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# Incomplete Recovery From Takotsubo Syndrome Is a Major Determinant of Cardiovascular Mortality

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**Background:** Although there is an apparent rapid and spontaneous recovery of left ventricular ejection fraction (LVEF) in patients with Takotsubo syndrome (TTS), recent studies have demonstrated a long-lasting functional impairment in those patients. The present study sought to evaluate the predictors of incomplete recovery following TTS and its impact on cardiovascular mortality.

**Methods and Results:** Patients with TTS between 2008 and 2018 were retrospectively enrolled at 3 different institutions. After exclusion of in-hospital deaths, 407 patients were split into 2 subgroups according to whether their LVEF was >50% (recovery group; n=341), or ≤50% (incomplete recovery group; n=66) at the chronic phase. Multivariate logistic regression analysis found that LVEF (odds ratio [OR]: 0.94; 95% confidence interval [CI]: 0.91–0.98; P<0.001) and C-reactive protein levels (OR: 1.11; 95% CI: 1.02–1.22; P=0.02) at discharge were independent predictors of incomplete recovery. At a median follow up of 52 days, a higher cardiovascular mortality was evident in the incomplete recovery group (16% vs. 0.6%; P<0.001).

**Conclusions:** This study demonstrated that incomplete recovery after TTS is characterized by residual systemic inflammation and an increased cardiac mortality at follow up. Altogether, the present study findings determined that patients with persistent inflammation are a high-risk subgroup, and should be targeted in future clinical trials with specific therapies to attenuate inflammation.

**Key Words:** Ejection fraction; inflammation; Mortality; Takotsubo syndrome

**T**akotsubo syndrome (TTS) is an acute and usually reversible heart failure syndrome characterized by typical regional wall motion abnormalities, often resulting from stressful, emotional or physical triggering events. Patients with this syndrome have characteristic ballooning of the left ventricle (LV), with subsequent prompt restoration of normal or near normal left ventricular ejection fraction (LVEF).

It has become obvious that TTS is not as benign as once thought, and acute episodes of TTS are associated with increased risk of mortality and morbidity.<sup>1</sup> Prior investigations have found that mortality in patients with TTS is high and is similar to that of patients diagnosed with acute coronary syndromes (ACS).<sup>2</sup> Despite a substantial recovery in systolic function, recent studies highlighted that TTS

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results in a long-term heart failure phenotype with persistent subclinical cardiac dysfunction.<sup>3,4</sup> Recent advances in the pathophysiology of TTS have emphasized the key role for catecholamine's surge, which triggers a switch in the  $\beta$ -2 adrenergic signaling from Gs to Gi-protein leading to further cardiodepression. Moreover, several investigations have determined that there is involvement of residual inflammation with symptomatic and functional impairment associated with persistent subclinical cardiac dysfunction.<sup>3,5</sup> Scally et al demonstrated that TTS was associated with a marked increase in markers of myocardial inflammation such as sustained myocardial edema on

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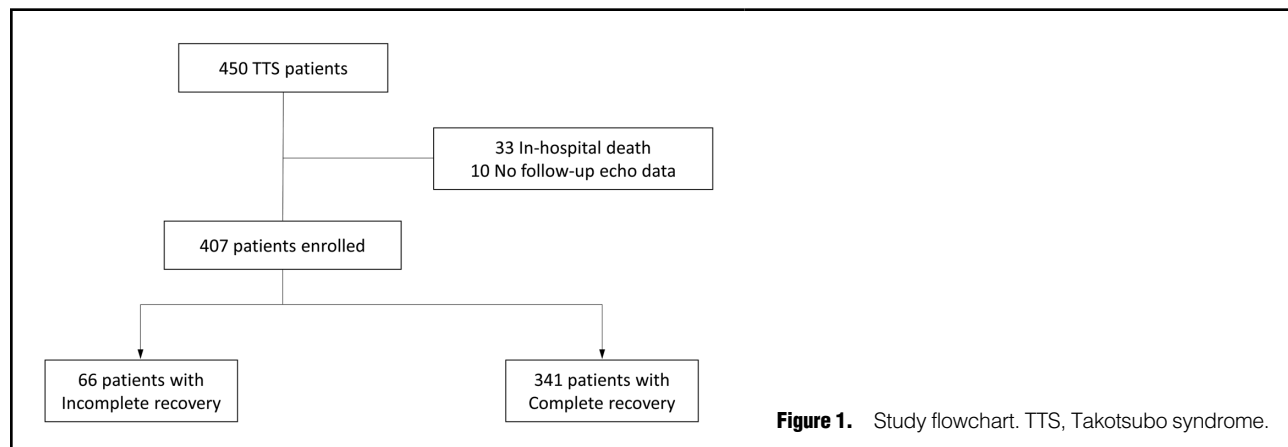
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magnetic resonance imaging (MRI) and with a substantial concomitant reduction in myocardial phosphocreatine ratio (PCr/ATP) as an indicator of energetic impairment.<sup>3</sup> Most recently, we clarified that the enhanced myocardial damage in TTS patients was related to a systemic inflammatory response syndrome, which was also associated with long-term cardiovascular mortality.<sup>5</sup>

Although the persistent inflammation and subclinical cardiac dysfunction in TTS patients have been delineated by recent studies, the noxious impact of incomplete recovery following TTS on long-term outcomes has not been investigated. In the present study, we sought to evaluate the long-term impact of incomplete recovery following TTS (LVEF  $\leq 50\%$  at the chronic phase) on cardiovascular outcomes and its determinants in a large cohort of unselected TTS patients.

## Methods

### Study Design and Population

We conducted a multicenter, retrospective study from September 2008 to September 2018 at 3 different institutions (Colmar, Haguenau, and Strasbourg, France). Among the 62,214 coronary angiograms recorded in the cardiac catheterization laboratory database, we identified patients with suspected TTS by using the key words “stress”, “takotsubo”, or “catecholamine”. The diagnosis of TTS was made according to the European Society of Cardiology Heart Failure Association criteria.<sup>6,7</sup> Patients with acute coronary occlusion, percutaneous coronary intervention, myocarditis, and cardiac arrest at first medical contact were excluded from the study. Two cardiologists reviewed all the cases and those were recorded in the Alsace Takotsubo (ATAK) registry. All participants gave their written informed consent prior to being admitted to the study. The investigation conforms with the principles outlined in the Declaration of Helsinki.

### Clinical and Biological Assessments

Baseline characteristics included medical history, cardiovascular risk factors, medications, electrocardiogram at the time of admission, coronary angiograms, and echocardiographic assessments. Serial biological parameters, including C-reactive protein (CRP), white blood cells count, brain natriuretic peptide (BNP), and troponin I, were measured on admission, at peak, and at discharge.

### Echocardiographic Assessments

Transthoracic echocardiography (TTE) was performed on admission, at discharge, and at follow up. Follow-up echocardiography was available for 407 patients, with a median follow up of 52 days (interquartile range [IQR]: 19–367 days). LVEF was assessed using 2-dimensional TTE and the biplane Simpson method from the apical 4- and 2-chamber views. Follow-up LVEF was assessed using MRI if the TTE was not performed. Left ventricular regional wall motion abnormalities were evaluated by visual assessments of multiple apical and short-axis views. Right ventricular (RV) wall motion was evaluated by visual assessment for the detection of RV involvement.

### Clinical Outcomes

In-hospital complications including arrhythmias, cardiogenic shock, and death were collected by careful reviewing of the patient electronic medical records. The follow up of patients was conducted via telephone interviews, using a standardized questionnaire about health status and symptoms from the family physician or the hospital records.

The primary endpoint of the study was cardiovascular mortality (a composite of death resulting from myocardial infarction, sudden cardiac death, heart failure, stroke, TTS recurrence, or resulting from other cardiovascular causes). The secondary endpoints included TTS recurrence and heart failure hospitalization.

### Statistical Analysis

Categorical variables are expressed as numbers (%), and continuous variables are expressed as mean  $\pm$  SD or median and interquartile values. Differences between the 2 groups, consisting of incomplete and complete recovery groups, were assessed with an unpaired Student's t-test for continuous variables that showed normal distributions and with the Wilcoxon test for continuous variables with skewed distributions. Chi-squared tests or Fisher's exact tests were used to analyze categorical variables. Univariate and multivariate logistic regression analyses were performed to identify independent predictors of incomplete recovery. Variables with P values  $< 0.05$  in univariate analyses were included in the multivariate analyses. The area under the receiver-operating characteristic (ROC) curves were constructed to identify the optimal cut-off values of LVEF and CRP levels at discharge to predict incomplete recovery. Associated sensitivity, specificity, positive predic-

	Incomplete recovery (n=66)	Complete recovery (n=341)	P value
Age, years	72±13	70±14	0.16
Male	16 (24)	39 (11)	0.005
Height, cm	164±9	163±8	0.26
Body weight, kg	69±19	66±15	0.13
Hypertension	35 (53)	202 (59)	0.35
Diabetes	14 (21)	62 (18)	0.56
Dyslipidemia	28 (42)	146 (43)	0.95
Current smoker	14 (21)	59 (17)	0.45
Coronary artery disease	25 (41)	115 (37)	0.57
Cerebrovascular disease	10 (15)	37 (11)	0.32
Peripheral artery disease	16 (25)	58 (17)	0.15
Psychiatric history	24 (36)	111 (33)	0.55
Dementia	10 (15)	22 (6)	0.02
Cancer history	17 (26)	75 (22)	0.50
Pheochromocytoma	0 (0)	2 (0.6)	1.00
Pacemaker	8 (12)	10 (3)	0.003
Previous TTS	4 (6)	8 (2)	0.11
Supraventricular arrhythmia	22 (33)	49 (14)	<0.001
Medication			
β-blocker	20 (33)	73 (22)	0.08
Antiarrhythmic drug	12 (18)	35 (10)	0.07
Trigger			0.31
Unknown	18 (27)	76 (22)	
Physical stress	33 (50)	156 (46)	
Emotional stress	15 (23)	109 (32)	
Symptom			
Dyspnea	31 (47)	134 (39)	0.25
Syncope	2 (3)	13 (4)	1.00
QTc, ms	488±53	464±48	0.007

Values are presented as n (%) or mean±SD. TTS, Takotsubo syndrome.

tive value (PPV), negative predictive value (NPV), and overall accuracy were also calculated. The association between incomplete recovery after TTS and cardiovascular mortality was evaluated using the Cox proportional hazards model. Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated. Event rates over time were summarized using Kapla-Meier estimates, and log-rank tests were used to perform comparisons between incomplete and complete recovery patients. P values of <0.05 were considered to indicate statistical significance. All analyses were performed using JMP 13 software® (SAS Institute, Cary, NC, USA).

## Results

### Patient Characteristics

The patient flow through the study is shown in **Figure 1**. A total of 450 TTS patients were identified and enrolled in the ATAK registry. After exclusion of in-hospital deaths (n=33) and patients whose echocardiographic data at follow up were not available (n=10), 407 patients were included in the present study. The patients were divided into 2 groups according to the LVEF ≤50% (incomplete recovery; n=66) or >50% (complete recovery; n=341) at follow up. Baseline characteristics, TTE and biological parameters are reported in **Tables 1** and **2**. More males (24% vs. 11%, P=0.005),

prolonged QT interval (488±53 ms vs. 464±48 ms, P=0.007), higher incidence of dementia (15% vs. 6%, P=0.02), prior pacemaker implantation (12% vs. 3%, P=0.003), and history of supraventricular arrhythmia (33% vs. 14%, P<0.001) were observed in patients who had an incomplete recovery (**Table 1**). The incomplete recovery was associated with lower LVEF on admission (34±9% vs. 40±11%, P<0.001) and at discharge (44±9% vs. 54±11%, P<0.001), RV involvement (12% vs. 2%, P=0.003), and poorer LVEF improvement (**Table 2**). Higher biological inflammatory parameters on admission, at peak, and discharge were recorded for patients with an incomplete recovery. The BNP levels were elevated on admission and at peak, but turned out to be similar at discharge. In contrast, troponin levels were equivalent between the 2 groups throughout the whole period. Likewise, the breakdown of medications at discharge were comparable between the 2 groups (**Supplementary Table 1**).

### Predictors of Incomplete Recovery Following TTS

In univariate logistic regression analysis, male sex, dementia, prior pacemaker implantation, history of supraventricular arrhythmia, LVEF on admission and at discharge, white blood cell counts at peak, CRP and BNP levels on admission, at peak, and at discharge were significant predictors of incomplete recovery at follow up (**Table 3**).

	Incomplete recovery (n=66)	Complete recovery (n=341)	P value
<b>Echocardiogram</b>			
LVEF on admission, %	34±9	40±11	<0.001
LVEF at discharge, %	44±9	54±11	<0.001
LVEF at follow up, %	45±6	63±6	<0.001
Time to follow up, days	74 (7–445)	52 (20–339)	0.62
<b>Improvement of LVEF</b>			
Difference between discharge and admission, %	10±11	13±13	0.049
Difference between follow up and admission, %	11±10	23±13	<0.001
<b>Types of TTS</b>			
Apical	46 (70)	242 (71)	0.81
Midventricular	16 (24)	87 (26)	0.82
Basal	2 (3)	6 (2)	0.62
RV involvement	7 (12)	8 (2)	0.003
<b>Baseline</b>			
WBC, 10 <sup>9</sup> /L	12.2±5.3	11.1±5.1	0.10
Hb, g/dL	12.7±1.9	12.9±1.8	0.31
Platelet, 10 <sup>9</sup> /L	261±114	267±100	0.68
Creatinine, μmol/L	90±98	75±44	0.06
eGFR, mL/min/1.73 m <sup>2</sup>	74±28	77±27	0.39
CRP, mg/dL	1.5 (0.4–7.2)	0.7 (0.3–3.5)	0.009
BNP, ng/L	685 (204–1,296)	331 (111–869)	0.004
Troponin I, μg/L	1.0 (0.2–2.2)	1.1 (0.3–3.5)	0.15
<b>Peak</b>			
WBC, 10 <sup>9</sup> /L	14.1±6.3	12.4±5.6	0.03
CRP, mg/dL	4.8 (1.0–13.2)	2.3 (0.4–7.3)	0.009
BNP, ng/L	883 (345–1,932)	506 (226–1,164)	0.02
Troponin I, μg/L	1.8 (0.5–4.5)	2.4 (0.9–5.4)	0.10
<b>Time to peak (day)</b>			
WBC	0 (0–2)	0 (0–1)	0.35
CRP	1 (0–3)	1 (0–2)	0.58
BNP	0 (0–2)	0 (0–2)	0.77
Troponin I	0 (0–1)	0 (0–1)	0.65
<b>Discharge</b>			
WBC, 10 <sup>9</sup> /L	8.6±3.9	7.9±3.1	0.10
CRP, mg/dL	1.9 (0.6–4.6)	0.8 (0.3–2.0)	<0.001
BNP, ng/L	378 (149–836)	273 (142–535)	0.06
Troponin I, μg/L	0.3 (0.06–1.2)	0.4 (0.1–1.4)	0.14

Values are presented as n (%), mean±SD, or median (interquartile range). BNP, brain natriuretic peptide; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; LVEF, left ventricular ejection fraction; RV, right ventricular; TTS, Takotsubo syndrome; WBC, white blood cell.

Multivariate logistic regression analysis for the variables on admission revealed that prior pacemaker implantation (odds ratio [OR]: 4.08; 95% CI: 1.04–15.94;  $P=0.04$ ) and LVEF (OR: 0.96; 95% CI: 0.93–0.99;  $P=0.007$ ) were the sole independent predictors of incomplete recovery (Table 4). Among the patients who received an additional follow-up echocardiography after discharge ( $n=319$ ), male sex (OR: 2.83; 95% CI: 1.11–7.25;  $P=0.03$ ), a history of supraventricular arrhythmia (OR: 3.49; 95% CI: 1.33–9.13;  $P=0.01$ ), LVEF (OR: 0.94; 95% CI: 0.91–0.98;  $P<0.001$ ), and CRP levels (OR: 1.11; 95% CI: 1.02–1.22;  $P=0.02$ ) were independent predictors of an incomplete recovery (Supplementary Table 2 and Table 4).

The ROC curves demonstrated that the area under the curves for LVEF and CRP levels at discharge for predict-

ing incomplete recovery at follow up were 0.72 (95% CI: 0.64–0.78) and 0.63 (95% CI: 0.53–0.73), respectively (Supplementary Figure 1). The cut-off values to predict incomplete recovery were 51% for LVEF at discharge (sensitivity 85%, specificity 54%, PPV 21%, NPV 96%, accuracy 58%) and 1.65 mg/dL for CRP at discharge (sensitivity 57%, specificity 71%, PPV 24%, NPV 91%, accuracy 69%). Figure 2 shows that incomplete recovery arose more frequently from patients with both LVEF ≤50% and CRP levels ≥1.65 mg/dL at discharge ( $P<0.001$ ).

### Long-Term Clinical Outcomes Following TTS

Long-term outcomes were available for 384 (94%) patients, with a median follow up of 750 days (IQR: 242–1,518 days). Cardiovascular mortality was more frequent in the incom-

**Table 3. Univariate Analysis for the Prediction of Incomplete Recovery Following TTS**

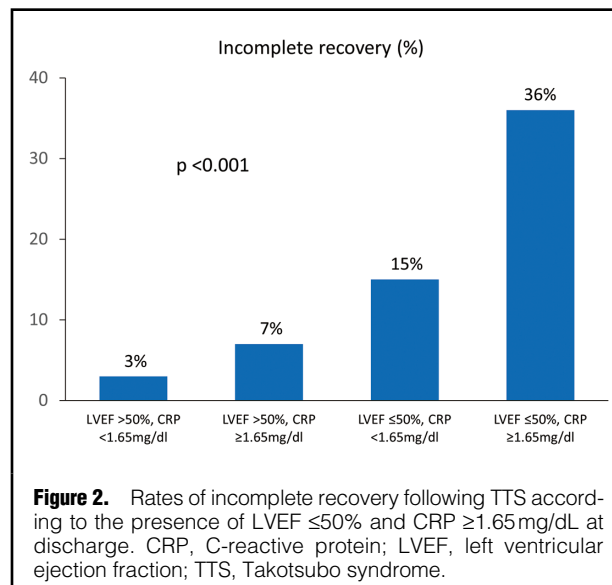
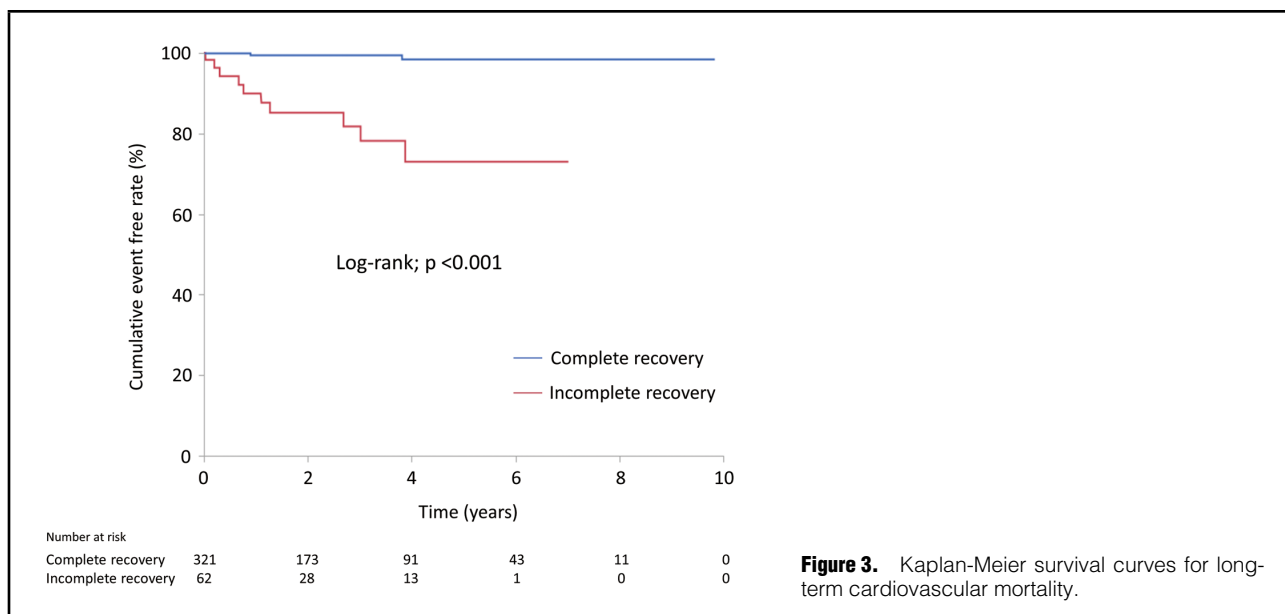
	OR (95% CI)	P value
Age, years	1.01 (0.99–1.04)	0.17
Male	2.48 (1.29–4.77)	0.007
Height, cm	1.02 (0.99–1.06)	0.26
Body weight, kg	1.01 (1.00–1.03)	0.13
Hypertension	0.78 (0.46–1.32)	0.35
Diabetes	1.21 (0.63–2.32)	0.56
Dyslipidemia	0.98 (0.58–1.68)	0.95
Current smoker	1.29 (0.70–2.47)	0.45
Coronary artery disease	1.18 (0.67–2.06)	0.57
Cerebrovascular disease	1.47 (0.69–3.12)	0.32
Peripheral artery disease	1.59 (0.84–2.98)	0.15
Psychiatric history	1.18 (0.68–2.05)	0.55
Dementia	2.58 (1.16–5.74)	0.02
Cancer history	1.23 (0.67–2.26)	0.50
Pacemaker	4.65 (1.76–12.27)	0.002
Previous TTS	2.73 (0.80–9.35)	0.11
Supraventricular arrhythmia	2.98 (1.64–5.40)	<0.001
Medication		
$\beta$ -blocker	1.70 (0.94–3.08)	0.08
Antiarrhythmic drug	1.92 (0.94–3.94)	0.07
Trigger		
Unknown	1.31 (0.72–2.38)	0.38
Physical stress	1.19 (0.70–2.01)	0.53
Emotional stress	0.63 (0.34–1.16)	0.14
Symptom		
Dyspnea	1.37 (0.81–2.32)	0.25
Syncope	0.79 (0.17–3.58)	0.76
Echocardiogram		
LVEF on admission, %	0.95 (0.93–0.98)	<0.001
LVEF at discharge, %	0.93 (0.90–0.95)	<0.001
Types of TTS		
Apical	0.93 (0.52–1.66)	0.81
Midventricular	0.93 (0.50–1.72)	0.82
Basal	1.74 (0.34–8.81)	0.50
Admission		
WBC, $10^9/L$	1.04 (0.99–1.09)	0.10
Hb, g/dL	0.93 (0.80–1.07)	0.31
Platelet, $10^9/L$	1.00 (1.00–1.00)	0.68
Creatinine, $\mu\text{mol/L}$	1.00 (1.00–1.01)	0.10
eGFR, mL/min/1.73 m <sup>2</sup>	1.00 (0.98–1.01)	0.38
CRP, mg/dL	1.05 (1.01–1.09)	0.009
BNP, per 100 ng/L	1.03 (1.00–1.06)	0.04
Troponin I, $\mu\text{g/L}$	0.99 (0.94–1.05)	0.84
Peak		
WBC, $10^9/L$	1.05 (1.00–1.09)	0.04
CRP, mg/dL	1.04 (1.01–1.07)	0.01
BNP, per 100 ng/L	1.02 (1.00–1.05)	0.047
Troponin I, $\mu\text{g/L}$	1.01 (0.99–1.04)	0.38
Discharge		
WBC, $10^9/L$	1.07 (0.99–1.15)	0.10
CRP, mg/dL	1.15 (1.07–1.23)	<0.001
BNP, per 100 ng/L	1.05 (1.01–1.09)	0.02
Troponin I, $\mu\text{g/L}$	0.87 (0.74–1.04)	0.13
Medication at discharge		
ACE-inhibitors	0.98 (0.57–1.69)	0.95
ARBs	0.92 (0.39–2.16)	0.85
$\beta$ -blockers	1.02 (0.57–1.82)	0.96
Calcium channel blockers	0.32 (0.07–1.38)	0.13
Statins	0.84 (0.48–1.45)	0.53

ACE, angiotensin-converting enzyme; ARBs, angiotensin-receptor blockers; CI, confidence interval; OR, odds ratio. Other abbreviations as in Table 2.

**Table 4. Multivariate Analyses for the Prediction of Incomplete Recovery Following TTS**

	OR (95% CI)	P value
<b>Predictors on admission (n=407)</b>		
Male	2.12 (0.94–4.78)	0.07
Dementia	2.32 (0.88–6.13)	0.09
Pacemaker	4.08 (1.04–15.94)	0.04
Supraventricular arrhythmia	2.02 (0.90–4.55)	0.09
LVEF, %	0.96 (0.93–0.99)	0.007
CRP, mg/dL	1.03 (0.98–1.08)	0.22
BNP, per 100 ng/L	1.01 (0.98–1.04)	0.61
<b>Predictors at discharge (n=319)</b>		
Male	2.83 (1.11–7.25)	0.03
Body weight, kg	1.02 (1.00–1.04)	0.08
Cancer history	1.22 (0.48–3.12)	0.67
Pacemaker	2.19 (0.53–9.02)	0.28
Supraventricular arrhythmia	3.49 (1.33–9.13)	0.01
LVEF, %	0.94 (0.91–0.98)	<0.001
CRP, mg/dL	1.11 (1.02–1.22)	0.02

Abbreviations as in Tables 2,3.

**Figure 2.** Rates of incomplete recovery following TTS according to the presence of LVEF ≤50% and CRP ≥1.65 mg/dL at discharge. CRP, C-reactive protein; LVEF, left ventricular ejection fraction; TTS, Takotsubo syndrome.**Figure 3.** Kaplan-Meier survival curves for long-term cardiovascular mortality.

plete recovery group as compared with the complete recovery group (16% vs. 0.6%,  $P<0.001$ ) (Supplementary Table 3). The Kaplan-Meier survival analysis shows that patients who had an incomplete recovery had a significant higher incidence of cardiovascular death during long-term follow up (log-rank:  $P<0.001$ ) (Figure 3). In addition, a sensitivity analysis was performed by dividing patients into groups according to the median echo follow-up duration. The Kaplan-Meier curves clarified that the magnitude of incomplete recovery in predicting cardiovascular mortality was comparable between the patients who received follow-up echocardiography at 52 days or before and after 52 days (Supplementary Figure 2). The incidence of secondary outcomes including TTS recurrence and heart failure hospitalization were similar between the 2 groups (3% vs.

4%,  $P=1.00$  and 13% vs. 9%,  $P=0.45$ , respectively) (Supplementary Table 3).

### Predictors of Cardiovascular Mortality

By using Cox regression analysis, prior cerebrovascular events (HR: 3.79; 95% CI: 1.01–12.04;  $P=0.048$ ), physical stress as a trigger of TTS (HR: 3.43; 95% CI: 1.03–15.51;  $P=0.045$ ), incomplete recovery (HR: 28.87; 95% CI: 7.61–187.81;  $P<0.001$ ), WBC counts on admission and at peak, creatinine levels on admission, CRP levels on admission, at peak, and at discharge, and BNP levels at discharge were associated with cardiovascular mortality at long-term follow up (Supplementary Table 4). In contrast, no relationship was evident between cardiovascular mortality and LVEF on admission or at discharge.



## Discussion

The current multicenter study drawn from a cohort of 407 patients is the first study to specifically evaluate the impact of incomplete LVEF recovery following TTS on adverse clinical outcomes. The salient results of the present study are as follows: (1) incomplete recovery (LVEF  $\leq 50\%$  at chronic phase) was observed in 16% of TTS patients; (2) an elevated CRP level at discharge was an independent factor of incomplete recovery; and (3) the rate of cardiovascular mortality was significantly higher in patients who had an incomplete recovery compared to those who had a complete recovery.

### Left Ventricular Dysfunction Following TTS

Numerous historic studies have reported resolution of LV systolic function after the acute TTS episode, basing this assessment on LVEF. The systematic review by Gianni et al showed LVEF improving from 20% to 49% on admission to 60% to 76% at follow up, and a recent report from Templin et al confirmed this in a more contemporary cohort, with a mean LVEF improving from 41.1% to 59.9% by 60 days.<sup>1,8</sup> Consistent with these findings, our study demonstrated that the mean LVEF of TTS patients improved from 39.2% to 60.4% at median follow-up time of 52 days.

Despite the macroscopic recovery, recent observations indicated that TTS may not always manifest as a fully reversible phenomenon, suggesting persistence of microscopic changes at the cellular level to some degree.<sup>9,10</sup> In clinical practice, these residual changes might largely account for the evolution of certain conditions, including persistent diastolic dysfunction and subclinical LV dysfunction with variable symptomatology among TTS survivors. A recent observational study including 205 TTS patients demonstrated an improvement of diastolic function in only 28% of cases in the recovery phase (mean  $38 \pm 16$  days after admission), whereas the remaining 72% had an unchanged or worsening diastolic function.<sup>9</sup> Neil et al compared 36 TTS patients to 19 age-matched female controls and found the LVEF normalized by the 3-month reassessment, but the global longitudinal strain (GLS) assessed by speckle echocardiography was impaired acutely ( $-12.7$  vs.  $-20\%$ ,  $P < 0.001$ ) and remained impaired at 3 months ( $-17.9\%$  vs.  $-20\%$ ,  $P = 0.003$ ).<sup>10</sup> Impaired GLS at 3 months was associated with both persistent N-terminal proBNP elevation and impaired quality of life. In a recent case control study, a low exercise capacity and metabolic performance were found to be persistent 20 months after TTS onset.<sup>3</sup> Apical T1 prolongation, as a possible marker of microscopic fibrosis, together with subtle alteration of the left apical strain and the wringing motion “twist” were evidenced in TTS patients, whereas no difference in LVEF could be observed. Although numerous studies have proven the existence of subclinical LV dysfunction following TTS, given the rarity of this disease, no study has specifically investigated the impact of subtle LV systolic dysfunction following TTS on long-term clinical outcomes. Our observation drawn from 407 TTS patients was the first study to specifically examine the impact of impaired LVEF at the recovery phase on long-term clinical outcomes. Although we found the prevalence of incomplete recovery (16%) to be similar to prior studies,<sup>9</sup> the large cohort enables us to extensively evaluate the outcomes of those patients.

### Interplay Between Inflammation and Incomplete Recovery

Inflammatory activation, both systemic and intramyocardial, are well documented in TTS. A number of studies have revealed an elevation of plasma CRP,<sup>11,12</sup> whereas intramyocardial inflammatory activation has been documented by myocardial biopsy,<sup>13</sup> technetium pyrophosphate imaging,<sup>14</sup> and MRI.<sup>15</sup> Recent insights have emphasized the importance of an adaptive immune response triggered by cardiomyocyte necrosis in the time course of TTS.<sup>5,16</sup> An infiltration of immune cells into the damaged myocardium could also trigger a process named sterile inflammation, as the immune system is activated despite the lack of any discernible infectious insult. In an experimental model of stress-induced takotsubo-like cardiomyopathy, Wilson et al described the temporal course of a chronic inflammatory response post-induction, with an initial early influx of neutrophils into myocardial tissue followed by macrophages that are typical of a pro-inflammatory M1 phenotype.<sup>13</sup> Interestingly, they suggested that the improvement of LVEF correlated positively with the percentage of anti-inflammatory M2 macrophages. These mechanisms could lead to ongoing inflammation, as reflected by elevated interleukin (IL)-6 levels at 5 months after TTS onset.<sup>16</sup> Moreover, TTS was recently characterized by a myocardial macrophage inflammatory infiltrate, together with an increase in systemic pro-inflammatory cytokines that persist for at least 5 months, suggesting a low-chronic inflammatory state.<sup>17</sup> Recent cardiac MRI data supported these findings, showing that TTS is characterized by a state of intra-myocardial edema secondary to a global left ventricular inflammatory response, which is detectable early after the index event and persists well beyond the resolution of segmental LV contractile dysfunction.<sup>18</sup> In line with these findings, our study demonstrated that the residual inflammation was apparent at discharge in a substantial proportion of TTS patients who had an incomplete recovery. Our finding points to the fact that in case of ongoing inflammation, severe alteration of the myocardium may lead to long-term LVEF impairment.

### Impact of Incomplete Recovery on Cardiovascular Mortality

Despite a well-recognized early mortality rate, few studies have described the physiological and clinical status of these patients in the long term. Although the persistent subclinical LV dysfunction holds true for a number of TTS patients, given the scarce availability of data regarding this topic, it remains unclear whether the LV dysfunction affects long-term clinical outcomes. To date, prior studies have indicated that an impaired LVEF, diastolic dysfunction, and GLS evaluated on admission were associated with long-term adverse events.<sup>1,4,19</sup> However, the majority of TTS patients experience improvement of their LV function within 4–8 weeks following TTS onset,<sup>1,9,10</sup> suggesting that reassessments of LV function at the recovery phase may be more appropriate to predict long-term outcomes. Therefore, it is noteworthy that our study with a large cohort underlined the noxious impact of incomplete recovery on long-term clinical outcomes. In addition, persistent LV dysfunction and systemic inflammation could also pave the way to arrhythmias, as observed in the early phase and possibly causing fatal events.<sup>20,21</sup> Accordingly, we could evidence prolonged QT duration in patients who had an incomplete recovery. In experimental studies, various pro-inflammatory cytokines such as TNF- $\alpha$  and IL-6 are demonstrated to induce action potential duration and QT prolongation by



decreasing transient outward current  $I_{to}$  or by enhancing L-type calcium current.<sup>22</sup> Altogether, the present data identify patients who have had an incomplete recovery of LV function as a vulnerable high-risk subgroup requiring close follow up.

### Future Perspective

Originally believed to be a benign disease, prior investigations have shown that TTS has morbidity and mortality rates that are comparable to those of ACS.<sup>1</sup> Unlike in ACS, guidelines for long-term management are lacking as no prospective randomized clinical trials have been performed in the TTS population.<sup>6</sup> In a large observational study, the use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers was associated with improved survival at 1-year follow up, whereas no evidence of any survival benefit was found for the use of  $\beta$ -blockers.<sup>1</sup>

Interestingly, special attention has been given to treatments specifically targeting inflammation in patients with coronary artery disease (CAD). In the Canakinumab Antiinflammatory Thrombosis Outcomes Study (CANTOS), canakinumab, a monoclonal antibody inhibiting IL-1 $\beta$ , reduced the level of high-sensitivity CRP and resulted in a modestly lower risk of the composite endpoint in patients with chronic CAD.<sup>23,24</sup> Moreover, the Colchicine Cardiovascular Outcomes Trial (COLCOT) has recently indicated the use of low-dose colchicine (0.5 mg once a day), an anti-inflammatory agent that works by inhibiting tubulin polymerization and microtubule formation, on secondary prevention after acute myocardial infarction.<sup>25</sup> Although further investigations are required for the role of inflammation in TTS patients, therapies to attenuate persistent inflammation in TTS patients represent an appealing subject for future research. Our study indicates that TTS patients with persistent LV dysfunction and inflammation appear to be appropriate candidates for anti-inflammatory therapies.

### Study Limitations

We acknowledge the following limitations. First, owing to the retrospective nature of our study, there are inherent limitations related to confounding known or unknown factors. Second, the time points of echocardiography at the follow-up varied, indicating that the LVEF may have improved and that certain patients may have been misclassified due to the recovery of LVEF in the long-term. Third, the evaluation of inflammation was restricted to CRP. Other parameters such as cytokine measurements or monocyte counts may have been assessed. Finally, the echocardiographic evaluations at discharge and at follow up were not standardized and were not assessed by a central Echo Core Lab.

### Conclusions

Among patients with TTS, incomplete recovery was associated with a significantly higher incidence of cardiovascular mortality at long-term follow up. A residual inflammatory response at discharge was evident as an independent factor of incomplete recovery. These observations suggest modulators of inflammation could be potential therapeutic options.

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### Disclosures

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### IRB Information

The present study was approved by the Research Ethics Committee of Strasbourg Hospital (2016-9 24022016) and the requirement for informed consent was waived by the Ethics Committee.

### Data Availability

The deidentified participant data will not be shared.

### References

- Templin C, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M, et al. Clinical features and outcomes of Takotsubo (Stress) cardiomyopathy. *N Engl J Med* 2015; **373**: 929–938.
- Redfors B, Vedin R, Angerås O, Råmunddal T, Petursson P, Haraldsson I, et al. Mortality in Takotsubo syndrome is similar to mortality in myocardial infarction: A report from the SWEDEHEART registry. *Int J Cardiol* 2015; **185**: 282–289.
- Scally C, Rudd A, Mezincescu A, Wilson H, Srivanasan J, Horgan G, et al. Persistent long-term structural, functional, and metabolic changes after stress-induced (Takotsubo) cardiomyopathy. *Circulation* 2018; **137**: 1039–1048.
- Citro R, Rigo F, D'Andrea A, Ciampi Q, Parodi G, Provenza G, et al. Echocardiographic correlates of acute heart failure, cardiogenic shock, and in-hospital mortality in Tako-tsubo cardiomyopathy. *JACC Cardiovasc Imaging* 2014; **7**: 119–129.
- Lachmet-Thébaud L, Marchandot B, Matsushita K, Dagrenat C, Peilleux M, Sato C, et al. Systemic inflammatory response syndrome is a major determinant of cardiovascular outcome in Takotsubo syndrome. *Circ J* 2020; **84**: 592–600.
- Ghadri JR, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, et al. International Expert Consensus Document on Takotsubo Syndrome (Part II): Diagnostic Workup, Outcome, and Management. *Eur Heart J* 2018; **39**: 2047–2062.
- Ghadri JR, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, et al. International expert consensus document on Takotsubo syndrome (Part I): Clinical characteristics, diagnostic criteria, and pathophysiology. *Eur Heart J* 2018; **39**: 2032–2046.
- Gianni M, Dentali F, Grandi AM, Sumner G, Hiralal R, Lonn E. Apical ballooning syndrome or Takotsubo cardiomyopathy: A systematic review. *Eur Heart J* 2006; **27**: 1523–1529.
- Sun T, Ming Z, Liu Z, Lennon RJ, Yang SW, Kwon TG, et al. Prevalence of diastolic function and clinical impact on long-term outcome in Takotsubo cardiomyopathy. *Int J Cardiol* 2017; **244**: 7–12.
- Neil CJ, Nguyen TH, Singh K, Raman B, Stansborough J, Dawson D, et al. Relation of delayed recovery of myocardial function after Takotsubo cardiomyopathy to subsequent quality of life. *Am J Cardiol* 2015; **115**: 1085–1089.
- Morel O, Sauer F, Imperiale A, Cimarelli S, Blondet C, Jesel L, et al. Importance of inflammation and neurohumoral activation in Takotsubo cardiomyopathy. *J Card Fail* 2009; **15**: 206–213.
- Madhavan M, Borlaug BA, Lerman A, Rihal CS, Prasad A. Stress hormone and circulating biomarker profile of apical ballooning syndrome (Takotsubo cardiomyopathy): Insights into the clinical significance of B-type natriuretic peptide and troponin levels. *Heart* 2009; **95**: 1436–1441.
- Wilson HM, Cheyne L, Brown PAJ, Kerr K, Hannah A, Srinivasan J, et al. Characterization of the myocardial inflammatory response in acute stress-induced (Takotsubo) cardiomyopathy. *JACC Basic Transl Sci* 2018; **3**: 766–778.
- Ito K, Sugihara H, Katoh S, Azuma A, Nakagawa M. Assessment of Takotsubo (apical) cardiomyopathy using 99mTc-tetrofosmin myocardial SPECT: Comparison with acute coronary syndrome. *Ann Nucl Med* 2003; **17**: 115–122.
- Neil C, Nguyen TH, Kucia A, Crouch B, Sverdlow A, Chirkov Y, et al. Slowly resolving global myocardial inflammation/oedema in Tako-Tsubo cardiomyopathy: Evidence from T2-weighted cardiac MRI. *Heart* 2012; **98**: 1278–1284.

16. Sattler S, Couch LS, Harding SE. Takotsubo syndrome: Latest addition to the expanding family of immune-mediated diseases? *JACC Basic Transl Sci* 2018; **3**: 779–781.
17. Scally C, Abbas H, Ahearn T, Srinivasan J, Mezincescu A, Rudd A, et al. Myocardial and systemic inflammation in acute stress-induced (Takotsubo) Cardiomyopathy. *Circulation* 2019; **139**: 1581–1592.
18. Wittstein IS, Thiemann DR, Lima JA, Baughman KL, Schulman SP, Gerstenblith G, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med* 2005; **352**: 539–548.
19. Alashi A, Isaza N, Faulx J, Popovic ZB, Menon V, Ellis SG, et al. Characteristics and outcomes of patients with Takotsubo syndrome: Incremental prognostic value of baseline left ventricular systolic function. *J Am Heart Assoc* 2020; **9**: e016537.
20. Jesel L, Berthon C, Messas N, Lim HS, Girardey M, Marzak H, et al. Ventricular arrhythmias and sudden cardiac arrest in Takotsubo cardiomyopathy: Incidence, predictive factors, and clinical implications. *Heart Rhythm* 2018; **15**: 1171–1178.
21. El-Battrawy I, Lang S, Ansari U, Tülümen E, Schramm K, Fastner C, et al. Prevalence of malignant arrhythmia and sudden cardiac death in Takotsubo syndrome and its management. *Europace* 2018; **20**: 843–850.
22. Lazzerini PE, Capecchi PL, Laghi-Pasini F. Systemic inflammation and arrhythmic risk: Lessons from rheumatoid arthritis. *Eur Heart J* 2017; **38**: 1717–1727.
23. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 2017; **377**: 1119–1131.
24. Ridker PM, Libby P, MacFadyen JG, Thuren T, Ballantyne C, Fonseca F, et al. Modulation of the interleukin-6 signalling pathway and incidence rates of atherosclerotic events and all-cause mortality: Analyses from the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS). *Eur Heart J* 2018; **39**: 3499–3507.
25. Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. *N Engl J Med* 2019; **381**: 2497–2505.

### Supplementary Files

Please find supplementary file(s);  
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