ORIGINAL RESEARCH

Clinical Predictors and Prognostic Impact of Recovery of Wall Motion Abnormalities in Takotsubo Syndrome: Results From the International Takotsubo Registry

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***Background*—**Left ventricular (LV) recovery in takotsubo syndrome (TTS) occurs over a wide-ranging interval, varying from hours to weeks. We sought to investigate the clinical predictors and prognostic impact of recovery time for TTS patients.

***Methods and Results*—**TTS patients from the International Takotsubo Registry were included in this study. Cut-off for early LV recovery was determined to be 10 days after the acute event. Multivariable logistic regression was used to assess factors associated with the absence of early recovery. In-hospital outcomes and 1-year mortality were compared for patients with versus without early recovery. We analyzed 406 patients with comprehensive and serial imaging data regarding time to recovery. Of these, 191 (47.0%) had early LV recovery and 215 (53.0%) demonstrated late LV improvement. Patients without early recovery were more often male (12.6% versus 5.2%; P=0.011) and presented more frequently with typical TTS (76.3% versus 67.0%, P=0.040). Cardiac and inflammatory markers were higher in patients without early recovery than in those with early recovery. Patients without early recovery showed unfavorable 1-year outcome compared with patients with early recovery (P=0.003). On multiple logistic regression, male sex, LV ejection fraction <45%, and acute neurologic disorders were associated with the absence of early recovery.

***Conclusions*—**TTS patients without early LV recovery have different clinical characteristics and less favorable 1-year outcome compared with patients with early recovery. The factors associated with the absence of early recovery included male sex, reduced LV ejection fraction, and acute neurologic events.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT01947621. **(*J Am Heart Assoc*. 2019;8: e011194. DOI: 10.1161/JAHA.118.011194.)**

Key Words: outcome • recovery • takotsubo syndrome • wall motion abnormalities

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Clinical Perspective

What Is New?

- Left ventricular recovery in takotsubo syndrome varies from days to weeks.
- Patients with early left ventricular recovery have a different clinical phenotype and more favorable outcomes compared with patients without early recovery.
- Factors associated with absence of early recovery were male sex, reduced left ventricular ejection fraction, and acute neurologic events.

What Are the Clinical Implications?

- The findings of this study highlight that takotsubo syndrome patients without early recovery have worse outcomes compared with patients with early recovery and thus should be monitored closely.
- Prospective studies are needed to unravel the pathophysiological mechanisms of left ventricular recovery in patients with takotsubo syndrome.

Takotsubo syndrome (TTS) is an acute heart failure syndrome characterized by left ventricular (LV) dysfunction and peculiar patterns of wall motion abnormalities (WMA).[1–4] Although this condition typically affects postmenopausal women and is often preceded by emotional or physical triggers, recent studies have demonstrated that TTS is more heterogeneous than previously thought.[1,5–9] Several studies have shown that TTS, which has typically been considered a benign disease, may represent a serious illness with mortality rates comparable to acute coronary syndrome in the acute phase and with a high rate of adverse events at long-term follow-up.[1,10,11]

Despite the recent progress in understanding TTS, many uncertainties remain. Recovery from LV dysfunction is a pivotal defining characteristic of TTS. However, the pathophysiological mechanisms underlying the LV dysfunction are still unclear and the clinical aspects of recovery have scarcely been investigated. Previous studies have shown that most patients with TTS recover from LV dysfunction within 1 to 6 months, but wide interindividual variation in the duration of the recovery process has been reported.[1,12–14] Moreover, the clinical implications of recovery time in TTS are also uncertain. First, it is unclear whether the differences in the duration of recovery affect outcomes of TTS patients. Second, the specific clinical parameters that influence or predict the duration of the LV recovery process are unknown. Finally, patients with higher risk of late resolution of WMA cannot currently be identified during the acute phase. This last issue might be of particular importance because this patient population may require longer monitoring and supportive therapy to improve outcomes.

In this analysis, we aimed to assess the clinical features of TTS patients without early resolution of WMA and to compare their outcomes to those of patients with early resolution of WMA. Furthermore, clinical parameters associated with the absence of early recovery were investigated.

Methods

Study Population

Data were collected from the InterTAK Registry (International Takotsubo Registry, www.takotsubo-registry.com),[15] which is a multicenter, prospective, and retrospective observational registry established at the University Hospital Zurich in 2011. The authors declare that all supporting data are available within the article. The study design, methods, and objectives were reported recently in a previous study.[1] TTS was defined based on InterTAK Diagnostic Criteria.[3] Medical records were reviewed by investigators at the University Hospital Zurich. Uncertain cases were reviewed by core team members at the University Hospital Zurich, and the decision for inclusion or exclusion was reached by consensus. Follow-up information was obtained from medical records, telephone interviews, or clinical visits. The study protocol was reviewed by the respective local ethics committee or investigational review board at each collaboration site. Given the partly retrospective nature of the study, ethics committees of most study centers waived the need for informed consent. At centers for which the ethics committees or investigational review boards required informed consent or from which patients were included prospectively, formal written consent was obtained from patients or surrogates.

Recovery Analysis

Recovery was defined as complete resolution of WMA in follow-up echocardiography or cardiac magnetic resonance imaging compared with the initial echocardiogram or ventriculogram. Patients were divided into 2 groups based on the presence or absence of WMA recovery within 10 days after TTS onset. Accordingly, patients who demonstrated recovery within 10 days of the index event were assigned to the early recovery group, whereas patients with persistent WMA after 10 days were allocated to the group without early recovery (Figure 1). These groups were compared to explore the differences in clinical profiles and outcomes. Patients who could not be categorized in one of the groups (eg, patients with documentation of resolution of WMA after several weeks without recovery information at previous time points) were not included in the analysis.

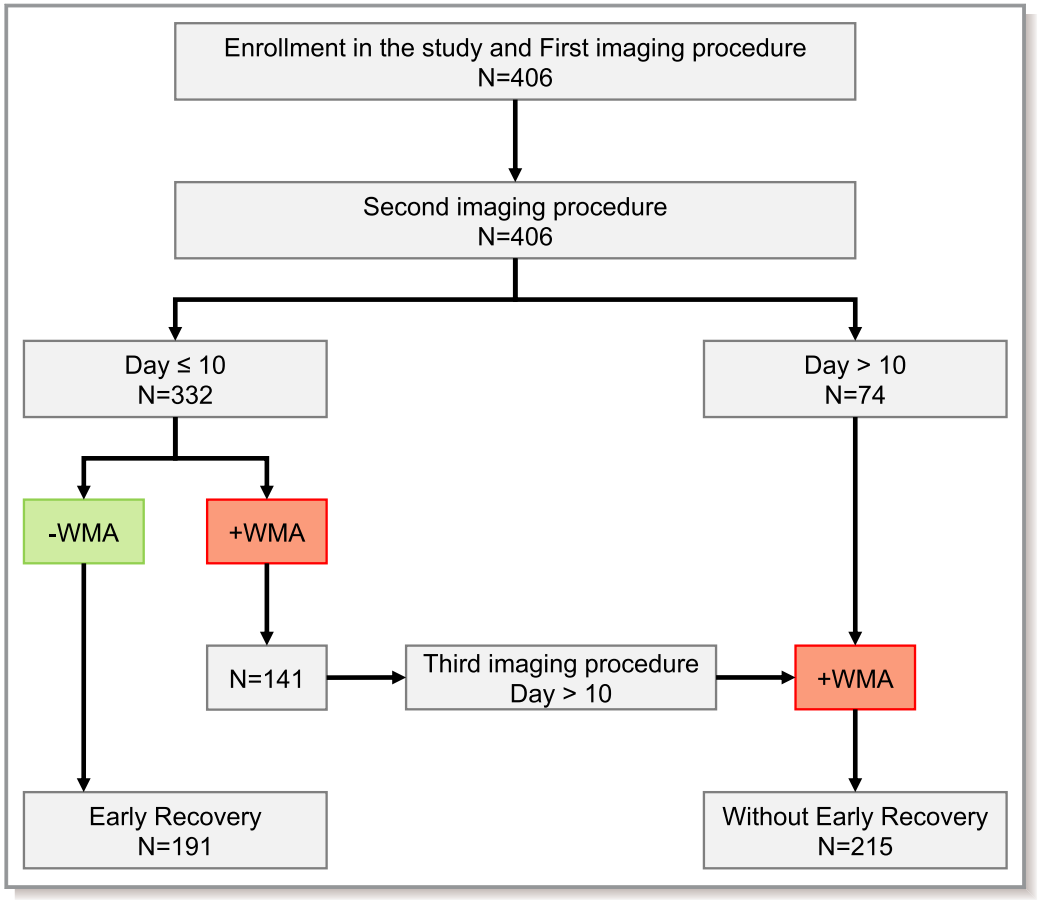

Figure 1. Study flowchart. +WMA indicates persistent wall motion abnormalities; −WMA, complete resolution of wall motion abnormalities.

Study Outcomes

Data regarding in-hospital complications (cardiogenic shock, death, ventricular thrombus) and their management (invasive or noninvasive ventilation, catecholamine administration) were recorded. The main outcome measure of this analysis was 1-year mortality. Patients whose follow-up was shorter than 10 days or who died during the first 10 days after TTS event were excluded from the analysis. Consequently, the qualifying events for outcome analysis were recorded from the 11th day after admission. Factors associated with the absence of early recovery in TTS patients were also investigated.

Statistical Analyses

Continuous variables are reported as mean±SD or median with interquartile range, whereas categorical variables are presented as frequency with percentage. Continuous variables were compared using the Mann–Whitney *U* test, whereas the Pearson χ^2 test (or Fisher exact test, as appropriate) was used for the comparison of categorical variables. Survival estimates were assessed using Kaplan–Meier curves, and group differences were evaluated with the log-rank test. Multivariable logistic regression was used to identify the parameters associated with the absence of early recovery in TTS patients. Covariates with $P<0.05$ at baseline comparison between the groups (with versus without early recovery) were included in the multivariable model; a multiple regression imputation analysis was then performed to account for missing values. The cut-off for statistical significance was set at a 2-sided *P* value <0.05. Odds ratios are reported with the respective 95% CIs. Analyses were computed with SPSS statistical software, version 23.0 (IBM Corp). Figures were created with Prism 7 software (GraphPad).

Results

Patient Characteristics

Of 406 patients, 191 (47%) were assigned to the early recovery group (Figure 1). In the early recovery group, median time to WMA resolution was 5 days (interquartile range: 3–7 days). In the group without early recovery, follow-up imaging

assessment was performed at a median of 30 days (interquartile range: 14–57 days). The baseline features of the 2 study groups are shown in Table. Patients without early resolution of WMA were more often male (12.6% versus 5.2%, *P*=0.011) and were more likely to have physical triggers (46.5% versus 35.1%, *P*=0.020) compared with patients with early resolution of WMA. Patients without early resolution of WMA had higher prevalence of comorbidities, particularly acute neurologic disorders, such as intracranial bleeding, stroke or seizure (9.6% versus 1.7%, *P*=0.001), and malignancies (22.1% versus 12.2%, *P*=0.010). TTS patients without early resolution of WMA presented with typical TTS more frequently (76.3% versus 67.0%, *P*=0.040) and had lower LV ejection fraction (LVEF) on admission (37.3±10.7% versus 43.7±11.9%, *P*<0.001). Moreover, patients without early resolution of WMA presented with higher values of troponin, CRP (C-reactive protein), and white blood cell counts on admission.

Outcomes

Patients without early resolution of WMA required invasive and noninvasive ventilation more frequently compared with patients with early resolution of WMA (26.0% versus 14.7%, *P*=0.005). Moreover, a trend toward a higher rate of cardiogenic shock was observed in TTS patients without early resolution of WMA (15.0% versus 8.9%, *P*=0.06). Interestingly, a significantly higher prevalence of ventricular thrombus was shown in TTS patients without early resolution of WMA (2.9% versus 0.0%, *P*=0.030). In addition, inotropic agents were more frequently used in patients in the group without early recovery, although the difference was not significant (16.7% versus 11.0%, *P*=0.10). Patients without early resolution of WMA had a significantly higher mortality rate at 1-year compared with patients with early recovery of WMA (7.4% versus 1.3%, *P*=0.003; Figure 2).

Factors Associated With Absence of Early Recovery

Multivariable logistic regression analysis was conducted, including covariates with significant differences (*P*<0.05) at baseline between patients with and without early recovery (Figure 3). We identified male sex, LVEF <45%, and a composite of acute neurologic events as factors associated with the absence of early recovery. The results remained similar after excluding the composite of acute neurologic disorders from the multivariable model (Figure S1).

Discussion

To our knowledge, this study is the largest investigating the predictors and prognostic impact of absence of early recovery in TTS. The study had 3 main findings: (1) patients with longer recovery time for WMA were more frequently male, had a higher prevalence of physical triggers initiating TTS, presented more commonly with typical TTS (apical ballooning), and presented with lower LVEF and higher troponin and inflammatory marker levels on admission; (2) male sex, LVEF <45%, and concomitant acute neurologic events were associated with the absence of early recovery in TTS; and (3) delayed resolution of WMA was associated with higher mortality at 1-year.

On multivariable analysis, male sex, depressed LVEF, and acute neurologic comorbidities were identified as risk factors associated with the absence of early recovery. These results are clinically important because patients with these characteristics should be monitored closely after hospitalization, given the higher risk of potential clinical complications. A previous study by Shiomura et al reported brain natriuretic peptide levels, body mass index, and nonuse of calcium channel blockers as independent predictors for delayed LV recovery. However, the difference in their findings may be due to the small size of that study (n=60).[16]

Rates of cardiogenic shock and invasive or noninvasive ventilation were higher in the group without early recovery. In addition, patients with longer WMA recovery duration appeared to be more susceptible to ventricular thrombus formation, most likely because of the extent of myocardial involvement and longer impairment of LV function. Nevertheless, a complicated acute course of the disease might adversely impact the recovery rate. The fact that those with prolonged recovery presented with higher troponin levels and lower LVEF supports this interpretation. It may just take more time to recover from a severely depressed LVEF than from a mild impairment of pump function.

Patients without early resolution of WMA had significantly elevated inflammatory markers, but these findings were not significant on multivariable analysis. Higher levels of inflammatory markers may have affected the outcome; however, inflammatory response could be due to the preexisting comorbidities in these patients. Indeed, TTS patients with longer recovery from WMA more commonly experienced acute neurologic conditions, which are known to be associated with elevated CRP levels. Similarly, it is known that neurologic disorders may lead to profound cardiac damage with pathological changes including contraction band necrosis, found in autopsied patients with sudden unexpected death in epilepsy as well as in TTS patients.[17,18] In this regard, TTS patients with acute neurologic comorbidities might have more severe "neurocardiac damage" with longer LV recovery times.

Schwarz et al recently reported persistent WMA at 4-month follow-up despite overall normalization of LVEF in some TTS patients.[19] The researchers noted subtle cardiac

Table. Patient Characteristics

Characteristic	TTS With Early Recovery (n=191)	TTS Without Early Recovery (n=215)	*P* Value
Demographics			
Female sex	181/191 (94.8)	188/369 (87.4)	0.011
Age, y	64.2±13.0 (n=191)	66.1±12.8 (n=215)	0.13
Symptoms and triggers			
Chest pain	131/175 (74.9)	127/192 (66.1)	0.07
Dyspnea	90/175 (51.4)	98/195 (50.3)	0.82
Physical trigger	67/191 (35.1)	100/215 (46.5)	0.020
Emotional trigger	60/191 (31.4)	62/215 (28.8)	0.57
Cardiac biomarkers			
Troponin on admission—factor increase in ULN*	5.96 (1.89–13.15); n=156	7.29 (2.00–23.54); n=168	0.040
Creatine kinase on admission—factor increase in ULN	0.83 (0.52–1.20); n=148	0.84 (0.48–1.43); n=141	0.92
BNP on admission—factor increase in ULN†	4.97 (2.44–12.80); n=57	9.87 (2.74–27.07); n=65	0.12
Inflammatory markers			
CRP on admission, mg/L	3.35 (1.03–8.98); n=132	5.10 (2.30–18.40); n=125	0.005
WBC on admission, $10^3/\mu L$	9.00 (7.11–11.65); n=169	10.40 (7.67–12.65); n=185	0.010
ECG on admission			
Sinus rhythm	161/169 (95.3)	172/185 (93.0)	0.36
Atrial fibrillation	7/169 (4.1)	12/185 (6.5)	0.33
AV block (I, II, or III)	5/169 (3.0)	17/185 (9.2)	0.020
ST-segment elevation	63/169 (37.3)	72/185 (38.9)	0.75
ST-segment depression	9/169 (5.3)	14/185 (7.6)	0.39
T-wave inversion	72/169 (42.6)	79/185 (42.7)	0.99
QTc, ms	457.4±46.8 (n=140)	459.8±43.7 (n=151)	0.64
Imaging and hemodynamic findings			
Apical type	128/191 (67.0)	164/215 (76.3)	0.040
LV ejection fraction, %‡	43.7±11.9 (n=169)	37.3±10.7 (n=191)	<0.001
LV end-diastolic pressure, mm Hg	21.3±8.9 (n=114)	22.2±7.6 (n=114)	0.40
Heart rate, beats/min	87.7±22.5 (n=151)	91.3±23.3 (n=162)	0.17
Systolic blood pressure, mm Hg	131.3±33.3 (n=157)	131.8±30.0 (n=166)	0.67
Cardiovascular risk factors/history			
Hypertension	124/188 (66.0)	133/210 (63.3)	0.56
Diabetes mellitus	29/186 (15.6)	29/210 (13.8)	0.62
Hypercholesterolemia	58/183 (31.7)	82/207 (39.6)	0.10
Coexisting medical condition			
Acute intracranial bleeding, stroke/TIA, seizure	3/173 (1.7)	20/208 (9.6)	0.001
Past or chronic neurologic disorders	24/172 (14.0)	46/205 (22.4)	0.035
Acute psychiatric disorders	18/173 (10.4)	19/208 (9.1)	0.68
Past or chronic psychiatric disorders	47/172 (27.3)	53/205 (25.9)	0.75
Cancer (total)	22/181 (12.2)	44/199 (22.1)	0.010
Medication on admission			
ACE inhibitor or ARB	52/156 (33.3)	60/163 (36.8)	0.52
Beta-blocker	59/156 (37.8)	47/164 (28.7)	0.08

Continued

Table. Continued

Characteristic	TTS With Early Recovery (n=191)	TTS Without Early Recovery (n=215)	*P* Value
Calcium-channel antagonist	9/156 (5.8)	8/163 (4.9)	0.73
Statin	23/156 (14.7)	25/163 (15.3)	0.88
Aspirin	50/156 (32.1)	49/163 (30.1)	0.70
In-hospital complications and management			
Cardiogenic shock	17/191 (8.9)	32/214 (15.0)	0.06
Death	5/191 (2.6)	7/215 (3.3)	0.71
Catecholamine use	21/191 (11.0)	36/215 (16.7)	0.10
Ventricular thrombus	0/189 (0.0)	6/210 (2.9)	0.030
Invasive or noninvasive ventilation	28/191 (14.7)	56/215 (26.0)	0.005

Values are mean ± SD, no./total n (%), or median (interquartile range). ACE indicates angiotensin-converting-enzyme; ARB, angiotensin-receptor blocker; AV block, atrioventricular block; BNP, brain natriuretic peptide; CRP, C-reactive protein; IQR, interquartile range; LV, left ventricular; QTc, QT interval corrected for heart rate; TIA, transient ischemic attack; TTS, takotsubo syndrome; ULN, upper limit of the normal range; WBC white blood cell count.

*Including ULNs for troponin T, high-sensitivity troponin T, and troponin I.

†Including ULNs for brain natiuretic peptide and the N-terminal of prohormone brain natiuretic peptide.

‡LV ejection fraction (%): information from catheterization or echocardiography, if both available: catheterization.

deformations and impaired contraction as assessed by LV twist and strain analysis. Moreover, a previous study by Scally et al reported impaired cardiac energetic status and the development of a heart failure phenotype on long-term follow-up in some TTS patients.[20] These results suggest the occurrence of prolonged impairment of cardiac function despite visual assessment suggestive of recovery of WMA and LVEF improvement. This surprising persistence of cardiac functional impairments in TTS should be evaluated further; the issue of "incomplete recovery" is a relatively new concept, and its mechanisms and clinical implications are unknown.[20,21]

We sought to provide parameters that are relatively easy to obtain in daily clinical practice to detect TTS patients with potentially longer recovery times for WMA. Our results suggest the importance of clinical vigilance in TTS patients, particularly those with prolonged resolution of WMA. Future studies evaluating therapeutic strategies are needed to

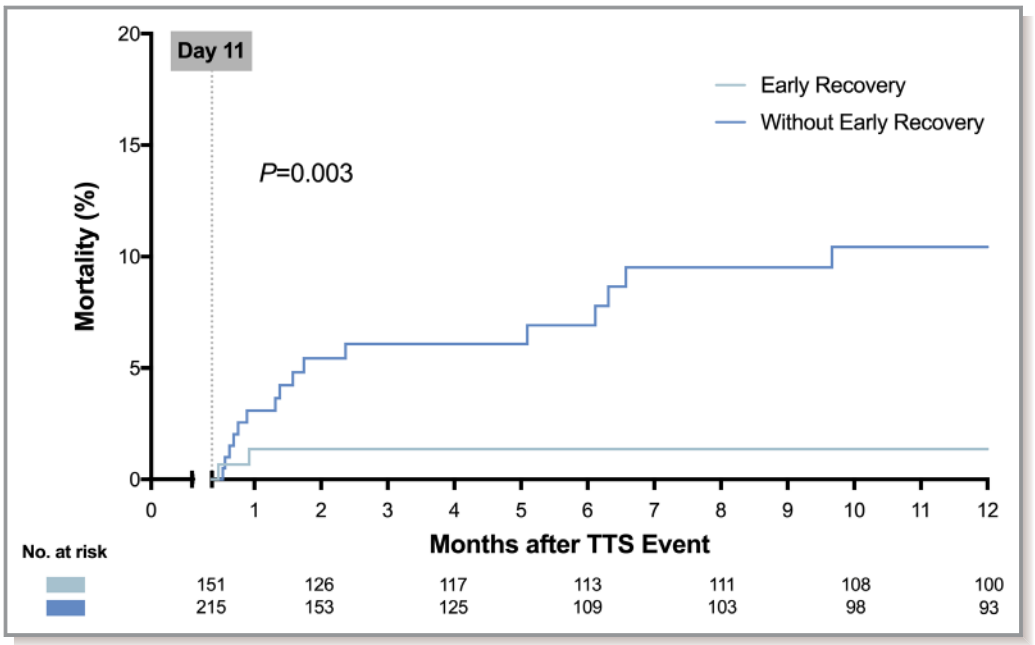

Figure 2. Long-term outcome in takotsubo syndrome (TTS) patients with and without early recovery. Kaplan–Meier survival analysis demonstrated significant differences in 1-year mortality in TTS patients without early recovery than in those with early recovery (*P*=0.003).

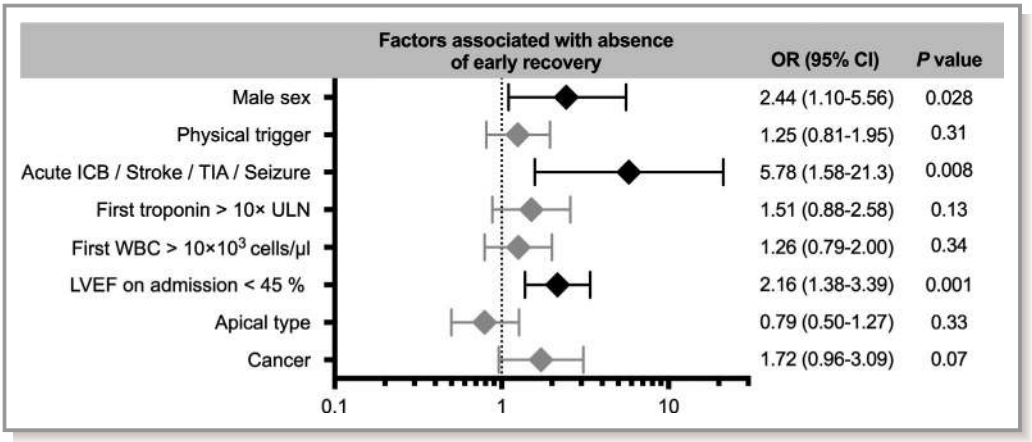

Figure 3. Factors associated with absence of early recovery. Multivariable logistic regression, adjusted for potential confounders, demonstrated that male sex, left ventricular ejection fraction <45%, and acute neurologic comorbidities were factors associated with the absence of early recovery in takotsubo syndrome. Error bars represent 95% CI. Black rhombi indicate statistical significance; gray rhombi are not statistically significant. ICB indicates intracranial bleeding; LVEF, left ventricular ejection fraction; OR, odds ratio; TIA, transient ischemic attack; ULN, upper limit of the normal range; WBC, white blood cell count.

accelerate LV recovery and to improve long-term prognosis in TTS patients.

Study Limitations

This study is partly retrospective in nature and is based on an international multicenter registry. Moreover, the dichotomous classification of those with and without early recovery may influence our results because a priori imaging time points were not selected. The vast majority of imaging studies were performed by echocardiography; cardiac magnetic resonance imaging was not performed in all patients because data went back to 1998, when cardiac magnetic resonance imaging was not broadly and systematically available.[22] The multivariable analysis did not demonstrate an association between physical triggers and the absence of early recovery, likely because of the sample size of the study. Multivariable logistic regression analysis was used to investigate the covariates associated with the absence of early recovery, given the retrospective limitation of assessing the exact time to recovery. Furthermore, multivariable assessment of survival was not performed because of the limited number of events at follow-up, which prevented the establishment of an accurate and reliable model.

Conclusions

This study offers new insights into the clinical impact of LV recovery time in TTS patients. Patients without early LV recovery have higher prevalence of in-hospital complications and higher mortality and should be monitored closely. Further prospective studies are needed to uncover the actual mechanism underlying LV recovery in TTS.

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Disclosures

None.

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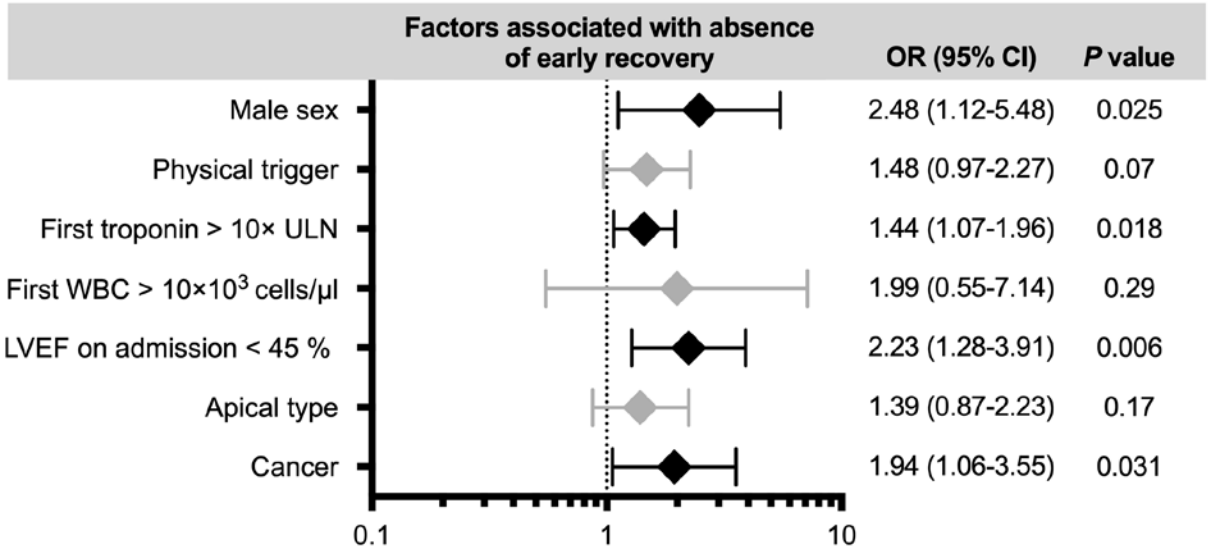
SUPPLEMENTAL MATERIAL

Figure S1. Multivariate logistic regression



Multivariate logistic regression revealed similar results both before and after excluding the composite of acute neurologic disorders.
Error bars represent 95% confidence interval.
Black rhombi indicate statistical significance; grey rhombi not statistically significant.
C.I., confidence interval; LVEF, left ventricular ejection fraction; OR, odds ratio; ULN, upper limit of the normal range; WBC, white blood cell count.