

Clinical Research

Novel Prognostic Insights in Multivalvular Disease: The Crucial Role of Right Ventricular–Pulmonary Artery Coupling

Davide Margonato, MD,^{a,b} Eleonora Suvini, MD,^a Giacomo Ingallina, MD,^a Giorgio Fiore, MD,^a Vincenzo Rizza, MD,^a Francesco Ancona, MD,^a Stefano Stella, MD,^a Federico Biondi, MD,^a Monica Barki, MD,^a Ludovica Bognoni, MD,^a Francesco Maisano, MD,^{c,d} Giovanni Benfari, MD,^e Joao L. Cavalcante, MD,^b Maurice Enriquez-Sarano, MD,^b Marco Metra, MD,^{a,d} Yan Topilsky, MD,^f and Eustachio Agricola, MD^{a,d}

^a Cardiovascular Imaging Unit and Cardiology Department, Cardiothoracic Department, IRCCS San Raffaele Scientific Institute, Milan, Italy

^b Cardiovascular Imaging Research Center and Valve Science Center, Minneapolis Heart Institute and Foundation, Minneapolis, Minnesota, USA

^c Cardiac Surgery Unit, Cardiothoracic Department, IRCCS San Raffaele Scientific Institute, Milan, Italy

^d Vita-Salute University San Raffaele, Milan, Italy

^e Section of Cardiology, University of Verona, Verona, Italy

^f Department of Cardiology, Tel Aviv Medical Center, Tel Aviv, Israel

See editorial by Maeder and Rizas, pages 1959–1963 of this issue.

ABSTRACT

Background: To our knowledge, the prognostic role of right ventricular–pulmonary artery coupling (RV-PAC) in the context of multiple valvular heart disease (MVD) has so far not been evaluated. Therefore, in this study we assessed the prognostic role of surrogate of RV-PAC in patients affected by one of the most common MVDs: moderate mitral regurgitation (MR) with concomitant moderate tricuspid regurgitation (TR).

Methods: We collected comprehensive data of patients with coexisting moderate MR and moderate TR at 2 centers between 2014 and 2021. The outcome of interest was all-cause death. RV-PAC was estimated using the tricuspid annular plane systolic excursion/pulmonary artery systolic pressure (TAPSE/PASP) ratio.

Results: In the 905 patients included in our study (median age 78 years, 53% female), the relative hazard of the outcome analysis identified ≤ 0.36 as the TAPSE/PASP threshold associated with a

RÉSUMÉ

Contexte : Le rôle pronostique du couplage ventricule droit-artère pulmonaire (cVD-AP) en présence d'une cardiopathie valvulaire multiple (CPVM) n'a encore jamais été étudié. Nous avons tâché d'évaluer le rôle pronostique d'un marqueur de substitution du cVD-AP chez des patients atteints de l'une des CPVM les plus fréquentes, l'insuffisance mitrale (IM) modérée avec régurgitation tricuspide (RT) modérée concomitante.

Méthodologie : Nous avons recueilli des données exhaustives sur les patients présentant une IM et une RT modérées concomitantes suivis dans deux centres entre 2014 et 2021. Le critère d'évaluation qui nous intéressait était le décès toutes causes confondues, et nous avons estimé le cVD-AP en fonction du rapport entre l'excursion systolique du plan de l'anneau tricuspide et la pression artérielle pulmonaire systolique (ESPA/PAPS).

Résultats : Chez les 905 patients inclus (âge médian de 78 ans, 53 % de femmes), le seuil du rapport ESPA/PAPS associé à un risque > 1 était $\leq$

Keywords: mitral regurgitation; pulmonary artery systolic pressure; right ventricle; tricuspid regurgitation

Corresponding author: Dr Davide Margonato

E-mail: margonato.davide@hsr.it

Linkedin: <https://www.linkedin.com/in/davide-margonato-2a7084173/>

See page 2064 for disclosure information.

Received for publication March 5, 2026. Accepted May 12, 2026.

<https://doi.org/10.1016/j.cjca.2026.05.005>

0828-282X/© 2026 Canadian Cardiovascular Society. Published by Elsevier Inc. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

In the past decade, a large amount of data have emerged confirming the high prevalence of multiple valvular heart disease (MVD), defined as coexisting stenosis or regurgitant lesion affecting at least 2 cardiac valves.^{1–3} Despite being a common and clinically relevant problem, the management of patients with MVD is still a major challenge for clinicians. In fact, due to the hemodynamic interdependence of concomitant valvular lesions, appropriate quantification of each

hazard > 1.0 . At baseline, TAPSE/PASP ≤ 0.36 was associated with worse New York Heart Association class, greater prevalence of atrial fibrillation, and worse remodeling of left- and right-sided chambers (all $P < 0.005$). After a median follow-up of 2.3 years, compared to patients with TAPSE/PASP > 0.36 , those with a low TAPSE/PASP ratio showed significantly worse survival ($P < 0.001$), and TAPSE/PASP ≤ 0.36 remained a powerful predictor of outcome after adjustment for crucial clinical and echocardiographic variables. Finally, the nested Cox regression model showed an incremental prognostic role of TAPSE/PASP compared with its constituents TAPSE and PASP as separate variables (P value of improved model fit = 0.008).

Conclusions: In this large cohort of patients with moderate MR + moderate TR, RV-PAC estimated by TAPSE/PASP was strongly associated with worse baseline clinical presentation and poor long-term prognosis.

valvular disease (VD) severity by echocardiography may be complex. Also, prognostic markers validated in isolated VD have been only marginally assessed in the setting of MVD, where their applicability remains uncertain.⁴ This gap is particularly evident in patients with nonsevere MVD, who represent a large proportion of those with this condition in real-world practice but for whom long-term prognostic data and risk stratification tools are scarce, often leading to delayed recognition and potential undertreatment.¹

The tricuspid annular plane systolic excursion/pulmonary artery systolic pressure (TAPSE/PASP) ratio, a noninvasive echocardiographic surrogate of right ventricular–pulmonary artery coupling (RV-PAC),⁵ was shown to be independently associated with outcome in large cohorts of patients with severe tricuspid and mitral regurgitation (TR and MR, respectively).^{6–8} As TAPSE/PASP captures the interaction between RV contractility and its afterload, this measurement could be crucially associated with the prognosis of MVD patients, but its role in this context has yet to be fully explored.

Importantly, coexisting moderate MR and TR represents one of the most prevalent MVD phenotypes.^{1,4} In this setting, the relative absence of advanced chamber remodeling and the technical limitations that often affect TAPSE/PASP assessment in severe TR may allow this noninvasive index to more reliably reflect the interaction between the RV and the pulmonary circulation driven by the combined hemodynamic burden of both valve diseases. Thus, in this study we aimed to assess the prognostic role of RV-PAC estimated by TAPSE/PASP by focusing on a large cohort of patients with moderate MR and concomitant moderate TR.

Methods

Study population

In this observational, retrospective, multicenter study we included patients referred to clinical echocardiography between January 2014 and June 2021 at 2 quaternary centers:

0,36 d'après l'analyse du risque relatif d'atteindre le critère d'évaluation. Au début de l'étude, un rapport ESPAT/PAPS $\leq 0,36$ était associé à une classe NYHA (New York Heart Association) moins favorable, à une plus grande prévalence de la fibrillation auriculaire et à un moins bon remodelage des cavités gauche et droite (toutes les valeurs $p < 0,005$). Après un suivi médian de 2,3 ans, les résultats relatifs à la survie étaient nettement moins bons chez les patients dont le rapport ESPAT/PAPS était faible par rapport à ceux dont le rapport ESPAT/PAPS était $> 0,36$ ($p < 0,001$); un rapport ESPAT/PAPS $\leq 0,36$ est demeuré un facteur de prédiction puissant après ajustement pour tenir compte de variables cliniques et échocardiographiques essentielles. Enfin, un modèle de régression de Cox emboîté a montré le rôle pronostique différentiel du rapport ESPAT/PAPS par rapport à ses constituants (ESPAT et PAPS) envisagés séparément (valeur p de l'amélioration de l'ajustement du modèle = 0,008).

Conclusions : Dans cette vaste cohorte de patients présentant une IM et une RT modérées, le cVD-AP estimé à l'aide du rapport ESPAT/PAPS a été étroitement associé à un tableau clinique moins bon au départ et à un pronostic défavorable à long terme.

San Raffaele Hospital (Milan, Italy) and Tel-Aviv Medical Center (Tel Aviv, Israel). All patients underwent comprehensive clinical and echocardiographic evaluation and had coexisting moderate MR and TR, as defined by the multiparametric approach recommended by clinical guidelines.^{9,10} The patients also had noninvasive quantification of RV-PAC with TAPSE/PASP ratio and available clinical follow-up data. Exclusion criteria for the study were: 1) any concomitant severe valvular heart disease and 2) history of previous mitral valve (MV) or tricuspid valve (TV) intervention, either surgical or percutaneous.

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by our institutional review boards (LOCOMOTRI study protocol, approved by ethics committees of the San Raffaele Scientific Institute and Tel Aviv Medical Center), and the research reported adhered to **Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)** guidelines. Informed consent provided by the patients allowed for retrospective de-identified data collection.

Clinical evaluation and echocardiography protocol

A complete clinical evaluation for symptoms was performed. Data including functional New York Heart Association (NYHA) class, major comorbidities (summed as Charlson Comorbidity Index [CCI] score), and baseline hemoglobin and renal function were collected. A history of chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate < 60 mL/min per m^2 ; coronary artery disease (CAD) was defined as a history of angiographically documented coronary stenosis $> 50\%$ in a major epicardial vessel; and atrial fibrillation (AF) was defined as any documented history of paroxysmal, persistent, or permanent AF.

All patients were evaluated using complete transthoracic echocardiography (TTE), performed at rest with a commercially available ultrasound system (Vivid E9 and Vivid E95, General Electric Healthcare, Milwaukee, WI, and Epic 7 and IE 33, Philips, Amsterdam, The Netherlands) for

morphologic and functional data according to the corresponding guideline.¹¹ Data were collected from the first available TTE during the designated period of investigation that identified moderate MR and TR patients without exclusion criteria for enrollment and were extracted without alteration or reinterpretation for the study. Quantification of valvular heart disease was performed according to specific guidelines.^{9,10} The constituents of the crucial variable of interest, TAPSE/PASP, were obtained as follows: TAPSE was measured as the maximum apical excursion of the basal right ventricular (RV) free wall segment in systole by M mode, and PASP was estimated by Doppler echocardiography using the modified Bernoulli equation to estimate the RV-right atrial (RA) pressure gradient and adding an estimate of RA pressure, which was estimated based on inferior vena cava size and collapsibility according to current guideline recommendations, acknowledging the intrinsic limitations of this noninvasive approach.^{9,10}

Outcome

The outcome of interest was all-cause death (ACD); follow-up and survival data were extracted from the electronic health records or via phone interview.

Statistical analysis

Normality was assessed using the Shapiro-Wilk test and all continuous variables were non-normally distributed. Therefore, they are presented as median (interquartile range [IQR]) and compared between groups using the Mann-Whitney *U* test. Categorical variables are expressed as count (percent) and were compared using the χ^2 test. Parsimonious models were used to represent the relationships between TAPSE/PASP and the hazard of having the outcome during follow-up: the cutoff value was obtained from the estimated threshold value that exceeded a hazard ratio of 1.0, along with the whole confidence interval (CI), to specifically discriminate normal vs pathologic values in the absence of a reference range in this specific clinical context. Logistic regression analysis was used to identify baseline covariates associated with TAPSE/PASP less than or equal to the pathologic threshold of association with outcome. Survival curves were estimated using the Kaplan-Meier method and compared between TAPSE/PASP groups using a log-rank test. Cox proportional hazards analysis was used to test the excess hazard ratio of TAPSE/PASP as a continuous variable and of patients with TAPSE/PASP under the pathologic threshold (with 95% CI) for the endpoint, and the convention of limiting the number of independent variables to 1 for every 10 events in the adjustment models was followed; adjustment models included variables with a biologically plausible association with outcome, represented in the first clinical model by age, gender, CCI, CKD, CAD, and AF, and in the second echocardiographic model by left ventricular ejection fraction (LVEF), stroke volume indexed (SVi) E/E', left atrial end-systolic volume indexed (LASVi), and right atrial end-systolic area (RAESA). Moreover, nested Cox regression models were built incrementally to assess the adjunctive prognostic role of TAPSE/PASP compared with its constituents (TAPSE and PASP). In cases of a variable

presenting missing values exceeding 5% of the study population, the exact number of patients with available data was reported in the relative table, so no imputation methods were required. Statistical analysis was performed using R version 4.0 in an RStudio environment (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study patients

During the study period, 905 patients met the inclusion criteria and represented our final study population. The baseline characteristics of the entire cohort are reported in [Table 1](#). Median age was 78 (68-85) years (53% female); 327 (36%) patients had a history of CAD and 548 (60%) had a history of CKD. Median CCI was 4.4 (3.0-6.0), and 222 (34%) patients were in NYHA functional class III/IV.

Echocardiographic parameters showed that most patients had mildly reduced LVEF, RV systolic function was normal according to TAPSE, and pulmonary arterial pressures were elevated; median TAPSE/PASP was 0.38 (0.28-0.51) ([Table 1](#)).

TAPSE/PASP prognostic threshold

The observed threshold of TAPSE/PASP ratio for excessive risk of the outcome was ≤ 0.36 ([Fig. 1](#)). When dividing the overall population according to this cutoff, patients with RV-PA uncoupling (TAPSE/PASP ≤ 0.36) were older, less often female, and had a greater frequency of CAD, AF, DM, and CKD vs those with TAPSE/PASP > 0.36 ; moreover, they had higher CCI and lower NYHA functional class ([Table 1](#)). Echocardiographic data showed these patients had worse biventricular systolic function, lower SVi values, larger RA volumes, and higher RA pressures compared to patients with TAPSE/PASP > 0.36 . [Supplemental Table S1](#) presents baseline clinical and echocardiographic characteristics stratified according to MR mechanisms and highlights the expected differences between organic and functional phenotypes.

On multivariable analysis, factors that remained significantly associated with TAPSE/PASP ≤ 0.36 at baseline were AF (odds ratio [OR] 2.11, 95% confidence interval [CI] 1.14-3.89, $P = 0.017$), RAESA (OR 1.04, 95% CI 1.01-1.09, $P = 0.042$), and RA pressure (OR 1.24, 95% CI 1.17-1.31, $P < 0.001$; [Table 2](#)).

Association of TAPSE/PASP with outcome

After a median follow-up of 2.3 [0.8-3.4] years, ACD occurred in 312 (32%) patients; overall, survival was 79% (76%-82%) at 1 year, 69% (66%-73%) at 2 years, and 61% (58%-65%) at 3 years.

During follow-up, occurrence of the outcome was strikingly higher for patients with TAPSE/PASP ≤ 0.36 ([Fig. 2](#)); this result was confirmed both in patients with organic MR ($n = 421$, 46%) and those with functional MR ($n = 484$, 54%; [Supplemental Fig. S1](#)). Univariable and multivariable analysis with comprehensive adjustment clinical and echocardiographic models showed that TAPSE/PASP, as a continuous variable, was significantly associated with higher risk for the outcome (adjusted HR in Model 1 per 0.1

Table 1. Baseline clinical characteristics of the overall population and according to TAPSE/PASP prognostic threshold

	Overall population (n = 905)	TAPSE/PASP > 0.36 (n = 495; 55%)	TAPSE/PASP ≤ 0.36 (n = 410; 45%)	P value
Age (years)	78 (68-85)	77 (67-84)	79 (69-86)	0.010*
BSA (m ²)	1.78 (1.64-1.94)	1.78 (1.63-1.94)	1.79 (1.64-1.93)	0.751
BMI (kg/m ²)	25.1 (23.0-28.1)	25.2 (23.2-28.0)	24.9 (22.9-28.3)	0.619
Gender (female)	478 (53%)	279 (57%)	199 (48%)	0.023*
Hypertension	620 (68%)	335 (67%)	285 (69%)	0.681
Dyslipidemia	397 (44%)	224 (45%)	173 (42%)	0.436
Diabetes mellitus	269 (30%)	124 (25%)	145 (35%)	0.002*
History of CAD	327 (36%)	148 (30%)	179 (43%)	< 0.001*
Prior CABG	29 (3%)	17 (4%)	12 (3%)	0.577
AF	314 (35%)	154 (31%)	160 (39%)	0.027*
CIED	91 (10%)	39 (8%)	52 (13%)	0.040*
CKD	548 (60%)	264 (53%)	284 (69%)	< 0.001*
COPD	59 (7%)	32 (6%)	27 (7%)	0.218
CCI	4.4 (3.0-6.0)	4.0 (3.0-5.0)	5.0 (3.0-6.0)	< 0.001*
NYHA class				< 0.001*
I	284 (31%)	189 (39%)	95 (23%)	
II	399 (44%)	185 (37%)	188 (39%)	
III/IV	222 (24%)	121 (24%)	101 (25%)	
eGFR (mL/min per m ²)	48 (32-66)	55 (37-73)	42 (29-61)	< 0.001*
Hb (g/dL)	11.1 (9.3-12.7)	11.2 (9.4-13.0)	11.0 (9.2-12.3)	0.103
Echocardiographic parameters				
LVEDDi (mm/m ²)	28 (24-32)	28 (24-32)	28 (25-32)	0.915
LVEF (%)	45 (35-60)	55 (40-60)	40 (30-55)	< 0.001*
SVi (mL/m ²)	32 (25-40)	36 (29-44)	28 (23-36)	< 0.001*
SVi ≤ 35 (mL/m ²)	461 (51%)	198 (40%)	263 (63%)	< 0.001*
Average E/e [†]	15 (12-20)	16 (11-20)	15 (13-20)	0.471
LAVi (mL/m ²)	50 (43-66)	50 (42-66)	50 (43-67)	0.866
TAPSE (mm)	18 (15-22)	21 (18-24)	15 (13-18)	< 0.001*
PASP (mm Hg)	48 (38-59)	40 (32-47)	55 (50-69)	< 0.001*
TAPSE/PASP	0.38 (0.28-0.51)	0.50 (0.43-0.64)	0.27 (0.22-0.32)	< 0.001*
RAESA (cm ²)	21 (17-26)	18 (15-22)	23 (19-28)	< 0.001*
RAP (mm Hg)	10 (5-15)	5 (5-10)	15 (10-20)	< 0.001*

Data expressed as median (interquartile range) or as number (%).

AF, atrial fibrillation; BMI, body mass index; BSA, body surface area; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCI, Charlson Comorbidity Index; CIED, cardiac implantable electronic device; CKD, chronic kidney disease, defined as eGFR < 60 mL/min; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; LAVi, left atrial volume indexed; LVEDDi, left ventricular end-diastolic diameter indexed; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; RAESA, right atrial end-systolic area; RAP, right atrial pressure; SVi, stroke volume indexed; TAPSE, tricuspid annular plane systolic excursion.

* Statistically significant.

† n = 595 patients.

TAPSE/PASP increase = 0.83, 95% CI 0.76-0.89, $P < 0.001$; adjusted HR in Model 2 per 0.1 TAPSE/PASP increase = 0.77, 95% CI 0.71-0.82, $P < 0.001$; [Table 3](#)). Furthermore, TAPSE/PASP ≤ 0.36 was a powerful predictor of outcome as compared with TAPSE/PASP > 0.36, in both our adjustment models (adjusted HR in Model 1 = 1.59, 95% CI 1.24-2.05, $P < 0.001$; adjusted HR in Model 2 = 2.04, 95% CI 1.34-3.12, $P < 0.001$; [Table 3](#)).

A sensitivity analysis restricted to patients with preserved LVEF (LVEF ≥ 50%, n = 460, 51%) corroborated similar findings to the entire cohort ([Supplemental Table S2](#)). In an exploratory analysis of the subgroup of 112 patients with follow-up echocardiography available (median time from baseline to follow-up echocardiogram: 776 [526-1489] days), worsening of MR and TR severity was assessed according to baseline TAPSE/PASP status. Patients with TAPSE/PASP ≤ 0.36 (n = 30) showed a numerically higher prevalence of progression to severe TR and MR compared with the 83 patients with TAPSE/PASP > 0.36 (46% and 17% vs 26% and 8%, respectively).

During follow-up, 36 patients underwent mitral or tricuspid intervention: 35 mitral (27 surgical, 8 percutaneous)

and 12 tricuspid (10 surgical, 2 percutaneous) procedures were performed. The proportion of patients undergoing valve intervention was similar between groups stratified by TAPSE/PASP (≤ 0.36 vs > 0.36), with no significant difference (5% vs 3%, $P = 0.454$); TAPSE/PASP ≤ 0.36 and as continuous variable remained associated with outcome, even when accounting for valvular intervention in our adjustment models ([Supplemental Table S3](#)).

Finally, the TAPSE/PASP ratio showed incremental prognostic value in associating with the outcome compared with its constituents, as it improved model fit in a nested regression model including TAPSE and PASP as separate variables (model χ^2 increase = 7, $P = 0.008$; [Fig. 3](#)).

Discussion

In this study we have evaluated for the first time the role of RV-PAC, as assessed by TAPSE/PASP ratio, in a large cohort of MVD patients specifically affected by concomitant moderate MR and TR. The key findings of this multicenter study are ([Central Illustration](#)):

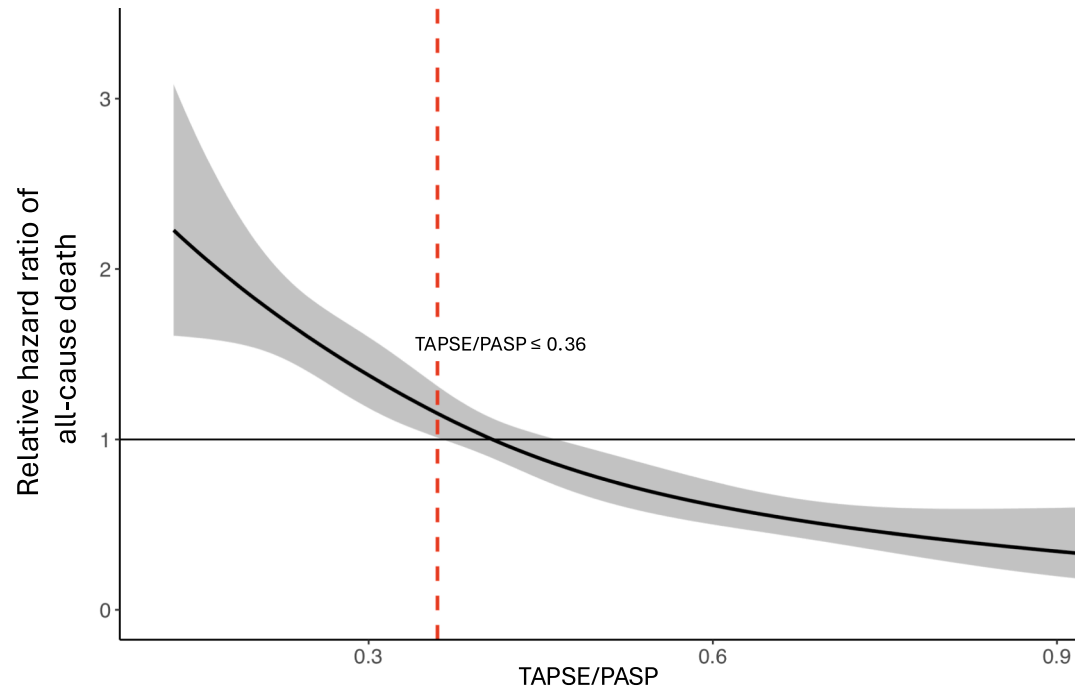


Figure 1. Plot shows the relationships between TAPSE/PASP and the hazard of having the outcome during follow-up: TAPSE/PASP $\leq$ 0.36 exceeded the 1.0 relative hazard for the outcome, along with the whole confidence interval (shaded grey contour). PASP, pulmonary artery systolic pressure; TAPSE, tricuspid annular plane systolic excursion.

- 1 Low TAPSE/PASP was associated with worse baseline clinical status; that is, more comorbidities, worse symptoms, and more advanced cardiac remodeling at presentation.
- 2 At 2 years, the TAPSE/PASP cutoff of $\leq$ 0.36 was strongly associated with worse outcome.
3. This cutoff remained a powerful predictor of outcome, even after comprehensive adjustment for relevant clinical and echocardiographic confounders.
4. The TAPSE/PASP ratio significantly improved the model fit when added to its constituents in our nested model, suggesting a more comprehensive clinical assessment of MVD patients by RV-PAc compared with TAPSE and PASP as single components.

Table 2. Multivariable analysis showing baseline variables associated with TAPSE/PASP $\leq$ 0.36

Parameter	OR (95% CI)	P value
Age	1.00 (0.98-1.03)	0.524
Gender	0.92 (0.53-1.62)	0.800
CAD	1.58 (0.87-2.85)	0.126
DM	1.47 (0.82-2.65)	0.287
CKD	1.08 (0.58-1.99)	0.797
AF	2.11 (1.14-3.89)	0.017*
CCI	1.07 (0.93-1.25)	0.324
LVEF (%)	0.99 (0.97-1.01)	0.462
SVi (mL/m ²)	0.98 (0.95-1.00)	0.091
RAESA (cm ²)	1.04 (1.01-1.09)	0.042*
RAP (mm Hg)	1.24 (1.17-1.31)	< 0.001*

CI, confidence interval; OR, odds ratio (see Table 1 for other abbreviations).

* Statistically significant.

Upon taking all of these findings into account, we have provided the first evidence of the prognostic role of TAPSE/PASP even in the context of MVD, corroborating its systematic measurement for patients with moderate MR and TR.

TAPSE/PASP in the context of MVD

Moderate MR and TR frequently coexist, reflecting the high prevalence of MVD in contemporary practice.^{1,3,4,12} Population-based registries and multicenter surveys have shown that up to one third of patients with significant left-sided VD present concomitant TR, with different etiologies such as degenerative, atrial functional, or postradiation therapy.^{1-3,13-15} The bidirectional hemodynamic interactions between chronic MR and TR establish a vicious circle of pressure and volume overload that ultimately affects biventricular geometry and performance,^{4,16,17} which explains why this specific MVD combination is associated with long-term poor prognosis.¹⁸⁻²⁰ Despite this frequent and clinically relevant association, prognostic markers applicable to patients with MVD remain poorly defined, particularly in the case of nonsevere MVD, and management decisions are often based on the experience on isolated VD rather than on integrated functional assessment.²¹

Within this complex interplay, RV-PAc emerges as a meaningful parameter to capture the balance between RV contractility and its afterload. The TAPSE/PASP ratio, as a noninvasive surrogate of RV-PAc, integrates these hemodynamic forces and provides a unified expression of right-sided adaptation to chronic afterload, thus representing a key marker for risk stratification with established prognostic

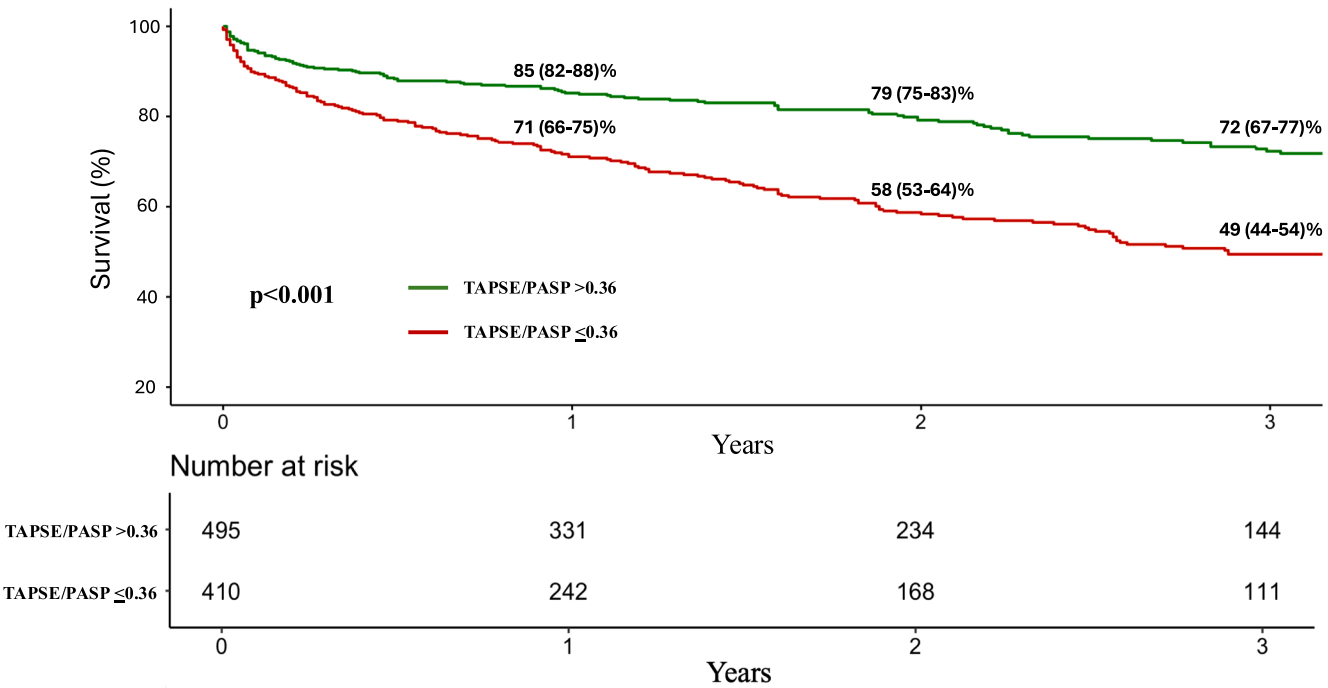


Figure 2. During follow-up, patients with TAPSE/PASP ≤ 0.36 (red line) showed excessive risk of outcome occurrence vs patients with TAPSE/PASP > 0.36 (green line). PASP, pulmonary artery systolic pressure; TAPSE, tricuspid annular plane systolic excursion.

relevance.²² Accordingly, in the specific setting of combined MR and TR, the hemodynamic burden on the RV is not merely additive but synergistic. Chronic MR increases pulmonary venous pressure and may lead to postcapillary pulmonary hypertension, thereby raising RV afterload, whereas concomitant TR promotes progressive right-sided volume overload and RA dilation. The coexistence of these lesions may therefore accelerate RV-PA uncoupling by simultaneously increasing afterload and impairing effective forward flow, creating a distinct pathophysiologic milieu that differs from isolated left- or right-sided VD.

The interpretation of RV-PA uncoupling in this cohort deserves consideration, given the heterogeneity of patients with concomitant moderate MR and TR. In patients with organic MR, a low TAPSE/PASP ratio may identify a subgroup with pulmonary vascular involvement, RV dysfunction, or both, suggesting a more advanced hemodynamic phenotype not solely explained by the mitral lesion. In such cases, correction of MR alone may not fully address the underlying pathophysiology. Conversely, in functional MR, particularly in the setting of AF and/or left ventricular

dysfunction, low TAPSE/PASP may reflect a broader cardiopulmonary syndrome, integrating left-sided dysfunction, postcapillary pulmonary hypertension, and secondary right-sided remodeling. In this context, TAPSE/PASP should be interpreted as a marker of global hemodynamic impairment rather than valve severity alone, with potential implications for risk stratification and clinical management.

Our study has provided a novel perspective by showing that RV-PA uncoupling, represented in this context by the distinct threshold of TAPSE/PASP ≤ 0.36 , is already associated with adverse clinical and echocardiographic characteristics at baseline, even in patients with only moderate MR and TR. Uncoupled patients exhibited more advanced symptom burden, higher NYHA functional class, worse left and right chamber remodeling, and impaired indices of biventricular systolic function. Of note, our optimal prognostic TAPSE/PASP cutoff, which we identified from the value that exceeded an HR for the outcome of 1.0 along with the whole CI, either matched^{23,24} or closely approximated⁶ the prognostic values reported in the literature, supporting its robustness across different clinical settings.

Table 3. Univariable and multivariable hazard ratio of TAPSE/PASP for the outcome

	Univariable model		Multivariable model 1		Multivariable model 2	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
TAPSE/PASP (per 0.1 increment)	0.72 (0.63-0.83)	< 0.001	0.83 (0.76-0.89)	< 0.001	0.77 (0.71-0.82)	< 0.001
TAPSE/PASP > 0.36	Reference		Reference		Reference	
HR, TAPSE/PASP ≤ 0.36	2.13 (1.62-2.59)	< 0.001	1.59 (1.24-2.05)	< 0.001	2.04 (1.34-3.12)	< 0.001

HR, hazard ratio.

Model 1: adjusted on age, gender, CCI, CKD, CAD, and AF; Model 2: adjusted on LVEF, SVi, E/E', LAVi, and RAESA (see Tables 1 and 2 for abbreviations).

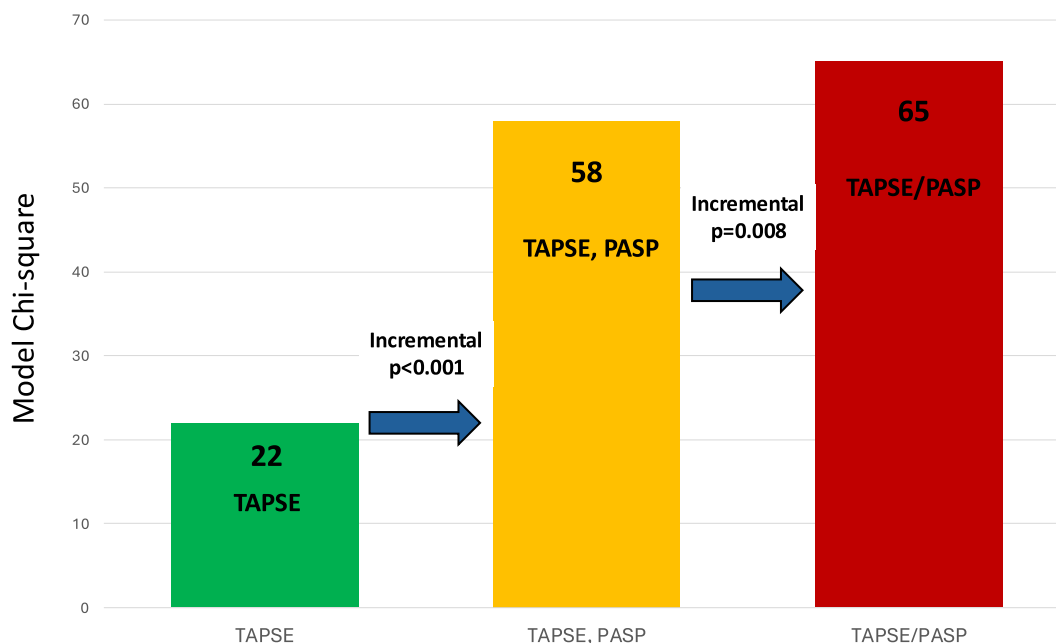


Figure 3. Nested regression models showing the incremental prognostic value of PASP when added to a basal model with TAPSE, and of TAPSE/PASP ratio added on top of a model including its singular constituents, TAPSE and PASP. Note the significant χ^2 change between models. PASP, pulmonary artery systolic pressure; TAPSE, tricuspid annular plane systolic excursion.

Upon multivariable analysis, AF, RAESA, and RA pressure remained significantly associated with low TAPSE/PASP. This pattern is physiologically coherent: AF and RA enlargement and pressure increase represent downstream consequences of the combined mitral-tricuspid burden, both contributing to and reflecting RV-PA uncoupling.

The relatively high prevalence of mildly reduced LVEF in our cohort also deserves consideration. In patients with degenerative MR, this finding may reflect a more advanced disease stage or subclinical myocardial dysfunction not fully captured by MR severity grading. In contrast, in functional MR, reduced LVEF likely represents the underlying myocardial disease and may identify a potential therapeutic target, as optimization of medical therapy and rhythm control could influence both MR severity and overall hemodynamic status. This further highlights the complexity of multivalvular disease, in which conventional severity parameters may be insufficient to describe the global disease burden, whereas integrated measures, such as TAPSE/PASP, may better reflect the global cardiopulmonary interaction and disease stage.^{22,25,26}

TAPSE/PASP and association with outcome

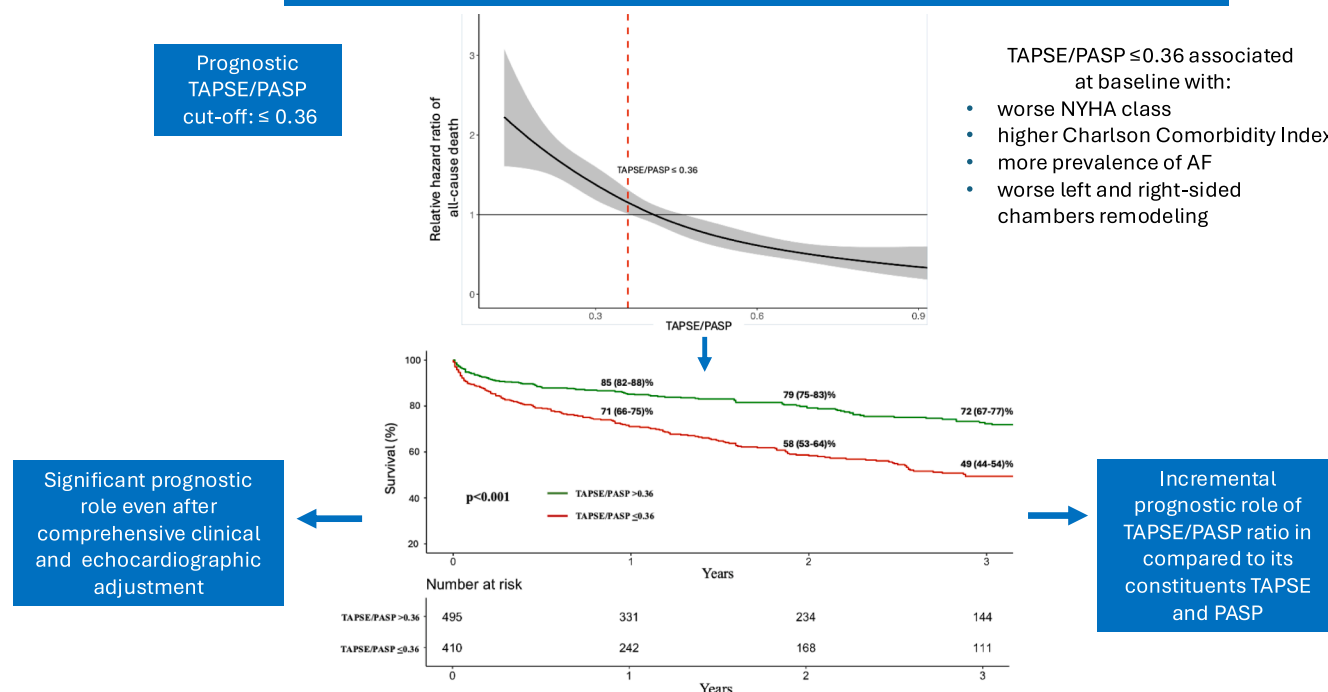
Our outcome analysis further reinforces this interpretation. Accordingly, uncoupled patients experienced significantly higher ACD during follow-up, regardless of MR etiology, and TAPSE/PASP, both as a continuous variable and at ≤ 0.36 , remained associated with outcome after adjustment for relevant clinical and echocardiographic parameters, even when excluding patients with biventricular systolic dysfunction. These findings from a cohort of patients with moderate MR and TR are in line with prior investigations of isolated severe valve disease. In secondary TR,

TAPSE/PASP < 0.31 mm/mm Hg independently predicted mortality,⁶ whereas, among patients with secondary MR enrolled in the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation (COAPT) trial, advanced RV-PA uncoupling identified those at highest risk of death and heart failure hospitalization, irrespective of treatment allocation,⁷ and TAPSE/PASP improvement after mitral edge-to-edge repair was associated with a reduced risk of mortality at roughly 2 years.⁸

Notably, our nested models showed that the integrated representation of contractility and afterload by TAPSE/PASP provided incremental prognostic information over their isolated assessment, confirming even in this specific context that this ratio conveys information not captured by isolated measures of RV contractility or afterload. Although only exploratory, follow-up echocardiographic data available in a subgroup suggested that baseline RV-PA uncoupling may also identify patients with a less favorable valvular trajectory over time.

The findings presented have practical implications. First, routine assessment of TAPSE/PASP could be easily implemented in the echocardiographic evaluation of patients with moderate MR and TR, providing a physiologic complement to regurgitant valve quantification. Identifying RV-PA uncoupling in patients with only moderate regurgitant lesions could help clinicians identify those patients already in a phase of hemodynamic maladaptation and in need of closer monitoring or earlier referral. Second, the coupling approach may refine timing and more appropriate patient selection for invasive treatment: physiologic parameters reflecting global circulatory adaptation, rather than lesion severity alone, may prove more appropriate to guide therapeutic decision-making. Third, TAPSE/PASP could serve

Prognostic role of TAPSE/PASP in 905 patients with concomitant moderate MR and TR



Central Illustration. In a large cohort of patients with concomitant moderate MR and TR, the identified threshold of TAPSE/PASP, which exceeded 1.0, along with the whole confidence interval of the hazard ratio of all-cause death, ≤ 0.36 , was significantly associated with worse clinical presentation and remodeling of both left- and right-sided chambers. This threshold was an independent predictor of outcome, even after comprehensive adjustment modeling, and outperformed its singular constituents, TAPSE and PASP, in associating with outcome in nested Cox models. MR, mitral regurgitation; PASP, pulmonary artery systolic pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

as a dynamic marker to evaluate response to therapy: improvement in coupling after intervention may indicate effective ventricular-arterial realignment and could be explored as a surrogate endpoint in future studies of patients with MVD.

Limitations

This retrospective study had intrinsic design limitations. Although the prognostic role of the TAPSE/PASP ratio has been explored and affirmed in recent years in different clinical contexts, we did not report results on the correlation between our echocardiographic measurement and invasive RV-PaC evaluation. It must be highlighted that TAPSE/PASP, although appealing due to its simplicity and feasibility via TTE, is only a noninvasive surrogate of RV-PaC. Thus, the TAPSE/PASP ratio may introduce compounding errors due to mutual load dependence and measurement inaccuracies. Moreover, we could not provide information on whether our TAPSE/PASP ratio provided the best predictive value compared with other echocardiographic measurements of RV-PaC (such as RV free-wall longitudinal strain/PASP ratio or RV fractional area change/PASP ratio). We also did not report complete data on MR and TR progression/regression during follow-up,

which may be considered another limitation as they may have affected long-term outcome. Furthermore, whether TAPSE/PASP provides prognostic information across different TR etiologies will require further study, as it was outside the scope of the present work. Finally, we could not fully verify whether the deaths were due to cardiovascular causes.

In this study of a large cohort of patients with concomitant moderate MR and TR, RV-PA uncoupling, as assessed by TAPSE/PASP ratio, identified patients at higher risk of events during follow-up, independently of relevant clinical and echocardiographic variables, thus highlighting its crucial prognostic role in this specific MVD combination.

Data Availability

Data sharing may be considered upon reasonable request to the corresponding author.

Ethics Statement

The research reported in this study adhered to STROBE guidelines and the study protocol was performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and approved by the ethics committees of the San Raffaele Scientific Institute and Tel Aviv Medical Center.

Patient Consent

The authors confirm that patient consent is not applicable to this article, as this is a retrospective study using de-identified data; therefore, the institutional review board did not require specific consent from the patients.

Funding Sources

The authors have no funding sources to declare.

Disclosures

The authors have no conflicts of interest to disclose.

References

1. Tribouilloy C, Bohbot Y, Kubala M, et al. Characteristics, management, and outcomes of patients with multiple native valvular heart disease: a substudy of the EURObservational Research Programme Valvular Heart Disease II Survey. *Eur Heart J* 2022;43:2756-66. Erratum in: *Eur Heart J* 2022;43:2813.
2. Andell P, Li X, Martinsson A, et al. Epidemiology of valvular heart disease in a Swedish nationwide hospital-based register study. *Heart* 2017;103:1696-703.
3. Dreyfus J, Komar M, Attias D, et al. Tricuspid regurgitation: frequency, clinical presentation, management and outcome among patients with severe left-sided valvular heart disease in Europe. Insights from the ESC-EORP Valvular Heart Disease II survey. *Eur J Heart Fail* 2024;26:994-1003.
4. Donal E, Unger P, Coisne A, et al. The role of multi-modality imaging in multiple valvular heart diseases: a clinical consensus statement of the European Association of Cardiovascular Imaging of the European Society of Cardiology. *Eur Heart J Cardiovasc Imaging* 2025;26:593-608. Erratum in: *Eur Heart J Cardiovasc Imaging* 2025;26:609. doi:10.1093/ehjci/jeaf075.
5. Tello K, Wan J, Dalmer A, et al. Validation of the tricuspid annular plane systolic excursion/systolic pulmonary artery pressure ratio for the assessment of right ventricular-arterial coupling in severe pulmonary hypertension. *Circ Cardiovasc Imaging* 2019;12:e009047.
6. Fortuni F, Butcher SC, Dietz MF, et al. Right ventricular-pulmonary arterial coupling in secondary tricuspid regurgitation. *Am J Cardiol* 2021;148:138-45.
7. Brener MI, Lurz P, Hausleiter J, et al. Right ventricular-pulmonary arterial coupling and afterload reserve in patients undergoing transcatheter tricuspid valve repair. *J Am Coll Cardiol* 2022;79:448-61.
8. Adamo M, Inciardi RM, Tomasoni D, et al. Changes in right ventricular-to-pulmonary artery coupling after transcatheter edge-to-edge repair in secondary mitral regurgitation. *JACC Cardiovasc Imaging* 2022;15:2038-47.
9. Lancellotti P, Pibarot P, Chambers J, et al. Multi-modality imaging assessment of native valvular regurgitation: an EACVI and ESC Council of Valvular Heart Disease position paper. *Eur Heart J Cardiovasc Imaging* 2022;23:e171-232.
10. Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography developed in collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr* 2017;30:303-71.
11. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015;16:233-70. Erratum in: *Eur Heart J Cardiovasc Imaging* 2016;17:412. doi:10.1093/ehjci/jew041. Erratum in: *Eur Heart J Cardiovasc Imaging* 2016;17:969. doi:10.1093/ehjci/jew124.
12. Mehr M, Karam N, Taramasso M, et al. Combined tricuspid and mitral versus isolated mitral valve repair for severe MR and TR: an analysis from the TriValve and TRAMI registries. *JACC Cardiovasc Interv* 2020;13:543-50.
13. Margonato D, Morosato M, Rizza V, et al. The prevalence, aetiologies, and clinical consequences of tricuspid regurgitation associated with severe degenerative mitral regurgitation. *Eur Heart J Cardiovasc Imaging* 2024;26:150-60.
14. Kagiya N, Mondillo S, Yoshida K, Mandoli GE, Cameli M. Subtypes of atrial functional mitral regurgitation: imaging insights into their mechanisms and therapeutic implications. *JACC Cardiovasc Imaging* 2020;13:820-35.
15. Cutter DJ, Schaapveld M, Darby SC, et al. Risk of valvular heart disease after treatment for Hodgkin lymphoma. *J Natl Cancer Inst* 2015;107:djv008.
16. Grimaldi A, Vermi AC, Pappalardo F, et al. The pivotal role of echocardiography in the assessment of multivalvular heart disease. *Minerva Cardioangi* 2013;61:229-42.
17. Unger P, Clavel MA, Lindman BR, Mathieu P, Pibarot P. Pathophysiology and management of multivalvular disease. *Nat Rev Cardiol* 2016;13:429-40.
18. Essayagh B, Benfari G, Antoine C, et al. The MIDA-Q mortality risk score: a quantitative prognostic tool for the mitral valve prolapse spectrum. *Circulation* 2023;147:798-811.
19. van Wijngaarden AL, Mantegazza V, Hiemstra YL, et al. Prognostic impact of extra-mitral valve cardiac involvement in patients with primary mitral regurgitation. *JACC Cardiovasc Imaging* 2022;15:961-70.
20. Essayagh B, Antoine C, Benfari G, Maalouf J, Michelena HI, Crestanello JA, et al. Functional tricuspid regurgitation of degenerative mitral valve disease: a crucial determinant of survival. *Eur Heart J* 2020;41:1918-29.
21. Praz F, Borger MA, Lanz J, et al. 2025 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2025;46:4635-6.
22. Androschuk V, Long E, Chehab O, et al. The prognostic value of right ventricle-pulmonary artery coupling in valve interventions: systematic review and meta-analysis. *JACC Cardiovasc Interv* 2026;19:174-88.
23. Guazzi M, Bandera F, Pelissero G, et al. Tricuspid annular plane systolic excursion and pulmonary arterial systolic pressure relationship in heart

- failure: an index of right ventricular contractile function and prognosis. *Am J Physiol Heart Circ Physiol* 2013;305:H1373-81.
24. Ghio S, Guazzi M, Scardovi AB, et al. Different correlates but similar prognostic implications for right ventricular dysfunction in heart failure patients with reduced or preserved ejection fraction. *Eur J Heart Fail* 2017;19:873-9.
25. Margonato D, Enriquez-Sarano M, Nishihara T, et al. Quantitative identification of high-risk tricuspid regurgitation by cardiac magnetic resonance. *Circulation* 2025;152:1769-80.
26. Hahn RT, Badano L, Praz F, et al. The last decade in tricuspid regurgitation: how imaging shaped a field. *JACC Cardiovasc Imaging* 2025;18:1013-41.

Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at <https://doi.org/10.1016/j.cjca.2026.05.005>