Heliyon 10 (2024) e32378

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Association between echocardiographic velocity time integral ratio of mitral valve and left ventricular outflow tract and clinical outcomes post transcatheter edge-to-edge mitral valve repair

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ARTICLE INFO

Keywords:
Mitral regurgitation
Transcatheter edge-to-edge repair
Prognosis
Velocity time integral

ABSTRACT

Background: Residual mitral regurgitation (MR) is frequent after transcatheter edge-to-edge repair (TEER). There is controversy regarding the clinical impact of residual MR and its quantitative assessment by transthoracic echocardiography (TTE), which is often challenging with multiple eccentric jets and artifact from the clip. The utility of the velocity time integral (VTI) ratio between the mitral valve (MV) and left ventricular outflow tract (LVOT), ($VTI_{MV/LVOT}$), a simple Doppler measurement that increases with MR, has not been assessed post TEER.
Methods: Baseline characteristics, clinical outcomes, and TTE data from patients who underwent TEER between 2014 and 2021 across three academic centers were retrospectively analyzed. Post-procedure TTEs were evaluated for $VTI_{MV/LVOT}$ in the first three months after TEER. One-year outcomes including all-cause and cardiac mortality, major adverse cardiac events, and MV reintervention were compared between patients with high $VTI_{MV/LVOT}$ ($\geq$2.5) and low ($<$2.5).
Results: In total, 372 patients were included (mean age 78.7 ± 8.8 years, 68 % male, mean pre-TEER ejection fraction of 50.5 ± 14.7 %). Follow up TTEs were performed at a median of 37.5 (IQR 30–48) days post-procedure. Patients with high $VTI_{MV/LVOT}$ had significantly higher all-cause mortality (HR 2.10, $p = 0.003$), cardiac mortality (HR 3.03, $p = 0.004$) and heart failure admissions (HR 2.28, $p < 0.001$) at one-year post-procedure. There was no association between raised $VTI_{MV/LVOT}$ and subsequent MV reintervention.
Conclusion: High $VTI_{MV/LVOT}$ has clinically significant prognostic value at one year post TEER. This tool could be used to select patients for consideration of repeat intervention.

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https://doi.org/10.1016/j.heliyon.2024.e32378
Received 7 May 2024; Accepted 3 June 2024
Available online 5 June 2024

1. Introduction

Severe mitral regurgitation (MR) is associated with increased risk of heart failure, atrial fibrillation, and sudden cardiac death [1]. Minimally invasive intervention of the mitral valve (MV) with transcatheter edge-to-edge repair (TEER) has been validated for the treatment of severe MR in high surgical risk patients and has become increasingly utilized in this population [2]. In addition to guideline-directed medical therapy, TEER has been seen to result in improved patient outcomes including heart failure admissions and overall survival [3]. While TEER has been identified as a safer alternative with fewer post-surgical adverse events compared to invasive surgical valve intervention, its short-term efficacy, as measured by a reduction in MR or the necessity for re-intervention, has been demonstrated to be inferior [4]. Of clinical significance, multiple studies have reported that post-operative moderate or severe MR following a TEER is not uncommon, and predicts worse long-term outcomes including progressive MR, higher rates of hospitalizations, and poorer survival [2,5–7]. In such patients, repeat intervention could be considered.

Despite these well-known prognostic implications of residual MR, there are many challenges related to its accurate quantification post TEER on transthoracic echocardiography (TTE). Several factors cloud the measurement of post-procedural MR including multiple eccentric regurgitant jets, acoustic shadowing by the clip, and the merging of multiple small jets [8–10]. Although different measurements and techniques have been suggested, no formal consensus guideline strategies exist regarding accurate assessment of residual/recurrent MR post TEER [9]. Additionally, iatrogenic mitral stenosis (MS) is a rare but potentially severe complication after TEER for which valve surgery is the only option [11]. Therefore, a comprehensive evaluation of valvular function following TEER intervention is critical.

Beyond validated quantitative and qualitative parameters, the ratio of the mitral inflow velocity time integral (VTIMV) to left ventricular outflow tract (LVOT) velocity time integral (VTI_{LVOT}) has been demonstrated to be accurate at detecting bioprosthetic MV dysfunction [12,13]. This ratio has been shown to detect both regurgitant and stenotic valves. Hemodynamically, significant MR increases forward flow through the MV with a simultaneous reduction in systemic flow through the LVOT, resulting in an elevation of the VTI ratio [12]. It can also affect pulmonary hypertension and its sequalae. On the other hand, significant MS markedly increases the VTIMV as a reflection of a reduced MV orifice area, with also potential reduction in forward flow through the LVOT, resulting in a raised VTI ratio [12]. Despite the demonstrated use of this ratio in bioprosthetic MV, the utility of this ratio in the population undergoing a TEER has not been assessed.

This study aims to evaluate the clinical utility of echocardiographically derived ratio of VTI_{MV} to VTI_{LVOT} as a means of assessing post TEER MV dysfunction and to analyze the prognostic value of this ratio for mortality, major adverse cardiovascular events, and need for subsequent MV intervention.

2. Methods

2.1. Population

This retrospective observational study reviewed all consecutive patients who underwent a TEER of the MV utilizing MitraClip™ (Abbott Laboratories, Chicago, Illinois, USA) between 07/01/2014 and 12/30/2021 across three tertiary hospitals in the United States (Mayo Clinic Rochester, Mayo Clinic Arizona, Mayo Clinic Florida). Patients under the age of 18 years were excluded. This study was approved by the Mayo Clinic Institution Review Board. Baseline characteristics were retrospectively collected from electronic medical records using EPIC Hyperspace Production (Epic Systems Corporation, Verona, Wisconsin, US).

2.1.1. Echocardiographic evaluation

Included patients underwent pre-operative comprehensive two-dimensional TTE (Philips iE33; Philips Medical Systems; GE Vivid E9, GE Healthcare) within one year prior to TEER and subsequent post-procedural TTE within three months after TEER. Only

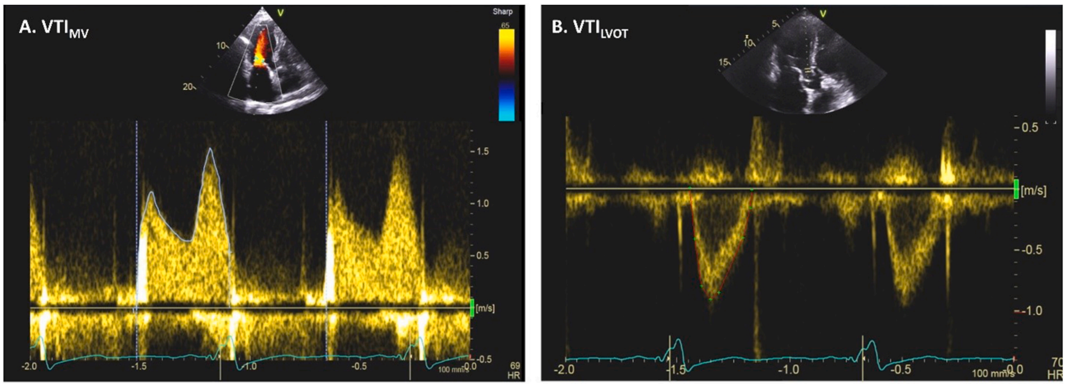

Fig. 1. Doppler echocardiographic measurements of velocity-time integral (VTI) of the mitral valve (MV) in **panel A** and left ventricular outflow tract (LVOT) in **panel B.**

outpatient post-procedural TTE was assessed to minimize the influence of hemodynamic variability secondary to procedural loading conditions. If multiple preoperative TTEs were available in the prespecified period, the closest one to the procedure was chosen; if multiple post-procedural TTEs were available, the earliest one was selected.

Two dimensional and Doppler imaging with dedicated pulsed-wave and continuous wave Dopplers were performed in accordance with current American Society of Echocardiography (ASE) guidelines [14]. Images were retrospectively reviewed. VTI of the MV (VTI_{MV}) and LVOT (VTI_{LVOT}) were manually measured for each patient on pre- and post-procedure TTEs. Specifically, VTI_{MV} was measured on continuous wave Doppler of mitral inflow on apical four chamber view (Fig. 1A). VTI_{LVOT} was measured on pulsed-wave Doppler of the LVOT on apical three chamber view (Fig. 1B). Two values were recorded and averaged for each measurement to improve accuracy, while five beats were recorded and averaged in patients with atrial fibrillation. A ratio of VTI_{MV} and VTI_{LVOT} ($VTI_{MV/LVOT}$) was calculated for each patient pre- and post-procedure by dividing VTI_{MV} by VTI_{LVOT}. A cutoff for high $VTI_{MV/LVOT}$ was determined as ≥ 2.5 as per previously published literature [12,15].

Final impression of residual MR severity, according to assessment of multiparametric qualitative, quantitative, and semi-quantitative methods was also documented pre- and post-procedure by experienced cardiologists with certification for special competency in echocardiography from the National Board of Echocardiography [16]. Baseline pre-operative TTE data including left ventricular ejection fraction (EF) using biplane Simpson's method, right ventricular systolic pressure (RVSP), left and right ventricular dimensions, left atrial volume index (LAVI), and mean transmitral gradient were abstracted from TTE reports.

3. Outcomes

All patient data was retrospectively reviewed for clinical outcomes at one-year post TEER, which included all-cause and cardiac mortality, major adverse cardiac outcome (MACE) involving heart failure admission, stroke, or myocardial infarction, and re-intervention of the MV. Comparisons of clinical outcomes were made between patients with high $VTI_{MV/LVOT}$ (≥ 2.5) and low $VTI_{MV/LVOT}$ (<2.5) on post TEER TTE. Frequency of MV re-intervention was further analyzed in patients with a mean transmitral gradient $\leq$ 5 mmHg, given contraindication for repeat TEER in patients with high transmitral gradient due to high risk of mitral stenosis [17,18].

3.1. Statistical analysis

Baseline characteristics at the time of TEER including demographics and comorbidities were collected and presented as either frequencies and percentages (n, %) for nominal values or mean ± standard deviation or median (interquartile range) for continuous variables according to distribution. Patient population was separated into two groups based on post-operative $VTI_{MV/LVOT}$. Comparisons between groups were performed using independent samples student t-tests or non-parametric tests for continuous variables and Chi-square test for nominal variables. To evaluate the association between $VTI_{MV/LVOT}$ and outcomes, univariable and multivariable analyses using Cox Regression models were performed. Kaplan-Meier curves were used for survival estimates. All statistical analysis was performed using Microsoft Excel and SPSS Statistical Software Suite (Version 28.0, IBM Statistics, New York, USA). Statistical significance was defined as two-tailed p value < 0.05.

Table 1
Baseline demographics and echocardiographic measurements for overall patient cohort and separated by $VTI_{MV/LVOT}$ cutoff of ≥ 2.5.

Baseline characteristics	Overall patient cohort n = 372	Low $VTI_{MV/LVOT}$ (<2.5) N = 264	High $VTI_{MV/LVOT}$ (≥2.5) N = 108	p-value (Low vs High VTI ratio)
Sex, male, n (%)	253 (68 %)	177 (67 %)	76 (70 %)	0.34
Age at time of TEER (years), mean ± SD	78.7 ± 8.8	78.7 ± 9.1	78.7 ± 8.2	0.77
Hypertension, n (%)	304 (82 %)	222 (84 %)	82 (76 %)	0.27
Diabetes, n (%)	108 (29 %)	74 (28 %)	34 (31 %)	0.39
Atrial fibrillation/flutter, n (%)	117 (31 %)	184 (70 %)	76 (70 %)	0.32
Etiology of MR, n (%)				0.50
Primary MR	254 (68 %)	183 (69 %)	71 (66 %)	
Secondary MR	118 (32 %)	81 (31 %)	37 (34 %)	
Prior ischemic heart disease, n (%)	128 (34 %)	93 (35 %)	35 (32 %)	0.29
Prior valvular intervention, n (%)	66 (18 %)	47 (18 %)	19 (18 %)	0.33
Prior aortic valve intervention, n (%)	47 (13 %)	33 (13 %)	14 (13 %)	0.36
Prior tricuspid valve intervention, n (%)	18 (5 %)	13 (5 %)	5 (5 %)	0.34
Prior mitral valve intervention, n (%)	19 (5 %)	12 (5 %)	7 (6 %)	0.63
Pre-TEER Echocardiographic parameters, mean ± SD				
Ejection fraction (%)	51.5 ± 14.7	50.55 ± 14.96	50.53 ± 13.99	0.94
Right ventricular systolic pressure (mmHg)	48.4 ± 18.3	50.58 ± 15.51	51.02 ± 14.58	0.75
LV dimension (d) (mm)	54.5 ± 18.4	54.73 ± 19.56	53.92 ± 15.33	0.72
LV dimension (s) (mm)	38.6 ± 15.8	38.57 ± 16.04	38.60 ± 15.35	0.95
Left atrial volume index (mL/m^2), median (IQR)	59.00 (28.25)	58.00 (27.00)	62.00 (37.25)	0.05
$VTI_{MV/LVOT}$	1.5 ± 0.6	1.4 ± 0.5	1.7 ± 0.6	<0.001

4. Results

A total of 648 patients were identified to have undergone TEER at our institutions between 07/01/2014 and 12/30/2021. Overall, 372 patients were included in this study with the remainder excluded due to incomplete TTE or follow-up data. There were no significant differences between the excluded and included cohorts in regard to age, sex, baseline EF and IHD (Supplementary table 1). Mean patient age was 78.7 ± 8.8 years and 68 % were male.

Baseline pre-procedure characteristics are described in Table 1. The most common comorbidity was hypertension, diagnosed in 82 % of patients. Diabetes and atrial fibrillation were present in 29 % and 31 % of patients, respectively. A total of 128 (34 %) patients had a diagnosis of coronary artery disease prior to TEER. Overall, 66 (18 %) patients had undergone previous valve intervention with 19 (5 %) patients having a prior MV intervention (either surgical or percutaneous). In 254 (68 %) patients the etiology of MR was primary with the remaining 118 (32 %) having secondary MR. No significant differences were seen between patients with high and low $VTI_{MV/LVOT}$ regarding baseline characteristics.

Pre-procedure TTE measurements are also presented in Table 1. TTEs occurred at a median of 28 (interquartile range [IQR] 7–29) days prior to TEER. Mean left ventricular EF was 51.5 % ± 14.7 % with a range from 15 % to 78 %. Overall, 215 (57.8 %) patients had impaired left ventricular systolic function as defined by EF < 50 %. The mean RVSP was elevated at 48.4 ± 18.3 mmHg. No significant differences were noted between patients with high and low $VTI_{MV/LVOT}$ regarding pre-TEER TTE measurements, except for a slightly higher pre-TEER $VTI_{MV/LVOT}$ in the high post-TEER $VTI_{MV/LVOT}$ group.

Post TEER TTEs occurred at a median of 37.5 (IQR 30–48) days post-procedure. There was no significant difference in the time to post TEER TTEs between the groups (39 days in low $VTI_{MV/LVOT}$ group compared to 36 days in high $VTI_{MV/LVOT}$ group, $p = 0.057$). Majority of patients (264, 71.0 %) had a low $VTI_{MV/LVOT}$ (<2.5), with the remainder (108, 29.0 %) having a high $VTI_{MV/LVOT} \geq 2.5$, Table 2**.** On expert multiparametric qualitative, semi-quantitative and quantitative assessment of post TEER TTEs, 58 patients (16 %) had a MR grading of moderate-severe or severe, while majority of the cohort had an MR grading of moderate or less (314, 84 %). The mean overall transmitral gradient post TEER was 4.22 ± 2.06 mmHg. Correlation between MR multiparametric impression vs $VTI_{MV/LVOT}$ was performed. In the 314 cases identified as ≤ moderate, 239 were also classified as low $VTI_{MV/LVOT}$ (239/314, 76 %). Of the 58 patients classified as moderate-severe or severe MR according to multiparametric impression, 33 were classified as high $VTI_{MV/LVOT}$ (33/58, 57 %). There was a significant positive correlation ($p < 0.001$) between multiparametric impression of MR and $VTI_{MV/LVOT}$, however the correlation was weak at 0.264 using nominal correlation testing. Correlation between MV mean gradient vs $VTI_{MV/LVOT}$ also had significant positive correlation ($p < 0.001$), however this was also weak-moderate (point biserial correlation for categorical and numerical variables 0.398).

Univariate Survival analysis – post TEER Echo measurements:

At one year follow up, 63 (16.9 %) patients died (Table 3). Of these, 24 (38 %) died of cardiac causes and 39 (62 %) patients died of non-cardiac causes. On univariable analysis, patients with high $VTI_{MV/LVOT} \geq 2.5$ had significantly increased risk of all-cause mortality (hazard ratio [HR] 2.10 [95%CI 1.28–3.45], $p = 0.003$, Fig. 2A), cardiac mortality (HR 3.03 [95%CI 1.36–6.76], $p = 0.004$, Fig. 2B), and MACE (HR 2.20 [95%CI 1.44–3.34], $p < 0.001$, Fig. 2C). This last finding was driven mainly by an increased risk in heart failure admissions (HR 2.28 [95%CI 1.40–3.70], $p < 0.001$, Fig. 2D), as risk of stroke and myocardial infarction were not significantly associated with high $VTI_{MV/LVOT}$ (HR 1.04 [95%CI 0.27–4.02], $p = 0.957$; and HR 1.23 [95%CI 0.31–4.91, $p = 0.773$, respectively).

A second analysis was performed to evaluate if the individual components of the $VTI_{MV/LVOT}$ ratio were associated with clinical outcomes. Univariable analysis of Doppler derived TTE measurements showed no significant relationship between VTI_{MV} and mortality (HR 1.01 [95%CI 0.99–1.03], $p = 0.323$) or MACE (HR 1.01 [95%CI 0.99–1.03], $p = 0.088$). Similarly, there was no significant risk associated with low post TEER VTI_{LVOT}, using a cutoff for reduced VTI_{LVOT} as < 17 cm, with mortality (HR 0.30 [95%CI 0.47–1.26], $p = 0.302$) and MACE (HR 0.71 [95%CI 0.71–1.67], $p = 0.707$).

Additional univariate analysis evaluated frequency of re-intervention of MV within the first year of TEER. High $VTI_{MV/LVOT} \geq 2.5$ was not statistically associated with re-intervention (HR 1.75 [95%CI 0.66–4.59], $p = 0.268$, **Fig. 3A). This result remained unchanged when evaluating only patients with transmitral gradient ≤ 5 mmHg (n = 292, HR 1.26 [95%CI 0.34–4.77], p = 0.729).**

Conversely, overall post-TEER multiparametric expert impression of MR, as "moderate-severe" or "severe" was significantly associated with MV-reintervention within one-year post TEER, compared to patients with MR multiparametric impression as "moderate", "mild-moderate", or "mild" (HR 6.61 [95%CI 2.55–17.13], p < 0.001, Fig. 3B).

Multivariate analysis using Cox Regression models adjusting for age, sex, diabetes, hypertension, atrial fibrillation, pre-operative EF and RVSP, and multiparametric expert impression of post TEER mitral regurgitation found high $VTI_{MV/LVOT}$ to be an independent

Table 2
Post TEER echocardiographic measurements for overall patient cohort and separated by $VTI_{MV/LVOT}$ cutoff of ≥2.5.

Mitral valve evaluation post-TEER	Overall patient cohort n = 372	Low $VTI_{MV/LVOT}$ (<2.5) N = 264	High $VTI_{MV/LVOT}$ (≥2.5) N = 108	p-value (Low vs High VTI ratio)
Mitral regurgitation severity on multiparametric expert assessment (moderate-severe or severe), n (%)	58 (15.6 %)	25 (9.5 %)	33 (30.6 %)	<0.001
Mitral valve inflow mean gradient (mmHg), mean ± SD	4.22 ± 2.06	3.73 ± 1.80	5.45 ± 2.16	<0.001
Mitral valve inflow VTI, mean ± SD	39.7 ± 12.3	35.9 ± 9.6	49.1 ± 13.1	<0.001
Left ventricular outflow tract VTI, mean ± SD	18.7 ± 4.8	19.6 ± 4.9	16.5 ± 4.6	<0.001

Table 3
Clinical outcomes at one year post TEER, for patients grouped by Low and High $VTI_{MV/LVOT}$.

Clinical outcomes at one year follow up	Low $VTI_{MV/LVOT}$ (<2.5) n = 264	High $VTI_{MV/LVOT}$ (≥2.5) n = 108	p-value
All-cause mortality, n (%)	35 (13.3 %)	28 (25.9 %)	**0.003**
Cardiac mortality, n (%)	11 (4.2 %)	13 (12.0 %)	**0.004**
MACE, n (%)	49 (18.6 %)	39 (36.1 %)	**<0.001**
Heart failure admissions, n (%)	36 (13.6 %)	30 (27.8 %)	**<0.001**
Stroke, n (%)	7 (2.3 %)	3 (2.8 %)	0.957
Myocardial infarction, n (%)	6 (2.3 %)	3 (2.8 %)	0.772
Re-intervention of mitral valve, n (%)	10 (3.8 %)	7 (6.5 %)	0.251

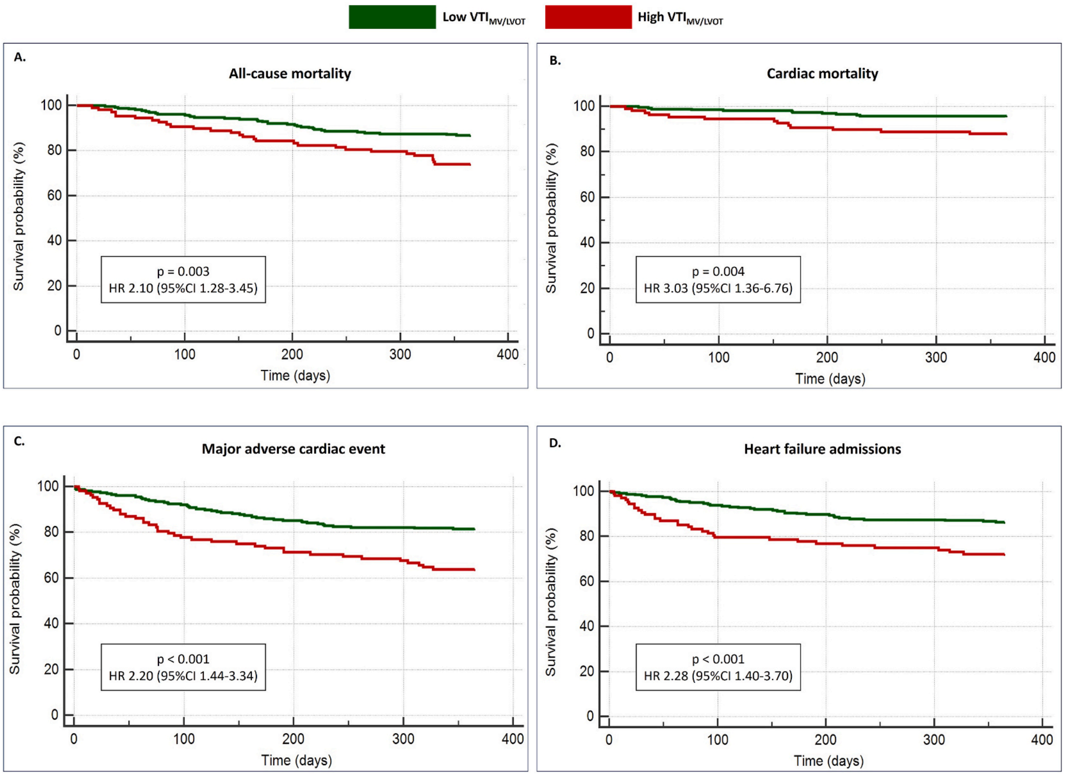

Fig. 2. Kaplan-Mayer curves for clinical outcomes at one year post MV TEER. **A.** Depicts overall all-cause mortality; **B**. Depicts mortality from cardiac causes; **C.** Depicts risk of major adverse cardiac events; **D.** Depicts risk of heart failure admissions. VTI: velocity-time integral; MV: mitral valve; LVOT: left ventricular outflow tract.

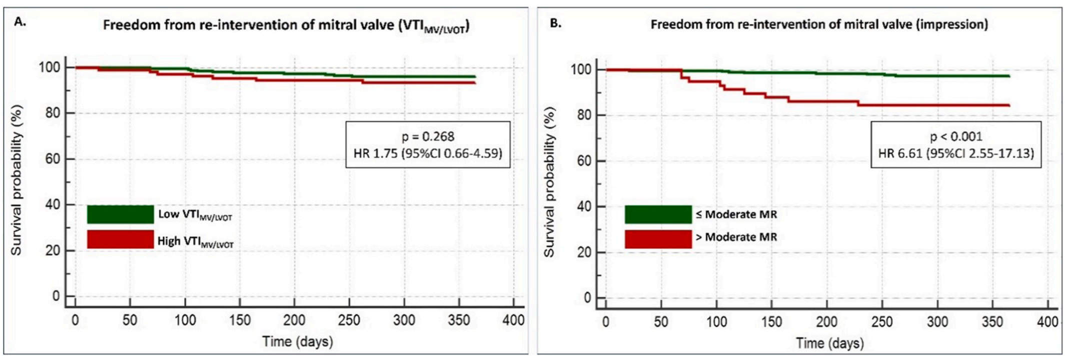

Fig. 3. Kaplan-Mayer curves depicting risk of re-intervention of MV one year post TEER. **A.** Risk associated with $VTI_{MV/LVOT}$ ratio; **B**. Risk associated with expert impression of residual MR from multiparametric quantitative and semi-quantitative assessment. VTI: velocity-time integral; MV: mitral valve; LVOT: left ventricular outflow tract; MR: mitral regurgitation.

risk factor for all measured outcomes at one year follow-up. High $VTI_{MV/LVOT}$ was the strongest predictor of all-cause mortality with HR 2.25 (95%CI 1.28–3.94, p = 0.005) (Table 4). High $VTI_{MV/LVOT}$ was also an independent risk factor for cardiac death (HR 2.75 [95%CI 1.12–6.80], p = 0.028) (Table 5), MACE (HR 2.03 [95%CI 1.28–3.20], p = 0.002) (Table 6I), and heart failure readmission (HR 2.24 [95%CI 1.33–3.76], p = 0.002) (Table 7).

5. Discussion

This study, among one of the largest studies of post TEER patients, highlights the clinical utility of the easy to acquire Doppler $VTI_{MV/LVOT}$ ratio in evaluating residual MV dysfunction compared to traditional methods. Furthermore, to our knowledge this is the first study to present the prognostic value of the $VTI_{MV/LVOT}$ ratio in a TEER cohort. Despite the well-known prognostic implication of residual MV dysfunction after TEER, its evaluation and quantification are challenging and often inaccurate [2,6,9]. Traditional echocardiographic parameters for assessing MR are often invalid post TEER, including PISA which assumes a single jet and constant flow [3,9]. Prior studies have suggested alternative methods of MR quantification though none have been thoroughly validated [8,9].

One proposed method of MR quantification following TEER is the assessment of vena contracta area (VCA) on 3-dimensional Doppler transesophageal echocardiography (TEE). Avenatti et al. found a significant improvement in VCA post TEER, with high VCA correlating with expert consensus of ≥ moderate MR [19]. There was, however, significant overlap in the VCA values for incremental severity of MR. Dietl et al. also evaluated the clinical utility of VCA, with patients undergoing follow-up TEE at four weeks post TEER [20]. This small study of 29 patients showed a correlation between the degree of reduction in VCA and clinical improvement in 6-min walk test. Ikenaga et al. suggested the assessment of pulmonary vein flow on TEE may correlate with residual MR [10]. Clinically, these methods require invasive TEE imaging following TEER and do not present a practical method of routine long-term surveillance for residual MV dysfunction.

Non-invasively, alternative imaging has also been suggested, though not validated. Hamilton-Craig et al. suggested the use of cardiac magnetic resonance imaging (MRI) to quantify residual MR post TEER, finding superior reproducibility compared to echocardiographic assessment [21]. However, they reported more than 30 % of their cohort were unable to undergo MRI due to arrhythmia or non-compatible devices. They also noted technical limitations of this method including artifact from the clips and non-perpendicular regurgitant flow that was unable to be captured [21]. Overall, though non-invasive, cardiac MRI has also not been validated and does not appear to be a practical technique for post TEER MV assessment.

Studies have previously demonstrated the utility of $VTI_{MV/LVOT}$ ratio in assessment of MV dysfunction following invasive surgical intervention, however it has not previously been assessed in MV TEER. As early as 1999, the use of Doppler derived $VTI_{MV/LVOT}$ was suggested for the evaluation of residual MR following surgical MV replacement. At that time, Olmos et al. suggested a cutoff of ≥2.5 to distinguish significant MR in mechanical prosthetic MVs [15]. In 2017, Luis et al. found $VTI_{MV/LVOT}$ to be a strong predictor of valve dysfunction in bioprosthetic MVs, with an overall specificity and sensitivity of 74.3 % and 75.5 % respectively, using a cutoff of $VTI_{MV/LVOT} \geq 2.3$ as abnormal (odds ratio (OR) 10.34, 95%CI 6.43–16.61, $p < 0.001$) [13]. Spencer et al. confirmed this, finding a cutoff $VTI_{MV/LVOT} > 2.5$ to have a sensitivity of 100 % and specificity of 95 % in detecting significant bioprosthetic MV dysfunction [12]. Palmiero et al. evaluated a similar ratio, $VTI_{MV/aortic\ valve}$, in patients post TEER of the MV. This group found a significant relationship between a ratio cutoff ≥1.02 and severe MR at six months post TEER, with a sensitivity of 87 % and specificity of 90 % [22]. The current study presents the reproducibility and reliability of the $VTI_{MV/LVOT}$ ratio. Using the cutoff value of $VTI_{MV/LVOT} \geq 2.5$ as previously documented, we have found this ratio to be valid for use in post TEER patients. Furthermore, there was a significant but weak correlation between the $VTI_{MV/LVOT}$ ratio and both expert multiparametric impression of residual MR and post-TEER MV mean gradient.

Importantly, in addition to quantification of residual valve dysfunction, our study has demonstrated that the $VTI_{MV/LVOT}$ ratio has significant prognostic value in the post TEER cohort. Previously, studies have identified several risk factors associated with poor prognosis post TEER. Sugiura et al. identified pre-operative left atrial volume to be an independent risk factor for recurrent MR and subsequent heart failure hospitalization and overall mortality [23]. Intra-operatively during TEER, additive and maximum vena contracta on TEE immediately after clip deployment were associated with significant persistent MR at one- and six-months follow-up [8]. Also, intra-operatively, another study has suggested pulmonary venous waveforms to be predictive of cardiac re-hospitalization at one-year post TEER [24]. In the current study, TTE measurement of $VTI_{MV/LVOT}$ has been obtained at the first outpatient TTE, to minimize impact of fluid status or hemodynamic instability. The COAPT trial in 2019 found pre-operative RVSP and Society of

Table 4
Multivariable analysis of all cause-mortality.

VARIABLE	HR	95%CI	p-value
$VTI_{MV/LVOT}$	**2.25**	**1.28–3.94**	**0.005**
Age	0.99	0.95–1.02	0.461
Sex	1.26	0.67–2.38	0.480
Diabetes	1.25	0.73–2.23	0.447
Hypertension	1.31	0.61–2.80	0.488
Ejection fraction	1.00	0.98–1.02	0.704
RVSP	1.01	1.00–1.03	0.104
Atrial Fibrillation	**2.17**	**1.04–4.53**	**0.039**
Mitral regurgitation on multiparametric impression	0.96	0.47–1.96	0.909

Table 5
Multivariable analysis of cardiac mortality.

VARIABLE	HR	95%CI	p-value
$VTI_{MV/LVOT}$	**2.75**	**1.12–6.80**	**0.028**
Age	1.04	0.97–1.11	0.259
Sex	1.06	0.38–2.91	0.918
Diabetes	1.87	0.74–4.74	0.189
Hypertension	4.65	0.61–35.15	0.137
Ejection fraction	0.99	0.96–1.03	0.626
RVSP	**1.03**	**1.00–1.06**	**0.035**
Atrial Fibrillation	2.05	0.59–7.09	0.258
Mitral regurgitation on multiparametric impression	1.32	0.47–3.76	0.600

Table 6
Multivariate analysis of major adverse cardiac event.

VARIABLE	HR	95%CI	p-value
$VTI_{MV/LVOT}$	**2.03**	**1.28–3.20**	**0.002**
Age	0.98	0.96–1.01	0.237
Sex	1.07	0.66–1.73	0.793
Diabetes	1.17	0.73–1.88	0.516
Hypertension	1.33	0.73–2.44	0.355
Ejection fraction	1.00	0.98–1.01	0.541
RVSP	**1.02**	**1.00–1.03**	**0.033**
Atrial Fibrillation	1.14	0.69–1.89	0.606
Mitral regurgitation on multiparametric impression	1.39	0.82–2.38	0.225

Table 7
Multivariate analysis of heart failure readmission.

VARIABLE	HR	95%CI	p-value
$VTI_{MV/LVOT}$	**2.24**	**1.33–3.76**	**0.002**
Age	0.98	0.95–1.02	0.324
Sex	0.87	0.50–1.51	0.624
Diabetes	1.43	0.85–2.20	0.184
Hypertension	1.35	0.66–2.77	0.415
Ejection fraction	0.99	0.97–1.00	0.110
RVSP	**1.02**	**1.00–1.04**	**0.031**
Atrial Fibrillation	1.37	0.76–2.50	0.299
Mitral regurgitation on multiparametric impression	1.04	0.55–1.97	0.899

Thoracic Surgeons (STS) score to be independent predictors of mortality and heart failure admission post TEER, however they are not specific for MV dysfunction [3]. Conversely, a study by Paranskaya et al. found no significant relationship between STS score and adverse outcomes after TEER [6].

To our knowledge, this is the first study to evaluate the prognostic value of post-TEER Doppler derived $VTI_{MV/LVOT}$ in TEER patients. Significantly, we found $VTI_{MV/LVOT}$ to independently predict all-cause mortality, cardiac mortality, MACE, and heart failure readmission at one year post procedure. This finding remained consistent when adjusting for expert multiparametric assessment of residual MR. Furthermore, there was no significance of the individual components (VTI_{LVOT} and VTI_{MV}) on clinical outcomes. This is different from findings of a recent study by Gentile et al. on native valve MR, which assessed only VTI_{LVOT} and found a significant relationship between this measurement and cardiac death [25]. Our findings suggest that the value of the ratio is more significant than any of each separate component, hence challenging any hypothesis that these findings may be related only to an improvement in VTI_{LVOT} secondary to a stroke volume increase after TEER. Therefore, this ratio may identify a cohort of patients who are at significantly higher risk for adverse outcome post TEER and may benefit from closer follow-up in the post-operative period. It may also suggest an avenue for more aggressive medical management in these patients, in particular in the setting of heart failure symptoms.

As described in the EVEREST II study, re-intervention of the MV post TEER is required in up to 28 % of patients at five years after intervention, however this study found only just over 5 % of patients required further intervention if they were event-free in the first 12 months [26]. High $VTI_{MV/LVOT}$ was not associated with re-intervention of the MV within one-year post TEER, even when analyzing only the population with a postoperative mean transmitral gradient of ≤ 5 mmHg [9]. Clinically, this is not altogether unsurprising as referral for re-intervention is often case-specific and historically relies upon both qualitative and quantitative assessment of residual MR, often via TEE. However, given the prognostic value of high $VTI_{MV/LVOT}$, this may assist in identifying patients with poor prognosis that may benefit from closer surveillance and more thorough imaging assessment for potential intervention of the MV.

5.1. Future directions

In the rapidly evolving era of artificial intelligence (AI), this easy to attain and highly reproducible measure may open the door for future machine learning models to predict prognosis and risk stratify patients undergoing TEER. This concept was discussed by Zweck et al., in 2021, who utilized AI to predict mortality at one-year post TEER. Their model incorporated metabolic factors including urea, hemoglobin, creatinine as well as mean arterial pressure, showing superiority in mortality prediction compared to traditional cardiovascular risk factors and previously reported risk scores [27]. This model, however, did not incorporate any echocardiographic measurements. Future studies may explore the potential utility of $VTI_{MV/LVOT}$ within similar AI algorithms.

6. Limitations

Though this study assesses one of the largest post TEER cohorts for clinical outcomes, it is limited in its duration of follow up. Outcomes are presented at one-year post-TEER, however longer follow-up may add to clinical utility of the $VTI_{MV/LVOT}$ ratio. Furthermore, the retrospective nature of this study may limit its overall validity in the global population. Of our TEER cohort, 276/648 (42.6 %) patients were excluded from analysis due to incomplete TTE follow up. This excluded cohort was evaluated and was noted to have no significant differences from the included cohort in regard to age, sex, baseline EF, and history of IHD. However, there is an potential risk of selection bias in the exclusion of these patients. Results of this study were not adjudicated by a core lab. Future prospective studies may allow for validation of this tool in a larger cohort.

7. Conclusions

$VTI_{MV/LVOT}$ is a valuable and easily obtainable measure for quantitatively evaluating and prognosticating patients post TEER. It is independently associated with significant mortality and morbidity at one-year post-procedure and identifies a cohort of patients that may benefit from increased post-operative surveillance and more aggressive medical management, including redo TEER where indicated.

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary Table 1
Baseline characteristic analysis of excluded cohort (n = 276) and included cohort (n = 372).

	Excluded cohort (N = 276)	Included cohort (N = 372)	p value
Age at time of TEER, years, mean ± SD	78.3 (10.1)	78.7 (8.8)	0.643
Sex (male), n (%)	171 (62.4 %)	244 (65.6 %)	0.404
Ischemic Heart Disease, n (%)	78 (28.3 %)	128 (34.4 %)	0.097
Baseline left ventricular ejection fraction (%), mean ± SD	51.4 ± 14.8	50.5 ± 14.7	0.457

CRediT authorship contribution statement

Isabel G. Scalia: Data curation, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. **Juan M. Farina:** Data curation, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. **Rachel Wraith:** Data curation, Investigation, Validation, Writing – review & editing. **Lisa Brown:** Data curation, Investigation, Visualization, Writing – review & editing. **Mohammed Tiseer Abbas:** Data curation, Investigation, Visualization, Writing – review & editing. **Milagros Pereyra:** Data curation, Investigation, Visualization, Writing – review & editing. **Mohamed Allam:** Data curation, Investigation, Visualization, Writing – review & editing. **Ahmed K. Mahmoud:** Investigation, Visualization, Writing – review & editing. **Moaz A. Kamel:** Investigation, Visualization, Writing – review & editing. **Timothy Barry:** Investigation, Visualization, Writing – review & editing. **F. David Fortuin:** Investigation, Visualization, Writing – review & editing. **Steven J. Lester:** Investigation, Visualization, Writing – review & editing. **John Sweeney:** Investigation, Visualization, Writing – review & editing. **Kristen A. Sell-Dottin:** Investigation, Visualization, Writing – review & editing. **Mohamad Alkhouli:** Investigation, Visualization, Writing – review & editing. **David R. Holmes:** Investigation, Visualization, Writing – review & editing. **Chieh-Ju Chao:** Investigation, Visualization, Writing – review & editing. **Said Alsidawi:** Investigation, Visualization, Writing – review & editing. **Chadi Ayoub:** Investigation, Supervision, Visualization, Writing – review & editing. **Reza Arsanjani:** Conceptualization, Investigation, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

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

References

[1] M. Enriquez-Sarano, C.W. Akins, A. Vahanian, Mitral regurgitation, Lancet. 373 (9672) (2009) 1382–1394.
[2] A. Hassan, M.F. Eleid, Recurrent mitral regurgitation after MitraClip: defining success and predicting outcomes, Circ Cardiovasc Interv 15 (3) (2022) e011837.
[3] F.M. Asch, P.A. Grayburn, R.J. Siegel, S. Kar, D.S. Lim, J.G. Zaroff, et al., Echocardiographic outcomes after transcatheter leaflet approximation in patients with secondary mitral regurgitation: the COAPT trial, J. Am. Coll. Cardiol. 74 (24) (2019) 2969–2979.
[4] T. Feldman, E. Foster, D.D. Glower, S. Kar, M.J. Rinaldi, P.S. Fail, et al., Percutaneous repair or surgery for mitral regurgitation, N. Engl. J. Med. 364 (15) (2011) 1395–1406.
[5] N. Buzzatti, M. De Bonis, P. Denti, F. Barili, D. Schiavi, G. Di Giannuario, et al., What is a "good" result after transcatheter mitral repair? Impact of 2+ residual mitral regurgitation, J. Thorac. Cardiovasc. Surg. 151 (1) (2016) 88–96.
[6] L. Paranskaya, G. D'Ancona, I. Bozdag-Turan, I. Akin, S. Kische, G.R. Turan, et al., Residual mitral valve regurgitation after percutaneous mitral valve repair with the MitraClip(R) system is a risk factor for adverse one-year outcome, Cathet. Cardiovasc. Interv. 81 (4) (2013) 609–617.
[7] S. Higuchi, M. Orban, L. Stolz, N. Karam, F. Praz, D. Kalbacher, et al., Impact of residual mitral regurgitation on survival after transcatheter edge-to-edge repair for secondary mitral regurgitation, JACC Cardiovasc. Interv. 14 (11) (2021) 1243–1253.
[8] E. Pozo Osinalde, A. Salinas Gallegos, X. Gordillo, L. Nombela Franco, P. Marcos-Alberca, P. Mahia, et al., Correlation of intraprocedural and follow up parameters for mitral regurgitation grading after percutaneous edge-to-edge repair, J. Clin. Med. 11 (9) (2022).
[9] W.A. Zoghbi, F.M. Asch, C. Bruce, L.D. Gillam, P.A. Grayburn, R.T. Hahn, et al., Guidelines for the evaluation of valvular regurgitation after percutaneous valve repair or replacement: a report from the American society of echocardiography developed in collaboration with the society for cardiovascular angiography and interventions, Japanese society of echocardiography, and society for cardiovascular magnetic resonance, J. Am. Soc. Echocardiogr. 32 (4) (2019) 431–475.
[10] H. Ikenaga, J. Yoshida, A. Hayashi, T. Nagaura, S. Yamaguchi, F. Rader, et al., Usefulness of intraprocedural pulmonary venous flow for predicting recurrent mitral regurgitation and clinical outcomes after percutaneous mitral valve repair with the MitraClip, JACC Cardiovasc. Interv. 12 (2) (2019) 140–150.
[11] K. Al-Azizi, M. Szerlip, Mitral stenosis after MitraClip: how to avoid and how to treat, Curr. Cardiol. Rep. 22 (7) (2020) 50.
[12] R.J. Spencer, K.G. Gin, M.Y.C. Tsang, T.S.M. Tsang, P. Nair, P.K. Lee, et al., Doppler parameters derived from transthoracic echocardiography accurately detect bioprosthetic mitral valve dysfunction, J. Am. Soc. Echocardiogr. 30 (10) (2017) 966–973 e1.
[13] S.A. Luis, L.A. Blauwet, H. Samardhi, C. West, R.A. Mehta, C.R. Luis, et al., Usefulness of mitral valve prosthetic or bioprosthetic time velocity index ratio to detect prosthetic or bioprosthetic mitral valve dysfunction, Am. J. Cardiol. 120 (8) (2017) 1373–1380.
[14] C. Mitchell, P.S. Rahko, L.A. Blauwet, B. Canaday, J.A. Finstuen, M.C. Foster, et al., Guidelines for performing a comprehensive transthoracic echocardiographic examination in adults: recommendations from the American society of echocardiography, J. Am. Soc. Echocardiogr. 32 (1) (2019) 1–64.
[15] L. Olmos, G. Salazar, J. Barbetseas, M.A. Quinones, W.A. Zoghbi, Usefulness of transthoracic echocardiography in detecting significant prosthetic mitral valve regurgitation, Am. J. Cardiol. 83 (2) (1999) 199–205.
[16] W.A. Zoghbi, D. Adams, R.O. Bonow, M. Enriquez-Sarano, E. Foster, P.A. Grayburn, 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. 30 (4) (2017) 303–371.
[17] D.S. Lim, H.C. Herrmann, P. Grayburn, K. Koulogiannis, G. Ailawadi, M. Williams, et al., Consensus document on non-suitability for transcatheter mitral valve repair by edge-to-edge therapy, Structural Heart 5 (3) (2021) 227–233.
[18] V. Bora, K.N. Brown, P. Agasthi, M.J. Lim, Catheter Management of Mitral Regurgitation, StatPearls Publishing, 2023 Feb 25 [Available from: https://www.ncbi.nlm.nih.gov/books/NBK536988/.
[19] E. Avenatti, G.B. Mackensen, K.C. El-Tallawi, M. Reisman, L. Gruye, C.M. Barker, et al., Diagnostic value of 3-dimensional vena contracta area for the quantification of residual mitral regurgitation after MitraClip procedure, JACC Cardiovasc. Interv. 12 (6) (2019) 582–591.
[20] A. Dietl, C. Prieschenk, F. Eckert, C. Birner, A. Luchner, L.S. Maier, et al., 3D vena contracta area after MitraClip(c) procedure: precise quantification of residual mitral regurgitation and identification of prognostic information, Cardiovasc. Ultrasound 16 (1) (2018) 1.
[21] C. Hamilton-Craig, W. Strugnell, N. Gaikwad, M. Ischenko, V. Speranza, J. Chan, et al., Quantitation of mitral regurgitation after percutaneous MitraClip repair: comparison of Doppler echocardiography and cardiac magnetic resonance imaging, Ann. Cardiothorac. Surg. 4 (4) (2015) 341–351.
[22] G. Palmiero, L. Ascione, C. Briguori, G. Carlomagno, C. Sordelli, R. Ascione, et al., The mitral-to-aortic flow-velocity integral ratio in the real world echocardiographic evaluation of functional mitral regurgitation before and after percutaneous repair, J. Intervent. Cardiol. 30 (4) (2017) 368–373.
[23] A. Sugiura, R. Kavsur, M. Spieker, C. Iliadis, T. Goto, C. Ozturk, et al., Recurrent mitral regurgitation after MitraClip: predictive factors, morphology, and clinical implication, Circ Cardiovasc Interv 15 (3) (2022) e010895.
[24] F.E. Corrigan 3rd, J.H. Chen, A. Maini, J.C. Lisko, L. Alvarez, N. Kamioka, et al., Pulmonary venous waveforms predict rehospitalization and mortality after percutaneous mitral valve repair, JACC Cardiovasc Imaging 12 (10) (2019) 1905–1913.
[25] F. Gentile, F. Buoncristiani, P. Sciarrone, L. Bazan, G. Panichella, S. Gasparini, et al., Left ventricular outflow tract velocity-time integral improves outcome prediction in patients with secondary mitral regurgitation, Int. J. Cardiol. 392 (2023) 131272.
[26] T. Feldman, S. Kar, S. Elmariah, S.C. Smart, A. Trento, R.J. Siegel, et al., Randomized comparison of percutaneous repair and surgery for mitral regurgitation: 5-year results of EVEREST II, J. Am. Coll. Cardiol. 66 (25) (2015) 2844–2854.
[27] E. Zweck, M. Spieker, P. Horn, C. Iliadis, C. Metze, R. Kavsur, et al., Machine learning identifies clinical parameters to predict mortality in patients undergoing transcatheter mitral valve repair, JACC Cardiovasc. Interv. 14 (18) (2021) 2027–2036.