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Right ventricular-pulmonary arterial uncoupling and ventricular-secondary mitral regurgitation: Relationship with outcomes in advanced heart failure

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BACKGROUND: Secondary mitral regurgitation (MR) is common in heart failure with reduced ejection fraction (HFrEF) and is associated with poor outcomes. However, there is little evidence regarding secondary MR in advanced HFrEF. Poor outcomes for MR intervention suggest a need for further risk stratification.

METHODS: Patients were assessed with echocardiography, right heart catheterization (RHC), and cardiopulmonary exercise testing. Ventricular-secondary MR was identified by echocardiography and categorized as mild, moderate, or severe according to guidelines. RV ability to compensate for pulmonary pressure rise was assessed by RV-pulmonary artery (PA) coupling, calculated as ratio of tricuspid annular plane systolic excursion (TAPSE), and systolic pulmonary artery pressure (SPAP) (echocardiography for TAPSE and RHC for SPAP). Primary end-point was a composite of all-cause mortality, urgent heart transplantation, or mechanical circulatory support.

RESULTS: Four hundred and fifty-six patients with ventricular-secondary MR were followed up for a median of 2.39 years, with 237 reaching a primary end-point. Severe MR conferred a worse prognosis than mild or moderate ((hazard ratio) HR 2.6, $p < 0.001$). Right atrial pressure was predictive of survival. RV-PA uncoupling, defined as TAPSE/SPAP below median value of 0.37, was associated with reduced survival across all severities of MR ($p < 0.001$).

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CONCLUSIONS: Ventricular-secondary MR is common and severity correlates with adverse prognosis in advanced heart failure. RV-PA uncoupling can improve risk stratification in all grades of MR severity, particularly with PA pressure determined invasively.

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Background

Advanced heart failure is defined by the persistence of severe heart failure symptoms and signs with severe impairment of exercise capacity, severe cardiac dysfunction, and episodes of congestion or low cardiac output despite optimal guideline-directed medical therapy (GDMT).[1] Patients with advanced heart failure require assessment of suitability for heart transplantation, mechanical circulatory support, or palliative care.

Secondary mitral regurgitation (MR) is common in heart failure and associated with a worse prognosis.[2-4] Severe secondary MR affects 10% of all patients with heart failure and 25% of patients with heart failure with reduced ejection fraction (HFrEF).[5] The incidence and impact on outcomes of secondary MR in advanced heart failure are less well defined.[6]

Secondary MR can be ventricular-secondary, which is characteristic of HFrEF. Ventricular-secondary MR is caused by left ventricular dilatation and spherical remodeling with papillary muscle displacement, mitral valve leaflet tenting, and reduction in coaptation length. It is also caused by left ventricular systolic dysfunction and systolic dyssynchrony, with impaired and delayed papillary muscle contraction, further impairing mitral valve closure. Secondary MR can also be atrial-secondary, which is more characteristic of heart failure with preserved ejection fraction. Atrial-secondary MR is caused by left atrial dilatation and dysfunction due to diastolic dysfunction and/or atrial fibrillation. An atrial-secondary component can accompany ventricular-secondary or primary MR when the left atrium dilates and/or atrial fibrillation occurs.

The severity of secondary MR is dynamic,[2] being affected by afterload, preload, heart rhythm and rate, and by systolic dyssynchrony.[7] Consequently, secondary MR can improve with GDMT, including cardiac resynchronization therapy and heart rhythm and rate control when needed.[7,8] This suggests that secondary MR is just a marker of heart failure severity and the severity of secondary MR should be reassessed following optimization of heart failure treatment.[9] However, secondary MR may progress on GDMT[10] or may fail to improve, becoming the driver of the heart failure syndrome. Persistent symptomatic severe MR despite optimal GDMT requires consideration of surgical or transcatheter mitral valve intervention.[11] Surgical mitral valve repair can result in reverse remodeling and improved left ventricular systolic function[12] but does not improve outcomes compared to medical treatment alone[13] or to mitral valve replacement,[14,15] and is associated with higher rates of recurrent secondary MR. Transcatheter edge-to-edge repair (TEER) reduced all-cause mortality and rehospitalization for heart failure in the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (trial) (COAPT) trial,[16] although benefit was confined to a subset of patients with less dilated left ventricles and more severe secondary MR.[16,17] Long-term outcomes remained poor despite TEER, with death or heart failure hospitalization in 73.6% of patients by 5 years.[18] Persistent poor outcomes, despite MR-specific treatment, suggest the need for further risk stratification in HFrEF with secondary MR.

In HFrEF, right ventricular (RV) dysfunction is present in 50% of cases,[19] and RV function (as estimated by tricuspid annular plane systolic excursion (TAPSE)) is a predictor of more advanced heart failure.[20] More so, RV dysfunction is an important prognostic factor in secondary MR.[21] Interestingly, severe MR does not seem to cause a drop in RV function,[22] although improvement in RV function was found following TEER in secondary MR.[23] RV-pulmonary artery (PA) uncoupling, the decreasing ability of the RV to cope with increasing pulmonary pressure,[24] has been associated with worse prognosis in heart failure patients,[25,26] including those with secondary MR.[27] RV-PA uncoupling was a powerful predictor of 2-year adverse outcomes in the COAPT patients, treated with TEER or not.[27]

Our study assessed the incidence and impact on outcomes of ventricular-secondary MR severity in advanced heart failure patients with HFrEF on GDMT, referred for consideration of heart transplantation. It also assessed the potential role of RV-PA uncoupling in this population, for further refining risk stratification.

Methods

Consecutive patients with advanced heart failure referred for consideration of heart transplantation at a single center in the UK underwent a series of investigations, including echocardiography, right heart catheterization (RHC), and cardiopulmonary exercise testing. All study procedures complied with local ethics protocols and research governance with informed consent obtained as required and in strict compliance with the International Society for Heart and Lung Transplantation ethics statement. Echocardiographic images were analyzed, to select and include in our study only patients with HFrEF and

ventricular-secondary MR. Patients with primary MR, atrial-secondary MR, previous surgical or transcatheter mitral valve intervention, arrhythmogenic cardiomyopathy, hypertrophic cardiomyopathy, and complex congenital heart disease were excluded. MR was graded as mild, moderate, and severe based on echocardiography, according to current recommendations.[9,28] TAPSE was measured from M-mode. The systolic pulmonary artery pressure (SPAP) was estimated on echocardiography from the tricuspid regurgitation (TR) velocity and the inferior vena cava respiratory variation.

Right atrial, right ventricular, pulmonary arterial, and pulmonary capillary wedge pressures were recorded from RHC using a PA flotation catheter (7Fr Swan Ganz catheter, Edwards Life Sciences, Irvine, CA). Cardiac output was estimated by Fick and thermodilution methods. RV-PA coupling was calculated as TAPSE divided by SPAP, using either the echocardiographic SPAP estimate or the RHC SPAP measurement.

All patients were followed up. The primary outcome was a composite of all-cause mortality, urgent heart transplantation, or mechanical circulatory support (with veno-arterial extra-corporeal membrane oxygenation or any form of ventricular assist device). Follow-up was censored at the time of routine heart transplantation, which was not considered a primary outcome event.

Summary statistics are presented as mean (standard deviation) if normally distributed on visual inspection or median [interquartile range]. Data were analyzed with a Cox regression analysis and group comparisons using log-rank tests and linear regression where appropriate. SPSS Statistics version 25 (SPSS Software, IBM Corporation, Armonk, NY), R-studio (RStudio, Boston, MA), and Graphpad Prism version 10 (Graphpad Software, San Diego, CA) were used.

Results

Derivation of study population

Eight hundred and seventy-seven patients with advanced heart failure underwent heart transplant assessment from January 2010 until December 2021. Three hundred and eleven patients did not have MR and were excluded. A further 19 patients with primary MR, 78 patients with atrial-secondary MR, and 13 patients with arrhythmogenic cardiomyopathy/hypertrophic cardiomyopathy (who were not in other groups) were excluded. The final study population included 456 patients with ventricular-secondary MR and categorized into 155 mild, 150 moderate, and 151 severe (Figure 1). Baseline characteristics are shown in Table 1. Patients had significantly reduced LV ejection fraction (22% ± 7.6%), high symptom burden (median New York Heart Association 3) and were receiving guideline-directed therapy for heart failure appropriate to their year of assessment.

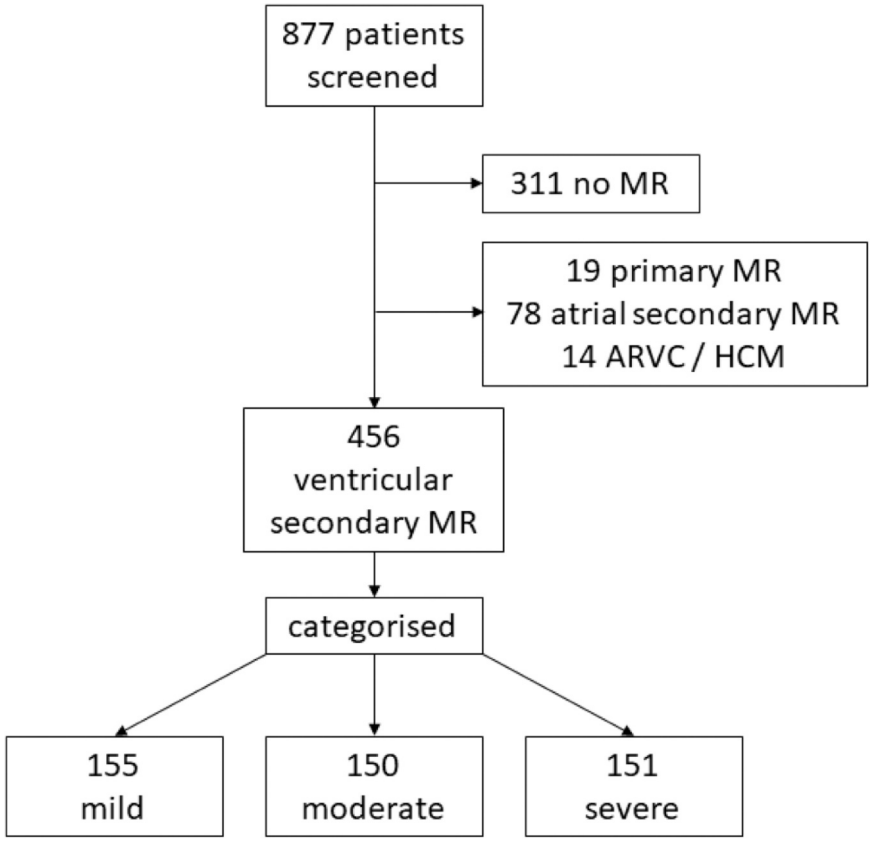

Figure 1 Study flowchart. HCM, hypertrophic cardiomyopathy; MR, mitral regurgitation.

Table 1 Demographic and Treatment Details of the Cohort

Demographic	All	Mild ($n = 142$)	Moderate ($n = 144$)	Severe ($n = 151$)	p-value ANOVA
Male, *n* (%)	342 (75%)	109 (77%)	106 (74%)	122 (81%)	0.133
Etiology, *n*	DCM 282, ICM 129, Other 45	83, 46, 2	89, 37, 4	102,45,1	
NYHA (mean)	2.83 ± 0.48	2.74 ± 0.48	2.78 ± 0.49	2.97 ± 0.44	< 0.001
NYHA (median)	3	3	3	3	
Proportion taking ACE inhibitor (%)	61.8	56.5	65	63.6	0.18
Proportion taking ARB (%)	21.5	19.5	21	23.8	0.686
Proportion taking ARNI (%)	11.8	15.6	9.8	10.6	0.214
Proportion taking beta blocker (%)	89.7	88.3	90.2	91.4	0.679
Proportion taking MRA (%)	86.2	85.7	86.7	85.4	0.891
LVIDd, cm	6.57 ± 10.9	6.2 ± 9.31	6.52 ± 10.6	7.11 ± 10.2	< 0.001
Left ventricular ejection fraction (%)	22.1 ± 7.6	25.1 ± 8.1	21.5 ± 8	19.6 ± 5.4	< 0.001
TAPSE, mm	16.6 ± 5.7	16.9 ± 4.4	16.7 ± 7.7	16.2 ± 4.3	0.514
6-min walk distance, m	310 ± 104	316 ± 111	306 ± 105	309 ± 96	0.739
Peak VO_2	13.6 ± 4.2	14 ± 4.3	13.7 ± 4.2	13 ± 4	0.135
Mean right atrial pressure, mmHg	10.7 ± 6.2	9.2 ± 5.8	11 ± 6.7	12.1 ± 5.7	< 0.001
Mean pulmonary artery pressure, mmHg	31 ± 11.7	25.1 ± 10.6	32.2 ± 12	35.7 ± 10	< 0.001
Mean pulmonary capillary wedge pressure, mm Hg	21.3 ± 9.3	16.3 ± 8.4	22.7 ± 9.2	24.9 ± 8	< 0.001
Pulmonary capillary V-wave, mmHg	27.9 ± 12.6	21.3 ± 11.1	28.7 ± 11.5	33.5 ± 12	< 0.001
Cardiac index Fick, liter/min/m^2	1.85 ± 0.58	2.09 ± 0.68	1.81 ± 0.52	1.62 ± 0.42	< 0.001
Cardiac index thermodilution, liter/min/m^2	1.9 ± 0.56	2.11 ± 0.59	1.9 ± 0.55	1.69 ± 0.46	< 0.001
RV stroke work index Fick, mmHg.ml/m^2	517 ± 293	475 ± 292	546 ± 303	531 ± 281	0.082
RV stroke work index thermodilution, mmHg.ml/m^2	537 ± 310	483 ± 275	583 ± 337	548 ± 312	0.017
NT pro BNP, pg/ml	4,089 ± 4,721	2,738 ± 3,932	3,759 ± 4,270	5,653 ± 5,324	< 0.001

Abbreviations: ACE, angiotensin-converting enzyme; ANOVA, analysis of variance; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor blocker neprilysin inhibitor; DCM, Dilated Cardiomyopathy; ICM, Ischaemic Cardiomyopathy; LVIDd, left ventricular internal dimension in diastole; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; RV, right ventricles; TAPSE, tricuspid annular plane systolic excursion.
p-values are by ANOVA comparing mild, moderate, and severe.

MR severity and event-free survival

Kaplan-Meier estimates of event-free survival, categorized by echocardiographic severity of MR, are presented in Figures 2 and 3. Severe secondary MR was a significant risk factor for adverse prognosis (hazard ratio compared to mild MR 2.6 (1.92-3.6), $p < 0.001$), while mild and moderate groups were not significantly different (hazard ratio for mild vs moderate 1.2 (0.88-1.8, $p = 0.2$).

Univariate and multivariate analysis

In univariate analysis using a Cox proportional hazards model, many variables were significant predictors of event-free survival (Table 2): left ventricular function measured by ejection fraction (LVEF), stroke work index or cardiac index; right ventricular function measured by TAPSE; measurements of pressure such as right atrial (RA) pressure, mean pulmonary artery pressure, or pulmonary capillary wedge pressure (PCWP); and right ventricular-pulmonary arterial (RV-PA) coupling as measured by TAPSE/SPAP and calculated using TAPSE from echocardiography and invasive PA pressure from the right heart catheter.

In multivariate analysis, the only significant variables were left ventricular internal dimension in diastole (LVIDd), VO_2 max, and right atrial pressure (Table 3).

Stepwise linear regression selected the variables of right atrial pressure, LVIDd, VO_2 max, and TAPSE/SPAP as predictive of the composite outcome with R-value of 0.391.

Right atrial and left atrial pressures

The association between the primary outcome measure and intra-cardiac filling pressures was examined.

Dividing the mild and moderate MR cohorts by elevated right atrial pressures (an RA pressure of greater than 10 mm Hg being used as a cut-off, this being the median in the dataset), those with elevated RA pressure had significantly reduced event-free survival compared to those

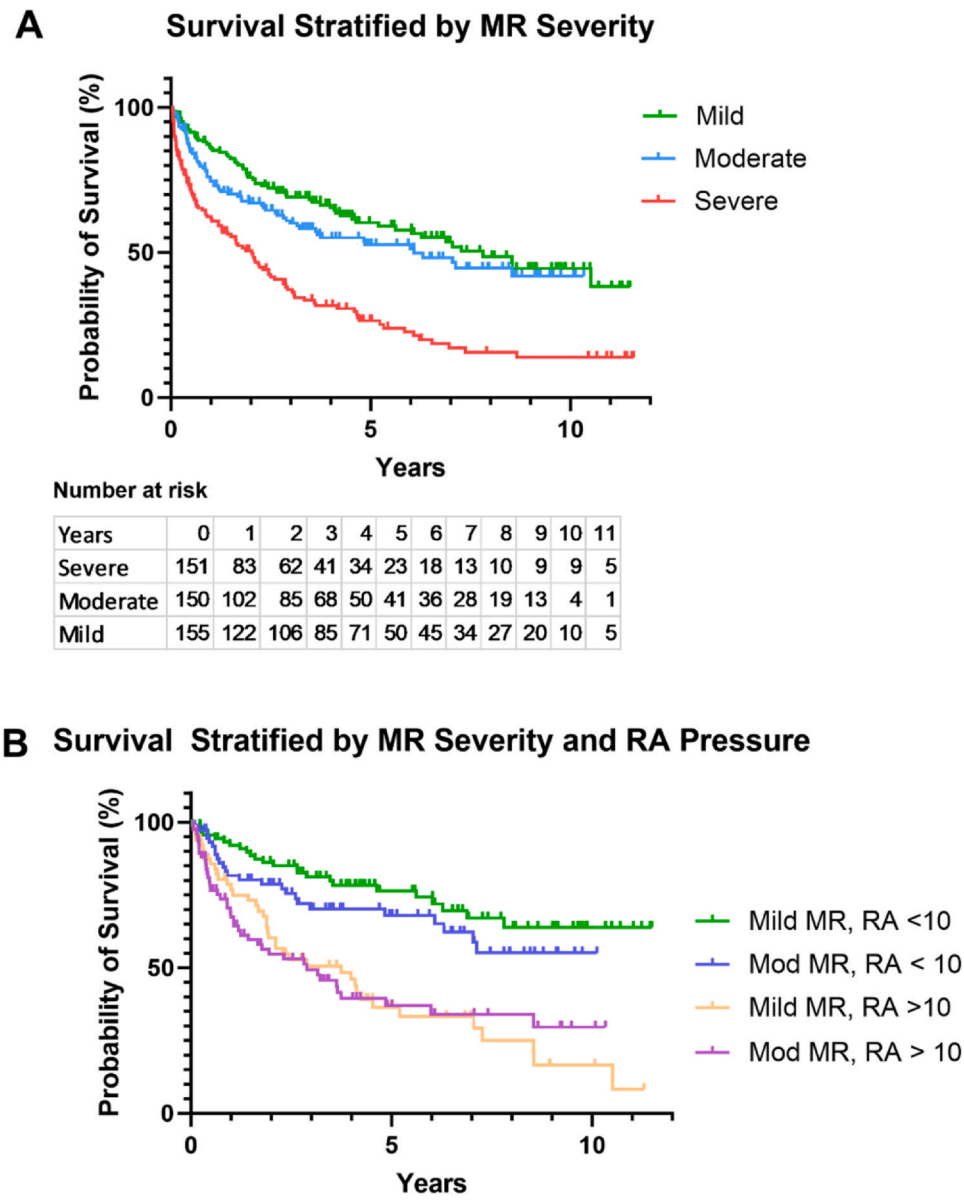

Figure 2 (A) Unadjusted event-free survival curves demonstrating survival by severity of mitral regurgitation. (B) Mild and moderate mitral regurgitation cohorts, divided by right heart failure (RHF) as determined by right atrial pressure > 10 mm Hg. MR, mitral regurgitation; RA, right atrium.

without ($p < 0.0001$, Figure 1B), except in the severe MR cohort, where there was no significant difference in survival between the RA > 10 and RA < 10 groups. Unsurprisingly, wedge pressure and RA pressure showed a positive correlation (slope 0.058, $R^2 = 0.33$, $p < 0.001$). Right atrial pressure was also higher in the severe MR cohort (12.1 ± 5.7 mm Hg) than the moderate (11 ± 6.7 mm Hg) and mild (9.1 ± 5.8 mm Hg) MR cohorts ($p < 0.0001$ for difference between groups).

Further stratification by wedge pressure is shown in Table 4. Looking at patients with elevated left atrium (LA) pressure (PCWP > 21 mmHg, the median in the dataset), those whose RA pressures were not elevated (RA pressure of < 10 mm Hg) had a significantly improved event-free survival compared with those RA pressures were elevated ($p < 0.001$).

Patients with RA pressure < 10 mm Hg and wedge pressure < 21 mm Hg had significantly greater event-free survival ($p < 0.001$, Table 4), which persisted across all MR severities (mild $p < 0.001$, moderate $p = 0.016$, severe $p = 0.032$ although in subgroup analysis this only remained significant for those with mild MR.

Right ventricular function

TAPSE was not significantly different across the different MR groups nor was there a correlation with pulmonary capillary wedge v-wave ($R^2 = 0.009$). Using the American Society of Echocardiography cut-off of a TAPSE of 17 mm to signify RV dysfunction,[29] RV dysfunction was predictive of reduced event-free survival ($p = 0.01$).

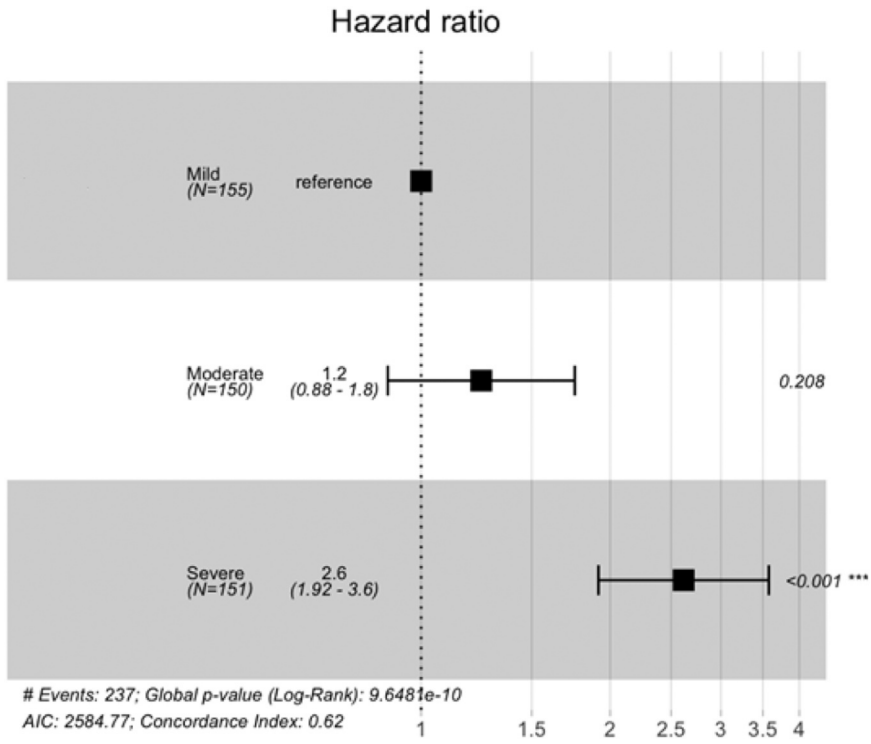

Figure 3 Comparative hazard ratios for moderate and severe mitral regurgitation compared to mild for a composite end-point of all-cause mortality, urgent heart transplantation, or mechanical circulatory support over a follow-up period of 2-12 years.

Pulmonary capillary v-wave correlated more strongly with systolic PA pressure in those with higher TAPSE ($R^2 = 0.703$ in TAPSE > 17 vs $R^2 = 0.528$ in TAPSE < 17).

There was no significant numerical trend for right ventricular stroke work index (RVSWi) to change by severity of MR, although there was a weak correlation between RVSWi and PCWP v-wave ($R^2 = 0.133$, $p < 0.001$). RVSWi had no association with the primary outcome measure, either in the univariate analysis or when divided into quartiles.

RV-PA uncoupling: Echocardiography and invasive data

The association between the primary outcome measure and right ventricular dysfunction, defined by RV-PA uncoupling, was examined. We defined RV-PA uncoupling as a TAPSE/SPAP of less than 0.37 (the median value of TAPSE/SPAP in our data), using invasively measured SPAP. Those with RV-PA uncoupling had significantly reduced event-free survival ($p < 0.001$, Figure 4). This effect was persistent across all MR severity groups (mild MR Figure 4A, $p = 0.003$, moderate MR Figure 4B, $p = 0.001$, severe MR Figure 4C, $p = 0.005$). Using a literature value of 0.4[30] as a cut-off, the outcome was similar. By reciever operator curve analysis, the optimal cutoff point was 0.459, (giving area under the curve of 0.67) which produced similar results, although there were small numbers in the severe MR group and the curves failed to separate.

TAPSE/SPAP was lower in those with elevated right heart pressures (as defined by RA pressure > 10 mm Hg), 0.53 ± 0.245 vs 0.334 ± 0.159, $p < 0.0001$, Figure 5. TAPSE/SPAP showed a negative correlation with RA pressure across all 3 MR severity groups ($R^2 = 0.279$, $p < 0.0001$, Figure 6). The correlation was present in all groups (mild MR group $R^2 = 0.299$, moderate MR group $R^2 = 0.253$) but very weak in the severe MR group ($R^2 = 0.114$).

Taking only patients with RA pressure lower than 10 mm Hg (218 in dataset, 90 with mild MR, 74 moderate, and 54 severe), patients with invasively derived RV-PA uncoupling still had a worse prognosis overall ($p < 0.001$, Figure 7). When subdivided by MR severity, there was no significant difference in those with mild MR (Figure 7A, $p = 0.254$), but moderate MR and severe MR retained significance (moderate Figure 7B, $p = 0.026$, severe Figure 7C, $p = 0.007$).

Looking at patients with elevated left atrial pressures (PCWP > 21 mm Hg), again RV-PA uncoupling was associated with lower event-free survival ($p = 0.001$), although this was not the case for those with low left atrial pressure. The correlation between RA pressure and TAPSE/SPAP, while present, was weak in those with high LA pressure ($R^2 = 0.104$, $p < 0.001$) and very weak in those with low LA pressure ($R^2 = 0.04$, $p = 0.032$).

RV-PA uncoupling: Echocardiography data only

Only 131 cases had complete echocardiographic estimation of SPAP: in many cases, the TR envelope was incomplete, there was inadequate TR to measure velocity or the TR was free-flowing, rendering calculations inaccurate. In some, the

Table 2 Univariate Cox Regression Analysis

Variable	*p*-value	Hazard ratio	Comments
MR moderate	0.208	1.247	
MR severe	1.53*e-09	2.618	
LVIDd	0.00308	1.018	Continuous
LVEF	0.00036	0.9667	Continuous
TAPSE	0.000736	0.9467	Continuous
VO_2 Max	6.18*e-10	0.8921	Continuous
6MWD	0.0107	0.9984	Continuous
TR mild	0.3186	0.7442	
TR moderate	0.2630	0.0194	
TR severe	0.0194	2.0349	
Cardiac Index – TD	1.07*e-11	0.3815	Continuous
Cardiac Index – Fick	1.11*e-09	0.4129	Continuous
RA pressure	3.16*e-15	1.082	Continuous
mPAP	1.19*e-13	1.041	Continuous
PCWP	5.37*e-13	1.052	Continuous
TPG	0.000135	1.047	Continuous
CPO – TD	1.1*e-10	0.1243	Continuous
CPO – Fick	9.17*e-09	0.154	Continuous
RVSWi – TD	0.996	1	Continuous
RVSWi – Fick	0.659	1	Continuous
LVSWi – TD	2.38*e-15	0.9992	Continuous
LVSWi – Fick	1.34*e-13	0.9992	Continuous
TAPSE/SPAP	1.81*e-10	0.2085	Continuous

Abbreviations: 6MWD, 6-minute walk distance; CPO, cardiac power output; LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal dimension in diastole; LVSWi, left ventricular systolic work index; mPAP, mean pulmonary artery pressure; MR, mitral regurgitation; PCWP, pulmonary capillary wedge pressure; RA, right atrial; RVSWi, right ventricular systolic work index; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TD, thermodilution; TPG, transpulmonary gradient; TR, tricuspid regurgitation.

Table 3 Multivariate Cox Regression Analysis

Variable	*p*-value
Left ventricular internal dimension in diastole (LVIDd, cm)	0.022
VO_2 max (ml/min/kg)	0.013
Right atrial pressure (mm Hg)	0.012

inferior vena cava could not be well seen. There were 29 data points available for mild MR, 53 for moderate, and 49 for severe. There was a modest correlation between echo-derived and invasively derived values ($R^2 = 0.309$, $p < 0.001$), with a tendency to over-estimate low PA pressure and under-estimate high PA pressure (equation of line $y = 0.509x + 22.56$).

The median point was 0.288, which was used as a cut-off to define RV-PA uncoupling. Again, this showed a group with significantly impaired survival ($p = 0.006$), although this association was lost in the subgroup with severe MR ($p = 0.461$).

Discussion

The association of secondary MR with adverse prognosis in heart failure and the relationship of this association with MR severity are well established by previous research,[3-5] however, with only limited evidence regarding advanced heart failure.[6]

Our study demonstrates the adverse prognostic impact of secondary MR in advanced heart failure and the importance of grading MR severity in these patients. Moreover, our study refined the assessment of secondary MR, based on current knowledge of mitral valve morphology and MR mechanisms from reference.[2] It is currently known that the 3 types of MR (primary, ventricular-secondary, and atrial-secondary) differ in prognosis and management strategy needs.[2,11] Presence of ventricular-secondary MR was an inclusion criterion for our study. The coexistence of an atrial-secondary component with the ventricular-secondary MR was accepted; however, pure atrial-secondary MR and primary MR were excluded. Ventricular-secondary MR was common in our study; present in more than 50% of patients attending for heart transplant assessment.

For purposes of the study, MR severity was reassessed in all patients following current recommendations,[9,28] updated in the light of recent evidence.[17] Previous European guidelines recommended using a lower threshold to grade secondary MR as severe, compared to primary MR. This lower threshold failed to predict response to specific MR treatment[17] compared to a threshold similar with primary MR,[16] triggering a change in European recommendations.[9] In our study, the severity of ventricular-secondary MR correlated with the risk of death, urgent heart transplantation, or mechanical circulatory support. The association of severe ventricular-secondary MR with adverse outcome was notably stronger than that of mild or moderate MR; this confirms the clinical benefit of grading ventricular-secondary MR using a similar threshold as for primary MR, to clearly distinguish the population at risk.

The strongest predictors of outcome for our patient population were VO_2 max, left ventricular size (LVIDd), and RA pressure. VO_2 max is well known to be a longstanding and robust predictor of benefit from transplant in advanced heart failure[31] and it is unsurprising to find that it is useful in this cohort. The left ventricular size is also a known

Table 4 Kaplan-Meier Survival Estimates in Years (95% Confidence Intervals in Brackets) Based on Left and Right Atrial Pressures

	Pulmonary capillary wedge pressure > 21	Pulmonary capillary wedge pressure < 21
Right atrial pressure > 10	3.62 (2.96-4.27)	5.06 (3.71-6.4)
Right atrial pressure < 10	5.55 (4.31-6.79)	8.02 (7.22-8.82)

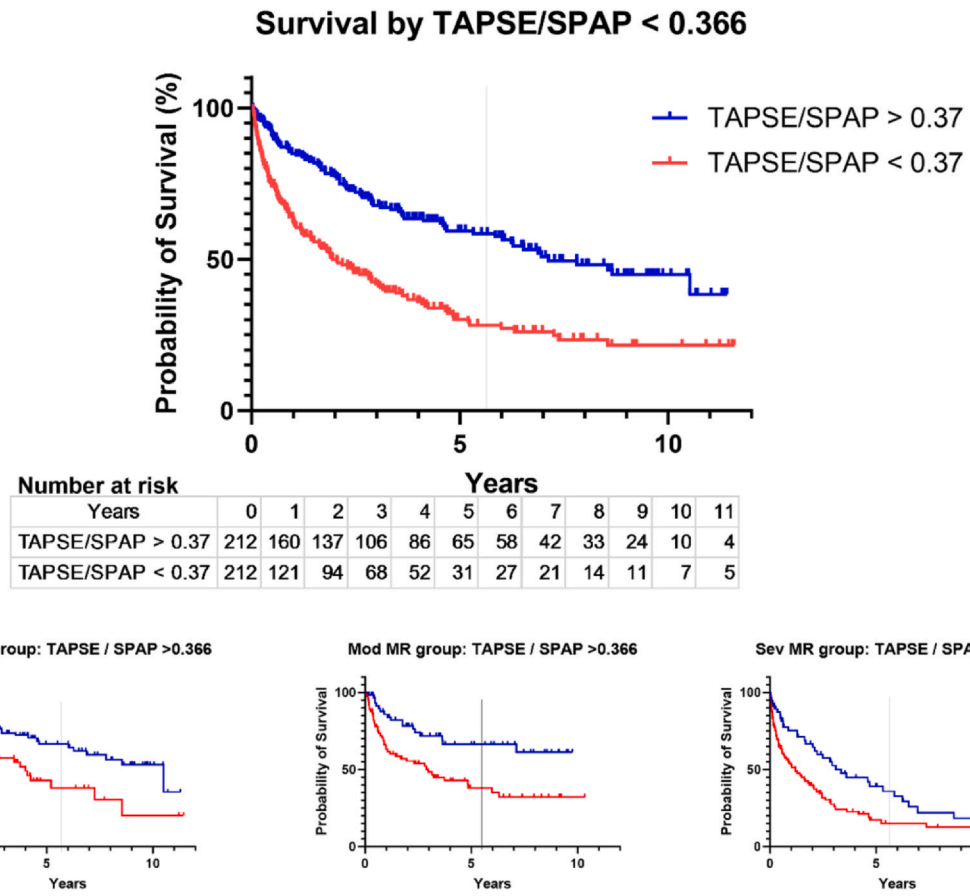

Figure 4 (A) Mild and moderate mitral regurgitation cohorts divided by right ventricular-pulmonary arterial uncoupling, as defined as TAPSE/SPAP of < 0.366. (B-D) Data are shown by mitral regurgitation severity. Black line indicates mean cohort survival of 5.8 years. SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion.

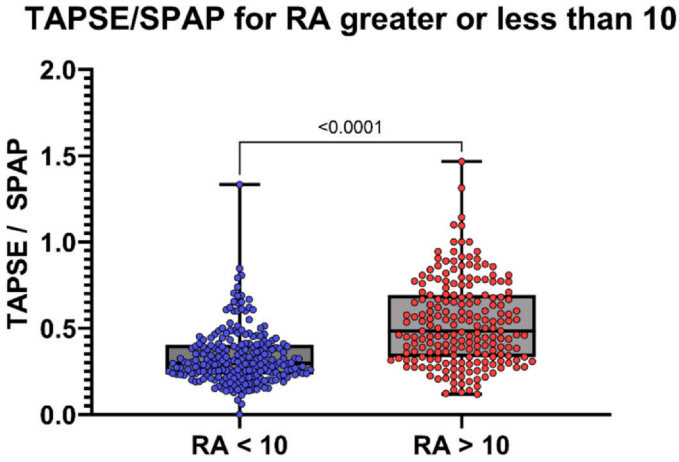

Figure 5 Tricuspid annular plane systolic excursion (TAPSE)/systolic pulmonary arterial pressure (SPAP) in those with and without right heart failure, as defined as right atrial pressure > 10 mm Hg. RA, right atrium.

predictor of adverse outcome in HFrEF[32]; it also correlates with lack of benefit from specific treatment (TEER) of secondary MR.[16,17]

It has been argued elsewhere[9] that ventricular secondary MR's increasing severity is simply a marker of a more dilated and more impaired ventricle rather than an independent marker of dysfunction. LVEDD increased and LVEF decreased in a stepwise fashion between MR groups ($p < 0.001$) hence this study cannot refute this.

Right atrial pressure

RA pressure < 10 mm Hg was a marker for improved survival in HFrEF with mild or moderate ventricular-secondary MR but not with severe MR. This suggests that persistence of severe MR despite effective offloading on optimal GDMT impacts survival. It also suggests that ventricular-secondary MR severity should be assessed following GDMT optimization with invasive measurement of RA pressure to confirm effective offloading. Our results confirm and strengthen current recommendations and guidelines for the assessment[9,28] and for the management[7,11] of secondary MR.

RV-PA uncoupling as a predictor of prognosis

Invasive assessment of intra-cardiac pressures and markers of RV failure, such as RV-PA uncoupling, allowed further risk stratification of ventricular-secondary MR.

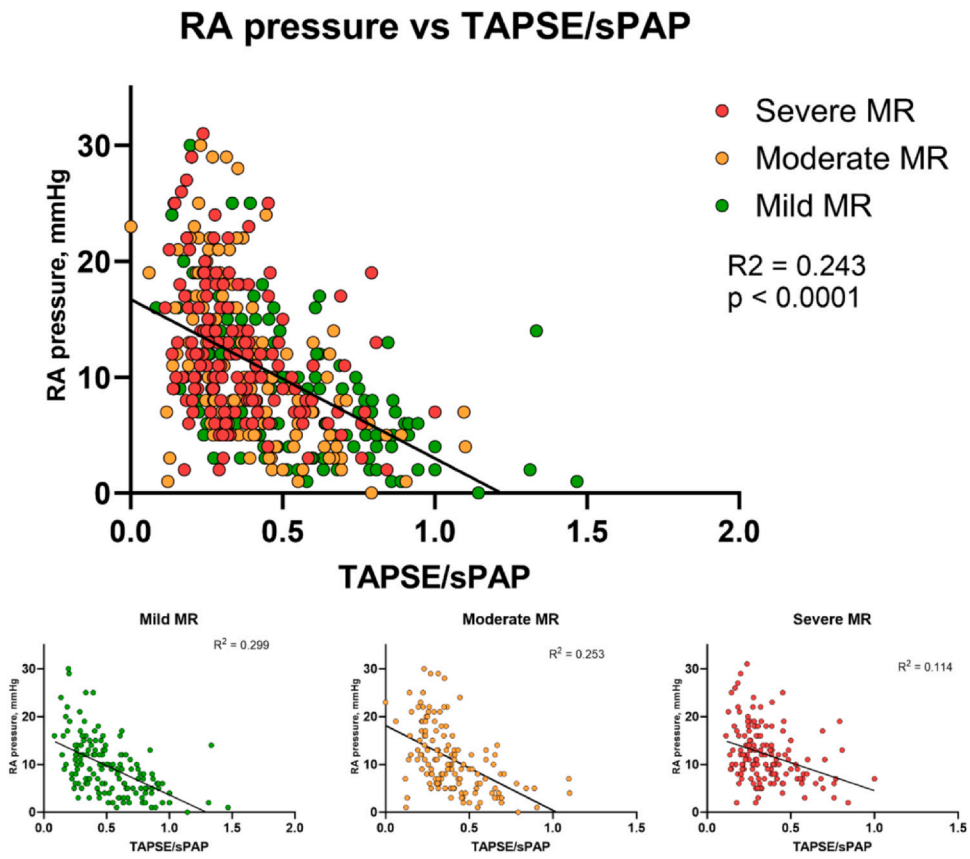

Figure 6 Correlation of tricuspid annular plane systolic excursion (TAPSE)/systolic pulmonary artery pressure (SPAP) against right atrial pressure (mm Hg). MR, mitral regurgitation; RA, right atrium.

RV-PA coupling predicts survival across all severities of MR. In Figure 4D, the Kaplan-Meier curves are seen to converge, but this only occurs after the median survival of the whole group (5.8 years), suggesting this is an effect of small group numbers. Moreover, RA pressure shows a good inverse correlation with TAPSE/SPAP. This suggests that patients with preserved RV-PA coupling have lower RA pressures as a reflection of preserved RV function. In patients with high wedge pressures, RV-PA coupling is protective with lower RA pressures and improved survival.

RV function (determined by TAPSE or RSWI) did not differ by MR severity, which may suggest, as previously proposed,[22] that MR is not a cause for RV function decline.

Our findings suggest that RV-PA uncoupling risk stratifies patients with advanced heart failure and ventricular-secondary MR, being associated with ineffective offloading on GDMT and consequent venous congestion as well as worse outcomes. This is in line with other similar studies, such as analysis of the COAPT data where RV-PA uncoupling was predictive of death or heart failure hospitalization in both the control and the TEER group.[27] Parallels can be also drawn with a growing body of evidence that RV-PA coupling indicates that the right ventricle is able to compensate for SPAP rise in idiopathic pulmonary hypertension and correlates with lower mortality in this condition.[33]

We have treated RV-PA uncoupling as a discrete entity rather than analyzing it as continuous data (although it remains a significant predictor when analyzed with Cox regression ($p < 0.001$ for mild MR, $p = 0.002$ for moderate MR, and $p = 0.005$ for severe MR). One issue is finding the ideal threshold to define RV-PA uncoupling: other studies have used different values and there is no clear ideal number. It seems likely that there is a threshold above which there is normal coupling, below which there is true uncoupling and a transition zone in between.

Benefit of invasive over echocardiographic studies

We show that invasively measured SPAP has superior predictive value compared to noninvasive SPAP estimated from echocardiography. Furthermore, in patients with advanced heart failure, estimation of SPAP based on echocardiography is often not feasible or inaccurate, hence we would recommend RHC to risk stratify these patients. Additionally, RHC consistently provides accurate RA pressure measurements needed to confirm effective offloading on GDMT.

Limitations

Our study performed a retrospective analysis of prospectively collected data for clinical purposes. Analysis was performed at a single point (the time of heart transplant

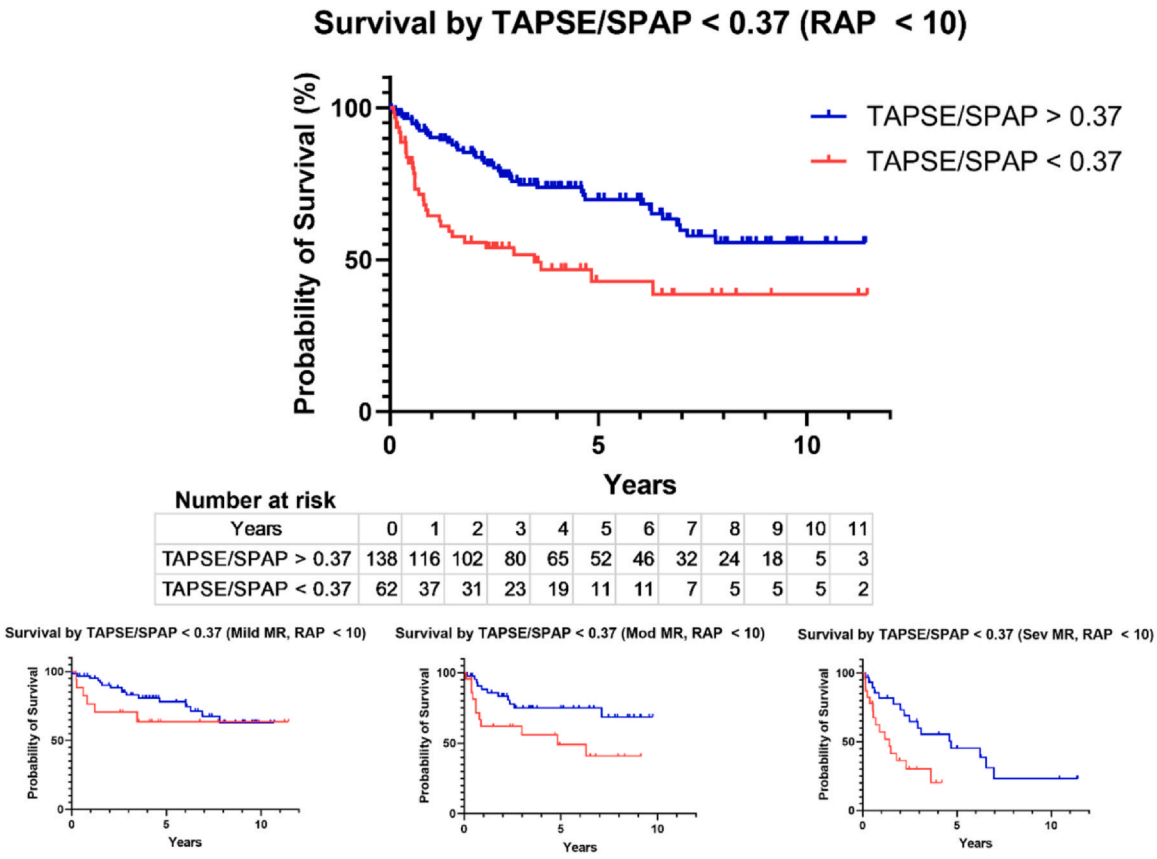

Figure 7 Patients with right atrial pressure less than 10 stratified by right ventricular-pulmonary arterial uncoupling. (B-D) Substratified by mitral regurgitation grade. MR, mitral regurgitation; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion.

assessment) and no longitudinal data are available. Data presented are unadjusted for multiple comparisons. The study is a single-center study. The composite end-point used includes events over which clinicians have some control (institution of mechanical circulatory support).

Conclusions

Ventricular-secondary MR is common in advanced heart failure, and MR severity correlates with the risk of death, mechanical cardiac support, or urgent heart transplantation. Right atrial pressure was a powerful marker of prognosis, emphasizing the need for effective offloading. RV-PA uncoupling confers adverse prognosis across all grades of MR severity, refining risk stratification. Overall, these data present a convincing argument for detailed right ventricular assessment in advanced heart failure patients with secondary MR to guide prognosis, highlighting the role of RHC, which may stratify patients for earlier intervention.

Understanding coupling as the ability of the RV to compensate for rise in SPAP and uncoupling as the threshold at which failure to do so occurs is important for several clinical scenarios. The threshold defining "uncoupling" may vary between those clinical scenarios and attempt to define a single threshold may not be useful. Future research should attempt to establish thresholds specifically for a certain condition, rather than reproduce thresholds found in the literature. Furthermore, future research should include invasive measures to establish those thresholds: a range of factors impact echo estimated SPAP in many clinical scenarios so RHC will produce clearer data, and analysis of pressure-volume loops may help better define the differences between coupling and uncoupling.

Disclosure statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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