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Overall impact of tethering and of its symmetric and asymmetric subtypes on early and long-term outcome of transcatheter edge-to-edge repair of significant mitral valve regurgitation

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ABSTRACT

Background: Tethering is a common condition of the mitral valve apparatus in the presence of significant regurgitation. Its impact on outcomes of transcatheter edge-to-edge repair (TEER) remains poorly characterized.
Methods: We appraised the prevalence, features, procedural details, and outcomes of patients with or without mitral valve tethering in a prospective multicenter observational study. The primary endpoint was the risk of cardiac death or rehospitalization for heart failure at mid-term follow-up.
Results: We included 2238 patients, 1467 (65.5 %) without tethering and 771 (34.5 %) with tethering (487 [21.8 %] with symmetric and 284 [12.7 %] with asymmetric tethering). Several differences in baseline features were evident among groups, yet procedural results were similar. After a median of 14 months, rates of cardiac death or rehospitalization for heart failure was significantly higher at unadjusted analysis in patients with tethering (191

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[24.8 %] vs. 272 [18.5 %] in those without tethering, $p = 0.001$), but weres similar between tethering subtypes ($p = 0.666$). At adjusted analysis, the presence of any tethering was no longer a significant predictor of cardiac death or rehospitalization for heart failure, and the same results were obtained focusing on tethering subtypes (all $p > 0.05$).

Conclusions: Tethering is common among patients with an indication to TEER, and is associated with adverse baseline and procedural features. In spite of this, device and procedural success rates are not significantly impacted by the presence of tethering that does not even have a negative prognostic effect at follow-up. Accordingly, tethering should not be considered a contraindication to TEER in suitable patients.

1. Introduction

Careful patient selection is paramount for TEER, and should entail detailed evaluation of the mechanisms and features of MR. [1] Tethering of the mitral valve is not uncommon in patients with significant mitral regurgitation, especially in case of secondary valve disease, and it involves symmetric or asymmetric displacement or pulling of the valve leaflets, adversely impacting on regurgitation severity. [2,3] Of note, tethering has previously been shown as a determinant of failure of surgical valve repair. [4] Moreover, tethering may also impact on the feasibility as well as acute and long-term results of TEER, as it may impede adequate grasping and thus effective clipping of the mitral leaflets. [5–7]

Previous data on the impact of tethering on acute and long-term results of TEER are limited, with conflicting reports on its role for clinical decision-making. [5,8,9] In particular, it is not clear whether tethering is simply an epiphenomenon of more adverse cardiac and valvular remodeling, or a specific unfavorable feature with an independent impact on acute results and follow-up outcomes of patients undergoing TEER. [5,7,10,11], This is even more true in current clinical practice, given the evolution in TEER devices and techniques that has extended the application of this therapy to more complex anatomic conditions. [12–14]

Thus, we aimed at appraising the features of patients with tethering undergoing TEER for significant MR, as well as quantifying the impact of tethering on procedural results and long-term outcomes, also trying to disentangle the independent prognostic impact of such anatomical feature, leveraging the evidence base stemming from the ongoing GIOTTO (GIse registry Of Transcatheter treatment of mitral valve regurgitaTiOn) prospective multicenter observational registry. [15]

2. Methods

This work was designed as an exploratory analysis stemming from the ongoing GIOTTO registry. Details of this registry have already been reported extensively, and its main features are also provided on an online trial registry (ClinicalTrials.gov identifier: NCT03521921). [15–19] Briefly, the GIOTTO study is an observational multicenter prospective study including all patients in whom TEER with the MitraClip was attempted at participating centers. All patients provided written informed consent for participation and study procedures. Indications, techniques and ancillary treatments were all at physicians' discretion, but established procedures were used for clinical screening, baseline imaging, and clinical as well as imaging evaluation. Transthoracic and transesophageal echocardiography was performed in all patients before TEER, enabling a comprehensive assessment of cardiac dimensions and function, and a detailed appraisal of mitral valve. On top of severity of regurgitation, coaptation depth (defined as the distance between the leaflet tips and the mitral annular plane) and tenting height (defined as the vertical distance from the annular plane to the leaflet coaptation point) were accurately measured by an expert echocardiographer.

Several outcomes were collected, ranging from device and procedural success to in-hospital adverse events, including death, bleeding, vascular complication, and duration of stay. Follow-up outcomes, including death, cardiac death, rehospitalization and rehospitalization for heart failure were also routinely evaluated and entered into a dedicated electronic case report form maintained by Airon Telematica, Milan, Italy. For the purpose of the present work focusing on tethering, we defined as primary outcome of interest the composite of cardiac death or rehospitalization for heart failure.

The analytical approach was based on distinguishing patients with tethering from those without, and then subdividing tethering into the asymmetric and symmetric subtypes during baseline transesophageal echocardiography, in keeping with Agricola et al. [20] Notably, tethering was defined as the apical and outward displacement of the mitral valve leaflets due to left ventricular remodeling, leading to restricted leaflet motion and impaired coaptation. We subclassified tethering into symmetric and asymmetric patterns based on assessment of leaflet displacement. Symmetric tethering was adjudicated when both anterior and posterior leaflets were equally displaced apically, resulting in a centrally directed regurgitant jet. Conversely, asymmetric tethering was adjudicated when one leaflet was more displaced than the other, leading to an eccentrically directed regurgitant jet. All echocardiography assessments were performed by TEER experienced operators and confirmed during multidisciplinary heart team meetings.

Descriptive variables are reported hereby as median (1st; 3rd quartile) and categorical variables as count (%). Mann-Withney U and Kolmogodorov-Smirnov tests were exploited for use for bivariate analysis of continuous variables, given their greater robustness and less lenience on outliers. Fisher exact test was used for categorical variables, except for computationally unsuitable scenarios, where chi-squared test was used. Thus, 5 sets of p values were generated: p for the overall comparison, p for the tethering vs no tethering comparison, p for the symmetric tethering vs no tethering comparison, p for the asymmetric tethering vs no tethering comparison, and p for the symmetric vs asymmetric tethering comparison. Time-to-event analysis was performed creating Kaplan-Meier plots and comparing failure curves with the Tarone-Ware test. In addition, Cox proportional hazard models were used, computing hazard ratios (HR) with 95 % confidence intervals, for bivariate and multivariable adjusted analyses. Computations were performed with Stata 18 (StataCorp, College Station, TX, USA). *P* values are reported throughout without any multiplicity adjustment, picking as cut-off a 0.05 two-tailed threshold. Notably, in all tables p for overall refers to the comparison of 'no tethering' vs 'symmetric tethering' vs 'asymmetric tethering';

3. Results

A total of 2238 patients in whom TEER was attempted at participating centers between 2016 and 2023 were included (Table 1). Notably, 1467 (65.5 %) did not exhibit tethering, whereas 771 (34.5 %) had tethering, with 487 (21.8 %) displaying symmetric and 284 (12.7 %) asymmetric subtypes. Several significant differences in baseline features were evident, including age, gender, functional class, history of smoking, chronic obstructive pulmonary disease, renal dysfunction, atrial fibrillation, carotid or peripheral artery disease, comorbidities such as diabetes mellitus, dyslipidemia, prior myocardial infarction, hospitalization for heart failure, prior implantation of pacemaker or implantable-cardioverter defibrillator, coronary artery disease, coronary revascularization, coronary artery bypass grafting, mitral valve repair, any

Table 1
Baseline features.

Feature	No tethering	Any tethering	Symmetric tethering	Asymmetric tethering	P overall*	P no vs any tethering	P no vs symmetric tethering	P no vs asymmetric tethering	P symmetric vs asymmetric tethering
Patients	1467	771	487	284	–	–	–	–	–
Age (years)	79 (72; 83)	76 (69; 81)	76 (69; 81)	75 (69; 81)	<0.001	<0.001	<0.001	<0.001	0.921
Female gender	576 (39.3 %)	245 (31.8 %)	153 (31.4 %)	92 (32.4 %)	0.002	0.001	0.002	0.033	0.810
Body mass index	24.7 (22.3; 27.7)	24.8 (22.3; 27.6)	24.6 (22.2; 27.3)	25.3 (22.6; 27.9)	0.126	0.782	0.416	0.101	0.041
Diabetes mellitus					<0.001	<0.001	<0.001	0.062	0.652
No	1121 (76.4 %)	534 (69.3 %)	332 (68.2 %)	202 (71.1 %)	–	–	–	–	–
Diet	28 (1.9 %)	30 (3.9 %)	22 (4.5 %)	8 (2.8 %)	–	–	–	–	–
Oral Rx	194 (13.2 %)	101 (13.1 %)	64 (13.1 %)	37 (13.0 %)	–	–	–	–	–
IDDM	124 (8.5 %)	106 (13.8 %)	69 (14.2 %)	37 (13.0 %)	–	–	–	–	–
Dyslipidemia	362 (24.7 %)	384 (49.8 %)	228 (46.8 %)	156 (54.9 %)	<0.001	<0.001	<0.001	<0.001	0.031
Hypertension	1062 (72.4 %)	344 (70.6 %)	344 (70.6 %)	216 (76.1 %)	0.921	0.450	0.215	0.215	0.112
Smoking history	124 (8.5 %)	201 (26.1 %)	119 (24.4 %)	82 (28.9 %)	<0.001	<0.001	<0.001	<0.001	0.202
Prior mitral repair	57 (3.9 %)	12 (1.6 %)	8 (1.6 %)	4 (1.4 %)	0.010	0.002	0.019	0.034	1
Prior myocardial infarction	384 (26.2 %)	343 (44.5 %)	201 (41.3 %)	142 (50.0 %)	<0.001	<0.001	<0.001	<0.001	0.020
Prior hospitalization for heart failure	730 (49.8 %)	523 (67.8 %)	323 (66.3 %)	200 (70.4 %)	<0.001	<0.001	<0.001	<0.001	0.263
Coronary artery disease	488 (33.3 %)	422 (54.7 %)	256 (52.6 %)	166 (58.5 %)	<0.001	<0.001	<0.001	<0.001	0.116
Prior revascularization	90 (26.9 %)	141 (36.8 %)	82 (36.0 %)	59 (38.1 %)	0.016	0.005	0.025	0.015	0.746
Prior CABG	171 (11.7 %)	145 (18.8 %)	89 (18.3 %)	56 (19.7 %)	<0.001	<0.001	<0.001	<0.001	0.634
Prior cardiac surgery	310 (21.1 %)	202 (26.2 %	121 (24.9 %)	81 (28.5 %)	0.013	0.008	0.089	0.008	0.271
Aortic valve disease					0.040	0.995	0.236	0.094	0.002
No	1037 (70.7 %)	551 (71.5 %)	366 (75.2 %)	185 (65.1 %)	–	–	–	–	–
Mild stenosis	34 (2.3 %)	18 (2.3 %)	10 (2.1 %)	8 (2.8 %)	–	–	–	–	–
Moderate stenosis	24 (1.6 %)	12 (1.6 %)	11 (2.3 %)	1 (0.4 %)	–	–	–	–	–
Regurgitation	350 (23.9 %)	180 (23.4 %)	95 (19.5 %)	85 (29.9 %)	–	–	–	–	–
Mixed disease	22 (1.5 %)	10 (1.3 %)	5 (1.0 %)	5 (1.8 %)	–	–	–	–	–
Prior PM implantation					<0.001	<0.001	<0.001	0.001	0.072
No	964 (65.7 %)	395 (51.2 %)	240 (49.3 %)	155 (54.6 %)	–	–	–	–	–
Monocameral	139 (9.5 %)	67 (8.7 %)	37 (7.6 %)	30 (10.6 %)	–	–	–	–	–
Bicameral	197 (13.4 %)	148 (19.2 %)	105 (21.6 %)	43 (15.1 %)	–	–	–	–	–
Biventricular	167 (11.4 %)	161 (20.9 %)	105 (21.6 %)	56 (19.7 %)	–	–	–	–	–
Prior ICD implantation	373 (25.4 %)	314 (40.7 %)	206 (42.3 %)	108 (38.0 %)	<0.001	<0.001	<0.001	<0.001	0.255
AF	242 (16.5 %)	240 (31.1 %)	143 (29.4 %)	97 (34.2 %)	<0.001	<0.001	<0.001	<0.001	0.171
Prior AF ablation	8 (0.6 %)	9 (1.2 %)	7 (1.4 %)	2 (0.7 %)	0.144	0.126	0.068	0.670	0.498
Prior LAAC	3 (0.2 %)	10 (1.3 %)	7 (1.4 %)	3 (1.1 %)	0.004	0.002	0.003	0.058	0.753
Peripheral artery disease	83 (5.7 %)	86 (11.2 %)	55 (11.3 %)	31 (10.9 %)	<0.001	<0.001	<0.001	0.002	0.906
Carotid artery disease	28 (1.9 %)	20 (2.6 %)	8 (1.6 %)	12 (4.2 %)	0.033	0.286	0.847	0.027	0.035
COPD	184 (12.5 %)	156 (20.2 %)	97 (19.9 %)	59 (20.8 %)	<0.001	<0.001	<0.001	<0.001	0.781
Frailty	275 (18.8 %)	384 (49.8 %)	240 (49.3 %)	144 (50.7 %)	<0.001	<0.001	<0.001	<0.001	0.710
Logistic EuroSCORE	10.5 (6.5; 17.7)	12.0 (6.3; 20.4)	12.1 (6.5; 20.9)	11.7 (6.3; 20.1)	0.143	0.059	0.058	0.303	0.552
EuroSCORE II	4.3 (2.6; 7.1)	5.5 (3.3; 9.9)	5.4 (3.3; 10.7)	5.7 (3.3; 8.8)	<0.001	<0.001	<0.001	<0.001	0.668
STS score	3.2 (1.7; 5.8)	3.7 (2.0; 6.3)	3.6 (2.0; 6.3)	3.8 (2.1; 6.3)	0.112	0.043	0.139	0.061	0.592
Prior syncope	51 (3.5 %)	40 (5.2 %)	22 (4.5 %)	18 (6.3 %)	0.070	0.056	0.334	0.030	0.313

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cardiac surgery, or left atrial appendage occlusion, as well as surgical risk and frailty scores (all $p < 0.05$). Notably, asymmetric tethering was more usually (but not invariably) associated with adverse clinical features than symmetric tethering (eg myocardial infarction, $p = 0.020$).

Focusing on echocardiographic features, tethering was also associated with significant differences in severity and etiology of mitral regurgitation, systolic function, cardiac dimensions, and presence of leaflet prolapse, flail or calcification (all $p < 0.05$)(Table 2). Notably, some adverse features were more common in patients with symmetric tethering (eg reduced left ventricular ejection fraction, $p = 0.011$).

Despite such remarkable differences, acute results and inhospital outcomes were largely similar irrespective of the presence or type of tethering, including device success and procedural success, even if patients with tethering required the implantation of more MitraClips ($p < 0.001$, Table 3).

Furthermore, we explored the impact of different MitraClip generations on success rates, according to the presence and features of tethering, with some evidence that last-generation MitraClip (i.e. XTr) may be associated with better acute results (Table 1S).

While final results in terms of regurgitation severity were similar in the groups under comparison, smoke like effect was more evidence in patients with tethering. Notably, no significant differences in inhospital rates of death, vascular complication, or bleeding were evident (all $p > 0.05$), with only marginally different hospital stays.

After a median follow-up of 14 months, the risk of cardiac death or rehospitalization for heart failure appeared significantly higher at unadjusted analysis in patients with tethering (191 [24.8 %] vs 272 [18.5 %] in those without tethering, $p = 0.001$), despite no significant differences according to tethering subtype (118 [24.2 %] for symmetric tethering vs 73 [25.7 %] for asymmetric tethering, $p = 0.666$)(Table 4). Similar trends were observed for death, rehospitalization, rehospitalization for heart failure and the composite of death or rehospitalization. Time-to-event analysis confirmed such differences (Fig. 1), with accompanying significant findings at unadjusted Cox proportional hazard analysis (Table 5). However, at multivariable adjusted analysis, even when using different modeling strategies (Table 5, Table 2S), the presence of any tethering was no longer a significant predictor of cardiac death or rehospitalization for heart failure, and the same results were obtained focusing on tethering subtypes (all $p > 0.05$). The same non-significant differences were found for the death, cardiac death or the composite of death or hospitalization, despite persistently significant differences at adjusted analyses for rehospitalization and rehospitalization for heart failure. Durability of MR reduction over time was satisfactory, overall as well as at subgroup analysis according to presence and type of tethering (Table 3, Table 4, Fig. 2).

Given the importance of disentangling the role of mitral regurgitation etiology on short- and long-term outcomes, we run several additional analyses, excluding patients with degenerative mitral regurgitation in unadjusted analysis, and adding mitral regurgitation etiology as covariate in multivariable analyses, showing that similar findings for both inhospital and follow-up outcomes were obtained throughout (Table 3S, Table 4S).

4. Discussion

This investigation originating from the ongoing prospective GIOTTO study provides a detailed perspective of the role of TEER in patients with mitral valve tethering. Indeed, while tethering often correlates with adverse patient and anatomic features, it did not significantly impact on clinical outcomes or their composite, once these potential confounding factors were correctly addressed. The implications of this work are substantial, as they imply that tethering per se should not be considered a contraindication against TEER, a key factor for decision-making, or an independent prognostic factor to manage patients after TEER.

The pathological mechanisms that cause significant MR are manifold, and indeed all structures forming the mitral apparatus should be considered in detail before placing an indication for a TEER procedure. [21,22] Among the various mechanisms potentially leading to regurgitation, tethering is not uncommon, and it is defined as displacement of the papillary muscles, such that leaflet motion tethers resulting in incomplete leaflet coaptation and secondary MR. [23] Typically, tethering is distinguished as symmetric or asymmetric, and may be present in primary or secondary MR. Usually, it is found much earlier in the natural history of the disease in case of functional MR. [24] Several follow-up studies evaluated patients with significant MR who were managed conservatively and highlighted the prognostic importance of tethering. Similarly, other studies, albeit of smaller size, showed the importance of this anatomic condition when MR was corrected with surgery or TEER. [5–9,25] Yet, the paucity of evidence limits the possibility of informed decision-making.

We hereby present a detailed analysis of a large prospective study on TEER with several generations of the MitraClip device, explicitly focusing on the presence vs absence of leaflet tethering at screening imaging, their correlates, their impact on procedural and also subsequent outcomes, at face value and after adjustment for other potentially relevant prognostic factors. We found indeed that tethering, especially symmetric, is not uncommon in individuals undergoing TEER, and that patients with tethering differ substantially from those without such features. For instance, those with tethering had more frequently cardiovascular risk factors, established atherosclerotic disease, functional class, and adverse surgical features. Similarly adverse characteristics were evident when cardiac dimensions and function were attentively appraised. Notably, for some of these features individuals with asymmetric and symmetric tethering did not differ significantly (eg functional class), whereas for some characteristics symmetric tethering was associated with worse figures (eg LVEF) and for others this applied to asymmetric tethering (eg history of prior myocardial infarction). Despite this veritable plethora of differences, short-term outcomes were

Table 1 (*continued*)

Feature	No tethering	Any tethering	Symmetric tethering	Asymmetric tethering	P overall*	P no vs any tethering	P no vs symmetric tethering	P no vs asymmetric tethering	P symmetric vs asymmetric tethering
NYHA Class					0.002	0.002	0.001	0.159	0.156
I	25 (1.7 %)	9 (1.2 %)	8 (1.7 %)	1 (0.4 %)	–	–	–	–	–
II	338 (23.1 %)	185 (24.1 %)	119 (24.5 %)	66 (23.3 %)	–	–	–	–	–
III	998 (68.2 %)	485 (63.2 %)	296 (61.0 %)	189 (66.8 %)	–	–	–	–	–
IV	102 (7.0 %)	89 (11.6 %)	62 (12.8 %)	27 (9.5 %)	–	–	–	–	–
Serum creatinine	1.2 (1.0; 1.7)	1.3 (1.0; 1.8)	1.3 (1.0; 1.8)	1.3 (1.1; 1.8)	0.011	0.003	0.032	0.012	0.537

* p for overall refers to the comparison of 'no tethering' vs 'symmetric tethering' vs 'asymmetric tethering'; AF = atrial fibrillation; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; ICD = implantable cardioverter-defibrillator; IDDM = insulin-dependent diabetes; LAAC = left atrial appendage closure; NYHA = New York Heart Association; PM = pacemaker; STS=Society of Thoracic Surgeons.

Table 2
Imaging and electrocardiographic features.

Feature	No tethering	Any tethering	Symmetric tethering	Asymmetric tethering	P overall*	P no vs any tethering	P no vs symmetric tethering	P no vs asymmetric tethering	P symmetric vs asymmetric tethering
Patients	1467	771	487	284	–	–	–	–	–
Severe mitral regurgitation	1166 (79.5 %)	580 (75.2 %)	369 (75.8 %)	211 (74.3 %)	0.061	0.024	0.086	0.057	0.666
MR etiology					<0.001	<0.001	<0.001	<0.001	0.002
Degenerative	625 (42.6 %)	85 (11.0 %)	66 (13.6 %)	19 (6.7 %)	–	–	–	–	–
Functional dilated	374 (25.5 %)	287 (37.2 %)	191 (39.2 %)	96 (33.8 %)	–	–	–	–	–
Functional ischemic	304 (20.7 %)	323 (41.9 %)	189 (38.8 %)	134 (47.2 %)	–	–	–	–	–
Mixed	164 (11.2 %)	76 (9.9 %)	41 (8.4 %)	35 (12.3 %)	–	–	–	–	–
LVEF (%)	46 (33; 59)	35 (26; 45)	32 (25; 44)	36 (28; 45)	<0.001	<0.001	<0.001	<0.001	0.011
LVEDD (mm)	57 (51; 64)	61 (55; 69)	61 (55; 69)	61 (54; 69)	<0.001	<0.001	<0.001	<0.001	0.500
LVESD (mm)	41 (33; 52)	48 (38; 57)	48 (39; 57)	47 (38; 56)	<0.001	<0.001	<0.001	<0.001	0.540
LVEDV (mL)	135 (102; 180)	167 (122; 210)	172 (122; 215)	160 (121; 208)	<0.001	<0.001	<0.001	<0.001	0.139
LVESV (mL)	69 (44; 111)	108 (70; 149)	113 (70; 153)	100 (68; 142)	<0.001	<0.001	<0.001	<0.001	0.049
Mean mitral gradient (mm Hg)	2 (1; 3)	2 (2; 3)	2 (1; 3)	2 (2; 2)	0.971	0.957	0.897	0.932	0.794
Leaflet prolapse	528 (36.0 %)	109 (14.1 %)	60 (12.3 %)	49 (17.3 %)	<0.001	<0.001	<0.001	<0.001	0.068
Leaflet flail	399 (27.2 %)	58 (7.5 %)	36 (7.4 %)	22 (7.8 %)	<0.001	<0.001	<0.001	<0.001	0.888
Coaptation depth (mm)	9 (7; 11)	9 (7; 12)	10 (7; 13)	9 (6; 12)	0.282	0.162	0.111	0.457	0.462
Tenting area (cm^2)	2.1 (1.6; 2.8)	2.1 (1.5; 3.0)	2.2 (1.6; 3.0)	2.0 (1.4; 2.9)	0.142	0.387	0.176	0.922	0.771
Severe calcification	52 (3.5 %)	55 (7.1 %)	28 (5.8 %)	27 (9.5 %)	<0.001	<0.001	0.047	<0.001	0.059
TR					0.078	0.013	0.036	0.201	0.937
No	83 (5.7 %)	29 (3.8 %)	18 (3.7 %)	11 (3.9 %)	–	–	–	–	–
Mild	561 (38.2 %)	283 (36.7 %)	182 (37.4 %)	101 (35.6 %)	–	–	–	–	–
Moderate	648 (44.2 %)	334 (43.3 %)	207 (42.5 %)	127 (44.7 %)	–	–	–	–	–
Severe	175 (11.9 %)	125 (16.2 %)	80 (16.4 %)	45 (15.9 %)	–	–	–	–	–
SPAP (mm Hg)	45 (38; 55)	45 (35; 55)	45 (35; 55)	45 (35; 55)	0.476	0.247	0.434	0.283	0.700
RBBB	24 (1.6 %)	32 (4.2 %)	12 (2.5 %)	20 (7.0 %)	<0.001	0.001	0.245	<0.001	0.004
LBBB	36 (2.5 %)	46 (6.0 %)	27 (5.5 %)	19 (6.7 %)	<0.001	<0.001	0.002	0.001	0.531

* p for overall refers to the comparison of 'no tethering' vs 'symmetric tethering' vs 'asymmetric tethering'; LBBB = left bundle branch block; LVEDD = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVESV = left ventricular end-systolic volume; MR = mitral regurgitation; RBBB = right bundle branch block; SPAP = systolic pulmonary artery pressure; TR = tricuspid regurgitation.

surprisingly similar, irrespective of the presence or subtype of tethering. This applied to device and procedural success rates, as well as clinically relevant inhospital outcomes. Subsequent event rates were apparently less reassuring, and suggested that tethering could indeed play an ominous role in shaping patient prognosis, such that fatal and non-fatal outcomes were largely disfavoring those with tethering. For this analysis there was no apparent disconnect between some symmetric and asymmetric tethering, with most events indeed being similarly more common with these valve defects than without. Yet, at the ultimate test, ie at multivariable adjusted analysis, tethering lost all its adverse prognostic role on fatal outcomes or their composite. In keeping with these results, and the significant association between tethering and rehospitalizations, two alternative hypothesis can be formulated. The first, which we consider more plausible, it that tethering is mainly a bystander and correlate of other patient features, in keeping with the apparently reassuring short-term results. An alternative hypothesis is that tethering is an independent prognostic feature, but mainly for non-fatal outcomes, at least in a relatively large registry such as GIOTTO. Notably, when focusing on surgical mitral valve repair, annuloplasty leveraging an relatively small ring, capable of reducing the distance of the mitral leaflet from the lateral septum, may yield better results. [26,27] A similar premise could apply to the results of TEER.

Irrespective of the above hypotheses, it is clear that, in light of prior evidence and our own results, the presence or subtype of tethering should not be considered per se as a contraindication to TEER. Conversely, the patient as a whole, in terms of clinical features, operative risk, and valve anatomy, should be appraised attentively. This holds true for routine practice, but also when considering expanding indications to other niche patient groups, or when designing future clinical studies. [28,29] At the same time, it is clear that our work indirectly reinforces the need for careful preprocedural imaging, subsequent careful planning, and then procedural personalization of TEER technique. [30,31] An intriguing question is indeed whether tethering in general, or one of its subtypes, warrants specific procedural choices or dedicated devices, even if the versatility of TEER makes it a competitive option in the present and near future. [32] On a somber note, the careful reader will have recognized that patients with tethering eventually received more MitraClips, and more of the XTr type. [13] Furthermore, on a cautionary note, patients with tethering also eventually showed a higher prevalence of smoke-like effect and a higher mitral valve gradient

Table 3
Procedural and inhospital details.

Feature	No tethering	Any tethering	Symmetric tethering	Asymmetric tethering	P overall*	P no vs any tethering	P no vs symmetric tethering	P no vs asymmetric tethering	P symmetric vs asymmetric tethering
Patients	1467	771	487	284	–	–	–	–	–
Effective MitraClip implantation	1460 (99.5 %)	768 (99.6 %)	484 (99.4 %)	284 (100 %)	0.500	1	0.717	0.607	0.301
Device success	1438 (98.0 %)	748 (97.0 %)	475 (97.5 %)	273 (96.1 %)	0.149	0.141	0.584	0.078	0.279
Procedural success	1406 (95.8 %)	737 (95.6 %)	467 (95.9 %)	270 (95.1 %)	0.792	0.825	1	0.524	0.590
MitraClips used					<0.001	<0.001	0.001	0.006	0.709
1	641 (43.7 %)	263 (34.1 %)	165 (33.9 %)	98 (34.5 %)	–	–	–	–	–
2	701 (47.8 %)	422 (54.7 %)	265 (54.4 %)	157 (55.3 %)	–	–	–	–	–
3 or more	118 (8.0 %)	83 (10.8 %)	54 (11.1 %)	29 (10.2 %)	–	–	–	–	–
Use of NT	759 (51.7 %)	498 (64.6 %)	308 (63.2 %)	190 (66.9 %)	<0.001	<0.001	<0.001	<0.001	0.311
Use of NTr	247 (16.8 %)	127 (16.5 %)	82 (16.8 %)	45 (15.9 %)	0.916	0.858	1	0.728	0.763
Use of XTr	587 (40.0 %)	186 (24.1 %)	121 (24.9 %)	65 (22.9 %)	<0.001	<0.001	<0.001	<0.001	0.601
Fluoroscopy time (minutes)	1.1 (0.6; 1.7)	1.0 (0.4; 1.7)	0.8 (0.4; 1.5)	1.3 (0.6; 1.7)	<0.001	<0.001	<0.001	0.598	<0.001
Smoke like effect	46 (3.1 %)	98 (12.7 %)	62 (12.7 %)	36 (12.7 %)	<0.001	<0.001	<0.001	<0.001	1
Final MVG (mm Hg)	3 (2; 4)	3 (2; 4)	3 (2; 4)	3 (2; 4)	0.071	0.046	0.021	0.551	0.265
Final MR					0.431	0.159	0.404	0.242	0.924
None	3,333,333,333	497 (64.5 %)	315 (64.7 %)	182 (64.1 %)	–	–	–	–	–
Mild	477 (32.5 %)	235 (30.5 %)	149 (30.6 %)	86 (30.3 %)	–	–	–	–	–
Moderate	52 (3.5 %)	21 (2.7 %)	13 (2.7 %)	8 (2.8 %)	–	–	–	–	–
Severe	19 (1.3 %)	18 (2.3 %)	10 (2.1 %)	8 (2.8 %)	–	–	–	–	–
Final SPAP (mm Hg)	40 (33; 49)	40 (32; 45)	40 (32; 45)	40 (32; 47)	0.056	0.025	0.019	0.349	0.387
Inhospital outcomes									
Death	37 (2.5 %)	25 (3.2 %)	16 (3.3 %)	9 (3.2 %)	0.547	0.344	0.420	0.542	1
Vascular complication	11 (0.8 %)	5 (0.7 %)	3 (0.6 %)	2 (0.7 %)	1	1	1	1	1
Bleeding	14 (1.0 %)	6 (0.8 %)	4 (0.8 %)	2 (0.7 %)	0.587	0.333	0.277	0.753	1
Total hospital stay (days)	5 (4; 8)	5 (4; 8)	5 (4; 8)	5 (4; 8)	0.009	0.009	0.002	0.548	0.122

* p for overall refers to the comparison of 'no tethering' vs 'symmetric tethering' vs 'asymmetric tethering'; MR = mitral regurgitation; MVG = mitral valve gradient; SPAP = systolic pulmonary artery pressure.

at postprocedural imaging, suggesting that some lesser evils must be accepted in case of tethering if a clinically impactful reduction in mitral regurgitation needs to be achieved. [17]

Despite its pros, this work has also many limitations. First, it is an observational study including patients treated in a variety of institutions by several operators, and using different approaches and techniques, as well as device generations, with evident underlying heterogeneity. [33] Furthermore, selection bias is clearly the elephant in the room in any real-world registry focusing on a complex procedure such as TEER such as the present one. Accordingly, our results cannot be immediately extrapolated to all patients with significant MR. In addition, while tethering definitions were shared and agreed upon pre hoc, there was no independent core lab analysis, and thus the detailed provided in the dedicated electronic case report form was accepted at face value. Similarly, detailed transesophageal imaging was performed in all cases, as TEER is by definition performed under such guidance, but only a selected number of echocardiographic features were entered into the study dataset, limiting our room for further exploratory analyses. Indeed, details on coaptation depth and tenting height were not routinely collected in the dedicated electronic case report form, impeding further analysis focusing on these features. Another drawback is the follow-up, which amounts to a median of 14 months. Accordingly, we cannot directly infer of long-term follow. Yet, the fact that procedural outcomes were similar irrespective of tethering and that a rather parsimonious adjusted model yielded non-significant results for the prognostic appraisal of this echocardiographic features leads us to opinionate that event at long-term it is unlikely that tethering will be a significant contributor to patient prognosis. The lack of multiplicity adjustment for p values is also a distinct limitation of our analyses, which, with the notable exception of those stemming from multivariable models, should be mainly regarded as hypothesis-generating. Finally, given the large number of patients included in the GIOTTO registry with tethering and degenerative MR, we preferred to also include them in the main analysis, which may appear counterintuitive. However, a detailed analysis conducted after excluding these patients was in agreement with the main findings of our work, ie that, despite several baseline difference between patients with vs without tethering, device and procedural success rates are not significantly impacted by the presence of tethering that does not even have a negative prognostic effect at follow-up.

In conclusion, tethering is a common finding among patients with an indication to TEER, and its most frequent form is the symmetrical subtype. Despite the fact that tethering is associated with other adverse

Table 4
Follow-up outcomes.

Feature	No tethering	Any tethering	Symmetric tethering	Asymmetric tethering	P overall*	P no vs any tethering	P no vs symmetric tethering	P no vs asymmetric tethering	P symmetric vs asymmetric tethering
Patients	1467	771	487	284	–	–	–	–	–
Cardiac death or rehospitalization for heart failure	272 (18.5 %)	191 (24.8 %)	118 (24.2 %)	73 (25.7 %)	0.002	0.001	0.007	0.007	0.666
Death or rehospitalization	408 (27.8 %)	282 (36.6 %)	181 (37.2 %)	101 (35.6 %)	<0.001	<0.001	<0.001	0.010	0.698
Cardiac death	176 (12.0 %)	115 (14.9 %)	71 (14.6 %)	44 (15.5 %)	0.132	0.055	0.156	0.117	0.754
Death	324 (22.1 %)	220 (28.5 %)	141 (29.0 %)	79 (27.8 %)	0.003	0.001	0.003	0.038	0.804
Rehospitalization	162 (11.0 %)	127 (16.5 %)	78 (16.0 %)	49 (17.3 %)	0.001	<0.001	0.005	0.005	0.688
Rehospitalization for heart failure	128 (8.7 %)	105 (13.6 %)	66 (13.6 %)	39 (13.7 %)	0.002	<0.001	0.003	0.011	1
Reintervention on mitral valve	12 (0.8 %)	13 (1.7 %)	9 (1.9 %)	4 (1.4 %)	0.133	0.088	0.073	0.312	0.777
NYHA class					0.002	0.006	0.011	0.005	0.035
I	183 (17.8 %)	94 (16.5 %)	70 (19.8 %)	24 (11.1 %)	–	–	–	–	–
II	634 (61.7 %)	324 (56.7 %)	189 (53.4 %)	135 (62.2 %)	–	–	–	–	–
III	201 (19.6 %)	137 (24.0 %)	86 (24.3 %)	51 (23.5 %)	–	–	–	–	–
IV	10 (1.0 %)	16 (2.8 %)	9 (2.5 %)	7 (3.2 %)	–	–	–	–	–
LVEF (%)	45 (31; 55)	35 (25; 45)	35 (25; 45)	35 (25; 46)	<0.001	<0.001	<0.001	<0.001	0.876
MVG (mm Hg)	4 (3; 5)	3 (3; 5)	3 (3; 4)	3 (3; 5)	0.049	0.014	0.024	0.141	0.746
MR					0.150	0.029	0.067	0.238	0.936
None	703 (49.2 %)	321 (42.9 %)	203 (42.9 %)	118 (42.9 %)	–	–	–	–	–
Mild	535 (37.4 %)	305 (40.8 %)	193 (40.8 %)	112 (40.7 %)	–	–	–	–	–
Moderate	141 (9.9 %)	85 (11.4 %)	52 (11.0 %)	33 (12.0 %)	–	–	–	–	–
Severe	51 (3.6 %)	37 (5.0 %)	25 (5.3 %)	12 (4.4 %)	–	–	–	–	–

* p for overall refers to the comparison of 'no tethering' vs 'symmetric tethering' vs 'asymmetric tethering'; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; MVG = mitral valve gradient; NYHA = New York Heart Association.

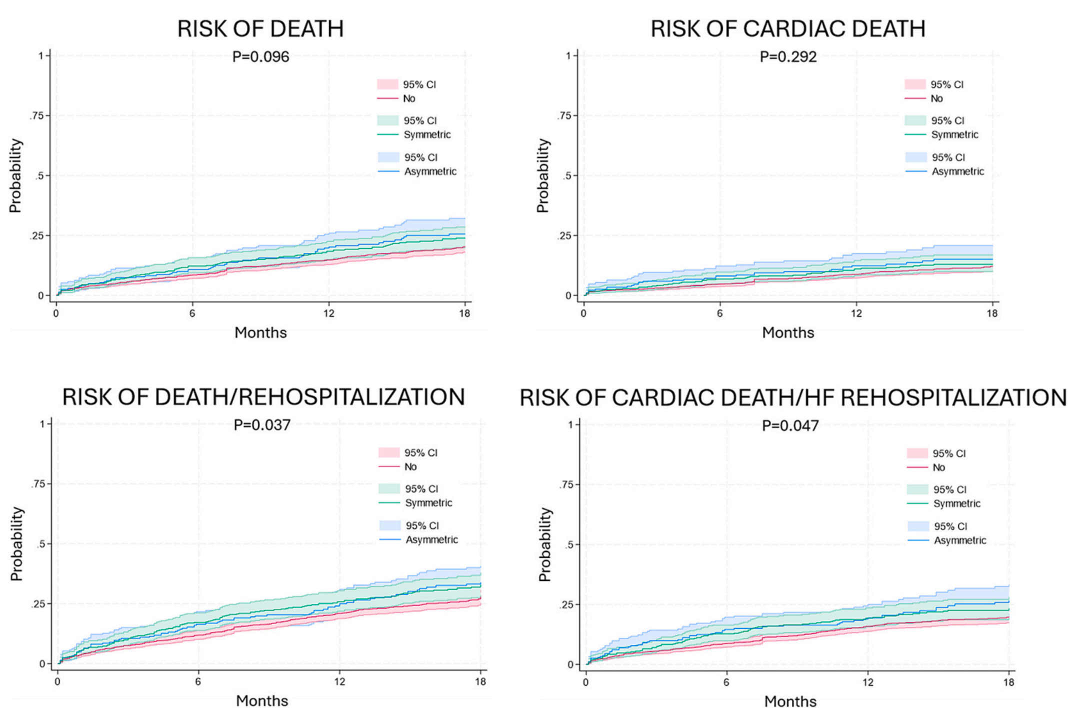

Fig. 1. Risk of death, cardiac death, death or rehospitalization, and cardiac death or rehospitalization according to the presence and type of tethering: no vs symmetric vs asymmetric. CI = confidence interval.

Table 5
Cox proportional hazard analysis for the risk of the primary endpoint (ie cardiac death or rehospitalization) and for other salient ones.

Outcome	Comparison	Analysis	Hazard ratio	95 % confidence interval	P
Cardiac death or rehospitalization for heart failure	Any tethering vs no tethering	Unadjusted	1.28	1.04–1.58	0.021
		Adjusted*	1.05	0.84-1.31	0.695
	Symmetric tethering vs no tethering	Unadjusted	1.23	0.96–1.58	0.099
		Adjusted*	0.98	0.76-1.27	0.882
	Asymmetric tethering vs no tethering	Unadjusted	1.38	1.03–1.84	0.033
		Adjusted*	1.14	0.84-1.55	0.397
	Asymmetric tethering vs symmetric tethering	Unadjusted	1.12	0.80–1.51	0.511
		Adjusted*	1.24	0.88-1.74	0.227
Death or rehospitalization	Any tethering vs no tethering	Unadjusted	1.29	1.11–1.51	0.001
		Adjusted*	1.12	0.96-1.32	0.159
	Symmetric tethering vs no tethering	Unadjusted	1.30	1.09–1.55	0.003
		Adjusted*	1.11	0.93-1.34	0.250
	Asymmetric tethering vs no tethering	Unadjusted	1.29	1.03–1.60	0.025
		Adjusted*	1.14	0.91-1.44	0.255
	Asymmetric tethering vs symmetric tethering	Unadjusted	0.99	0.75–1.27	0.939
		Adjusted*	1.05	0.82-1.35	0.698
Death	Any tethering vs no tethering	Unadjusted	1.28	1.07–1.51	0.006
		Adjusted*	1.09	0.90-1.31	0.379
	Symmetric tethering vs no tethering	Unadjusted	1.25	1.03–1.53	0.027
		Adjusted*	1.04	0.85-1.29	0.686
	Asymmetric tethering vs no tethering	Unadjusted	1.31	1.02–1.68	0.032
		Adjusted*	1.17	0.90-1.52	0.231
	Asymmetric tethering vs symmetric tethering	Unadjusted	1.05	0.80–1.39	0.729
		Adjusted*	1.12	0.84-1.49	0.429
Cardiac death	Any tethering vs no tethering	Unadjusted	1.23	0.97–1.59	0.089
		Adjusted*	0.96	0.75-1.24	0.778
	Symmetric tethering vs no tethering	Unadjusted	1.17	0.89–1.55	0.260
		Adjusted*	0.90	0.67-1.20	0.468
	Asymmetric tethering vs no tethering	Unadjusted	1.33	0.95–1.86	0.093
		Adjusted*	1.10	0.78-1.56	0.594
	Asymmetric tethering vs symmetric tethering	Unadjusted	1.13	0.78–1.66	0.520
		Adjusted*	1.24	0.84-1.83	0.289
Rehospitalization	Any tethering vs no tethering	Unadjusted	1.48	1.17–1.86	0.001
		Adjusted*	1.31	1.02-1.68	0.034
	Symmetric tethering vs no tethering	Unadjusted	1.27	0.96–1.69	0.098
		Adjusted*	1.24	0.94-1.65	0.130
	Asymmetric tethering vs no tethering	Unadjusted	1.45	1.04–2.04	0.030
		Adjusted*	1.43	1.02-2.00	0.037
	Asymmetric tethering vs symmetric tethering	Unadjusted	1.13	0.79–1.62	0.505
		Adjusted*	1.23	0.85-1.79	0.264
Rehospitalization for heart failure	Any tethering vs no tethering	Unadjusted	1.56	1.21–2.02	0.001
		Adjusted*	1.35	1.03-1.78	0.032
	Symmetric tethering vs no tethering	Unadjusted	1.52	1.13–2.05	0.006
		Adjusted*	1.31	0.96-1.79	0.092
	Asymmetric tethering vs no tethering	Unadjusted	1.63	1.13–2.33	0.008
		Adjusted*	1.44	0.99-2.09	0.057
	Asymmetric tethering vs symmetric tethering	Unadjusted	1.09	0.73–1.61	0.687
		Adjusted*	1.21	0.81-1.81	0.361

* adjusting for age, prior myocardial infarction, and left ventricular ejection fraction at baseline.

baseline and procedural features, device and procedural success rates are not significantly impacted by its presence, and even at follow-up, it does not confer an independent adverse prognostic effect. Accordingly, tethering should not be considered as a contraindication to TEER in suitable patients. However, further research is warranted to confirm these findings and to optimize TEER techniques and devices for patients with mitral valve tethering.

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CRediT authorship contribution statement

Nicola Corcione: Writing – review & editing, Methodology, Data curation, Conceptualization. **Paolo Ferraro:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Filippo Finizio:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Michele Cimmino:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Michele Albanese:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Alberto Morello:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Giuseppe Biondi-Zoccai:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Paolo Denti:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Antonio Popolo Rubbio:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Francesco Bedogni:** Writing – review & editing, Methodology, Funding

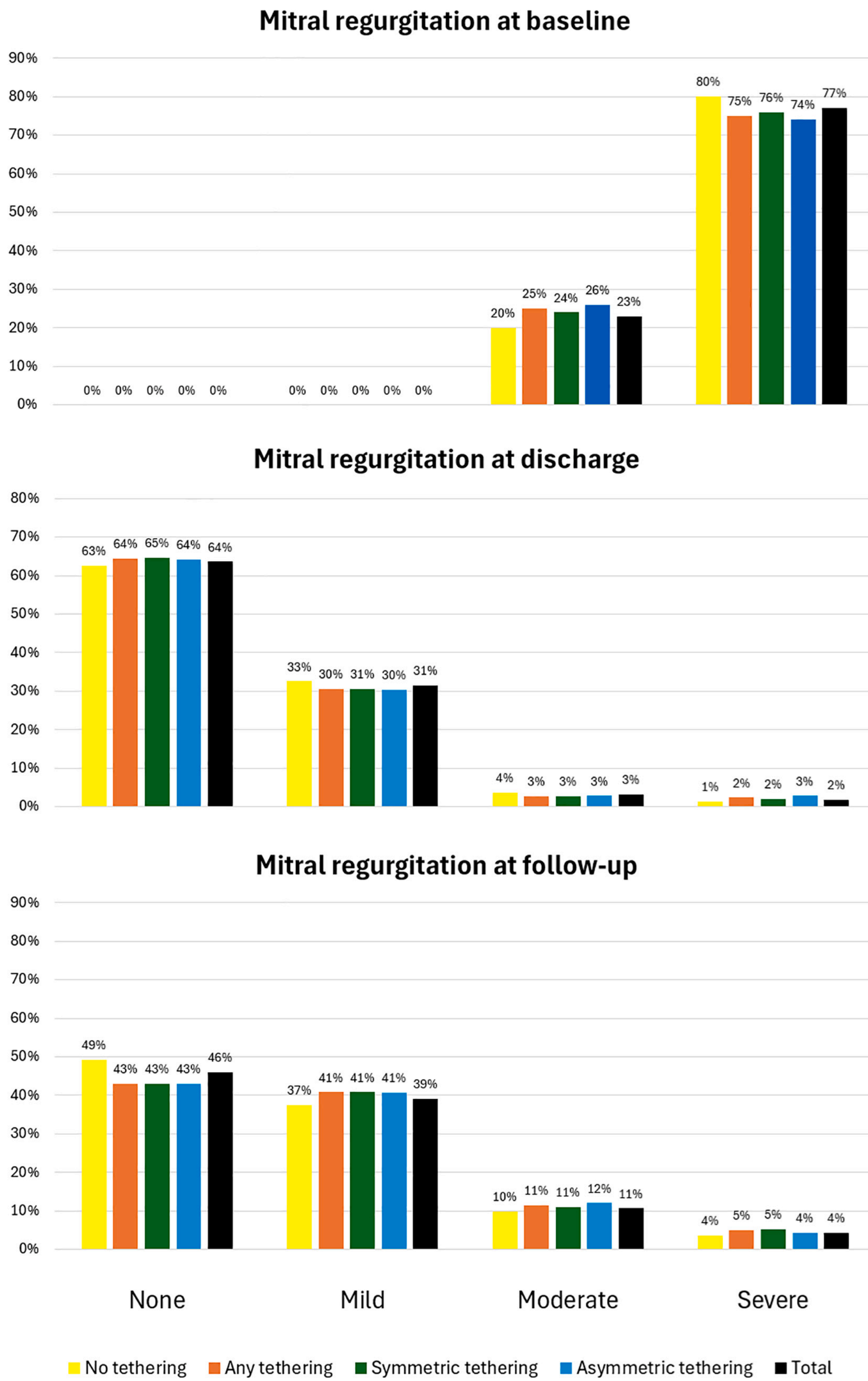

Fig. 2. Barplot displaying the extent of severity of mitral regurgitation at baseline, at discharge, and at follow-up, according to the presence and type of tethering, and overall.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2024.132874.

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