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ORIGINAL RESEARCH

OUTCOMES AND QUALITY

Clinical Characteristics and Outcomes of Patients With Takotsubo Syndrome Complicated With Acute Mitral Regurgitation

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ABSTRACT

BACKGROUND Acute mitral regurgitation (MR) is a serious complication of takotsubo syndrome (TTS). However, its incidence and prognostic implications are still poorly investigated.

OBJECTIVES This study aimed to assess the clinical characteristics, short- and long-term outcomes of patients with TTS complicated by acute, reversible, moderate or severe MR.

METHODS The study included TTS patients from the Takotsubo Italian Network multicenter registry. The primary outcome was the composite of in-hospital acute heart failure, cardiogenic shock, and mortality. Secondary outcomes included mortality and the recurrence of TTS at the longest available follow-up. The propensity score weighting technique was performed to account for potential confounders between patients with and without acute moderate or severe MR.

RESULTS The study included 1,025 patients (mean age 70 ± 11 years, 91.6% females); of them, 186 (18.2%) showed acute moderate or severe MR. Logistic regression analysis showed a significantly higher risk for the primary outcome (adjusted OR: 2.29; 95% CI: 1.83-2.88), acute heart failure (adjusted OR: 2.17; 95% CI: 1.70-2.77), and cardiogenic shock (adjusted OR: 2.46; 95% CI: 1.69-3.59) in patients with acute MR compared to those without. Also, the coexistence of left ventricular outflow tract obstruction with acute MR further increased the risk for the primary outcome (adjusted OR: 5.26; 95% CI: 3.22-8.59). At long-term follow-up (median 29 months), patients who developed acute MR during hospitalization showed a significantly higher risk of mortality (adjusted HR: 1.82; 95% CI: 1.21-2.74).

CONCLUSIONS In this real-world study, acute MR was associated with a significantly higher risk of adverse events during hospitalization and long-term mortality. Early echocardiographic detection of acute MR can support prognostic stratification and management of TTS patients. (JACC Adv. 2026;5:102522) © 2026 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

LV = left ventricle

LVEF = left ventricular ejection fraction

LVOTO = left ventriclar outflow tract obstruction

MR = mitral regurgitation

RV = right ventricle

SAM = systolic anterior movement

TIN = Takotsubo Italian network

TTS = takotsubo syndrome

It has been 35 years since Dr Sato's first description of takotsubo syndrome (TTS).[1] Since then, growing interest in this condition has led to an increasingly detailed understanding of its natural history. In this setting, the contribution of international registries has been crucial in both describing the clinical features and possible complications of the acute phase and the long-term prognosis. So over time, from the initial idea of a pathology that tended to be benign, we have moved to the concept of a cardiological emergency that, especially in the acute phase, has a mortality rate quite like that of acute coronary syndromes in the era of mechanical reperfusion.[2]

Among the complications having the greatest impact on the clinical course and mortality during the acute phase, dynamic mitral regurgitation (MR) plays a key role.[3-7]

Transient and reversible moderate or severe MR has been reported in 17% to 25% of TTS patients during the acute episode. It is a potentially serious complication often associated with hemodynamic instability, clinical deterioration, and heart failure.[3,4,8]

The hypothesized mechanisms underlying MR in TTS are multifactorial, primarily related to papillary muscle dysfunction, tethering of the mitral valve leaflets due to apical ballooning, and dynamic left ventricular (LV) outflow tract obstruction (LVOTO).[8-13]

However, the clinical impact related to the onset of moderate or severe MR in TTS is still poorly elucidated as currently available evidence comes from a few studies including a limited number of patients. Therefore, risk stratification, clinical management, patients' monitoring, and therapy are not standardized.

This study aimed at evaluating the incidence and the outcome implications of acute, reversible, moderate or severe MR in a large population of patients with TTS enrolled in the Takotsubo Italian Network (TIN) registry.

METHODS

STUDY POPULATION. This observational, multicenter cohort study included consecutive patients with TTS diagnosis admitted at 18 Italian hospitals and enrolled in the TIN register between January 2007 and December 2023. Patients were recruited according to the TIN diagnostic criteria, subsequently revised and incorporated by the Heart Failure Association and by the InterTAK Diagnostic Criteria (Supplemental Table 1).[14,15] The TIN registry characteristics and procedures have been previously described.[16,17] All patients underwent coronary angiography and left ventriculography to confirm TTS diagnosis. Hospitalization data were recorded through standardized forms and included patient demographics, cardiovascular risk factors, triggering factors, symptoms on admission, laboratory profile, electrocardiogram, echocardiographic findings, and pharmacological therapy at discharge. Local investigators obtained follow-up data during periodic clinical visits, telephonic interviews, or medical record revision.

For the present analysis, patients with TTS were divided into 2 groups based on the presence of acute moderate or severe MR during the hospitalization. The absence of information on MR during the hospitalization was considered an exclusion criterion for this study.

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The study protocol was approved by the coordinating center's Ethics Committee (CET ASREM) and by each enrolling site. Eligible patients were asked to participate in the TIN register after confirming their TTS diagnosis, and all patients provided informed written consent. Participants were not involved in determining the research question or outcome measures nor were they involved in recruitment, design, or implementation of the study.

MR ASSESSMENT. The presence and the severity of MR during the acute phase were routinely assessed by transthoracic echocardiography. All echocardiographic examinations were performed within 6 hours of admission or symptom onset as per theTIN registry criteria, before coronary angiography, and then repeated during hospitalization according to clinical judgment. All echocardiographic exams were performed at each center, certified by European Association of CardioVascular Imaging or Società Italiana di Ecocardiografia e CardioVascular Imaging, by expert noninvasive cardiologists (certified Società Italiana di Ecocardiografia e CardioVascular Imaging). Echocardiographic measurements were obtained in accordance with American Society of Echocardiography/European Association of CardioVascular Imaging guidelines.[18] MR was assessed using an integrative approach, including qualitative, semiquantitative, and quantitative echocardiographic measures according to current recommendations.[19,20] In all patients, MR was graded using Color flow imaging as absent/trivial, mild, moderate, or severe using the standardized criteria.[19,20] The severity of MR was confirmed, when available, using vena contracta measurement and/or the quantitative measure of the effective regurgitant orifice area and regurgitant volume by using the proximal isovelocity surface area method based on clinical judgment.

To ensure consistency in the assessment of MR severity, all recruiting cardiologists were authorized to enroll patients only after passing an online questionnaire. It was created with the aim of testing skills in the diagnosis and assessment of MR severity and ensuring a good quality of recruitment by each authorized center and cardiologist.

Acute MR has been defined as moderate or severe MR, detected at the first echocardiographic assessment, which is reduced to mild/trivial or absent at discharge, during follow-up or, in any case, at the time of recovery of LV systolic function and/or of resolution of LVOTO. Due to its dynamic nature, it is considered transient and reversible. Patients with a history of pre-existing moderate or severe MR, as well as those with persistent MR after LV recovery, were excluded from this analysis. The study selection process is summarized in Supplemental Figure 1.

STUDY OUTCOMES AND FOLLOW-UP. The primary outcome of the present study was the composite of in-hospital acute heart failure, cardiogenic shock, and mortality. Acute heart failure was defined as the presence of pulmonary edema, dyspnea, and/or oxygen desaturation requiring drug therapy; cardiogenic shock was defined by systolic blood pressure <90 mm Hg for >30 minutes or if maintenance of systolic blood pressure above this value was achieved with inotropic therapy, with clinical signs of impaired organ perfusion.[21-23]

The secondary outcomes included single components of the primary outcome that occurred during the hospitalization.

Other secondary outcomes of interest were death for any cause and the recurrence of TTS at the longest available follow-up. Recurrence of TTS was diagnosed if, after complete recovery of LV wall motional abnormalities following the index event, a new episode met the diagnostic criteria for TTS.

After hospital discharge, follow-up was performed through outpatient clinic visits, medical charts, or structured telephone interviews by local investigators. The occurrence of the TIN prespecified adverse clinical events was recorded.

STATISTICAL ANALYSIS. The normal distribution of continuous parameters was visually assessed through histograms and tested with the Kolmogorov-Smirnov test. Normally distributed variables were expressed as mean ± SD and compared using the Student's t-test; variables with a skewed distribution were reported as median and IQR and were compared with the Mann-Whitney U test. Categorical variables were reported as numbers and percentages and compared using the chi-square test or Fisher exact test, when appropriate.

To identify factors associated with acute MR, we fitted a generalized linear mixed model including a random intercept for the recruiting center to account for clustering in this multicenter registry. Variables statistically significant ($P < 0.05$) at univariable analysis, as well as variables considered clinically relevant in the context of acute MR in TTS were entered in the model. Results were reported as ORs with their 95% CIs.

To assess the risk of the primary and secondary outcomes during hospitalization according to the presence or absence of acute MR, we calculated the unadjusted and adjusted ORs with their 95% CIs using logistic regression models. To evaluate the effect of coexisting MR and LVOTO, we conducted

unadjusted and adjusted interaction analyses to assess the risk of in-hospital adverse events according to the presence of MR or LVOTO, or both.

Survival free from all-cause death and TTS recurrence during follow-up was displayed using Kaplan-Meier curves. To assess the risk of long-term adverse events, we calculated the unadjusted and adjusted HRs with their 95% CIs using Cox proportional hazards regression models. The proportional hazard assumption was verified by visually inspecting the log-log plots and with the Schoenfeld residuals test. Since the occurrence of death modifies the probability of TTS recurrence, competing risk analysis was conducted considering all-cause death as a competing risk to TTS recurrence. The Fine-Gray method was used to estimate the cumulative incidences of the study outcomes and determine the subdistribution hazard of TTS recurrence, which accounts for the competing risk of mortality.

For both the in-hospital and long-term outcome regression analyses, we employed the propensity score weighting technique to account for potential selection bias between patients with and without acute MR. The propensity score model was developed using a nonparsimonious approach and incorporating a large number of baseline covariates potentially related to the outcome and/or the exposure, regardless of their statistical significance or collinearity with other variables. The lists of covariates entered in the propensity score models are reported in Supplemental Table 2. After weighting, a standardized mean difference of <0.10 was achieved for all covariates included in the propensity score models, reflecting an optimal balance (Supplemental Figures 2 and 3). Propensity score trimming was performed to remove the individuals with extreme weights (at the 5th/95th percentile).

The rate of missing baseline values is shown in Supplemental Table 3. Missing data were handled using multiple imputations with the method of chained equations. Twenty imputed data sets were generated and combined using the Rubin rules.[24]

For all tests, a P value of <0.05 was considered statistically significant. Analysis was performed by using IBM SPSS Statistics Version 25 and R (version 4.2.3, R Foundation for Statistical Computing).

RESULTS

CLINICAL CHARACTERISTICS OF THE STUDY POPULATION. The study included 1025 TTS patients (mean age 70 ± 11 years, 91.6% females); acute, reversible, moderate or severe MR was reported in 186 patients (18.2%). The clinical characteristics of the study population are summarized in **Table 1**.

Patients with acute MR during the acute phase were significantly older compared to patients without ($P < 0.001$) and showed a higher percentage of hypertension ($P = 0.013$) and dyspnea at clinical presentation ($P = 0.001$).

Transthoracic echocardiography on admission showed that patients with acute MR had significantly lower LV ejection fraction (LVEF; 38 ± 9 vs 42 ± 10, $P < 0.001$) and a higher percentage of coexisting LVOTO (16.2% vs 4.8%, $P < 0.001$) and right ventricular (RV) involvement (12.4% vs 6.0%, $P = 0.003$), compared to patients without.

ESTIMATED OR OF ACUTE MODERATE OR SEVERE MR. Generalized linear mixed model multivariable logistic regression analysis showed that older age (OR: 1.03; 95% CI: 1.01-1.05), dyspnea on admission (OR: 1.62; 95% CI: 1.04-2.54), lower LVEF values (OR: 0.97; 95% CI: 0.95-0.99), LVOTO (OR: 3.77; 95% CI: 2.02-7.05), and RV involvement (OR: 1.59; 95% CI: 1.04-2.54) were independently associated with the presence of acute MR during the acute phase (**Table 2**).

IN-HOSPITAL OUTCOMES. Supplemental Table 4 reports the percentage of in-hospital adverse events in the study population. The primary outcome was reported in 185 patients (18.0%), with a significantly higher percentage in patients with acute MR compared to those without (35.5% vs 14.2%, $P < 0.001$). Acute heart failure (29.0% vs 11.4%, $P < 0.001$) and cardiogenic shock (12.9% vs 4.2%, $P < 0.001$) were also more frequently reported in patients with acute MR, but no statistical difference was observed in the percentage of death (3.8% vs 1.5%, $P = 0.125$) between groups.

The propensity score-weighted regression analysis showed that patients with acute MR had a significantly higher risk for the primary outcome (adjusted OR: 2.29; 95% CI: 1.83-2.88), acute heart failure (adjusted OR: 2.17; 95% CI: 1.70-2.77), and cardiogenic shock (adjusted OR: 2.46; 95% CI: 1.69-3.59), compared to patients without (**Table 3**). In-hospital death occurred in only 20 cases. The risk estimate for in-hospital mortality suggests a higher risk in patients with acute MR than in those without, although this difference was not statistically significant (adjusted OR: 1.54, 95% CI: 0.80-2.96; $P = 0.19$).

Conversely, there was no difference between the groups in terms of mortality risk.

The characteristics of patients according to the presence of MR and/or LVOTO are shown in

TABLE 1 Baseline Characteristics

	Overall Population (N = 1,025)	Acute MR (n = 186)	No Acute MR (n = 839)	*P* Value
Age, y	70 ± 11	74 ± 10	69 ± 12	<0.001
Female, n (%)	939 (91.6)	175 (94.1)	764 (91.1)	0.178
Cardiovascular risk factors and comorbidities				
Diabetes, n (%)	128 (12.5)	29 (15.6)	99 (11.8)	0.157
Hypertension, n (%)	669 (65.3)	136 (73.1)	533 (63.5)	0.013
Hypercholesterolemia, n (%)	443 (43.2)	82 (44.1)	361 (43.0)	0.792
Tobacco use, n (%)	228 (22.2)	39 (21.0)	189 (22.5)	0.644
CAD, n (%)	152 (14.8)	27 (14.5)	125 (14.9)	0.894
COPD, n (%)	156 (15.6)	26 (14.8)	130 (15.8)	0.730
Neurologic disorders, n (%)	100 (9.9)	18 (9.9)	82 (9.9)	0.988
Psychiatric disorders, n (%)	144 (14.3)	27 (15.3)	117 (14.1)	0.699
Endocrine disorders, n (%)	125 (12.5)	19 (10.8)	106 (12.9)	0.445
History of cancer n (%)	134 (13.2)	24 (13.1)	110 (13.2)	0.978
Menopause, n (%)	856 (91.2)	161 (92.0)	695 (91.0)	0.665
Clinical, echocardiographic and laboratory characteristics during the index event				
SBP at admission, mm Hg	128 ± 23	128 ± 25	128 ± 23	0.733
DBP at admission, mm Hg	75 ± 14	75 ± 15	75 ± 13	0.838
Heart rate, beats/min	85 ± 19	87 ± 17	84 ± 19	0.057
Chest pain, n (%)	690 (70.6)	113 (68.1)	577 (71.1)	0.442
Dyspnea, n (%)	183 (18.7)	46 (27.7)	137 (16.9)	0.001
Trigger				
Emotional (primary TTS), n (%)	480 (46.8)	77 (41.4)	403 (48.0)	0.238
Physical (secondary TTS), n (%)	186 (18.1)	39 (21.0)	147 (17.5)	
Unknown trigger, n (%)	359 (35.0)	70 (37.6)	289 (34.4)	
ST-segment elevation, n (%)	462 (46.0)	80 (44.4)	382 (46.4)	0.641
New-onset LBBB, n (%)	39 (3.9)	10 (5.6)	29 (3.5)	0.200
Troponin I peak, μg/L	3.3 (1.1-14.5)	4.4 (1.0-108.0)	3.2 (0.3-12.3)	0.095
GFR, mL/min	72.0 (56.9-88.9)	64.9 (49.2-81.1)	74.1 (57.9-89.8)	0.001
LVEF at admission, %	41.0 ± 9.7	38.1 ± 9.3	41.7 ± 9.6	<0.001
Apical form, n (%)	893 (87.1)	158 (84.9)	735 (87.6)	0.328
Atypical form, n (%)	132 (12.9)	28 (15.1)	104 (12.4)	0.328
LVOTO, n (%)	64 (6.9)	28 (16.2)	36 (4.8)	<0.001
RV involvement, n (%)	67 (7.2)	22 (12.4)	45 (6.0)	0.003
LV apical thrombus, n (%)	22 (2.2)	3 (1.6)	19 (2.4)	0.782
Inotropic agents, n (%)	71 (7.5)	28 (15.9)	43 (5.6)	<0.001
IABP, n (%)	28 (3.0)	13 (7.4)	15 (1.9)	<0.001
VT/VF, n (%)	22 (2.2)	4 (2.2)	18 (2.2)	1.000
LVEF at discharge, %	52.4 ± 9.0	51.6 ± 9.5	52.6 ± 8.9	0.259
Medications at discharge				
ASA, n (%)	714 (72.7)	120 (69.8)	594 (73.3)	0.340
$P2Y_{12}$ inhibitor, n (%)	345 (35.1)	46 (26.7)	299 (36.9)	0.011
Beta-blocker, n (%)	695 (70.8)	134 (77.5)	561 (69.3)	0.033
Oral anticoagulant, n (%)	108 (11.1)	26 (15.3)	82 (10.2)	0.055
RAASi, n (%)	432 (44.0)	85 (49.1)	347 (42.9)	0.133
Statin, n (%)	525 (53.5)	92 (53.5)	433 (53.5)	0.993

Values are mean ± SD or 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 2 Estimated Odds ratio of Acute Moderate or Severe MR in the Study Population

	Univariable			Adjusted		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Age	1.04	1.02-1.06	<0.001	1.03	1.01-1.05	0.009
Male	0.64	0.33-1.23	0.181	0.59	0.28-1.25	0.166
Diabetes	1.38	0.88-2.16	0.158			
Hypertension	1.56	1.10-2.22	0.013	1.13	0.72-1.78	0.586
Hypercholesterolemia	1.04	0.76-1.44	0.792			
Tobacco use	0.91	0.62-1.35	0.644			
CAD	0.97	0.62-1.52	0.894			
COPD	0.92	0.58-1.46	0.730			
Neurologic disorders	1.000	0.58-1.71	0.988			
Psychiatric disorders	1.09	0.70-1.72	0.699			
Endocrine disorders	0.82	0.49-1.37	0.446			
History of cancer	0.99	0.62-1.60	0.978			
Menopause	1.14	0.63-2.08	0.665			
SBP at admission	1.00	0.99-1.01	0.733			
DBP at admission	0.99	0.99-1.01	0.837			
Heart rate	1.01	1.00-1.02	0.058			
Chest pain	0.87	0.61-1.24	0.442			
Dyspnea	1.89	1.28-2.78	0.001	1.62	1.04-2.54	0.033
Emotional trigger (primary TTS)	0.76	0.49-1.17	0.210			
Physical trigger (secondary TTS)	1.39	0.90-2.13	0.134			
ST-segment elevation	0.93	0.67-1.28	0.641			
Troponin I peak	1.00	1.00-1.00	0.476			
GFR	0.99	0.99-1.00	0.578			
LVEF at admission	0.96	0.94-0.98	<0.001	0.97	0.95-0.99	0.004
Apical form	0.80	0.51-1.25	0.328	0.73	0.44-1.21	0.219
LVOTO	3.85	2.28-6.51	<0.001	3.77	2.02-7.05	<0.001
RV involvement	2.24	1.31-3.84	0.003	1.59	0.86-2.95	0.140

Abbreviations as in Table 1.

Supplemental Table 5. The unadjusted and adjusted interaction analyses for the risk of in-hospital adverse events according to the presence of MR and/or LVOTO are shown in **Table 4** and Supplemental Table 6. Patients with acute MR and LVOTO during the acute phase had the highest risk for the primary outcome (adjusted OR: 5.26; 95% CI: 3.22-8.59). The presence of LVOTO increased the risk for the primary outcome by 2.4 times in patients with acute MR; the presence of acute MR increased the risk of the primary outcome by 3.7 times in patients with LVOTO.

TABLE 3 Risk of Adverse In-Hospital Outcome in Patients With Acute Moderate or Severe MR

	Univariable			Adjusted		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Primary outcome[a]	3.33	2.33-4.76	<0.001	2.29	1.83-2.88	<0.001
Acute heart failure	3.17	2.16-4.64	<0.001	2.17	1.70-2.77	<0.001
Cardiogenic shock	3.40	1.97-5.88	<0.001	2.46	1.69-3.59	<0.001
Mortality	2.49	0.98-6.32	0.056	1.54	0.80-2.96	0.192

[a]Composite of acute heart failure, cardiogenic shock, and mortality occurring during the hospitalization.

Abbreviations as in Table 1.

LONG-TERM OUTCOMES. Of the 179 patients with acute MR discharged (7 died during hospitalization), 99 showed mild/trivial or absent MR at discharge, whereas the remaining 80 within 6 weeks. Follow-up information was available for 1,008 of 1,025 patients (17 patients were lost to follow-up). At a median follow-up of 29 months (IQR: 12-55), all-cause death was reported in 124 cases and TTS recurrence in 42. Kaplan-Meier curves are depicted in **Figure 1**. The propensity score-weighted Cox regression analysis showed that patients who developed acute MR during hospitalization had a significantly higher risk of mortality during long-term follow-up compared to those who did not (adjusted HR: 1.82; 95% CI: 1.21-2.74). Conversely, there was no difference for the risk of TTS recurrence between groups (adjusted HR: 1.22; 95% CI: 0.57-2.59). There was no violation of the proportional

hazard assumption in both the analyses for all-cause death and for TTS recurrence.

Competing risk analysis confirmed that there was no difference in the likelihood of TTS recurrence between patients with and without acute MR, with all-cause death as a competing risk (Supplemental Figure 4).

DISCUSSION

This is the first and largest multicenter cohort study designed to evaluate the incidence, patients' characteristics, in-hospital, and long-term outcomes of patients with TTS complicated with acute MR.

The main findings of this study can be summarized as follows.

1. Acute MR is a common complication of TTS, being reported in about 18% of patients.
2. Patients with acute MR are significantly older and have a significantly higher percentage of dyspnea on admission, more severe LV systolic dysfunction, and higher percentage of coexisting LVOTO and RV involvement compared to patients without.
3. Acute MR is independently associated with a higher risk of adverse events during the hospitalization, including acute heart failure and cardiogenic shock. The coexistence of acute MR with LVOTO results in a heightened risk of adverse events, including death.
4. The occurrence of acute, reversible MR during the hospitalization is associated with significantly lower survival at long-term follow-up.

In this real-world multicenter registry, the occurrence of acute, reversible, moderate or severe MR was reported in about 1/5 of TTS patients. This percentage is consistent with previous observational studies, which reported an incidence ranging from 17% to 25%.[9,25-27]

Patients with acute MR showed a distinct clinical phenotype characterized by older age and higher percentage of dyspnea on admission.

Parodi et al[25] reported acute significant MR in 14 of 68 TTS patients (20.6%); these patients were older, albeit in the absence of statistical significance, than those without acute MR. Moreover, in a single-center study on 47 TTS patients, Izumo et al[9] reported older age in TTS patients complicated by acute MR.

Acute MR in the context of LV dysfunction is usually related to papillary muscle displacement and bileaflet tethering. In some patients with elongated anterior leaflet or myocardial hypertrophy, especially with sigmoid interventricular septum, the reorientation of hemodynamic intraventricular drag forces may generate a "distortion" effect with consequent systolic anterior movement (SAM) of the anterior mitral leaflet and/or chordae. Subsequently, hypercontractility of the basal segments along with myocardial edema (which further increases the thickness of the interventricular septum) may lead to high-flow velocity in a narrowed LVOT, facilitating a Venturi effect on the mitral apparatus. In this context, significant MR is a result of SAM, LVOTO, and altered leaflet coaptation.[11,12]

However, describing the pathogenic mechanism of MR in TTS was not among our objectives. This study investigated the clinical course of patients with MR with (16.2%) or without LVOTO. From a speculative point of view, it is reasonable to assume that in patients without LVOTO there is a different underlying pathogenetic mechanism of MR. However, we cannot rule out a bystander effect of LVOTO in some cases of acute MR and we cannot rule out forms with mixed mechanisms.[3,4,8,9,11,12,28]

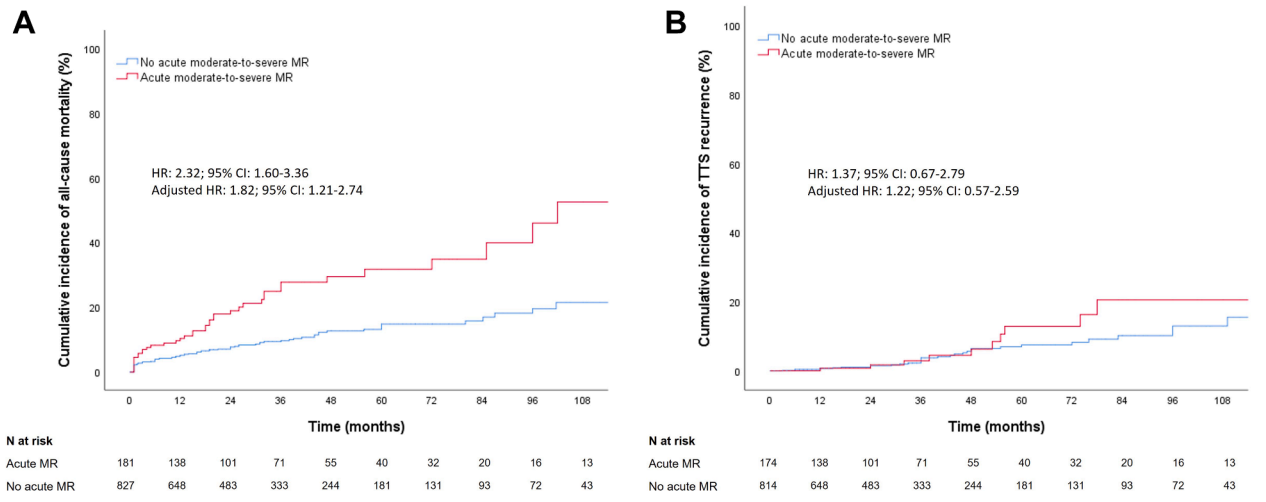
TABLE 4 Propensity Score Weighting-Adjusted Interaction Analysis for risk of In-Hospital Adverse Events According to the Presence of MR and/or LVOTO

	LVOTO Absent	LVOTO Present	Effect of LVOTO in Patients With MR
Primary composite outcome			
MR absent	1.00 (Ref)	1.41 (0.77, 2.57) $P = 0.265$	-
MR present	2.15 (1.69, 2.74) $P < 0.001$	5.26 (3.22, 8.59) $P < 0.001$	2.44 (1.51, 3.97) $P < 0.001$
Effect of MR in patients with LVOTO	-	3.73 (1.79, 7.78) $P < 0.001$	$P_{interaction} = 0.162$
Acute heart failure			
MR absent	1.00 (Ref)	1.13 (0.56, 2.26) $P = 0.732$	-
MR present	2.02 (1.56, 2.62) $P < 0.001$	4.28 (2.57, 7.13) $P < 0.001$	2.12 (1.28, 3.49) $P = 0.003$
Effect of MR in patients with LVOTO	-	3.79 (1.68, 8.58) $P = 0.001$	$P_{interaction} = 0.151$
Cardiogenic shock			
MR absent	1.00 (Ref)	3.56 (1.64, 7.72) $P = 0.001$	-
MR present	2.24 (1.46, 3.43) $P < 0.001$	11.58 (6.39, 21) $P < 0.001$	5.17 (2.96, 9.04) $P < 0.001$
Effect of MR in patients with LVOTO	-	3.26 (1.38, 7.66) $P = 0.007$	$P_{interaction} = 0.442$
Death			
MR absent	1.00 (Ref)	NA[a]	-
MR present	0.91 (0.43, 1.92) $P = 0.806$	7.34 (3.1, 17.38) $P < 0.001$	8.06 (3.24, 20.07) $P < 0.001$
Effect of MR in patients with LVOTO	-	NA[a]	$P_{interaction} = 0.985$

The risk estimates are reported as adjusted OR (95% CI). Analysis conducted on 927 patients with available information on LVOTO. Composite of acute heart failure, cardiogenic shock, and mortality occurring during the hospitalization. [a]No death was reported in patients with LVOTO and without MR.

NA = not available; other abbreviations as in Table 1.

FIGURE 1 Cumulative Incidence Curves



(A) All-cause death and (B) TTS recurrence. MR = mitral regurgitation; TTS = takotsubo syndrome.

The coexistence of LVOTO in TTS patients with acute MR is extremely variable among prior studies, probably due to their small sample size that was suboptimal for capturing the actual rates of complications in TTS. Parodi et al[25] reported SAM of the mitral valve leaflets in 36% of patients with acute MR, and Izumo et al[9] in 50% of cases. Conversely, in a study on 47 TTS patients, Haghi et al[26] reported LVOTO in none of the 9 patients with acute MR.

In this study, we found an independent association between the presence of acute MR and RV involvement. This association may reflect the severe ventricular dysfunction in patients with acute MR, which can result in biventricular TTS forms. Although RV involvement in patients with TTS and severe LVEF reduction at admission has been associated with long-term adverse outcomes, our study shows for the first time that the negative prognostic impact of MR is independent of the coexistence of these 2 conditions.

The echocardiographic evidence of acute MR identified a subset of patients with a significantly higher risk profile for adverse events during hospitalization, including acute heart failure and cardiogenic shock. This result is consistent with the study by Parodi et al[25] who reported significantly worse Killip class on admission and higher use of intra-aortic balloon pump in TTS patients with acute significant MR.

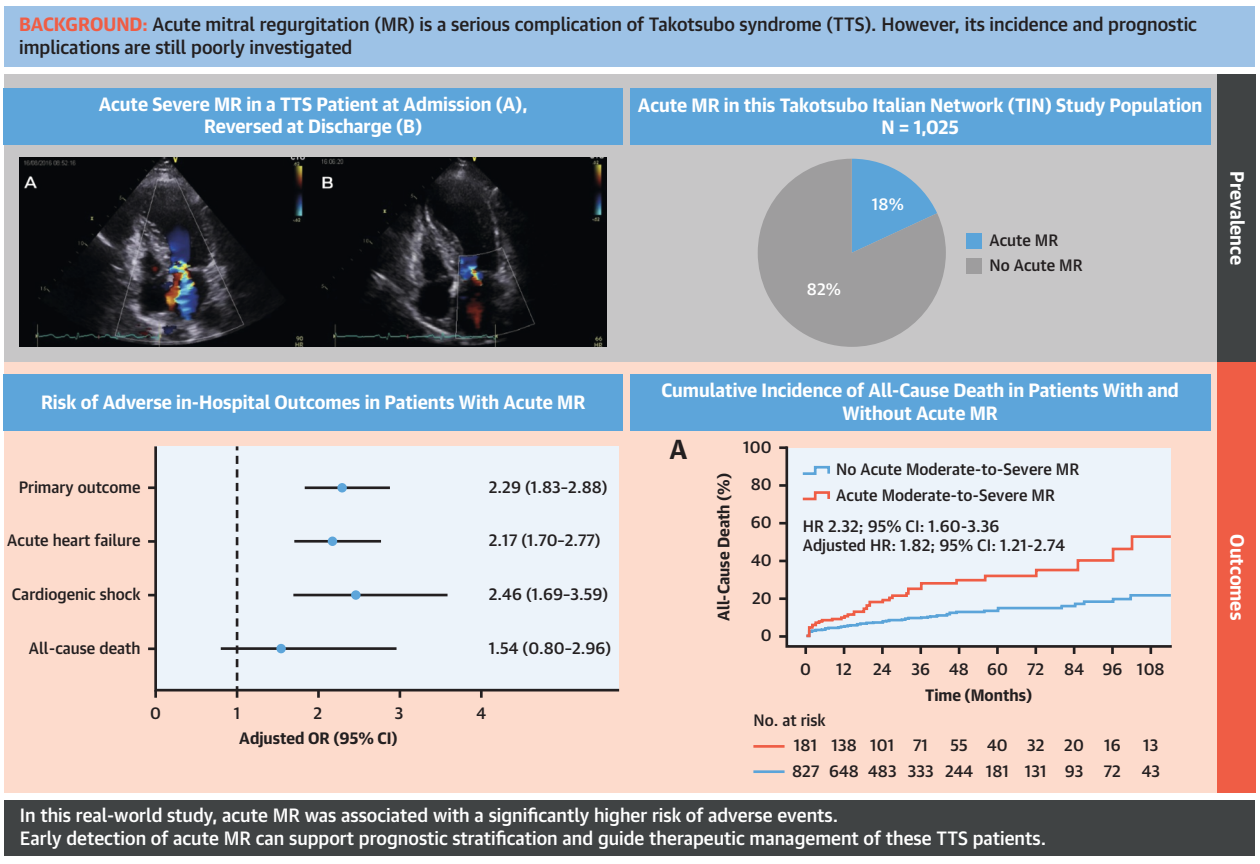
Furthermore, we found that the coexistence of LVOTO in patients with acute MR dramatically increased the primary composite outcome and its components, including mortality.

Acute MR, associated with SAM of the mitral valve and LVOTO, is a severe clinical condition often associated with cardiogenic shock, which implies challenging therapeutic management. This study demonstrates that the combination of MR and LVOTO markedly increases the risk of in-hospital adverse events. These results suggest that the goal of patient monitoring and therapy should not only be the resolution of LVOTO but also the reduction of MR degree.

The study uses a well-defined cohort of TTS patients with serial echocardiographic evaluations, allowing for a dynamic assessment of MR resolution over time. The resolution of MR parallels the recovery of LV function, indicating that it is a functional and reversible phenomenon rather than a marker of intrinsic mitral valve disease. Despite its transient and reversible nature, acute MR carried a significantly higher risk of long-term mortality compared to TTS patients without this complication.

This result could be attributed to differences in patient characteristics and some residual bias in data balancing. However, we conducted a propensity score-weighted Cox regression analysis, which

CENTRAL ILLUSTRATION **Clinical Characteristics and Outcome of Takotsubo Syndrome With Acute Mitral Regurgitation**



Silverio A, et al. JACC Adv. 2026;5(2):102522.

included multiple covariates that could exert a confounding effect.

That said, this result fits with the existing evidence on TTS, which demonstrates how multiple conditions observed during the acute phase, although completely regressing within days or weeks, can impact patients' long-term outcomes. A previous study from the International Takotsubo Registry including 2078 TTS patients reported that the occurrence of cardiogenic shock during the acute phase was associated with higher mortality at long-term follow-up.[21] In a previous study on 326 TTS patients, lower LVEF values on admission were associated with a higher rate of major adverse cardiac events in the long term.[29] Also, a study including 839 TTS patients from the GEIST registry reported that RV involvement correlated with higher mortality at follow-up.[30] Notably, the presence of acute MR has a negative impact on the long-term prognosis of TTS patients regardless of coexistence with severe LV dysfunction and RV involvement. Another consideration is the growing evidence of the long-lasting persistence of subclinical cardiac systolic and diastolic dysfunction in TTS patients after the acute phase, secondary to microscopic fibrosis following myocardial edema resolution and impaired myocardial energetic and calcium homeostasis.[31-33] It is conceivable that patients with more severe TTS forms have a higher grade of persistent structural and metabolic impairment after discharge. This long-lasting myocardial impairment may contribute to the worse long-term outcome of patients who developed acute MR. However, these controversial issues of TTS natural history require further investigations.

STUDY LIMITATIONS. Owing to the observational nature of this study, our results should be considered

hypothesis-generating. Although a robust study design and rigorous statistical analysis, including propensity score weighting technique, were implemented to account for potential selection bias between patients with and without acute MR, some concealed confounders may remain.

The design of this registry-based study does not allow for a definitive determination of causality between acute MR and adverse outcomes in patients with TTS. Therefore, the study findings should be interpreted as associations and cannot be used to prove direct cause-and-effect relationships.

Given the intensive care setting of TTS patients during the acute phase, especially when acute complications occur, it was not possible to systematically perform a quantitative echocardiographic assessment of MR severity. For the same reason, cardiac magnetic resonance could not be performed during the acute phase. Even though all echocardiographic examinations were performed and reviewed by cardiologists trained in cardiovascular imaging, the study design did not include a core lab for central storage and exam revision.

In this study, we defined acute MR by excluding patients who had pre-existing moderate to severe MR. Although this approach could potentially introduce a bias, it allowed us to focus solely on patients with the acute form of MR (rather than those with prevalent MR) and to evaluate its impact on clinical outcomes. In this study, we excluded 9 patients with evidence of persistent moderate or severe MR during follow-up despite complete recovery of LV systolic function or LVOTO, when present. Indeed, the retrospective nature of this study did not allow us to exclude pre-existing moderate or severe MR in these patients, as we were not able to retrieve this information systematically.

Although we stratified patients by coexisting LVOTO, we cannot exclude cases with mixed mechanism of acute MR (both tethering and SAM of mitral leaflets).

In this study, we reported a significant association between acute MR and long-term mortality, but not with in-hospital mortality. Since death during hospitalization is not very frequent in TTS, the estimates of in-hospital mortality should be interpreted as exploratory.

CONCLUSIONS

Our real-world multicenter registry with a large and well-characterized cohort of TTS patients confirmed that acute MR was a frequent complication reported in about one-fifth of the patients. In the broad spectrum of the causes leading to acute MR, TTS should be considered as one of the most representative models. The clinical relevance of this condition is demonstrated by the statistical association with a higher risk of adverse events during the hospitalization, especially in patients with LVOTO. Also, the negative prognostic impact is not confined to the acute phase but portends a higher long-term mortality. The echocardiographic detection and monitoring of acute MR is of utmost importance in patients with TTS to guide patient management.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Acute MR is a serious complication of TTS. However, its incidence and prognostic implications remain poorly understood. This registry-based study is the largest to investigate the prognostic impact of acute MR. A significantly higher risk of adverse events during hospitalization and long-term mortality was observed in patients with acute MR compared to those without.

TRANSLATIONAL OUTLOOK: Further studies are needed to confirm these results.

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KEY WORDS acute mitral regurgitation, broken heart syndrome, left ventricular outflow tract obstruction, stress cardiomyopathy, takotsubo syndrome

APPENDIX For supplemental tables and figures, please see the online version of this paper.