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Left ventricular outflow tract velocity-time integral improves outcome prediction in patients with secondary mitral regurgitation

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ABSTRACT

Aims: Left ventricular outflow velocity-time integral (LVOT-VTI) has been shown to improve outcome prediction in different patients' subsets, with or without heart failure (HF). Nevertheless, the prognostic value of LVOT-VTI in patients with HF and secondary mitral regurgitation (MR) has never been investigated so far. Therefore, in the present study, we aimed to assess the prognostic value different metrics of LV forward output, including LVOT-VTI, in HF patients with secondary MR.

Methods and results: Consecutive patients with HF and moderate-to-severe/severe secondary MR and systolic dysfunction (i.e., left ventricular ejection fraction [LVEF] <50%) were retrospectively selected and followed-up for the primary endpoint of cardiac death. Out of the 287 patients analyzed (aged 74 ± 11 years, 70% men, 46% ischemic etiology, mean LVEF 30 ± 9%, mean LVOT-VTI 20 ± 5 cm), 71 met the primary endpoint over a 33-month median follow-up (16–47 months). Patients with an LVOT-VTI ≤17 cm ($n = 96$, 32%) showed the greatest risk of cardiac death (Log Rank 44.3, $p < 0.001$) and all-cause mortality (Log rank 8.6, $p = 0.003$). At multivariable regression analysis, all the measures of LV forward volume (namely LVOT-VTI, stroke volume index, cardiac output, and cardiac index) were predictors of poor outcomes. Among these, LVOT-VTI was the most accurate in risk prediction (univariable C-statistics 0.70 [95%CI 0.64–0.77]).

Conclusion: Left ventricular forward output, noninvasively estimated through LVOT-VTI, improves outcome prediction in HF patients with low LVEF and secondary MR.

1. Introduction

The hemodynamic characterization of patients with heart failure (HF), including the evaluation of forward left ventricular (LV) output, remains a cornerstone in the clinical practice to optimize outcome prediction [1]. However, since the gold standard cardiac catheterization is not feasible in large populations, the use of echocardiography-derived hemodynamic measures has been identified as a low-cost and more available noninvasive alternative, whose accuracy has been confirmed in landmark validation studies [2,3].

In particular, by the mean of Doppler-echocardiography, LV forward stroke volume (SV) is estimated as the product of the velocity-time

Abbreviation: BMI, body mass index; BSA, body surface area; CSA, cross-sectional area; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; EROA, effective regurgitant orifice area; GLS, global longitudinal strain; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; LVOTd, left ventricular outflow tract diameter; LVOT-VTI, left ventricular outflow tract velocity-time integral; MR, mitral regurgitation; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PISA, proximal isovelocity area; RV-FAC, right ventricle-fractional area change; SV, stroke volume; TAPSE, tricuspid annular plane systolic excursion.

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integral of the flow through the LV outflow tract (LVOT-VTI) and its cross-sectional area (LVOT-CSA) [3]. While LVOT-CSA assessment relies on a geometrical assumption, for which any error is squared, and may be difficult to obtain in case of suboptimal acoustic windows [4], LVOT-VTI may be easily measured in nearly all patients and has been shown to be highly reproducible even in the critical setting [4]. Furthermore, LVOT-VTI specifically expresses the forward LV output independently of cardiac remodelling and has been identified as an accurate parameter for risk prediction in patients with ischemic heart disease, HF, and pulmonary embolism [5–12].

While the echocardiographic evaluation of the forward LV flow has been shown to improve risk prediction also in patients with primary mitral regurgitation (MR) [13], no studies have investigated the role of this parameter in patients with MR secondary to LV systolic dysfunction, so far. Considering the high prevalence and detrimental impact of secondary MR [14,15], in the present study, we aimed to assess the prognostic value of the echocardiographic-derived measures of forward LV output, including LVOT-VTI, in a contemporary cohort of HF patients, LV systolic dysfunction, and secondary MR.

2. Methods

2.1. Subjects and study design

Consecutive patients referred to the echo-lab of our Center (Fondazione Monasterio, Pisa, Italy) between January 2015 and April 2021 were retrospectively screened. Whether a patient had undergone multiple exams within this timeframe, only the first one was taken into account. A diagnosis of HF with either reduced (HFrEF, LVEF $\leq$40%) or mildly reduced LVEF (HFmrEF, LVEF 41–49%) with moderate-to-severe or severe MR represented the inclusion criteria. Exclusion criteria were acute MR, primary MR (i.e., Barlow disease, rheumatic disease, endocarditis), uncorrected intracardiac/extracardiac shunts, more than mild aortic regurgitation, and hemodynamically significant LVOT obstruction since they may have affected the accuracy of LVOT-VTI assessment [3]. Since MR is dynamic and volume dependent, to reduce the risk of inaccuracy, only stable patients, not necessitating intravenous diuretic therapy at the time of the examination, were included. All patients underwent a clinical and bio-humoral evaluation, including the estimated glomerular filtration rate (eGFR, through the CKD-EPI formula) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations. The study protocol was approved by our Institutional Review Board. All the patients gave consent to the use of their anonymized data for research purposes, while no specific written form was required for this study since all the data were acquired for clinical indications.

2.2. Transthoracic echocardiography

A standard protocol was followed to acquire echocardiographic parameters, using commercially available instrumentations (Philips iE33 or EPIQ7, Andover, Massachusetts, USA) [16]. All exams were performed by either expert Cardiologists or certified Sonographers, under the supervision of an expert Cardiologist, and the images were stored in an own-property server. LV and atrial volumes were acquired from 2D images and indexed for body-surface area (BSA). LVEF was calculated through Simpson's method and diastolic function through a multiparametric algorithm. [17]

The severity of MR was graded following an integrated approach, accounting for both qualitative and quantitative data, and considered significant in case of vena contracta $\geq$5 mm, systolic blunting or flow reversal in the pulmonary veins, and dominant *E*-wave at mitral inflow pulsed-wave (PW) Doppler [18]. The effective regurgitant orifice area (EROA), regurgitant volume, and fraction were calculated through the proximal isovelocity area (PISA) method whenever possible but were not reported because missing in more than half of the study population.

The SV was estimated by the product of LVOT-VTI and CSA and indexed for BSA (SVi) [3]. LVOT-VTI was measured by tracing the envelope of the PW Doppler spectrum of systolic flow from the apical 5- or 3-chamber views, placing the sample volume within the LVOT proximal to the aortic cusps and moving apically to obtain a narrow spectral signal, with a rapid upstroke and an end-systolic click (Fig. 1) [4,19]. The diameter of the LVOT (LVOTd) was both measured in a zoomed longitudinal parasternal long-axis view at the annular level at mid-systole ($LVOTd_{measured}$) [20], and calculated ($LVOTd_{calculated}$) through the formula $5.7 \times BSA + 12.1$ [21]. The LVOT-CSA was then calculated as $LVOT - CSA = \pi \times (LVOTd/2)^2$ [4,19]. Cardiac output (CO) was estimated by the product of SV and heart rate and cardiac index (CI) as the ratio between CO and BSA [4,19]. In the case of atrial fibrillation, each measure was averaged over at least three-to-five consecutive cycles.

2.3. Follow-up

Patients were followed-up until December 2022 and their outcome status was determined by blinded investigators from the medical records or telephone interviews with the patients, their relatives, or General Practitioners. Cardiac death (i.e., death attributed to HF progression, myocardial infarction, or sudden cardiac death) was considered the primary endpoint of the study. All-cause mortality was a secondary endpoint.

2.4. Statistical analysis

Statistical analysis was performed by using SPSS (version 25.0, 2017, IBM Statistics, Armonk, New York, USA), and R software (version 3.4.0), and a 2-tailed *p*-value $\leq$0.05 was considered significant.

Quantitative values were reported as mean $\pm$ standard deviation (SD), or median (interquartile interval), while qualitative values as numbers or percentages. Comparisons between groups were performed through the unpaired Student *t*-test or the Mann-Whitney *U* test for quantitative variables, or the chi-square test for categorical variables. Bland-Altman plot analysis was used to assess bias and limits of agreement (defined as 95%CI around the mean) between $LVOTd_{measured}$ and $LVOTd_{calculated}$.

The optimal prognostic cut-off of LVOT-VTI for the primary endpoint was assessed through the maximally selected log-rank statistics [22]. Accordingly, the population was distinguished into two subgroups, which were compared for both baseline characteristics and risk of events, through Kaplan-Meier curves and the Log rank test. The predictive value of LVOT-VTI was also modeled with the p-spline smoothing method for the primary endpoint.

The univariable and multivariable predictors of cardiac death were identified through the Fine-Gray model for competing risks analysis, considering noncardiac death as a competing event. To avoid model overfitting, only the predictors with a univariable *p* value $\leq$0.05 were included in the final multivariable models. In this regard, to avoid collinearity issues, four different multivariable models were tested, each including one of the different metrics of LV forward output (namely LVOT-VTI, SVi, CO, and CI) and the other univariable predictors. Finally, the accuracy of different metrics of systolic function in predicting the risk of cardiac death was compared through the difference (Δ) in Harrell's C-statistics.

3. Results

Out of the 1531 HF patients screened, 287 (aged 74 $\pm$ 11 years, 70% men) matched the entry criteria and were included in the study (Supplemental Fig. 1). Most patients were symptomatic, showing a New York Heart Association (NYHA) class II (45%) or III (30%), despite being on guideline-recommended therapies (Table 1). According to the entry criteria, LVEF was compromised (mean LVEF 30 $\pm$ 9%, 89% HFrEF) and

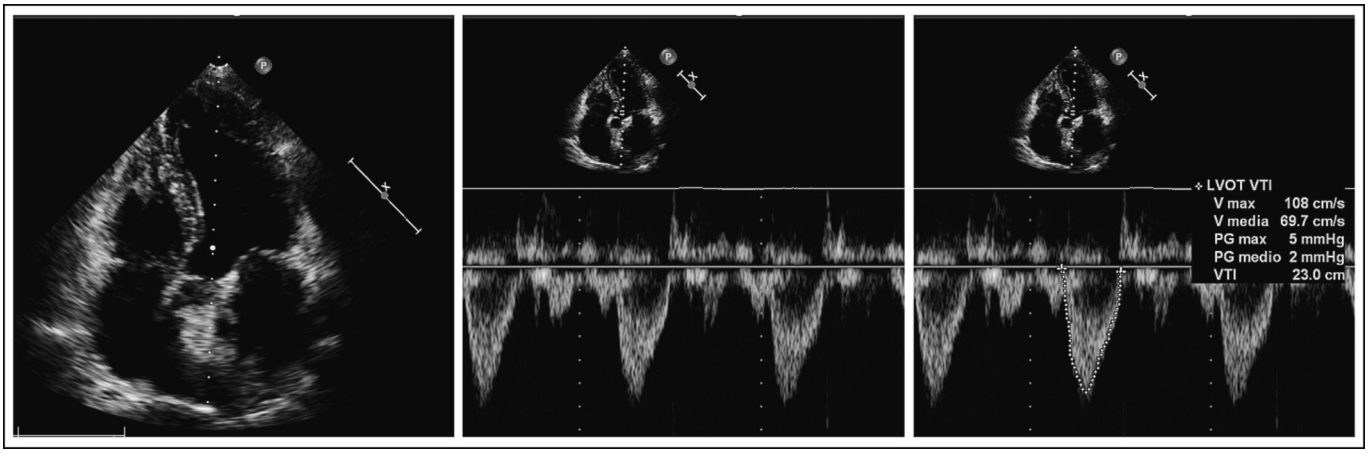

Fig. 1. Assessment of LVOT-VTI from a sample patient.
Left ventricular outflow tract velocity-time integral (LVOT-VTI) was measured by tracing the envelope of the PW Doppler spectrum of systolic flow from the apical 5- or 3-chamber views, placing the sample volume within the LVOT proximal to the aortic cusps and moving apically to obtain a narrow spectral signal, with a rapid upstroke and an end-systolic click [4,19].

Table 1
Characteristics of the study population according to the optimal prognostic cut-off of LVOT-VTI.

Variables	All patients $n = 287$	LVOT-VTI ≤ 17 cm ($n = 96$, 32%)	LVOT-VTI > 17 cm ($n = 191$, 68%)	p
Clinical features				
Age, years	74 ± 11	74 ± 12	74 ± 10	0.953
Men, n (%)	202 (70)	76 (79)	126 (66)	**0.028**
BMI, kg/m^2	27 ± 5	26 ± 4	27 ± 5	0.079
Ischemic etiology, n (%)	130 (46)	38 (40)	92 (49)	0.167
NYHA III-IV, n (%)	133 (47)	65 (68)	68 (36)	**<0.001**
Atrial fibrillation, n (%)	110 (39)	40 (42)	70 (37)	0.442
Hypertension, n (%)	121 (43)	38 (40)	83 (44)	0.527
Diabetes, n (%)	80 (28)	23 (24)	57 (30)	0.329
COPD, n (%)	49 (17)	14 (15)	35 (18)	0.507
Biohumoral data				
Hb, g/dL	12.6 ± 1.9	12.5 ± 1.8	12.7 ± 1.9	0.484
eGFR, mL/min/1.73 m^2	57 (39–75)	52 (37–71)	60 (43–76)	0.100
NT-proBNP, ng/L	3990 (1940–8414)	6067 (3220–14,003)	3098 (1450–5925)	**<0.001**
Treatment				
Beta-blockers, n (%)	241 (93)	76 (92)	165 (93)	0.618
ACEi/ARB, n (%)	154 (59)	43 (52)	111 (63)	0.105
ARNI, n (%)	46 (18)	18 (22)	28 (16)	0.294
MRA, n (%)	198 (76)	66 (79)	132 (75)	0.641
Furosemide, n (%)	236 (90)	79 (94)	157 (88)	0.131
ICD, n (%)	95 (33)	29 (30)	66 (35)	0.506
CRT, n (%)	82 (29)	27 (28)	55 (29)	0.891
Previous MVR, (%)	11 (4)	2 (2)	9 (5)	0.263

Values are mean ± SD, median (interquartile interval), or n (%). ACEi: angiotensin converting-enzyme inhibitors; ARB: angiotensin receptor blockers; ARNI: angiotensin receptor-neprilysin inhibitors; BMI: body mass index; COPD: chronic obstructive pulmonary disease; CRT: cardiac resynchronization therapy; eGFR: estimated glomerular filtration rate; Hb: hemoglobin; ICD: implantable cardioverter-defibrillator; LVOT-VTI: left ventricular outflow tract velocity-time integral; MRA: mineralocorticoid receptor antagonists; MVR: mitral valve repair/replacement; NT-proBNP: N-terminal pro–B-type natriuretic peptide; NYHA: New York Heart Association. Bold means "statistically significant".

all the patients showed at least moderate-to-severe MR. Left chambers were enlarged (mean left atrium volume index, LAVi 53 ± 17 mL/m^2; mean LV end-diastolic volume index, LVEDVi 107 ± 30 mL/m^2) (Table 2). The mean LVOT-VTI was 20 ± 5 cm and the $LVOTd_{measured}$ and $LVOTd_{calculated}$ were 21 ± 2 mm and 23 ± 1 mm, respectively, showing a modest agreement (−1.48 [95%CI -5.13-2.17], Supplemental Fig. 2). The mean SVi, CO, and CI were 39 ± 12 mL/m^2, 5.6 ± 2 L/min, and 2.9 ± 1.1 L/min/m^2, by using $LVOTd_{measured}$, and 45 ± 12 mL/m^2,

Table 2
Echocardiographic data of the study population according to the optimal prognostic cut-off of LVOT-VTI.

Variables	All patients n = 287	LVOT-VTI ≤ 17 cm (n = 96, 32%)	LVOT-VTI > 17 cm (n = 191, 68%)	p
LAVi, mL/m^2	53 ± 17	53 ± 15	53 ± 18	0.927
Vena contracta, mm	5.7 ± 0.9	5.7 ± 0.9	5.7 ± 0.9	0.738
E wave, cm/s	111 ± 34	106 ± 30	113 ± 36	0.120
E/e' average	17 ± 8	17 ± 8	18 ± 8	0.862
LVEDDi, mm/m^2	33 ± 5	32 ± 5	34 ± 5	**0.004**
LVESDi, mm/m^2	28 ± 5	28 ± 5	29 ± 5	0.357
LVEDVi, mL/m^2	107 ± 30	101 ± 28	110 ± 30	**0.013**
LVESVi, mL/m^2	76 ± 27	75 ± 25	76 ± 28	0.756
LVEF, %	30 ± 9	27 ± 7	32 ± 9	**<0.001**
SVi, mL	39 ± 12	28 ± 7	45 ± 10	**<0.001**
Heat rate, bpm	78 ± 17	84 ± 18	74 ± 15	**<0.001**
CO, mL/min	5.6 ± 2.0	4.5 ± 1.5	6.1 ± 2	**<0.001**
CI, mL/min/m^2	2.9 ± 1.1	2.3 ± 0.7	3.3 ± 1	**<0.001**
TAPSE, mm	18 ± 5	16 ± 5	19 ± 5	**<0.001**
S', cm/s	9.8 ± 2.7	9 ± 2.5	10.3 ± 2.7	**<0.001**
RV-FAC, %	36 ± 9	32 ± 9	38 ± 8	**<0.001**
TR velocity, cm/s	315 (290–340)	320 (290–350)	310 (290–340)	0.295
sPAP, mmHg	49 (42–57)	52 (45–59)	48 (42–56)	0.051
Severe TR, %	63 (22)	30 (31)	33 (17)	**0.003**

Values are mean ± SD, median (interquartile interval), or n (%). CI: cardiac index; CO: cardiac output; LAVi: left atrial volume/body-surface area; LVEDDi: left ventricular end-diastolic diameter/body-surface area; LVEDVi: left ventricular end-diastolic diameter/body-surface area; LVEF: left ventricular ejection fraction; LVESDi: left ventricular end-systolic diameter/body-surface area; LVESVi: left ventricular end-systolic volume/body-surface area; LVOT-VTI: left ventricular outflow tract velocity-time integral; RV-FAC: right ventricle-fractional area change; sPAP: systolic pulmonary arterial pressure; SVi: stroke volume/body-surface area; TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation. Bold means "statistically significant".

6.4 ± 2.2 L/min, and 3.4 ± 1.1 L/min/m^2, by using $LVOTd_{calculated}$, respectively.

3.1. Clinical correlates of LVOT-VTI

The optimal cut-off of LVOT-VTI in predicting the primary endpoint was 17 cm (Fig. 2). Accordingly, the study population was divided into two subgroups (Tables 1 and 2). Patients with reduced LVOT-VTI (n = 96, 32%) were more often males ($p = 0.028$), showed a higher NYHA class ($p < 0.001$), and a higher plasma concentration of NT-proBNP ($p < 0.001$). No differences were found for age, HF etiology, comorbidities, and treatments in the two LVOT-VTI subgroups (all $p > 0.05$). LVOT-VTI ≤17 cm was associated with smaller LV end-diastolic volume and diameter (both $p < 0.05$), worse LVEF, right ventricular systolic function, and tricuspid regurgitation (all $p < 0.001$).

3.2. Survival analysis

Over a 33-month median follow-up (16–47 months), 114 (40%) patients died: 71 patients for cardiac causes (62 of HF progression, 6 of sudden cardiac death, and 3 of acute myocardial infarction), and 43 patients for noncardiac causes. Thirty-seven patients (13%) underwent either mitral valve repair ($n = 28$) or replacement ($n = 9$) after a median 29-month (10–45 months) period, with no difference between patients with LVOT-VTI ≤17 or > 17 cm (9% vs. 15%, $p = 0.263$).

Reduced LVOT-VTI was associated with a higher risk of cardiac death (49% vs. 13%, hazard ratio [HR] 4.72 [95%CI 2.77–8.05], $p < 0.001$) (Fig. 3) and all-cause mortality (50% vs. 34%, HR 1.57 [95%CI 1.04–2.36], $p = 0.030$) (Supplemental Fig. 3). Similar findings were observed after excluding patients who had undergone mitral valve intervention before the study begin (Supplemental Fig. 4) or over the follow-up (Supplemental Fig. 5). The prognostic role of the selected cut-off was maintained across BSA (p for interaction = 0.608, Supplemental Fig. 6) and heart rate tertiles (p for interaction = 0.607, Supplemental Fig. 7).

At regression analysis (Table 3), reduced LVOT-VTI ($p < 0.001$), SVi ($p = 0.002$), CO ($p = 0.006$), and CI ($p = 0.003$), but not LVEF ($p = 0.254$), were associated with an increased risk of the primary endpoint, independently of the other univariable predictors. Similar findings were observed when SVi, CO, and CI were estimated by using $LVOTd_{calculated}$ (Supplemental Table 1).

Among the different metrics of systolic function, LVOT-VTI and SVi (by using $LVOTd_{calculated}$) showed the highest accuracy in predicting the risk of cardiac death (Table 4).

4. Discussion

This is the first study evaluating the prognostic value of the echocardiographic-derived measures of forward LV output in HF patients with low LVEF and secondary MR. Reduced forward LV output was associated with higher NYHA class, neurohormonal activation, and worse right ventricle function, despite smaller LV dimensions and no difference in age, HF etiology, comorbidities, and treatments. Although all the measures of forward LV output were independent predictors of poor outcomes, LVOT-VTI was the most accurate in risk prediction.

Representing a widely available, low-cost, and noninvasive alternative to cardiac catheterization, the echocardiographic-derived hemodynamic evaluation has been shown to provide valuable information in the assessment of cardiovascular patients in different clinical scenarios, optimizing outcome prediction [5–12]. Nevertheless, to the best of our knowledge, the prognostic significance of these measures had never been investigated so far in patients with low LVEF and secondary (or functional) MR. For example, while the prognostic significance of LVOT-VTI was previously documented in patients with advanced HF ($n = 100$,

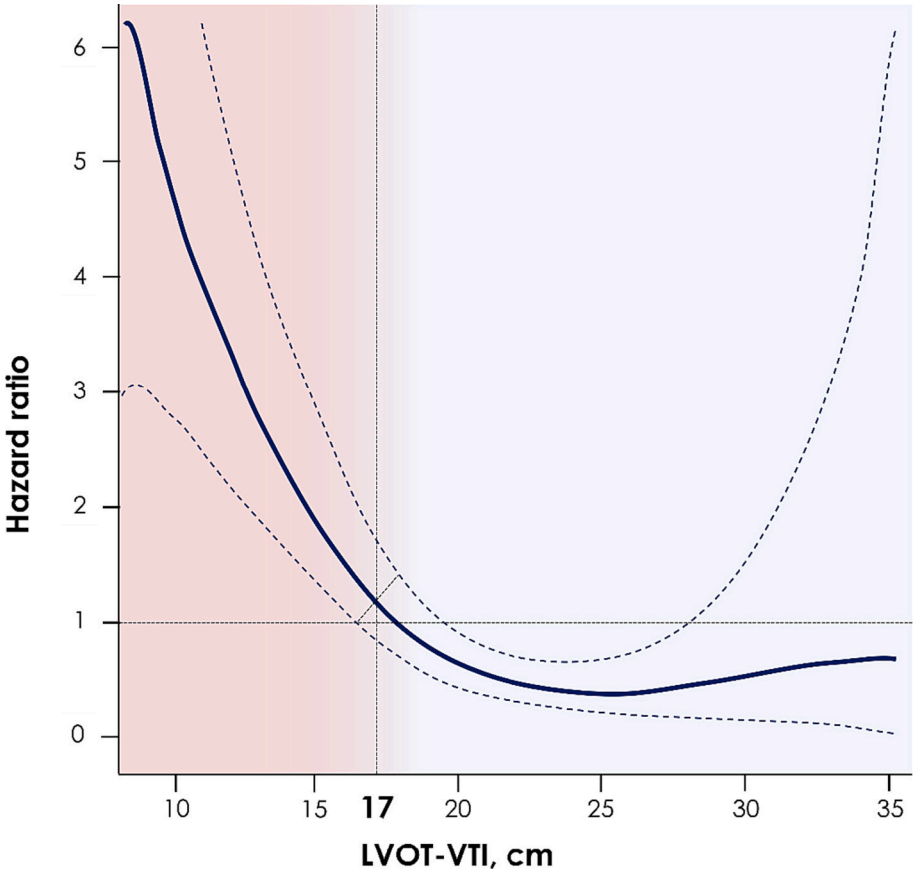

Fig. 2. P-spline curve for the risk of cardiac death according to LVOT-VTI values.
The spline curve shows the event-risk change with the decrease of LVOT-VTI. The dashed lines represent the upper and lower limits of 95% confidence interval for the curve. The optimal prognostic cut-off (17 cm) corresponds to the point where the spline curve, including the upper and lower limits of its 95% confidence interval, were above the hazard ratio = 1. LVOT-VTI: left ventricular outflow tract velocity-time integral.

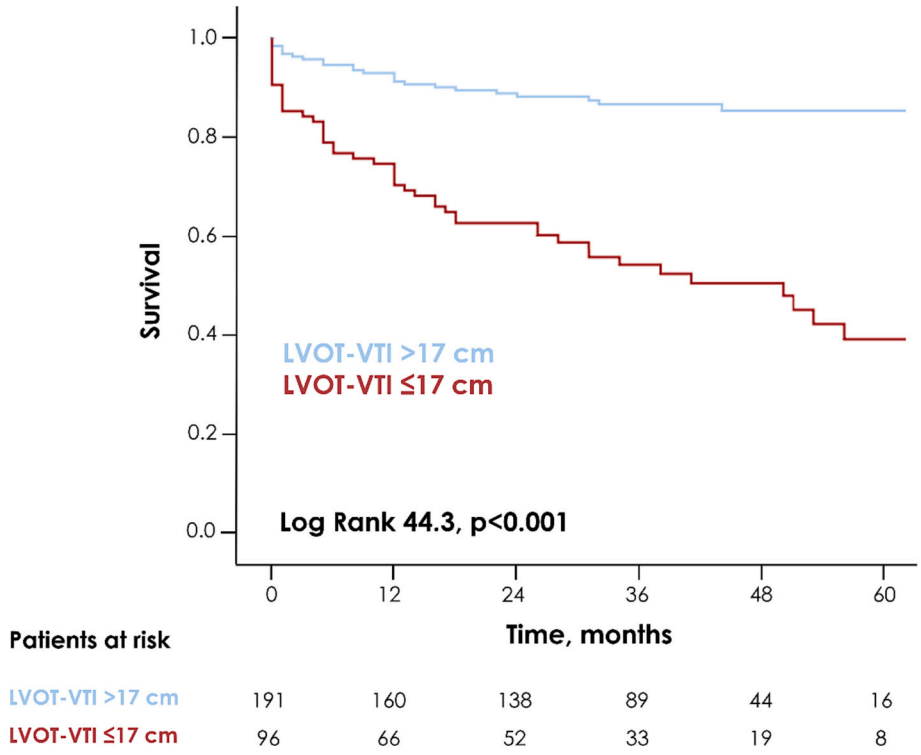

Fig. 3. Kaplan-Meier curves for cardiac death according to LVOT-VTI.
Patients with reduced LVOT-VTI (≤17 cm) showed a significantly higher risk of cardiac death over a 33-month median follow-up (16–47 months). LVOT-VTI: left ventricular outflow tract velocity-time integral.

mean LVEF 29 ± 17%) [8] and in a large cohort of patients admitted to cardiac intensive care unit ($n = 6957$, mean LVEF 47 ± 16%) [12], the impact of MR was not assessed in these studies. Furthermore, among 990 patients with stable coronary artery disease ($n = 990$), LVOT-VTI was an independent predictor of adverse outcomes independently of MR severity, though significant MR was more prevalent in the subset with LVOT-VTI ≤18 cm (25% vs. 16%, $p = 0.006$), underscoring the impact of MR on the forward LV output [23].

Notably, in our population, all the measures of forward LV output evaluated (namely LVOT-VTI, SVi, CO, and CI) were predictors of cardiac death, independently of other clinical, biohumoral, and echocardiographic variables. These findings are in line with those of a previous study on patients with primary MR ($n = 278$, LVEF 65 ± 5%), in which reduced forward LV flow was associated with an increased risk of a composite endpoint including mitral valve surgery and death [13].

Similar to other patients' subsets [5–12], LVOT-VTI and SVi outperformed the other metrics of forward LV output in risk stratification also in our population. By relying on heart rate, CO and CI may lack accuracy in predicting outcomes, since heart rate may vary on the same day, and may alter the calculation of CO, particularly in case of rhythm disorders or compensatory tachycardia [4,12]. On the other hand, the estimation of LVOT-CSA remains the major source of errors in the calculation of the SV, for different reasons: it relies on a geometrical assumption; any error in LVOTd is squared; the optimal site to measure LVOTd is debated [20]; the feasibility and reproducibility of LVOTd are low in case of suboptimal acoustic windows [4]. Accordingly, the C-statistics of SVi in predicting cardiac death were slightly higher when an estimated LVOTd (proportional to BSA) was used. [21] While the reliability of this formula remains to be confirmed in other populations, the prognostic accuracy was similar, but not superior, to that obtained by using LVOT-VTI only. Thus, estimating the SVi did not add any relevant information at the cost of a supplemental calculation.

To overcome these limitations, we proposed the use of LVOT-VTI to optimize risk stratification in these patients. Indeed, LVOT-VTI is measurable in nearly all patients and has been shown to be highly reproducible, even in the critical setting [4]. Furthermore, being LVOTd essentially constant, any variation in the SV depends on the changes in LVOT-VTI [4,24,25]. In line with this hypothesis, LVOT-VTI showed the highest C-statistics for the prediction of cardiac death, while the calculation of an optimal prognostic cut-off (17 cm) allowed an accurate stratification of patient risk over the follow-up (Log rank 44.3, $p < 0.001$). Interestingly, in a sub-analysis of the EVEREST II trial [26], percutaneous edge-to-edge mitral valve repair was associated with a greater hemodynamic and clinical improvement in the patients with a lower baseline forward LV flow. Considering the retrospective nature of the present work, further well-designed prospective studies should clarify whether the integration of LVOT-VTI with other clinical and instrumental parameters, such as EROA and GLS, may optimize the selection of the patients with HF and functional MR which could benefit more from mitral valve intervention.

4.1. Study limitations

As in nearly all the studies with a cross-sectional design [27,28], the impact of the longitudinal changes in echocardiographic measures, including LVEF and LVOT-VTI, remains to be evaluated, particularly in patients undergoing mitral valve intervention. Because of the retrospective nature of the work, other metrics of LV systolic function (e.g., GLS and 3D-LVEF) were not available in most of the patients. Therefore, their accuracy in risk prediction, compared with LVOT-VTI, remains to be investigated. Different confounders may affect LVOT-VTI values, including ethnicity, BSA, and heart rate during echocardiography [4]. In the present study, including exclusively white individuals, LVOT-VTI ≤17 cm was associated with a higher risk of cardiac death across both BSA and heart rate tertiles. Nevertheless, considering the monocentric design of the study, this cut-off should be used with caution in the case of extreme BSA and heart rate categories, while future studies are expected to test its accuracy in larger and more heterogeneous populations. Since

Table 3
Univariable and multivariable competing risks regression analyses for the prediction of cardiac death.

Predictors	Univariable model			Multivariable model 1			Multivariable model 2			Multivariable model 3			Multivariable model 4		
	SHR	95%CI	p	SHR	95%CI	p	SHR	95%CI	P	SHR	95%CI	P	SHR	95%CI	p
Age, years	**1.06**	**1.03–1.10**	**<0.001**	**1.05**	**1.01–1.10**	**0.021**	**1.06**	**1.01–1.11**	**0.012**	**1.06**	**1.02–1.10**	**0.007**	**1.06**	**1.02–1.11**	**0.005**
Female sex	0.71	0.40–1.26	0.245	–	–	–	–	–	–	–	–	–	–	–	–
BMI, kg/m^2	0.96	0.90–1.01	0.137	–	–	–	–	–	–	–	–	–	–	–	–
Ischemic etiology	1.15	0.69–1.91	0.583	–	–	–	–	–	–	–	–	–	–	–	–
NYHA class III-IV	**2.15**	**1.28–3.59**	**0.004**	1.25	0.71–2.22	0.437	1.17	0.65–2.10	0.595	1.31	0.73–2.32	0.373	1.28	0.72–2.30	0.399
Atrial fibrillation	1.31	0.79–2.19	0.293	–	–	–	–	–	–	–	–	–	–	–	–
Hypertension	1.03	0.62–1.72	0.904	–	–	–	–	–	–	–	–	–	–	–	–
COPD	0.71	0.34–1.50	0.376	–	–	–	–	–	–	–	–	–	–	–	–
Diabetes	0.89	0.49–1.61	0.713	–	–	–	–	–	–	–	–	–	–	–	–
Hb, g/dL	0.87	0.76–1.01	0.063	–	–	–	–	–	–	–	–	–	–	–	–
Ln (eGFR)	**0.39**	**0.24–0.63**	**<0.001**	0.55	0.29–1.04	0.068	0.59	0.31–1.14	0.116	0.64	0.33–1.25	0.192	0.67	0.34–1.30	0.235
Ln (NT-proBNP)	**1.93**	**1.53–2.44**	**<0.001**	1.26	0.93–1.73	0.131	**1.38**	**1.01–1.89**	**0.042**	**1.42**	**1.03–1.94**	**0.027**	**1.46**	**1.08–1.97**	**0.015**
MVR over follow-up	0.36	0.11–1.14	0.083	–	–	–	–	–	–	–	–	–	–	–	–
LAVi, mL/m^2	**1.01**	**1.00–1.03**	**0.037**	1.01	0.99–1.03	0.079	1.01	0.99–1.03	0.090	1.01	0.99–1.03	0.233	1.02	0.99–1.03	0.211
Vena contracta, mm	1.01	0.67–1.52	0.955	–	–	–	–	–	–	–	–	–	–	–	–
E/e' average	1.01	0.98–1.04	0.521	–	–	–	–	–	–	–	–	–	–	–	–
LVEDVi, mL/m^2	0.99	0.98–1.01	0.689	–	–	–	–	–	–	–	–	–	–	–	–
TAPSE, mm	**0.91**	**0.86–0.96**	**0.001**	0.96	0.90–1.01	0.183	0.95	0.89–1.01	0.096	**0.92**	**0.86–0.98**	**0.015**	**0.92**	**0.86–0.98**	**0.019**
sPAP, mmHg	1.02	0.99–1.04	0.106	–	–	–	–	–	–	–	–	–	–	–	–
Heart rate, bpm	1.01	0.99–1.02	0.128	–	–	–	–	–	–	–	–	–	–	–	–
LVEF, %	0.98	0.95–1.01	0.254	–	–	–	–	–	–	–	–	–	–	–	–
LVOT-VTI, cm	**0.86**	**0.80–0.91**	**<0.001**	**0.87**	**0.81–0.93**	**<0.001**	–	–	–	–	–	–	–	–	–
SVi, mL/m^2	**0.95**	**0.92–0.98**	**<0.001**	–	–	–	**0.95**	**0.92–0.98**	**0.004**	–	–	–	–	–	–
CO, L/min	**0.79**	**0.69–0.91**	**0.001**	–	–	–	–	–	–	**0.75**	**0.61–0.92**	**0.006**	–	–	–
CI, L/min/m^2	**0.66**	**0.51–0.86**	**0.002**	–	–	–	–	–	–	–	–	–	**0.55**	**0.38–0.81**	**0.003**

After having identified the univariable predictors of cardiac death, four multivariable models were tested, each including a different metric of LV forward output (namely LVOT-VTI, SVi, CO, and CI), and the other univariable predictors, to avoid collinearity issues. BMI: body mass index; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; Hb: hemoglobin; LAVi: left atrial volume/body-surface area; LVEDVi: left ventricular end-diastolic diameter/body-surface area; LVEF: left ventricular ejection fraction; LVOT-VTI: left ventricular outflow tract velocity-time integral; MVR: mitral valve repair/replacement; NT-proBNP: N-terminal pro–B-type natriuretic peptide; NYHA: New York Heart Association; SHR: sub-distribution hazard ratio; sPAP: systolic pulmonary arterial pressure; TAPSE: tricuspid annular plane systolic excursion. Bold means "statistically significant".

Table 4
Accuracy in the prediction of cardiac death of different metrics of left ventricular systolic function compared with LVEF.

Variable	C-statistics (95% CI)	Δ vs. LVEF	p
LVEF	0.59 (0.53–0.67)	–	–
LVOT-VTI	0.70 (0.64–0.77)	0.11 (0.02–0.20)	**0.018**
SVi	0.68 (0.62–0.75)	0.09 (0.00–0.18)	0.052
CO	0.63 (0.57–0.69)	0.03 (−0.05–0.13)	0.467
CI	0.63 (0.56–0.69)	0.03 (−0.05–0.13)	0.490
$^{*}SVi_{calculated}$	0.70 (0.64–0.77)	0.11 (0.03–0.20)	**0.012**
$^{*}CO_{calculated}$	0.64 (0.55–0.72)	0.04 (−0.07–0.14)	0.452
$^{*}CI_{calculated}$	0.64 (0.56–0.72)	0.04 (−0.06–0.17)	0.461

only patients with an LVEF <50% were included, the study design did not allow a proper assessment of the prognostic value of LVEF. However, LVOT-VTI has been shown to be an accurate predictor of poor outcomes also in HFpEF patients [10]. Furthermore, though functional MR has been recently described also in HFpEF patients, the related clinical and prognostic significance remains to be clarified. In this regard, since LVEF <50% was an inclusion criterion, any possible error in its assessment at the time of the exam may have led to some inaccuracy in the selection of patients with values around the upper limit. Similar to previous studies [27,29], MR severity was graded through an integrated approach, while EROA and regurgitant volume were not reported, because of the high frequency of missing values. While both the accuracy in stratifying MR severity and the prognostic value of these measures remains debated in patients with secondary MR [30,31], some inaccuracy in the classification of patients as having moderate-to-severe MR could not be excluded also using a multiparametric approach, particularly in the case of borderline findings. Finally, the relatively low number of patients undergoing mitral valve intervention during the follow-up period may have underestimated the related prognostic benefit, observing only a nonsignificant trend in regression analysis (Table 3, $p = 0.086$).

4.2. Next steps

Despite the acknowledged limitations, in this study, we documented the role of echocardiographic measures of forward LV output, particularly LVOT-VTI, in predicting risk in a specific cohort of HF patients with low LVEF and secondary MR on guidelines-recommended therapies. Future studies are expected to replicate our findings in larger populations and assess the impact of longitudinal changes in these parameters, particularly in response to interventions like mitral valve procedures. However, considering the accumulating evidence affirming the prognostic significance of LVOT-VTI across various clinical settings, advocating for a broader implementation of this low-cost noninvasive measure is warranted. Indeed, improving risk prediction in HF patients holds importance in customizing follow-up intensity, proactively anticipating clinical decline, offering advanced therapeutic options, and refining clinical trial designs, with the ultimate goal of improving outcomes.

5. Conclusions

In patients with HF, LVEF <50%, and moderate-to-severe or severe functional MR, the echocardiographic-derived measures of forward LV output (namely LVOT-VTI, SVi, CO, and CI) are independent predictors of cardiac death. Not relying on geometrical assumption and being easy-to-obtain, widely available, and highly reproducible, LVOT-VTI may represent an ideal parameter to assess systolic function and predict outcomes in this context. Future prospective studies are expected to investigate whether LVOT-VTI, along with other measures (such as EORA and GLS), may play some role in optimizing therapeutic choices.

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Declaration of Competing Interest

None.

Data availability

Data are available upon reasonable request.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2023.131272.

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