note in both subsets, higher mortality corresponds to higher SPAP. Abbreviations as in Figure 1.

management) is higher in mPHTN and even higher in sPHTN (Figure 7).

DISCUSSION

The present, large international cohort of patients with DMR (as unified cause), with prospectively quantified SPAP and regurgitation (of moderate or severe grade) at diagnosis in routine clinical practice, provides unique and new insights, underscoring the importance of SPAP elevation measured by Doppler echocardiography (Central Illustration).[5,6] Systematic SPAP assessment among moderate-to-severe DMR demonstrates that PHTN response to DMR is frequent, with 25% classic sPHTN (SPAP ≥50 mm Hg) but also 30% with the novel definition of mPHTN in DMR (ie, 35-49 mm Hg). Despite the strong link between SPAP and both age and DMR severity, PHTN critically and powerfully affects DMR survival under medical management, independently of quantified DMR severity, age, and any other determinant of outcome and in all patients' subsets. The essential novel finding is that the untoward impact of PHTN on DMR survival is not limited to classical threshold of SPAP ≥50 mm Hg but also affects outcomes at much lower levels, with mPHTN 35-49 mm Hg independently associated with excess mortality. Post mitral surgery, risks associated with elevated SPAP persist (although attenuated) but remain significant only for sPHTN. Early mitral surgery within 3 months of moderate/severe DMR diagnosis is associated with markedly lowered mortality in all PHTN subsets. However, absolute early surgery benefit, considerable for sPHTN, is also quite notable for mPHTN. Thus, the present reappraisal of PHTN in DMR identifies the new subset of mPHTN as marker of mortality risk under medical management, markedly reduced or eradicated by DMR surgical correction. Therefore,

FIGURE 5 **Forest Plot of Survival Under Medical Management**

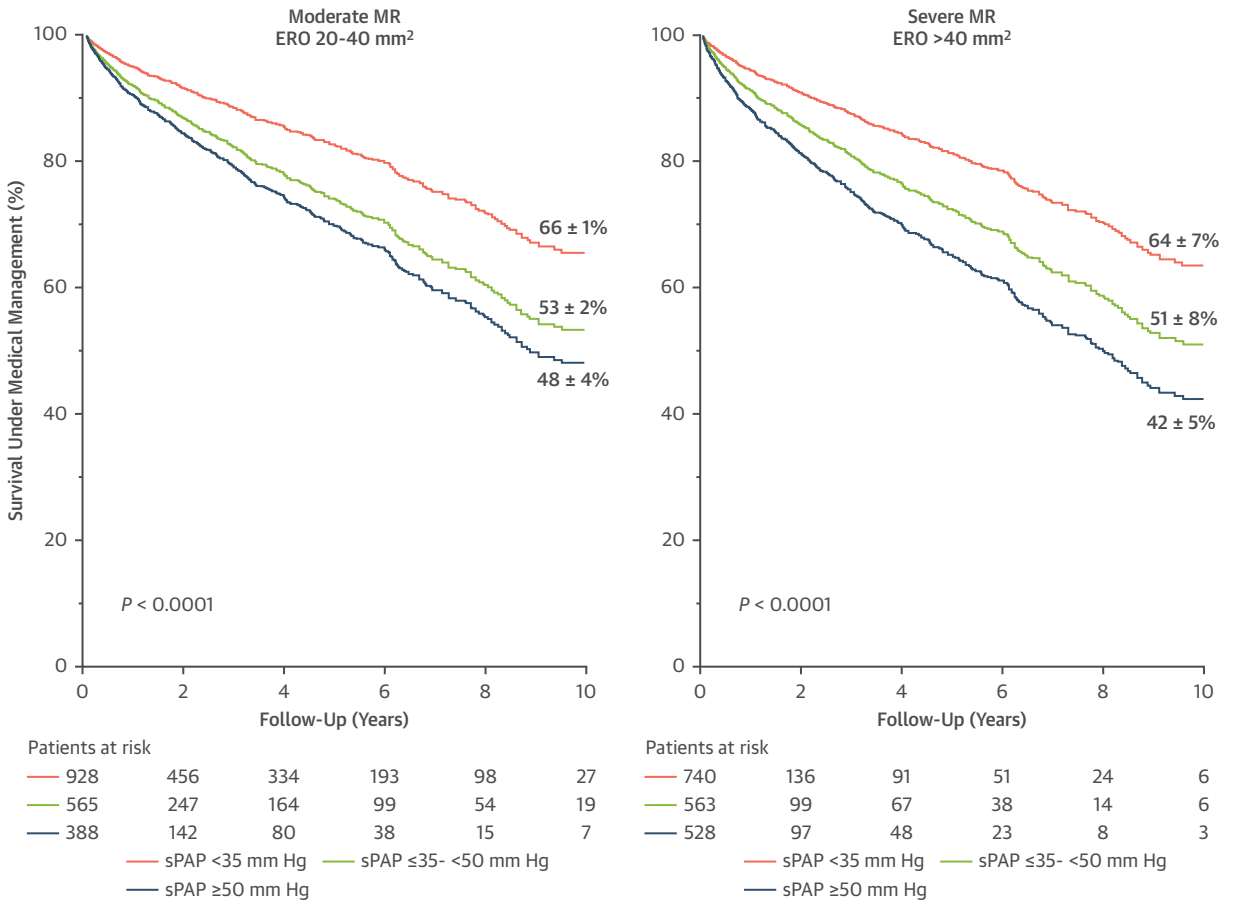


Forest plot displaying adjusted HRs for mortality with moderate PHTN (mPHTN) and severe PHTN (sPHTN) (vs no PHTN) in all subsets. AF = atrial fibrillation; ERO = effective regurgitant orifice; ES II = EuroSCORE II; other abbreviations as in Figure 5.

SPAP measured by Doppler echocardiography in routine practice is a powerful marker of DMR outcome, is extensively usable in most world regions, and should play a definite and crucial role in guiding DMR management and in considering early DMR correction.

PHTN IN DMR. PHTN in patients with MR was noted early by cardiac catheterization as consequence of LA pressure elevation with large V-wave associated with systolic regurgitation into LA.[26] This association was considered pathognomonic of severe MR, with the concept of MR severity essentially determining LA pressure elevation and in turn pulmonary pressures elevations.[27] However, hemodynamic studies promptly emphasized that severe MR may occur with normal LA pressures and diminutive V waves,[28] and that tall V waves may occur even without MR.[29] Thus, LA pressure is not only related to MR volume but also to atrial compliance and PHTN is strongly additionally dependent on pulmonary circulation compliance.[27,29] Thus, the exact link between DMR, currently most frequently causing organic MR in Western countries,[1] and PHTN remained uncertain, due to lack of studies with DMR quantitation. Even though a quantified functional MR link to elevated pulmonary pressure is established,[30] the present multicenter study is the first demonstrating that indeed DMR quantified severity is a major PHTN determinant but that several other factors play crucial roles, including LV diastolic filling characteristics[31] linked to reduced exercise capacity.[32] Whereas elevated E-wave classically reflects DMR severity,[33] our study shows that E/e′ and ERO are very weakly correlated, implying that elevated E/e′ reflects LV diastolic characteristics rather than DMR severity.

FIGURE 6 Survival Stratified by SPAP Categories and MR Severity

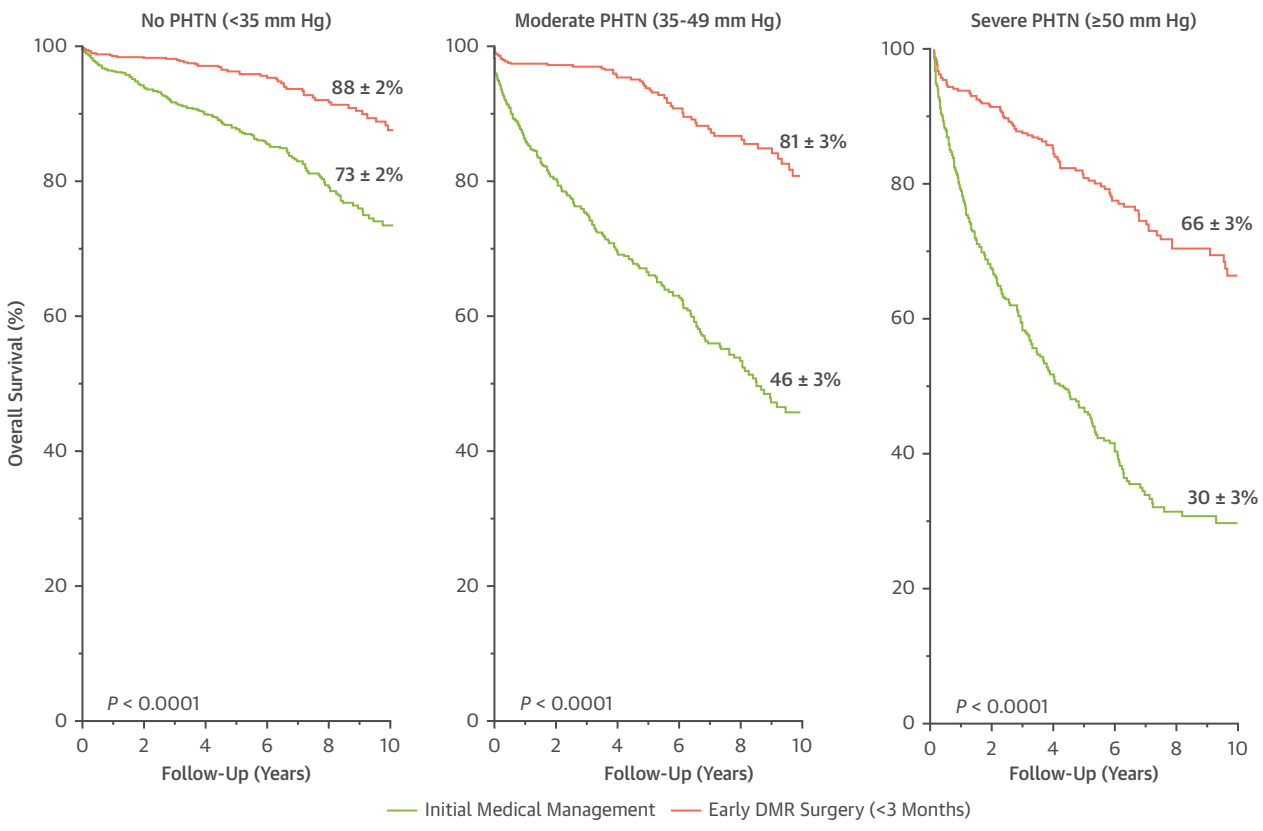


Kaplan-Meier curves for SPAP subsets under medical management, for moderate (left) and severe (right) mitral regurgitation (MR), and adjusted for age, sex, symptoms, EuroSCORE II, left ventricular ejection fraction ≤60%, left ventricular end-systolic diameter ≥40 mm (right). Note marked separation between curves in both panels, maintained throughout follow-up with considerable mortality with higher SPAP (≥50 mm Hg) but also moderate SPAP (35-49 mm Hg), and more severe MR. Abbreviations as in Figures 1 and 5.

Whereas reduced LA compliance associated with elevated LA pressure[27] may suggest that smaller LAs yield PHTN, such is not the case because LAVI is larger with PHTN, probably owing to the LA reaching extreme wall stiffness preventing LA dilatation compensatory effect.[34] One considerable contributor to PHTN is older age, which affects pulmonary vascular reactivity and is linked to PHTN in the general population.[35] These complex pathophysiologic factors[36] are crucial in considering the wide span of individual pulmonary hemodynamic response to DMR. This emphasizes the importance of measuring SPAP throughout the spectrum of DMR severity. However, the approach to measuring SPAP is confusing. Indeed, imperfect Doppler-echocardiographic correlations to invasive pressures[37] yielded invasive catheterization emphasis,[38] whereas DMR guidelines recommend Doppler-echocardiographic SPAP assessment.[5,6] Therefore, our study is crucial by its size, use of routine practice data, and multicenter nature, as well as by demonstrating that SPAP measured by Doppler echocardiography has strong, independent, and incremental prediction for outcome with narrow confidence interval in spline analysis. Thus, irrespective of considerations on precision of SPAP estimation by Doppler echocardiography, it has an important role to play in DMR management.

DMR OUTCOME AND MANAGEMENT: ROLE OF PHTN. Clinical guidelines focus exclusively on severe DMR and present diverging approaches whereby PHTN remains an important Class II indication for surgical

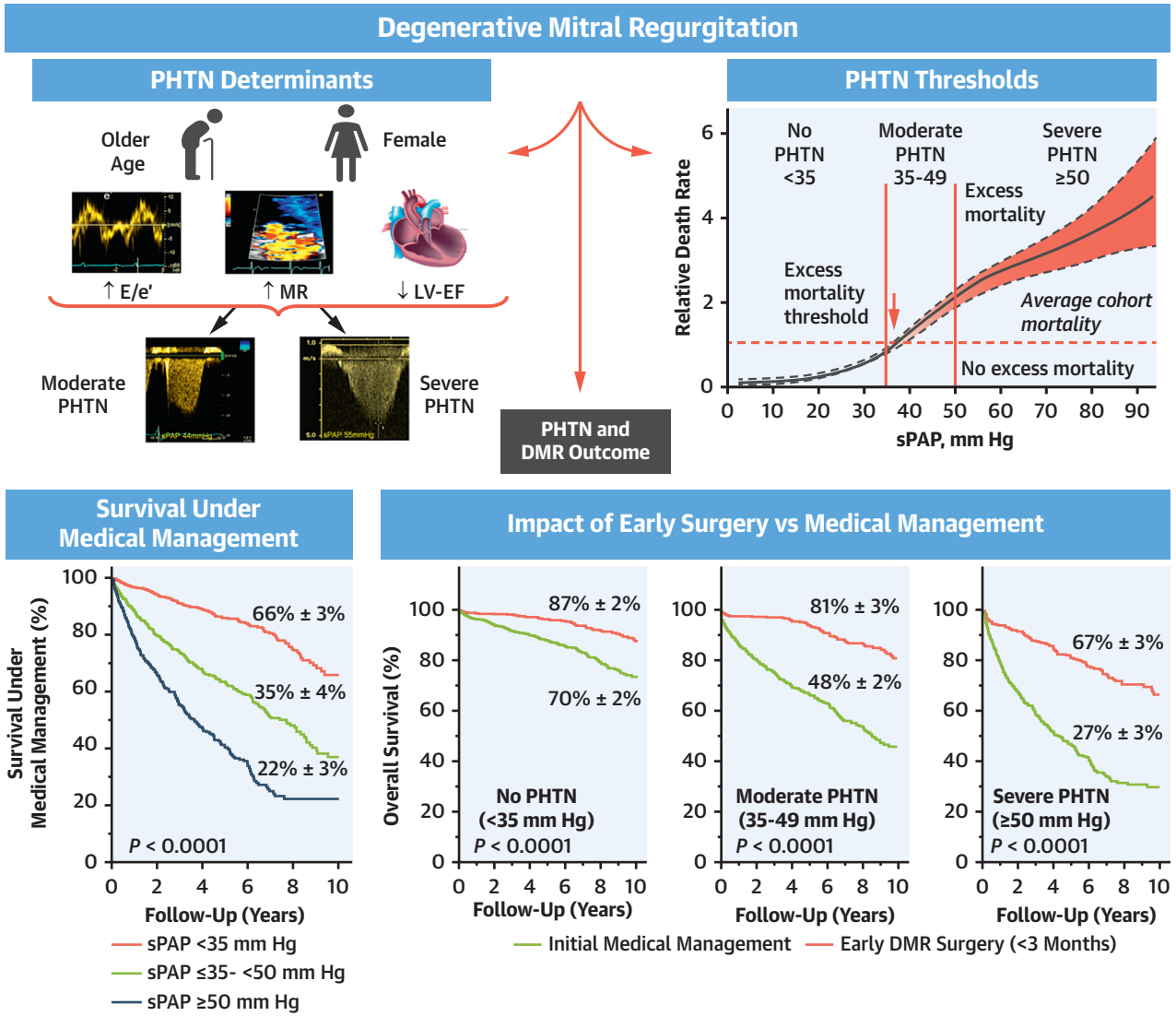
FIGURE 7 Survival Associated With Early Surgery (vs Continued Medical Management) Stratified by SPAP Subgroups



Landmark Kaplan-Meier survival curves for early mitral surgery (3 months) vs medical management with no (left), moderate (middle), and severe (right) PHTN. Note the absolute survival benefit in each category, considerable with severe PHTN but also substantial with moderate-PHTN. Abbreviations as in Figure 1.

correction in European guidelines,[5] whereas PHTN is not part of management algorithms in U.S. guidelines.[6] This divergence created confusion for risk assessment and surgical indications. Patients with DMR present often at an advanced age[1,3,4] with notable risk for surgery[10] that may discourage interventions, resulting in undertreatment.[1,39] Therefore, it is essential to balance surgical risks to DMR risk under medical management, which has a wide span[40] and for which PHTN has an important role to play. The current published data on PHTN may be considered discouraging for mitral interventions by emphasizing mediocre postinterventional/surgical outcomes with PHTN.[12-20] However, this would ignore risks under medical management related to PHTN, which are rarely reported,[11,41] or not accounting for comorbidity impact on outcome.[42] Thus, our large cohort provides incremental, novel information, demonstrating for the first time that SPAP is not just a surrogate for DMR severity, but is incremental to the ERO, RVol, and to all other clinical characteristics in predicting outcome. Also, for the first time, our large cohort demonstrates that excess mortality is not just the prerogative of sPHTN, but it is also observed with mPHTN with SPAP 35-49 mm Hg, consistent with calls for reducing pulmonary pressure thresholds in defining PHTN of any cause.[43] We also show that PHTN affects postoperative outcomes, but excess mortality is more muted than under medical management and is attached independently to sPHTN, whereas risks become insignificant for mPHTN. Thus, taking all this new information into consideration, sPHTN has, in our opinion, characteristics of a Class I criterion for intervention in severe DMR.[5,6] Symptoms and LV dysfunction were defined as Class I criteria based on cohort analyses, without randomized clinical trials, similarly to the present analysis. These Class I triggers (and sPHTN) require immediate DMR correction due to swift excess mortality under medical management,[44] but risk is not completely

CENTRAL ILLUSTRATION **Outcome Implications of Pulmonary Hypertension in Degenerative Mitral Regurgitation**



Essayagh B, et al. J Am Coll Cardiol Img. 2024;■(■):■-■.

(Top, left) Independent determinants of moderate (systolic pulmonary artery pressure [SPAP] 35-49 mm Hg) and severe pulmonary hypertension (PHTN) (SPAP ≥50 mm Hg). (Top, right) Spline curve of mortality risk according to SPAP. Note the threshold of 35 mm Hg for excess mortality. (Bottom, left) Survival under medical management stratified by SPAP categories. Note considerable mortality attached with sPHTN and even moderate PHTN. (Bottom, right) Landmark Kaplan-Meier survival curves for early mitral surgery (3 months) vs medical management with no (left), moderate (middle), and severe (right) PHTN. Note the absolute survival benefit in each category, which is considerable with severe PHTN but also substantial with moderate PHTN. DMR = degenerative mitral regurgitation; LVEF = left ventricular ejection fraction; MR = mitral regurgitation.

attenuated after DMR correction.[45] Conversely, mPHTN is less disastrous for outcomes but encouraging to promptly consider repair for DMR severe enough based on quantitative criteria, to restore life expectancy.[7,46] Surgical/interventional treatment of moderate DMR is not mentioned in current guidelines[5,6] but may deserve careful consideration (particularly guided by PHTN) if clinical trials demonstrate effectiveness in improving outcomes. If DMR is not severe enough to justify surgical/interventional repair, medical therapies developed for PHTN[43] may be considered but warrant future clinical

trials. Similarly, medical treatment of persistent PHTN after surgical/interventional repair warrants evaluation. Irrespective of remaining therapeutic questions, our novel data and outcomes emphasize the importance of including SPAP, measured by Doppler echocardiography in routine practice, among parameters guiding DMR management.

STUDY STRENGTHS AND LIMITATIONS. Although our cohort was identified retrospectively in each center, all measurements were performed prospectively by multiple operators and collected electronically without alteration, allowing us to merge a large international cohort of consecutive isolated DMR with considerable strength provided by routine-practice prospective DMR quantitation. Such a methodological approach ensures wide applicability to routine practice of DMR all-comers. Due to vagaries of death causes coding and legal restrictions for death certificate retrieval, cardiac mortality could not be analyzed, and we focused instead on the most robust endpoint of all-cause mortality under medical management. TR and SPAP assessment did not use saline nor ultrasound-enhancing agents as part of routine practice.

Patients with PHTN due to overt causes other than DMR were excluded from the present study, but PHTN is multifactorial and contributing conditions may be subtle. Nevertheless, the relationships among PHTN, quantified DMR, and left heart size and function are reassuring regarding the strong link between DMR and PHTN.

Catheterization, theoretically advised for definitive diagnosis of PHTN,[21] was used infrequently clinically in the present multicenter routine practice of DMR, concordant with valvular guidelines,[5,6] and with DMR's well-established causal relationship to PHTN (group 2). Indeed, only 4% of patients underwent right-heart catheterization precluding evaluation of prognostic value of this diagnostic modality. Use of tricuspid regurgitant velocity as an alternative to SPAP with recommended thresholds at 2.9 and 3.4 m/s[21] was tested, but in nested models , it became insignificant ($P = 0.42$) with incremental power left to SPAP ($P = 0.01$). Impact of exercise PHTN or coupling to right ventricular function[47] on DMR outcome remains uncertain without large registries.[48] Peak exercise SPAP can reach >60 mm Hg in healthy individuals,[49] and exercise in both European[5] and U.S. guidelines[6] is indicated for symptoms assessment rather than for exercise PHTN. Thus, methodologically there is no established and widely applicable alternative to Doppler-echocardiographic assessment of SPAP in routine practice of DMR. In aggregate, our data show mPHTN strong prognostic affects and improved survival after mitral surgery, and we believe it is crucial to consider DMR correction in this context, whereas other approaches may prove their prognostic usefulness in future research/trials.

CONCLUSIONS

The present study demonstrates in a large international cohort of isolated DMR with prospective quantitative DMR and SPAP assessment in routine practice that SPAP response to the MR is heterogeneous with frequent PHTN. Despite the link between DMR severity and SPAP, PHTN is strongly associated with poor outcome under medical management independently of DMR severity and all other characteristics. The very novel finding is that excess mortality emerges for SPAP levels much below previously touted thresholds. Moderate PHTN (SPAP 35-49 mm Hg) is of particular importance because it is linked to significant excess mortality under medical management, which is eliminated after surgical correction of DMR. Conversely, severe PHTN (≥50 mm Hg) is associated with more severe excess mortality, which is attenuated but not suppressed after surgical correction of DMR. Hence, the present reappraisal of PHTN in DMR shows that its assessment by Doppler echocardiography is critical in routine practice and should not only emphasize sPHTN, but also crucially mPHTN, to guide the clinical decision-making process and ultimately reduce DMR undertreatment.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: The present large international cohort of isolated, moderate, or severe DMR diagnosed in routine practice with prospective quantitative DMR and SPAP assessment demonstrates that PHTN is frequent and independently linked with poor outcome, not only for severe but also for moderate PHTN. Thus, in clinical practice it is essential to: 1) measure SPAP by Doppler echocardiography systematically at diagnosis of DMR simultaneously to DMR quantitation; 2) promptly indicate surgery for DMR considered severe by quantitative measures and with sPHTN; 3) promptly consider transcatheter intervention for DMR of prohibitive risk for surgery, considered severe by quantitative measures and with sPHTN; 4) consider early repair for patients with DMR considered severe by quantitative measures and with mPHTN; and 5) test medical therapy for PHTN in patients with limited DMR severity with PHTN. These therapeutic considerations guided by the PHTN response to DMR are essential to clinical decision-making and ultimately to reduce DMR undertreatment.

TRANSLATIONAL OUTLOOK: The PHTN response to DMR is highly variable and its determinants and mechanisms are poorly understood. Mechanistic research linking potential determinants, such as the stiffness of the LA or of the pulmonary bed, to biological mechanisms including proteomics and genomics in combination with DMR quantitation are in order to define the modulators of the individual response to DMR severity. Whether these yield metabolic pathways and therapies that can relieve the untoward consequences of PHTN in patients with DMR remains to be determined.

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KEY WORDS degenerative mitral regurgitation, echocardiography, mitral valve prolapse, pulmonary hypertension, survival

APPENDIX For expanded Methods and Results sections as well as supplemental tables, a figure, and references please see the online version of this paper.