

## **SUPPLEMENTAL APPENDIX**

### **Clinical Characteristics and Outcomes of Patients with Takotsubo Syndrome complicated with Acute Mitral Regurgitation**

#### **TABLE OF CONTENTS**

Table S1. TTS diagnostic criteria

Table S2. List of variables included in the propensity score models

Table S3. Missing values

Table S4. In-hospital adverse events

Table S5 Baseline characteristics of the study population according to the presence of acute MR and/or LVOTO.

Table S6. Unadjusted interaction analysis for the risk of in-hospital adverse events according to the presence of acute MR and/or LVOTO

Figure S1. Study selection process

Figure S2. Covariate balance in the propensity score weighted analysis for assessment of in-hospital adverse events

Figure S3. Covariate balance in the propensity score weighted analysis for assessment of long-term adverse events

Figure S4. Cause-specific risk curves for TTS recurrence and the competing risk of death between patients with and without acute MR at long-term follow-up.

## SUPPLEMENTAL TABLES

**Table S1. TTS diagnostic criteria**

<b>Tako-tsubo Italian Network diagnostic criteria</b>
<ol style="list-style-type: none"><li>1. Typical transient LV wall motion abnormalities extending beyond a single epicardial vascular distribution with complete functional normalization within 6 weeks.</li><li>2. Absence of potentially culprit coronary stenosis, or angiographic evidence of acute plaque rupture, dissection, thrombosis or spasm.<sup>a</sup></li><li>3. New and dynamic ST-segment abnormalities or T-wave inversion as well as new onset of transient or permanent LBBB.</li><li>4. Mild increase in myocardial injury markers (creatine kinase-mb value <math>\leq</math> 50 U/L).</li><li>5. Clinical and/or instrumental exclusion of myocarditis.</li><li>6. Post-menopausal woman (optional).<sup>b</sup></li><li>7. Antecedent stressful event (optional).<sup>b</sup></li></ol>
<b>Heart Failure Association diagnostic criteria</b>
<ol style="list-style-type: none"><li>1. Transient regional wall motion abnormalities of LV or RV myocardium which are frequently, but not always, preceded by a stressful trigger (emotional or physical).</li><li>2. The regional wall motion abnormalities usually extend beyond a single epicardial vascular distribution, and often result in circumferential dysfunction of the ventricular segments involved.<sup>c</sup></li><li>3. The absence of culprit atherosclerotic coronary artery disease including acute plaque rupture, thrombus formation, and coronary dissection or other pathological conditions to explain the pattern of temporary LV dysfunction observed (e.g. hypertrophic cardiomyopathy, viral myocarditis).</li><li>4. New and reversible ECG abnormalities (ST-segment elevation, ST depression, LBBB, T-wave inversion, and/or QTc prolongation) during the acute phase (3 months).<sup>d</sup></li><li>5. Significantly elevated serum natriuretic peptide (BNP or NT-proBNP) during the acute phase.</li><li>6. Positive but relatively small elevation in cardiac troponin measured with a conventional assay (i.e. disparity between the troponin level and the amount of dysfunctional myocardium present).<sup>e</sup></li><li>7. Recovery of ventricular systolic function on cardiac imaging at follow-up (3–6 months).<sup>f</sup></li></ol>
<b>International Takotsubo Diagnostic Criteria (InterTAK Diagnostic Criteria)</b>
<ol style="list-style-type: none"><li>1. Patients show transient <sup>g</sup> LV dysfunction (hypokinesia, akinesia, or dyskinesia) presenting as apical ballooning or midventricular, basal, or focal wall motion abnormalities. Right ventricular</li></ol>

involvement can be present. Besides these regional wall motion patterns, transitions between all types can exist. The regional wall motion abnormality usually extends beyond a single epicardial vascular distribution; however, rare cases can exist where the regional wall motion abnormality is present in the subtended myocardial territory of a single coronary artery (focal TTS).<sup>h</sup>

2. An emotional, physical, or combined trigger can precede the TTS event, but this is not obligatory.

3. Neurologic disorders (e.g. subarachnoid hemorrhage, stroke/transient ischaemic attack, or seizures) as well as pheochromocytoma may serve as triggers for takotsubo syndrome.

4. New ECG abnormalities are present (ST-segment elevation, ST-segment depression, T-wave inversion, and QTc prolongation); however, rare cases exist without any ECG changes.

5. Levels of cardiac biomarkers (troponin and creatine kinase) are moderately elevated in most cases; significant elevation of brain natriuretic peptide is common.

6. Significant coronary artery disease is not a contradiction in TTS.

7. Patients have no evidence of infectious myocarditis.<sup>h</sup>

8. Postmenopausal women are predominantly affected.

BNP, brain natriuretic peptide; LBBB, left bundle branch block; LV, left ventricular; NT-proBNP, n-terminal pro-brain natriuretic peptide; RV, right ventricular; TTS, takotsubo syndrome.

<sup>a</sup> Coronary angiography should be performed as soon as possible (ideally within 48 hours from admission); <sup>b</sup> Optional diagnostic criteria are not mandatory, but when positive they increase the likelihood of TTS syndrome diagnosis; <sup>c</sup> Acute, reversible dysfunction of a single coronary territory has been reported; <sup>d</sup> LBBB may be permanent after TTS, but should also alert clinicians to exclude other cardiomyopathies. T-wave changes and QTc prolongation may take many weeks to months to normalize after recovery of LV function; <sup>e</sup> Troponin-negative cases have been reported, but are atypical; <sup>f</sup> Small apical infarcts have been reported. Bystander subendocardial infarcts have been reported, involving a small proportion of the acutely dysfunctional myocardium. These infarcts are insufficient to explain the acute regional wall motion abnormality observed; <sup>g</sup> Wall motion abnormalities may remain for a prolonged period of time or documentation of recovery may not be

possible. For example, death before evidence of recovery is captured;<sup>h</sup> Cardiac magnetic resonance imaging is recommended to exclude infectious myocarditis and diagnosis confirmation of TTS.

**Table S2. List of variables included in the propensity score models.**

PS model	List of variables
In-hospital outcomes	Age, sex, hypertension, diabetes, hypercholesterolemia, tobacco use, menopause, CAD, COPD, endocrine disorders, psychiatric disorders, neurologic disorders, cancer, symptoms at admission (chest pain, dyspnea), trigger (emotional, physical, not identifiable), ST-segment elevation at admission, LVEF at admission, apical/atypical form, peak troponin I, glomerular filtration rate, right ventricular involvement, LVOTO
Long-term outcomes	Age, sex, hypertension, diabetes, hypercholesterolemia, tobacco use, menopause, CAD, COPD, endocrine disorders, psychiatric disorders, neurologic disorders, cancer, symptoms at admission (chest pain, dyspnea), trigger (emotional, physical, not identifiable), ST-segment elevation at admission, LVEF at admission, apical/atypical form, peak troponin I, glomerular filtration rate, complications during hospitalization (LV apical thrombus, acute heart failure, cardiogenic shock, right ventricular involvement, LVOTO), LVEF at discharge, and pharmacological therapy at discharge (acetylsalicylic acid, P2Y <sub>12</sub> inhibitors, oral anticoagulants, beta-blockers, RAASi, and statins).

BB, beta-blockers; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; HT, hypertension; LV, left ventricular; LVEF, left ventricular ejection fraction; LVOTO, left ventricular outflow tract obstruction; MR, mitral regurgitation; RAASi, renin-angiotensin-aldosterone system inhibitors; TTS, takotsubo syndrome.

**Table S3. Missing values**

	<b>Overall population (N = 1025)</b>
Age, years	0
Male sex, N (%)	0
Diabetes, N (%)	0
Hypertension, N (%)	0
Hypercholesterolemia, N (%)	0
Tobacco use, N (%)	0
CAD, N (%)	0
COPD, N (%)	27 (2.6)
Neurologic disorders, N (%)	17 (1.7)
Psychiatric disorders, N (%)	20 (2.0)
Endocrine disorders, N (%)	27 (2.6)
History of cancer N (%)	8 (0.8)
Menopause, N (%)	0
SBP at admission, mmHg	78 (7.6)
DBP at admission, mmHg	78 (7.6)
Heart rate, beats/min	67 (6.5)
Chest pain, N (%)	47 (4.6)
Dyspnea, N (%)	47 (4.6)
Trigger, N (%)	0
ST segment elevation, N (%)	21 (2.0)
New-onset LBBB, N (%)	21 (2.0)
Troponin I peak, $\mu\text{g/L}$	107 (10.4)
GFR, ml/min	270 (26.3)
LVEF at admission, %	42 (4.1)
Apical form, N (%)	0
Atypical form, N (%)	0
LVOTO, N (%)	98 (9.6)
RV involvement, N (%)	92 (9.0)

Apical thrombus, N (%)	44 (4.3)
Inotropic agents, N (%)	76 (7.4)
IABP, N (%)	78 (7.6)
Acute heart failure, N (%)	0
Cardiogenic, shock, N (%)	0
VT/VF, N (%)	34 (3.4)
Death, N (%)	0
LVEF at discharge, %*	220 (21.9)
ASA, N (%)*	24 (2.4)
P2Y <sub>12</sub> inhibitor, N (%)*	24 (2.4)
Oral anticoagulant, N (%)*	33 (3.3)
RAASi, N (%)*	24 (2.4)
BB, N (%)*	24 (2.4)
Statin, N (%)*	25 (2.5)

ASA, acetylsalicylic acid; BB, beta-blockers; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; GFR, glomerular filtration rate; IABP, intra-aortic balloon pump; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; LVOTO, left ventricular outflow tract obstruction; MR, mitral regurgitation; RAASi, renin-angiotensin-aldosterone system inhibitors; RV, right ventricular; SBP, systolic blood pressure; TTS, takotsubo syndrome; VF, ventricular fibrillation; VT, ventricular tachycardia.

\* Percentage calculated on 1006 patients discharged alive.

**Table S4. In-hospital and long-term adverse events.**

	<b>Overall population (N = 1025)</b>	<b>Acute MR (N = 186)</b>	<b>No Acute MR (N = 839)</b>	<b>p-value</b>
<b>In-hospital outcomes</b>				
Composite in-hospital outcome, N (%)	185 (18.0)	66 (35.5)	119 (14.2)	<0.001
Acute heart failure, N (%)	150 (14.6)	54 (29.0)	96 (11.4)	<0.001
Cardiogenic shock, N (%)	59 (5.8)	24 (12.9)	35 (4.2)	<0.001
Death, N (%)	20 (2.0)	7 (3.8)	13 (1.5)	0.125
<b>Long-term outcomes*</b>				
All-cause death, N (%)	124 (12.3)	43 (23.8)	81 (9.8)	<0.001
TTS recurrence, N (%)	42 (4.2)	10 (5.5)	32 (3.9)	0.313

MR, mitral regurgitation; TTS, takotsubo syndrome.

\* Percentage calculated on 1008 patients with available follow-up information.

**Table S5. Baseline characteristics of the study population according to the presence of acute MR and/or LVOTO.**

	Overall population (N = 927)	Acute MR		p-value	No Acute MR		p-value
		Without LVOTO (N = 145)	With LVOTO (N = 28)		Without LVOTO (N = 718)	With LVOTO (N = 36)	
Age, years	72 (63-78)	74.9±8.8	72.6±13.9	0.535	70 (61-77)	70.1±8.8	0.892
Female sex, n (%)	846 (91.3)	135 (93.1)	27 (96.4)	0.509	651 (90.7)	33 (91.7)	1.000
<b>Cardiovascular risk factors and comorbidities</b>							
Diabetes, n (%)	119 (12.8)	26 (17.9)	2 (7.1)	0.260	90 (12.5)	1 (2.8)	0.111
Hypertension, n (%)	610 (65.8)	109 (75.2)	18 (64.3)	0.233	456 (63.5)	27 (75.0)	0.161
Hypercholesterolemia, n (%)	405 (43.7)	66 (45.5)	10 (35.7)	0.339	317 (44.2)	12 (33.3)	0.202
Tobacco use, n (%)	211 (22.8)	32 (22.1)	7 (25.0)	0.734	165 (23.0)	7 (19.4)	0.622
CAD, n (%)	144 (15.5)	20 (13.8)	6 (21.4)	0.301	113 (15.7)	5 (13.9)	0.766
COPD, n (%)	151 (16.8)	20 (14.1)	4 (19.0)	0.518	120 (16.8)	7 (29.2)	0.115
Neurologic disorders, n (%)	93 (10.2)	14 (9.9)	3 (11.1)	0.738	75 (10.5)	1 (3.6)	0.347
Psychiatric disorders, n (%)	139 (15.3)	25 (17.6)	2 (9.1)	0.536	110 (15.5)	2 (6.3)	0.208
Endocrine disorders, n (%)	113 (12.6)	15 (10.6)	3 (14.3)	0.707	94 (13.2)	1 (4.2)	0.347
History of cancer n (%)	120 (13.1)	22 (15.5)	1 (3.6)	0.130	96 (13.5)	1 (2.8)	0.073
Menopause, n (%)	772 (88.3)	129 (91.5)	21 (75.0)	0.012	594 (88.7)	28 (80)	0.121
<b>Clinical, echocardiographic and laboratory characteristics during the index event</b>							
SBP at admission, mmHg	130 (110-142)	133.6±26.5	113 (107-130)	0.034	130 (110-140)	123.6±18.0	0.264
DBP at admission, mmHg	75 (66-84.5)	80 (70-89)	70 (59-75)	0.030	75 (66-84)	71.6±10.8	0.118

Heart rate, beats/min	85 (74-100)	90 (75-100)	99.3±18.1	0.228	84 (73-100)	86.5±16.4	0.430
Chest pain, n (%)	690 (70.6)	82 (65.1)	20 (74.1)	0.368	483 (69.9)	24 (66.7)	0.681
Dyspnea, n (%)	170 (19.3)	36 (28.6)	9 (33.3)	0.622	137 (16.9)	9 (25.0)	0.203
Trigger							
Emotional (primary TTS), n (%)	429 (46.3)	65 (44.8)	8 (28.6)	0.111	336 (46.8)	20 (55.6)	0.304
Physical (secondary TTS), n (%)	176 (19.0)	33 (22.8)	5 (17.9)	0.566	113 (18.5)	5 (13.9)	0.483
Unknown trigger, n (%)	327 (35.3)	49 (33.8)	15 (53.6)	0.047	252 (35.1)	11 (30.6)	0.577
ST segment elevation, n (%)	417 (45.8)	59 (41.8)	17 (60.7)	0.067	318 (45.0)	23 (63.9)	0.027
New-onset LBBB, n (%)	38 (4.2)	9 (6.4)	1 (3.6)	1.000	26 (3.7)	2 (5.6)	0.641
Troponin I peak, µg/L	3.2 (1.0-13.9)	4.1 (0.9-108.0)	4.9 (1.9-10.8)	0.840	3.1 (1.0-10.8)	2.4 (1.5-5.7)	<0.001
GFR, ml/min	74.0 (56.7-90.6)	66.4±28.7	69.1±20.6	0.762	75.6 (57.9-93.3)	56.0±23.9	0.108
LVEF at admission, %	40 (35-46)	38.8±8.2	41.0±11.1	0.959	41.2±9.6	41.4±7.6	0.394
Apical form, n (%)	802 (86.5)	124 (85.5)	24 (85.7)	1.000	619 (86.2)	35 (97.2)	0.073
Atypical form, n (%)	59 (6.4)	13 (9.0)	2 (7.4)	1.000	40 (5.6)	4 (11.4)	0.144
RV involvement, n (%)	67 (7.3)	19 (13.1)	3 (11.1)	1.000	40 (5.6)	5 (14.3)	0.034
LV Apical thrombus, n (%)	22 (2.5)	3 (2.1)	0 (0)	1.000	18 (2.6)	1 (3.6)	0.537
Inotropic agents, n (%)	59 (6.7)	18 (12.9)	7 (26.9)	0.066	34 (4.9)	0 (0)	0.625
IABP, n (%)	27 (3.1)	10 (7.2)	3 (11.5)	0.434	12 (1.7)	2 (8.0)	0.082
VT/VF, n (%)	20 (2.2)	4 (2.8)	0 (0)	1.000	13 (1.9)	3 (8.3)	0.041
LVEF at discharge, %	55 (46.5-60.0)	52.6±8.7	54.7±9.8	0.649	55 (46-60)	60 (51-65)	0.386
<b>Medications at discharge</b>							

ASA, n (%)	653 (72.6)	98 (70.5)	14 (63.6)	0.515	523 (74.1)	18 (56.3)	0.026
P2Y <sub>12</sub> inhibitor, n (%)	308 (34.3)	36 (25.9)	6 (27.3)	0.892	255 (36.1)	11 (34.4)	0.841
Beta-blocker, n (%)	632 (70.2)	106 (75.2)	19 (84.6)	0.293	487 (69.1)	20 (62.5)	0.432
Oral anticoagulant, n (%)	101 (11.3)	23 (16.5)	0 (0)	0.081	77 (10.9)	1 (4.2)	0.500
RAASi, n (%)	390 (43.4)	69 (48.9)	8 (36.4)	0.272	301 (42.8)	12 (37.5)	0.556
Statin, n (%)	475 (52.8)	75 (53.6)	8 (36.4)	0.133	375 (53.2)	17 (53.1)	0.994

Continuous normally distributed variables are expressed as mean  $\pm$  SD. Continuous non-normally distributed variables are expressed as median (IQR). ASA, acetylsalicylic acid; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; GFR, glomerular filtration rate; IABP, intra-aortic balloon pump; LBBB, left bundle branch block; LV, left ventricular; LVEF, left ventricular ejection fraction; LVOTO, left ventricular outflow tract obstruction; MR, mitral regurgitation; RAASi, renin-angiotensin-aldosterone system inhibitors; RV, right ventricular; SBP, systolic blood pressure; TTS, takotsubo syndrome; VF, ventricular fibrillation; VT, ventricular tachycardia.

**Table S6. Unadjusted interaction analysis for the risk of in-hospital adverse events according to the presence of MR and/or LVOTO**

PRIMARY COMPOSITE OUTCOME		LVOTO absent	LVOTO present	Effect of LVOTO in patients with MR
	MR absent	1 [Ref]	1.45 [0.66, 3.22] p=0.356	-
	MR present	2.83 [1.91, 4.19] p<0.001	7.06 [3.35, 14.87] p<0.001	2.5 [1.13, 5.52] p=0.024
	Effect of MR in patients with LVOTO	-	4.86 [1.7, 13.91] p=0.003	P <sub>interaction</sub> =0.346
ACUTE HEART FAILURE		LVOTO absent	LVOTO present	Effect of LVOTO in patients with MR
	MR absent	1 [Ref]	1.05 [0.4, 2.74] p=0.923	-
	MR present	2.77 [1.82, 4.2] p<0.001	5.93 [2.79, 12.62] p<0.001	2.14 [0.96, 4.8] p=0.063
	Effect of MR in patients with LVOTO	-	5.66 [1.74, 18.43] p=0.004	P <sub>interaction</sub> =0.263
CARDIOGENIC SHOCK		LVOTO absent	LVOTO present	Effect of LVOTO in patients with MR
	MR absent	1 [Ref]	3.45 [1.27, 9.42] p=0.015	-
	MR present	2.52 [1.3, 4.87] p=0.006	12.78 [5.51, 29.68] p<0.001	5.07 [1.99, 12.94] p=0.001
	Effect of MR in patients with LVOTO	-	3.7 [1.11, 12.33] p=0.033	P <sub>interaction</sub> =0.583
DEATH		LVOTO absent	LVOTO present	Effect of LVOTO in patients with MR
	MR absent	1 [Ref]	NA*	-
	MR present	1.18 [0.33, 4.2] p=0.795	9.28 [2.83, 30.4] p<0.001	7.85 [1.66, 37.1] p=0.009
	Effect of MR in patients with LVOTO	-	NA*	P <sub>interaction</sub> =0.987

The risk estimates are reported as OR with their 95% CI (in bracket squares). Analysis conducted on 927 patients with available information on LVOTO.

LVOTO, left ventricular outflow tract obstruction; MR, mitral regurgitation; NA, not available.

Composite of acute heart failure, cardiogenic shock and mortality occurring during the hospitalization. \* No death was reported in patients with LVOTO and without MR.

## **SUPPLEMENTAL FIGURES**

### **Figure S1. Study selection process**

MR, mitral regurgitation; TIN, Takotsubo Italian Network; TTS, takotsubo syndrome.

### **Figure S2. Covariate balance in the propensity score weighted analysis for assessment of in-hospital adverse events**

Love plot showing the unadjusted (red circles) and adjusted (blue circles) values of the absolute standardized difference before and after weighting. The dotted line represents the threshold value of  $\pm 0.1$  for the absolute standardized mean difference; standardized mean difference within the threshold value are conventionally considered an index of optimal balance achieved after weighting.

CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; LVOTO, left ventricular outflow tract obstruction; RV, right ventricular; TTS, takotsubo syndrome.

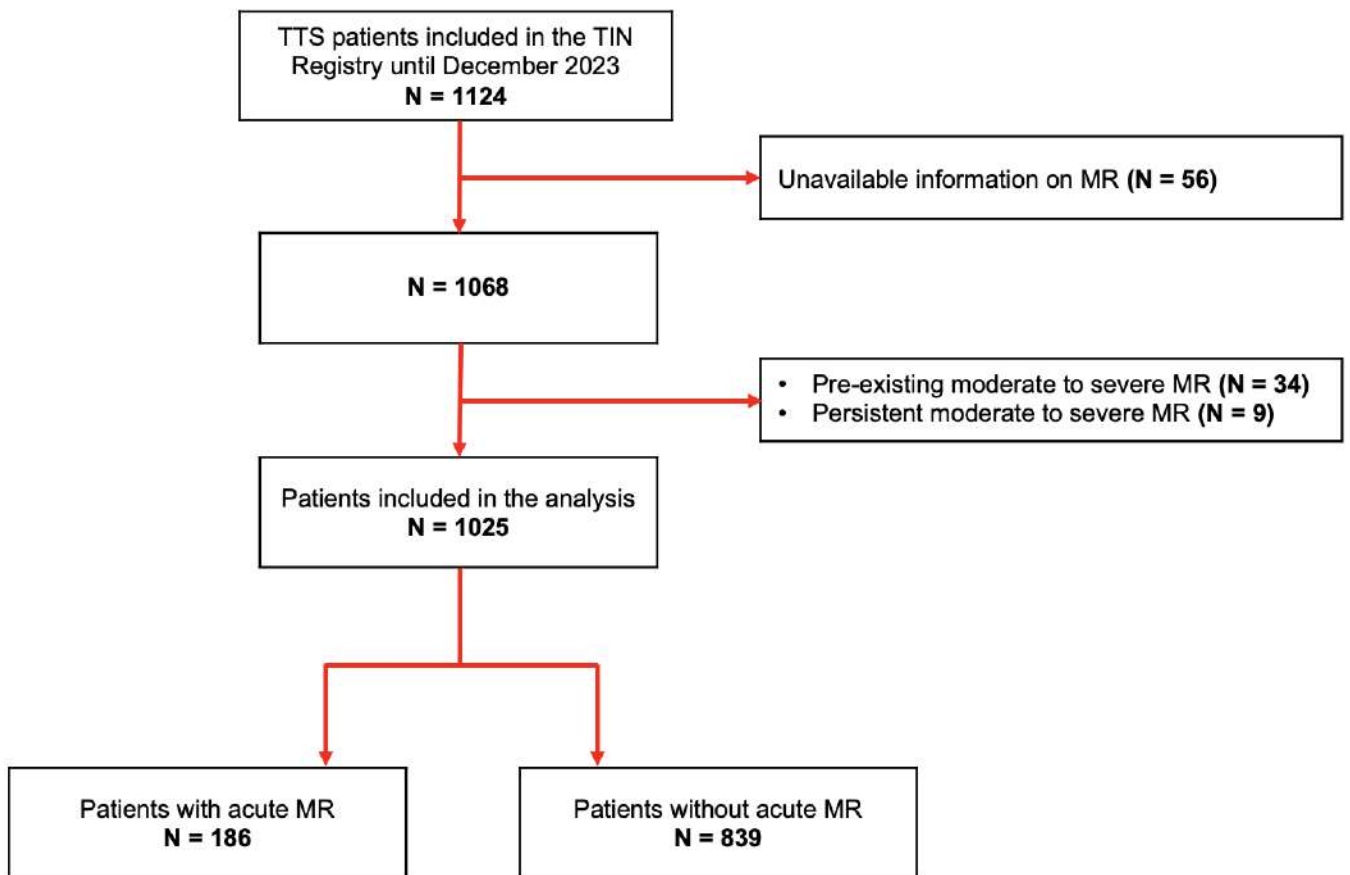
### **Figure S3. Covariate balance in the propensity score weighted analysis for assessment of long-term adverse events**

Love plot showing the unadjusted (red circles) and adjusted (blue circles) values of the absolute standardized difference before and after weighting. The dotted line represents the threshold value of  $\pm 0.1$  for the absolute standardized mean difference; standardized mean difference within the threshold value are conventionally considered an index of optimal balance achieved after weighting.

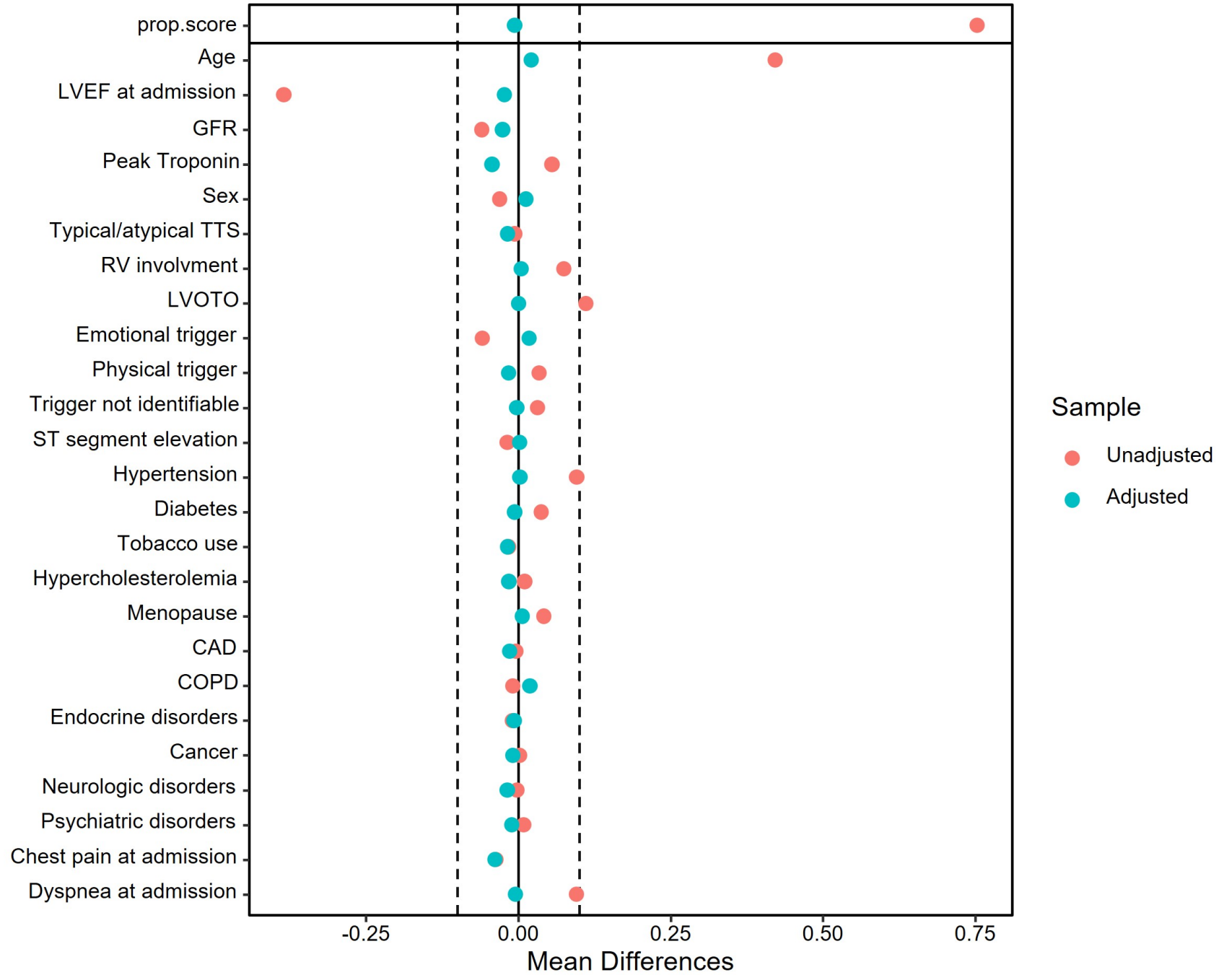
ASA, acetylsalicylic acid; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; LV, left ventricular; LVEF, left ventricular ejection fraction; LVOTO, left ventricular outflow tract obstruction; RAASi, renin-angiotensin-aldosterone system inhibitors; RV, right ventricular; TTS, takotsubo syndrome.

**Figure S4. Cause-specific risk curves for TTS recurrence and the competing risk of death between patients with and without acute MR at long-term follow-up.**

aHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio; MR, mitral regurgitation.



# Covariate Balance



### Covariate Balance

