

Prognostic role of TAPSE to PASP ratio in outpatients with left ventricular systolic dysfunction

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Abstract

Aims Few data are available regarding the role of tricuspid annulus plane systolic excursion to pulmonary artery systolic pressure (TAPSE/PASP), a measurement of right ventricular to pulmonary artery coupling, in patients with chronic heart failure and left ventricular systolic dysfunction.

Methods and results This retrospective single-centre study included outpatients with left ventricular systolic dysfunction (ejection fraction $\leq 50\%$) evaluated between January 2022 and December 2022. TAPSE/PASP was evaluated as a continuous variable and as tertiles according to its value on the first visit. The primary outcome of the study was a composite of all-cause mortality or heart failure (HF) events at the last available follow-up.

Results A total of 642 patients were included (mean age 71 ± 13 years, 78% male, mean left ventricular ejection fraction 40% [interquartile range 35–46]). Patients with lower TAPSE/PASP had more co-morbidities (i.e., atrial fibrillation, chronic kidney disease or previous cardiovascular implantable electronic device), an higher New York Heart Association class ($P < 0.001$), more signs of congestion ($P = 0.007$), and had more probability to receive intravenous furosemide during the visit ($P < 0.001$). After a median follow-up of 474 days [interquartile range 392–507 days], a total of 51 patients (8.0%) died (with 24 patients [3.8%] experiencing cardiovascular-related deaths), a total of 179 patients (28.1%) experienced a composite outcome, and 158 patients (24.8%) had HF events. Kaplan–Meier analysis showed that the estimated 1-year rate of the primary outcome was higher in the lowest tertile (38.0%), as compared with the intermediate (19.6%) and highest tertiles (14.9%; P -value log-rank < 0.001). TAPSE/PASP ratio as a continuous variable was independently associated with the primary outcome (adjusted hazard ratio for 0.1 mm/mmHg increase 0.91, 95% CI 0.84–0.98, $P = 0.009$), predominantly driven by a higher risk of HF events during follow-up. Analysing the impact of TAPSE/PASP tertiles on the primary outcome, an independent association was confirmed at multivariate analysis for the highest versus lowest tertile (adjusted hazard ratio 0.61, 95% CI 0.38–0.99, $P = 0.044$).

Conclusions TAPSE/PASP was independently associated with mortality or HF events among ambulatory patients with left ventricular systolic dysfunction.

Keywords Heart failure; Outpatients; PASP; TAPSE

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Introduction

In patients with chronic heart failure (HF), right ventricular (RV) dysfunction is a powerful prognostic indicator, irrespective of left ventricular (LV) ejection fraction (EF) (LVEF).¹ Invasive haemodynamics assessment is the gold standard to

evaluate RV function, and it also permits to analyse RV-pulmonary artery (RV-PA) coupling, which is the complex set of mechanisms with which the ventricle adapts its performance in response to variations in pressure and compliance of the downstream vessels.^{2,3} However, its clinical applicability is limited by its complexity, invasive nature, and associated

costs. Recently, a novel parameter indicative of RV performance and RV-PA coupling has been introduced, named tricuspid annulus plane systolic excursion to pulmonary artery systolic pressure (TAPSE/PASP) ratio. This parameter can be easily obtained through a standard transthoracic echocardiogram (TTE) and relates the longitudinal shortening of the right ventricle, representing its contractile capacity, to the consequent pressure generated.⁴ Importantly, this parameter was shown to be an independent predictor of mortality in several diseases including acute HF, regardless of LVEF, pulmonary hypertension and pulmonary embolism.^{4–8} Also, in outpatients with LV dysfunction, TAPSE/PASP ratio showed a prognostic impact, but data are limited and come from studies with small samples.^{9–11} For this reason, the objective of this study was to analyse the clinical and prognostic role of the TAPSE/PASP ratio in a cohort of outpatients with LV systolic dysfunction (i.e., LVEF $\leq$ 50%).

Methods

Study design

In this observational, retrospective, single-centre study, a total of 810 consecutive ambulatory patients with TTE-confirmed LVEF $\leq$ 50%, evaluated between January 2022 and December 2022 at the Cardiology Department of our Institute (Spedali Civili di Brescia, Brescia, Italy), were included. Patients were included regardless of the presence of signs and symptoms of congestion and need for diuretic treatment at time of inclusion. Patients with LVEF $>$ 50% and age $<$ 18 years old were not included. For the purposes of the present study, only patients with available data on TAPSE/PASP ratio at the index TTE were included in the final analysis ($n = 634$).

Institutional review board approval was waived for this study because of its retrospective design with collection of anonymized data and without any study-specific intervention. De-identified individual patient data on medical history, clinical presentation, echocardiography and laboratory findings, medical therapy and clinical outcomes were collected. Congestion and perfusion status at clinical presentation was described according to available guidelines and position statements.

Data collection and outcomes

De-identified individual patient data on medical history, clinical presentation, physical examination, medical therapy, echocardiography and laboratory data were recorded. Estimated glomerular filtration rate (eGFR) was calculated with Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

TTE was performed for all patients and the following parameters were collected: LVEF, presence and degree of mitral regurgitation (MR), PASP, TAPSE and inferior vena cava congestion. LVEF was calculated using the biplane Simpson method according to the international guidelines.¹² PASP was measured as the sum of the tricuspid regurgitation (TR) peak gradient at continuous Doppler and estimated right atrial pressure (based on inferior vena cava evaluation). TAPSE was evaluated as the maximum excursion with M-mode at the lateral tricuspid annulus from four-chamber apical view. The TAPSE/PASP ratio was calculated based on the two individual parameters. Information regarding follow-up was collected from review of hospital records, including hospitalizations and follow-up visits, and phone contact.

The primary outcome of the study was a composite of all-cause mortality or HF events (HFE) at the last available follow-up. Secondary outcomes included the two individual endpoints analysed separately. HFE was defined as an hospitalization, an emergency department visit, an urgent care visit, or an outpatient visit due to a primary diagnosis of HF or worsening HF, with need of intensification of therapy for HF, including significant increase of oral diuretics, the introduction or up-titration of intravenous diuretics, any other intravenous therapy for HF or mechanical support.

Statistical analysis

Patients were divided into three groups based on TAPSE/PASP ratio tertiles, and baseline characteristics, medical therapy, and outcomes were compared between these tertiles. Continuous variables are reported as mean $\pm$ SD or median and interquartile range (IQR), as appropriate, and compared using ANOVA or Kruskal–Wallis test, respectively. Categorical variables are reported as frequencies and percentages (%) and were compared using the chi-square test. Pairwise comparisons were also performed to evaluate between-groups differences across the three tertiles (adjusted P -values for multiple comparisons using the Tukey's method).

Kaplan–Meier analysis was performed to assess outcomes at the last available follow-up, and group comparisons were performed using the log-rank test. Univariate and multivariate Cox regression was conducted to evaluate the prognostic impact of the TAPSE/PASP ratio (both as a continuous variable and as tertiles) on the primary and secondary outcomes. At multivariate analyses, the prognostic impact of TAPSE/PASP ratio was adjusted for the following clinically relevant covariates: age, sex, body mass index (BMI), systolic blood pressure, chronic obstructive pulmonary disease, LVEF, and eGFR. Clinically relevant covariates were identified by previous studies.^{13–19} The results of the Cox regression analyses are reported as hazard ratios (HR) with 95% confidence

interval (CI). The continuous association between the risk of the primary endpoint and TAPSE/PASP ratio as a continuous variable was assessed by restricted cubic splines with three knots.

A “*P*-value” less than 0.05 was considered statistically significant. Statistical analyses were performed using STATA software version 16 (STATA Corp., College Station, Texas, USA).

Results

A total of 642 outpatients with LVEF $\leq$ 50% were included in the present study. The patients were stratified into tertiles based on TAPSE/PASP ratio: 222 patients (35%) had a low TAPSE/PASP ratio (<0.60 mm/mmHg, first tertile), 210 patients (33%) had an intermediate TAPSE/PASP ratio (0.60 to 0.90 mm/mmHg, second tertile), and 210 patients (33%) had a high TAPSE/PASP ratio (>0.90 mm/mmHg, third tertile).

Baseline characteristics

The mean age of the study population was 71 ± 13 years, and 502 (78%) patients were male. Patients with lower TAPSE/PASP values were older, had a higher New York Heart Association (NYHA) class and lower BMI compared with the other tertiles (Table 1). Regarding co-morbidities, patients with lower TAPSE/PASP were more commonly affected by atrial fibrillation, chronic kidney disease and they had more history of percutaneous valve interventions or implantation of cardiac electronic devices. These patients also had more frequently an HF hospitalization in the previous year than the others and more signs of congestion (orthopnoea and peripheral oedema) than those in the intermediate tertile (Table 1).

Medical therapy at the end of the first visit varied among the tertiles (Table 2). Angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), and angiotensin receptor-neprilysin inhibitors (ARNi) were less prescribed in the lowest TAPSE/PASP tertile. On the other hand, sodium-glucose co-transporter 2 inhibitors (SGLT2i) were more frequently prescribed in the lowest tertile than the highest tertile. Loop diuretics were prescribed more frequently in the lowest tertile than in the other groups, whereas use of mineralocorticoid receptor antagonists (MRA) was significantly higher in the intermediate versus highest tertile.

The median LVEF in the overall population was 40% (IQR 35%–46%), being lower in the patients with TAPSE/PASP <0.60 mm/mmHg (37% vs. 40% and 44%). Moreover, patients in the lowest tertile presented more dilated left atrial

dimensions and higher LV filling pressures (Table 3). The lowest TAPSE/PASP tertile had a higher prevalence of severe MR, RV dilation, dysfunction and severe TR (all $P < 0.001$).

Regarding laboratory data, significant differences were reported in renal function, NT-proBNP and haemoglobin levels among tertiles (Table 3). In particular, the lowest tertile exhibited lower eGFR, higher creatinine and urea levels, and higher NT-proBNP values.

Clinical outcomes

After a median follow-up of 474 days (IQR 392–507 days), a total of 51 patients (8.0%) died, with 24 patients (3.8%) experiencing cardiovascular -related deaths. Additionally, 158 patients (24.8%) had HFE, and a total of 179 patients (28.1%) experienced a composite outcome (death or HFE).

Kaplan–Meier analysis, as illustrated in Figure 1, reported the cumulative incidence of the primary outcome across the three TAPSE/PASP tertiles. The estimated 1-year rate of the primary outcome was higher in the lowest tertile (38.0%), as compared with the intermediate (19.6%) and highest tertiles (14.9%; *P*-value log-rank <0.001). The same was observed for the Kaplan–Meier estimated 1-year rates of the two individual secondary outcomes (Figures 2 and 3).

As shown in Table 4, the prognostic impact of TAPSE/PASP ratio as a continuous variable on the primary outcome was confirmed by both univariable and multivariable Cox regression analyses (adjusted HR for 0.1 mm/mmHg increase 0.91, 95% CI 0.84–0.98, $P = 0.009$). Figure 4 shows the relationship between the risk of the primary endpoint (HR relative to a minimum TAPSE/PASP value of 0.20 mm/mmHg) and TAPSE/PASP ratio as a continuous variable, highlighting a non-linear association (*P*-value for non-linearity = 0.002) with progressively lower risk of the primary endpoint at increasing TAPSE/PASP values. Analysing the impact of TAPSE/PASP tertiles on the primary outcome at univariable analyses, both the intermediate and highest tertiles were associated with a lower risk as compared to the lowest tertile. However, this result was confirmed only for the highest vs. lowest tertile at multivariable analyses (adjusted HR for highest vs. lowest tertile 0.61, 95% CI 0.38–0.99, $P = 0.044$; adjusted HR for intermediate vs. lowest tertile 0.68, 95% CI 0.44–1.04, $P = 0.073$). Regarding secondary outcomes (Table 4), a significant impact of TAPSE/PASP on all-cause mortality was shown at univariable analyses, but not confirmed at multivariable analyses. The significant association between TAPSE/PASP as a continuous variable and first HFE was confirmed at both univariable and multivariable analyses (adjusted HR for 0.1 mm/mmHg increase 0.91, 95% CI 0.84–0.98, $P = 0.013$). Conversely, only a non-significant trend towards a lower risk of HFE in the highest vs. lowest tertile was observed at multivariable analysis (adjusted $P = 0.063$).

Table 1 Baseline characteristics and clinical presentation according to tricuspid annular plane systolic excursion (TAPSE) /pulmonary artery systolic pressure (PASP) tertiles

	All patients (N = 642)	Low TAPSE/PASP (N = 222)	Intermediate TAPSE/PASP (N = 210)	High TAPSE/PASP (N = 210)	P-value
Baseline characteristics					
Age (years)	71 ± 13	74 ± 12	70 ± 12	68 ± 13	0.678
Male sex (%)	502 (78)	166 (75)	167 (80)	169 (81)	0.270
BMI (kg/m ²)	26 [23–29]	25 [23–29]	26 [23–28]	26 [24–30]	0.001
SBP (mmHg)	123 ± 17	121 ± 16	124 ± 17	126 ± 19	0.188
DBP (mmHg)	76 ± 10	75 ± 10	76 ± 10	77 ± 10	0.824
Heart rate (b.p.m.)	70 ± 12	72 ± 14	67 ± 10	69 ± 11	<0.001
Smoking habit (%)					0.103
Active	60 (9)	16 (7)	25 (12)	19 (9)	
Former	100 (16)	29 (13)	42 (20)	29 (14)	
Hypertension (%)	396 (62)	152 (69)	123 (60)	121 (59)	0.056
Dyslipidaemia (%)	321 (50)	111 (50)	115 (55)	95 (46)	0.227
Diabetes (%)	216 (34)	81 (37)	64 (31)	71 (35)	0.425
PAD (%)	59 (9)	23 (10)	15 (7)	21 (10)	0.433
Previous stroke/TIA (%)	73 (11)	28 (13)	25 (12)	20 (10)	0.632
AF (%)	313 (49)	148 (67)	91 (43)	74 (36)	<0.001
Previous MI (%)	259 (41)	88 (40)	93 (44)	78 (38)	0.403
CAD (%)	316 (50)	110 (50)	109 (52)	97 (47)	0.646
Previous PCI (%)	243 (38)	77 (35)	89 (42)	77 (38)	0.294
Previous CABG (%)	73 (11)	38 (17)	23 (11)	12 (6)	0.004
Any valve surgery (%)	56 (9)	24 (11)	17 (8)	15 (7)	0.354
Previous valve surgery					0.261
MV repair (%)	12 (2)	5 (2)	5 (2)	2 (1)	
MV replacement (%)	16 (3)	5 (2)	6 (3)	5 (2)	
AV replacement (%)	22 (3)	13 (6)	6 (3)	3 (2)	
Any PVI	56 (9)	24 (11)	17 (8)	15 (7)	0.372
Previous PVI					<0.001
MitraClip™	45 (7)	29 (13)	11 (5)	5 (2)	
TAVR	8 (1)	6 (3)	2 (1)	0 (0)	
Previous myocarditis (%)	18 (3)	2 (1)	9 (4)	7 (3)	0.087
Previous device implantation					<0.001
PM (%)	74 (12)	30 (14)	26 (13)	18 (9)	
ICD (%)	138 (22)	47 (21)	56 (27)	35 (17)	
CRT-D (%)	131 (21)	68 (31)	37 (18)	26 (13)	
CRT-P (%)	15 (2)	8 (4)	4 (2)	3 (2)	
Any CIED (%)	364 (57)	154 (70)	123 (59)	87 (41)	<0.001
COPD (%)	70 (11)	30 (14)	19 (9)	21 (10)	0.367
CKD (%)	217 (34)	105 (48)	62 (30)	50 (24)	<0.001
Dialysis (%)	8 (1)	4 (2)	3 (1)	1 (1)	0.456
History of cancer (%)	138 (22)	55 (25)	38 (18)	45 (22)	0.308
Depression (%)	26 (4)	11 (5)	11 (5)	4 (2)	0.170
Dementia					0.336
Mild impairment (%)	14 (2)	7 (3)	2 (1)	5 (2)	
Severe impairment (%)	3 (1)	0 (0)	2 (1)	1 (1)	
Clinical presentation					
De novo HF (%)	30 (5)	7 (3)	9 (4)	14 (7)	0.198
Previous HF hospitalization in the last year (%)	161 (25)	77 (35)	46 (22)	38 (18)	<0.001
Numbers of HF hospitalization in the last year					0.004
0 (%)	481 (77)	145 (68)	164 (79)	172 (83)	
1 (%)	114 (18)	46 (22)	40 (20)	28 (14)	
2 (%)	22 (4)	14 (7)	2 (1)	6 (3)	
3 (%)	8 (1)	5 (2)	2 (1)	1 (1)	
4 (%)	2 (0)	2 (1)	0 (0)	0 (0)	
NYHA class					<0.001
I (%)	299 (47)	70 (32)	109 (52)	120 (59)	
II (%)	273 (43)	114 (52)	93 (44)	66 (32)	
III (%)	58 (9)	33 (15)	8 (4)	17 (8)	
IV (%)	6 (1)	4 (2)	0 (0)	2 (1)	
NYHA class III–IV (%)	64 (10)	37 (17)	8 (4)	19 (9)	<0.001
Peripheral oedema (%)	112 (18)	49 (22)	23 (11)	40 (20)	0.007
Orthopnoea (%)	11 (2)	8 (4)	1 (1)	2 (1)	0.027
Rales > 1/3 lung fields (%)	17 (3)	9 (4)	4 (2)	4 (2)	0.284
IV diuretics (%)	39 (6)	28 (13)	5 (2)	6 (3)	<0.001

AF, atrial fibrillation; AV, aortic valve; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CIED, cardiac implantable electronic device; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT-D/P, cardiac resynchronization therapy – defibrillator/pacemaker; DBP, diastolic blood pressure; HF, heart failure; ICD, implantable cardiac defibrillator; IV, intra-venous; MI, myocardial infarction; MV, mitral valve; NYHA, New York Heart Association; PAD, peripheral arteries disease; PASP, pulmonary artery systolic pressure; PCI, percutaneous coronary intervention; PM, pace-maker; PVI, percutaneous valve intervention; SBP, systolic blood pressure; TAPSE, tricuspid annular plane systolic excursion; TAVR, transcatheter aortic valve replacement; TIA, transient ischaemic attack.

Discussion

Our observational, retrospective, single-centre study demonstrates that TAPSE/PASP ratio is independently associated with an increased risk of all-cause mortality or HFE in outpatients with LVEF $\leq 50\%$. The association between TAPSE/PASP ratio and adverse prognosis was confirmed both when assessing it as a continuous variable and also when stratifying patients based on tertiles of this ratio. The prognostic impact on the primary outcome was predominantly driven by a higher risk of HFE during the follow-up.

RV-PA uncoupling connotes an advanced stage of disease progression in left-sided heart disease, since it is indicative of a failure of the compensatory phase during which the right ventricle tries to adapt by increasing its contractility to compensate for the excess afterload and maintain pulmonary circulation. Although it could be hypothesized that RV dysfunction and RV-PA uncoupling are secondary and closely related to left HF,²⁰ previous studies have shown that RV dysfunction is not simply a consequence of increased afterload and passive congestion resulting from LV dysfunction, but it repre-

sents a more complex sign of left-sided HF, independent of LVEF, involving common biventricular myocardial processes.²¹

The TAPSE/PASP ratio is a reliable and non-invasive parameter for assessing the RV-PA coupling. Guazzi *et al.* proposed this method for estimating the RV capacity to develop contractile force based on longitudinal shortening and coupling it with the PA pressure, demonstrating its strong and independent predictive value for mortality.²² Ghio *et al.* showed that patients with PASP ≥ 40 mmHg plus TAPSE ≤ 14 mm had a poorer survival (adjusted HR 4.27, 95% CI 3.45–7.43, $P < 0.001$) than those with high PASP but preserved TAPSE; moreover, RV dysfunction associated with normal PASP did not carry additional risks.²³ Other studies have further validated this echocardiographic parameter by comparing it with invasive measurements obtained during cardiac catheterization, confirming its utility as a prognostic indicator.^{4,7} In the various clinical studies a substantial heterogeneity in the definition of RV-PA uncoupling was observed, with suggested TAPSE/PASP cut-off values varying from 0.27 to 0.58 mm/mmHg,²⁴ while in our population we

Table 2 Medical therapy at the end of the first visit according to tricuspid annular plane systolic excursion (TAPSE) /pulmonary artery systolic pressure (PASP) tertiles

	All patients (N = 642)	Low TAPSE/PASP (N = 222)	Intermediate TAPSE/PASP (N = 210)	High TAPSE/PASP (N = 210)	P-value
Beta-blocker (%)	592 (93)	207 (93)	196 (93)	189 (93)	0.956
ACEi (%)	160 (25)	44 (20)	46 (22)	70 (34)	0.001
ARB (%)	70 (11)	17 (8)	30 (14)	23 (11)	0.088
ARNI (%)	238 (37)	80 (36)	94 (45)	64 (31)	0.040
ARNI/ACEi/ARB (%)	466 (73)	141 (64)	169 (81)	156 (77)	<0.001
MRA (%)	400 (63)	146 (66)	141 (67)	113 (55)	0.026
Ivabradine (%)	24 (4)	9 (4)	6 (3)	9 (4)	0.683
SGLT2i					0.005
Dapagliflozin (%)	133 (21)	62 (28)	45 (22)	26 (13)	
Empagliflozin (%)	40 (6)	14 (6)	15 (7)	11 (5)	
Loop-diuretic					<0.001
Furosemide (%)	428 (67)	196 (88)	127 (61)	105 (52)	
Torsemide (%)	7 (1)	4 (2)	1 (1)	2 (1)	
Thiazide					0.680
Hydrochlorothiazide (%)	10 (2)	3 (1)	4 (2)	3 (2)	
Metolazone (%)	1 (1)	1 (1)	0 (0)	0 (0)	
Other (%)	1 (1)	1 (1)	0 (0)	0 (0)	
Loop-diuretic dose (mg)	69 $\pm$ 124	109 $\pm$ 150	53 $\pm$ 112	42 $\pm$ 86	<0.001
Beta-blocker dose (fraction of the target dose - %)	60 $\pm$ 50	60 $\pm$ 40	60 $\pm$ 40	60 $\pm$ 80	0.829
ARNI/ACEi/ARB dose (fraction of the target dose, %)	40 $\pm$ 40	30 $\pm$ 30	50 $\pm$ 40	40 $\pm$ 40	<0.001
MRA dose (fraction of the target dose, %)	50 $\pm$ 60	50 $\pm$ 60	50 $\pm$ 50	50 $\pm$ 60	0.415

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; MRA, mineralocorticoid receptor blocker; PASP, pulmonary artery systolic pressure; SGLT2i, sodium/glucose cotransporter 2 inhibitor; TAPSE, tricuspid annular plane systolic excursion.

Table 3 Baseline echocardiographic and laboratory data according to tricuspid annular plane systolic excursion (TAPSE) /pulmonary artery systolic pressure (PASP) tertiles

	All patients (N = 642)	Low TAPSE/PASP (N = 222)	Intermediate TAPSE/PASP (N = 210)	High TAPSE/PASP (N = 210)	P-value
Echocardiographic data					
Left ventricular ejection fraction (%)	40 [35–46]	37 [30–45]	40 [35–47]	44 [38–48]	<0.001
LV end-diastolic volume (mL)	134 [95–180]	145 [93–188]	140 [101–180]	112 [89–157]	0.006
LV end-diastolic diameter (mm)	59 [54–64]	60 [54–66]	59 [55–64]	58 [53–63]	0.049
Left atrial volume (mL)	85 [62–115]	109 [80–140]	75 [60–101]	70 [55–92]	<0.001
Left atrial diameter (mm)	45 [40–50]	49 [44–55]	44 [40–49]	42 [39–47]	<0.001
Diastolic pattern					<0.001
Normal	40 (67)	9 (4)	18 (9)	13 (7)	
Impaired relaxation	318 (52)	59 (27)	124 (61)	135 (68)	
Intermediate	42 (9)	19 (9)	13 (6)	10 (5)	
Restrictive	36 (6)	23 (10)	6 (3)	7 (4)	
Mitral regurgitation grade					<0.001
No/trivial (%)	27 (4)	7 (3)	7 (3)	13 (7)	
Mild (%)	205 (33)	29 (13)	89 (42)	87 (44)	
Moderate (%)	299 (47)	123 (55)	86 (41)	90 (45)	
Moderate/severe (%)	36 (6)	15 (7)	17 (8)	4 (2)	
Severe (%)	64 (10)	48 (22)	11 (5)	5 (3)	
Aortic stenosis grade					0.944
No/trivial (%)	533 (85)	189 (86)	175 (83)	169 (85)	
Mild/sclerosis (%)	84 (13)	27 (12)	31 (15)	26 (13)	
Moderate (%)	11 (2)	4 (2)	4 (2)	3 (2)	
Severe (%)	2 (0)	1 (1)	0 (0)	1 (1)	
Aortic regurgitation grade					0.184
No/trivial (%)	291 (46)	87 (40)	103 (49)	101 (51)	
Mild (%)	235 (37)	90 (41)	78 (37)	67 (34)	
Moderate (%)	98 (16)	43 (20)	27 (13)	28 (14)	
Severe (%)	5 (1)	1 (1)	2 (1)	2 (1)	
Right ventricular dilatation	141 (22)	89 (40)	31 (15)	21 (11)	<0.001
Right ventricular dysfunction	72 (12)	58 (26)	14 (7)	0 (0)	<0.001
Tricuspid regurgitation grade					<0.001
No/trivial (%)	75 (12)	3 (1)	19 (9)	53 (27)	
Mild (%)	289 (46)	58 (26)	121 (58)	110 (56)	
Moderate (%)	201 (32)	114 (52)	61 (29)	26 (13)	
Severe (%)	57 (9)	41 (19)	8 (4)	8 (4)	
TAPSE (mm)	20 [19–22]	18 [17–20]	20 [19–22]	21 [20–24]	<0.001
TAPSE/PASP (mm/mmHg)	0.7 [0.5–1]	0.5 [0.4–0.6]	0.7 [0.7–0.8]	1 [1–1.1]	<0.001
PASP (mmHg)	30 [20–35]	40 [35–45]	30 [25–30]	20 [20–20]	<0.001
Inferior vena cava diameter (mm)	17 [16–18]	18 [17–21]	17 [16–18]	17 [16–18]	<0.001
Central venous pressure (mmHg)	5 [5–5]	5 [5–10]	5 [5–5]	5 [5–5]	<0.001
Laboratory data					
eGFR < 30 mL/min/1.73 mg	77 (14)	43 (22)	20 (11)	14 (8)	<0.001
eGFR – CKD-EPI (mL/min/1.73 mg)	56 [38–75]	46 [33–64]	57 [44–81]	63 [44–81]	<0.001
Creatinine (mg/dL)	1.2 [1–1.6]	1.4 [1–1.9]	1.1 [0.9–1.5]	1.1 [0.9–1.5]	<0.001
Urea (mg/dL)	34 [27–55]	41 [32–72]	33 [27–55]	30 [25–35]	0.001
NT-proBNP (pg/mL)	1821 [636–3906]	2410 [1278–5165]	956 [317–2534]	922 [282–2899]	<0.001
Haemoglobin (g/dL)	14 [12–15]	13 [12–15]	14 [13–15]	14 [12–15]	0.002
Haematocrit (%)	41 [36–44]	40 [36–44]	42 [38–45]	42 [36–44]	0.103
Platelets (10 ⁹ /L)	209 [163–250]	200 [150–244]	210 [173–250]	224 [175–265]	0.017
Sodium (mmol/L)	139 [137–141]	139 [137–141]	139 [137–140]	138 [137–140]	0.018
Potassium (mmol/L)	4.3 [4–4.6]	4.3 [4–4.6]	4.3 [4.1–4.7]	4.2 [4–4.6]	0.353
Chloride (mmol/L)	100 [99–100]	100 [99–100]	100 [99–100]	100 [99–100]	0.873
AST (U/L)	25 [20–32]	24 [18–31]	25 [20–34]	25 [20–32]	0.493
ALT (U/L)	25 [18–32]	24 [17–32]	27 [19–35]	26 [20–32]	0.079
Total Bilirubin (mg/dL)	0.8 [0.6–0.9]	0.8 [0.6–0.9]	0.8 [0.6–1]	0.7 [0.6–0.9]	0.183
INR	1.2 [1–2]	1.2 [1.1–2]	1.1 [1–2.1]	1.1 [1–2]	0.114

ALT, alanine amino-transferase; AST, aspartate amino-transferase; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate; INR, international normalized ratio; NT-proBNP, N-terminal pro brain natriuretic peptide; PASP, pulmonary artery systolic pressure; TAPSE, tricuspid annular plane systolic excursion; TAVR, transcatheter aortic valve replacement.

identified a ratio below 0.60 mm/mmHg as associated with worse outcome. In our study, the patients in the lowest TAPSE/PASP tertiles had more HF hospitalizations in the

previous year, lower LVEF, a greater prevalence of severe MR, and had more frequently chronic kidney disease, as previously reported.^{9,10} Haemoglobin levels are lower in the

Figure 1 Kaplan–Meier analysis describing the cumulative incidence of the primary outcome (all-cause death or HF event) across the three tertiles of TAPSE/PAPS. HF, heart failure; PAPS, pulmonary artery systolic pressure; TAPSE, tricuspid annulus plane systolic excursion.

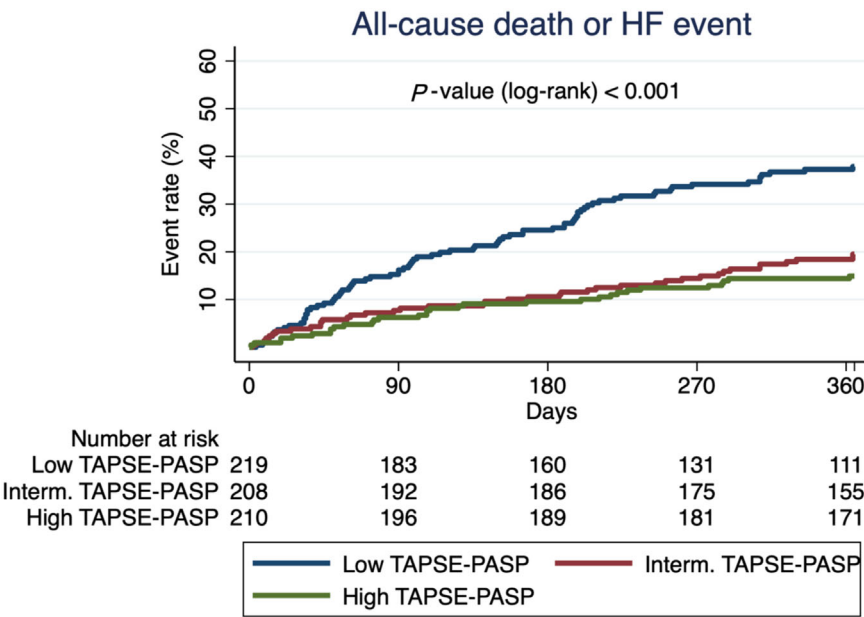
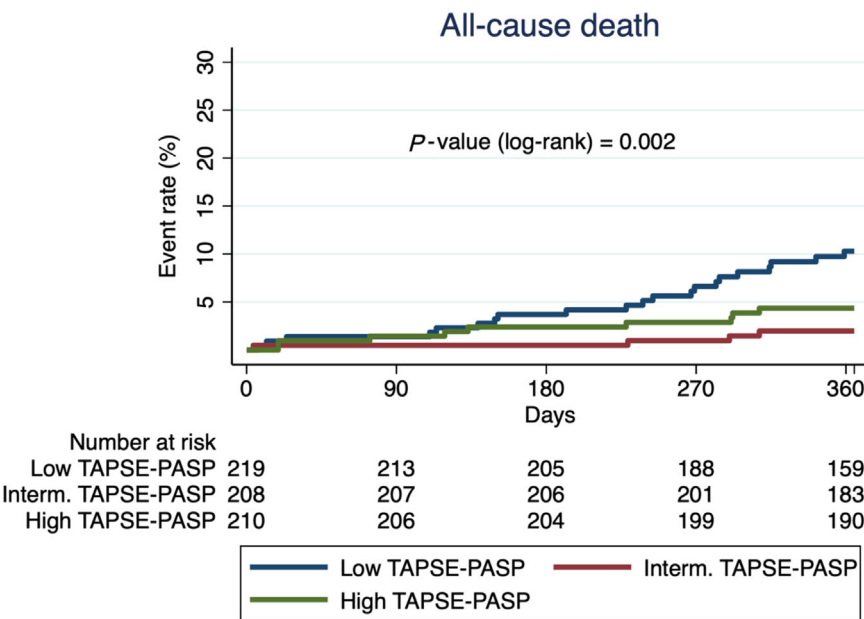


Figure 2 Kaplan–Meier analysis describing the cumulative incidence of the secondary outcome all-cause death across the three tertiles of TAPSE/PAPS. PAPS, pulmonary artery systolic pressure; TAPSE, tricuspid annulus plane systolic excursion.



lowest tertile, highlighting that these patients are more co-morbid and fragile.²⁵

Our study shows that TAPSE/PASP ratio has a significant prognostic impact for the composite outcomes of death and HFE in outpatients with LV systolic dysfunction, defined as LVEF ≤50%. These data confirm previous analyses in patients

with chronic HF, although we used a higher cut-off to identify patients with RV-PV uncoupling.^{9–11,23} For example, in the analysis of Guazzi *et al.* TAPSE/PASP emerged as a strong and independent predictor of mortality (HR 10.3, $P < 0.001$), with a <0.36 mmHg/mm threshold as the best identified cut-off.²² Palazzuoli *et al.* showed that a

Figure 3 Kaplan–Meier analysis describing the cumulative incidence of the secondary outcome HF event across the three tertiles of TAPSE/PASP. HF, heart failure; PASP, pulmonary artery systolic pressure; TAPSE, tricuspid annulus plane systolic excursion.

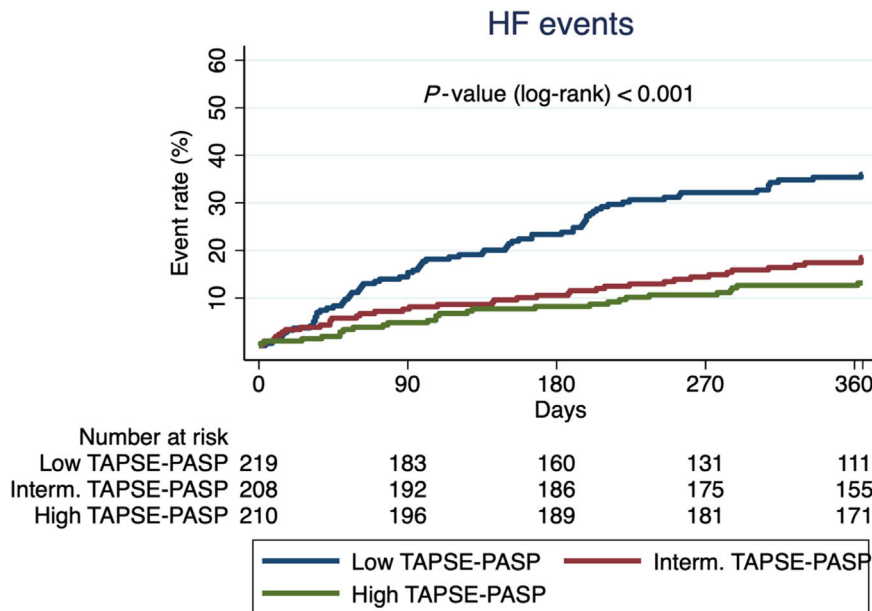


Table 4 Cox regression analysis for the prognostic impact of tricuspid annular plane systolic excursion (TAPSE)/pulmonary artery systolic pressure (PASP) ratio on clinical outcomes at last available follow-up

	Unadjusted		Adjusted model ^a	
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
Primary endpoint (composite of all-cause death or first HF event)				
TAPSE/PASP as continuous variable (per 0.1 mm/mmHg increase)	0.82 (0.77–0.87)	<0.001	0.91 (0.84–0.98)	0.009
TAPSE/PASP groups ^b				
Tertile 2 versus tertile 1	0.45 (0.32–0.63)	<0.001	0.68 (0.44–1.04)	0.073
Tertile 3 versus tertile 1	0.34 (0.23–0.49)	<0.001	0.61 (0.38–0.99)	0.044
All cause of death				
TAPSE/PASP as continuous variable (per 0.1 mm/mmHg increase)	0.86 (0.78–0.96)	0.009	0.96 (0.84–1.11)	0.610
TAPSE/PASP groups ^b				
Tertile 2 versus tertile 1	0.30 (0.14–0.63)	0.002	0.45 (0.18–1.16)	0.098
Tertile 3 versus tertile 1	0.50 (0.27–0.94)	0.033	1.01 (0.44–2.33)	0.982
First HF event				
TAPSE/PASP as continuous variable (per 0.1 mm/mmHg increase)	0.81 (0.76–0.87)	<0.001	0.91 (0.84–0.98)	0.013
TAPSE/PASP groups ^b				
Tertile 2 versus tertile 1	0.47 (0.33–0.68)	<0.001	0.72 (0.46–1.12)	0.149
Tertile 3 versus tertile 1	0.31 (0.21–0.48)	<0.001	0.62 (0.37–1.03)	0.063

Data are reported HR with 95%.

BMI, body mass index; CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; LVEF, left ventricular ejection function; SBP, systolic blood pressure.

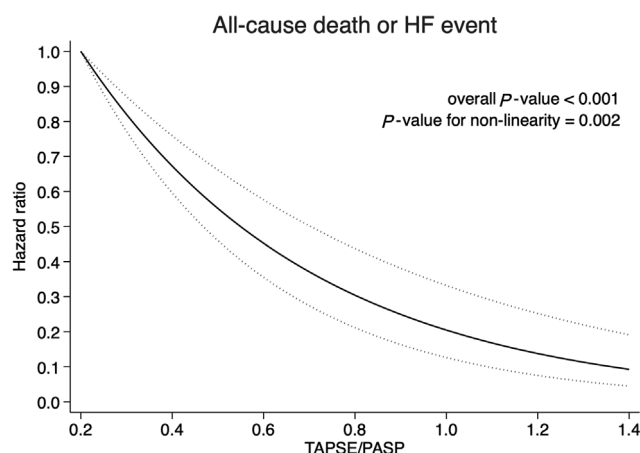
^aVariables included in the multivariate analysis: age, sex, BMI, SBP at inclusion; COPD; LVEF; GFR (CKD-EPI).

^bTertile 1: TAPSE/PASP < 0.60 mm/mmHg; tertile 2: TAPSE/PASP 0.60–0.90 mm/mmHg; tertile 3: TAPSE/PASP > 0.90 mm/mmHg.

TAPSE/PASP ratio < 0.425 mm/mmHg was associated with death and re-hospitalization for HF at 180-day at univariate analysis (HR 2.13, *P* < 0.001) but not at multivariate analysis (HR 0.89, *P* = 0.60).²⁶ Similarly, Bosch et al. showed that a TAPSE/PASP ratio < 0.48 mm/mmHg was associated with all-cause mortality and HF hospitalization in patients with HF, regardless of LVEF.²¹ In a recent meta-analysis of four

HF studies of patients with different LVEF values (two including patients with LVEF < 35%, one with LVEF < 45% and one with LVEF ≥ 45%), the risk of all-cause death was increased by 32% for each unit of reduction in TAPSE/PASP ratio, analysed as a continuous variable.²⁴ In our analysis, the prognostic impact of TAPSE/PASP ratio was even broader since the unadjusted risk for all-cause death was reduced by 18% for each

Figure 4 Spline curve describing the risk of the primary outcome (all-cause death or HF event) according to TAPSE/PASP values. The hazard ratio for all-cause death or HF event (relative to a minimum TAPSE/PASP value of 0.20 mm/mmHg) is shown on the y-axis whereas TAPSE/PASP as a continuous variable is shown on the x-axis. HF, heart failure; PAPS, pulmonary artery systolic pressure; TAPSE, tricuspid annulus plane systolic excursion.



increase in TAPSE/PASP of 0.1 mm/mmHg. These data in outpatients with LV dysfunction confirm the prognostic value of this parameter, that was already shown in patients with HF and preserved LVEF,^{1,6,27} making it useful in the whole spectrum of LVEF,²¹ as well as in other settings, such as acute HF,^{5,28} cardiac amyloidosis²⁹ or valvular heart disease.³⁰

Assessment of congestion is essential in the management of patients with HF, since it is a cause of frequent hospitalizations and it is also strongly associated with mortality.³¹ Congestion can affect right heart function parameters such as TAPSE, which improves during hospitalization with the optimization of haemodynamic compensation.^{32,33} In addition, PASP tends to increase in patients with a higher degree of congestion.³⁴ The final result is a reduction in TAPSE/PASP ratio. In our cohort, patients in the lowest tertile had higher NYHA class, more signs of congestion, and higher NT-proBNP concentration, confirming the interplay between congestion and RV-PA coupling.^{33,35,36} However, we confirmed the association between TAPSE/PASP and outcomes in a real-world population including patients with different degrees of congestion.

Worsening RV function and its ratio to pulmonary pressure is significantly associated not only with death, but also with an increased risk of HF hospitalizations independent of LVEF.³⁷ These events are associated with poorer quality of life, increased risks of hospitalization and death and are a major burden on healthcare resources.³¹ In our cohort, a 19% unadjusted reduction of first HFE was observed for each 0.1 mm/mmHg increase of TAPSE/PASP ratio. Hence, TAPSE/PASP ratio could be an important parameter for strat-

ifying the risk of incident HFE among stable, ambulatory patients with LV dysfunction.

Our study enrolled a real-world HF with reduced EF/HF with mildly reduced EF population from a high-volume HF centre. Analysing the distribution of HF medical therapy in the various tertiles, we observed that patients in the lowest tertile were less treated with ARNI/ACEi/ARB, while they were more treated with loop diuretics and SGLT2i. There has also been a trend towards greater use of MRAs without being statistically significant. Our results are in line with those found by Rosa *et al.* with a lower use of ACEi in patients with a lower TAPSE/PASP ratio and a higher use of diuretics. In contrast, MRA was also less used in patients with worse RV-PA coupling in their study.⁹ These differences in medical therapy might be theoretically explained by the greater degree of renal dysfunction and more signs of advanced HF in the lowest tertile.

Study limitations

Our study has several limitations. First, it is a retrospective, observational and single-centre study. Additionally, all data were reported by local investigators based on available medical records, without centralized analysis of echocardiographic images or independent adjudication of clinical events during follow-up. A larger sample size would have allowed for more robust analyses. Regarding echocardiographic parameters, TAPSE may be underestimated in patients who underwent prior cardiac surgery, while PASP may be underestimated in patients with severe TR. Congestion can also affect TAPSE values.^{33,35} Unfortunately, no data was available in the dataset for liver distension, jugular vein distension or third tone. Therefore, an accurate assessment of the concordance between signs and symptoms of systemic congestion and RV echocardiographic measurement was not possible. Furthermore, there is a certain inter-operator variability in the acquisition of echocardiographic images and in the calculation of both TAPSE and PASP. The 'a priori' selection of clinically relevant covariates for the multivariable analyses may have introduced some bias. Lastly, standardized cut-offs for the TAPSE/PASP ratio are not available.

Conclusions

Our study confirms the prognostic role of the TAPSE/PASP ratio in a single-centre, contemporary cohort of outpatients with left ventricular systolic dysfunction (LVEF ≤ 50%). Specifically, patients with TAPSE/PASP < 0.60 mm/mmHg had more co-morbidities, a more complex clinical profile, and a higher risk of all-cause mortality or HFE during follow-up.

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Conflict of interest

Dr. Pagnesi has received personal fees from Abbott Vascular, AstraZeneca, Boehringer Ingelheim, Novartis, Roche Diagnostics and Vifor Pharma. Dr. Adamo has received speaker fees

from Abbott Vascular and Medtronic. Dr. Metra has received consulting honoraria as a member of trial committees or advisory boards for Abbott Vascular, Actelion, Amgen, Bayer, Edwards Therapeutics, Servier, Vifor Pharma and Windtree Therapeutics. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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