Systemic Inflammatory Response Syndrome Is a Major Determinant of Cardiovascular Outcome in Takotsubo Syndrome

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**Background:** Recent insights have emphasized the importance of inflammatory response in takotsubo syndrome (TTS). We sought to evaluate the predictors of systemic inflammatory response syndrome (SIRS) and its impact on cardiovascular mortality after TTS.

**Methods and Results:** The 215 TTS patients were retrospectively included between September 2008 and January 2018. SIRS was diagnosed in 96 patients (44.7%). They had lower left ventricular ejection fraction (LVEF) on admission (34.5% vs. 41.9%; \( P < 0.001 \)) and higher peak brain natriuretic peptide and troponin. At a median follow-up of 518 days, SIRS was associated with increased in-hospital mortality (14.6% vs. 5.0%; \( P = 0.019 \)), overall mortality (29.4% vs. 10.8%; \( P = 0.002 \)), and cardiovascular mortality (10.6% vs. 2.1%; \( P = 0.026 \)). A history of cancer (OR, 3.36; 95% CI: 1.54–7.31; \( P = 0.002 \)) and LVEF <40% at admission (OR, 2.31; 95% CI: 1.16–4.58; \( P = 0.017 \)) were identified as independent predictors of SIRS. On multivariate Cox regression analysis, SIRS (HR, 12.8; 95% CI: 1.58–104; \( P = 0.017 \)), age (HR, 1.09; 95% CI: 1.02–1.16; \( P = 0.01 \)), and LVEF <40% at discharge (HR, 9.88; 95% CI: 2.54–38.4; \( P = 0.001 \)) were independent predictors of cardiovascular death.

**Conclusions:** SIRS was found in a large proportion of TTS patients and was associated with enhanced myocardial damage and adverse outcome in the acute phase. At long-term follow-up, SIRS remained an independent factor of cardiovascular death.

**Key Words:** Cardiovascular outcome; Inflammation; Mortality; Systemic inflammatory response syndrome; Takotsubo syndrome
Methods

Study Design and Subjects
We conducted a retrospective study from September 2008 to January 2018 at the University Hospital of Strasbourg, France. Patients with suspected TTS were identified out of 34,037 coronary angiograms recorded in the cardiac catheterization laboratory database, using the key words “stress”, “takotsubo” or “catecholamine”. The diagnosis of TTS was made according to the Madias or the international TTS criteria.7,8 Exclusion criteria included a diagnosis of myocarditis, absence of LVEF recovery at follow-up and cardiac arrest at first medical contact. Two cardiologists reviewed all the cases and the diagnosis of TTS was based on a consensus agreement. Cases were recorded in the Alsace Takotsubo (ATAK) registry. The study protocol was approved by the University institutional review board.

Clinical and Biological Assessment
All baseline clinical data and follow-up variables were recorded and entered into a secure, ethics-approved database, after careful review of patient medical electronic records. Baseline characteristics included medical history, cardiovascular risk factors, medication, electrocardiogram at admission, coronary angiograms and LVEF. LVEF was assessed using 2-D transthoracic echocardiography (TTE) and the biplane Simpson method. Serial biological parameters including C-reactive protein (CRP), white blood cell (WBC) count, brain natriuretic peptide (BNP) and troponin were measured at admission, peak (highest) and discharge. Emotional and physical stressors were defined according to the International Expert Consensus Document on Takotsubo Syndrome.8

SIRS Criteria and Definition
SIRS was defined as the presence of 2 of 3 of the following criteria 12–48 h after TTS diagnosis: (1) WBC count <4 or >12×10^9/L; (2) heart rate >90 beats/min; and (3) temperature <36 or >38°C. The standard definition of SIRS9 is usually based on the occurrence of 2 or more of the preceding criteria, with an additional tachypnea item defined as respiratory rate >20/min or pCO2 <32 mmHg, but this was not reliably assessed in the present study and was therefore excluded from the definition of SIRS.

Outcomes
In-hospital complications such as arrhythmia, cardiogenic shock and death were collected on careful review of the

| Table 1. TTS Patient Baseline Characteristics vs. SIRS Status  |
|---------------------------------------------------------------|
| Total TTS (n=215) vs. Non-SIRS (n=119) vs. SIRS (n=96) P-value |
| Female sex                                                   | 174 (80.1) vs. 102 (85.7) vs. 72 (75.0) 0.047          |
| Age (years)                                                  | 70.0±12.5 vs. 71.6±12.6 vs. 68.2±12.2 0.049          |
| Comorbidities                                                |                                                          |
| Dementia                                                     | 13 (6.0) vs. 7 (5.90) vs. 6 (6.3) 1.000                |
| Cancer                                                       | 55 (25.6) vs. 19 (16.0) vs. 36 (37.5) <0.001          |
| Cardiovascular risk factors                                  |                                                          |
| Hypertension                                                 | 118 (55.9) vs. 73 (61.3) vs. 45 (46.9) 0.034          |
| Diabetes mellitus                                            | 49 (22.8) vs. 30 (25.2) vs. 19 (19.8) 0.346          |
| Dyslipidemia                                                 | 81 (37.7) vs. 53 (44.5) vs. 28 (29.2) 0.021          |
| Current smoking                                              | 41 (19.1) vs. 20 (16.8) vs. 21 (21.9) 0.347          |
| Prior smoking                                                | 56 (26.0) vs. 27 (22.7) vs. 29 (30.2) 0.212          |
| Cardiovascular history                                       |                                                          |
| CAD or PAD                                                   | 51/214 (23.8) vs. 23/119 (19.3) vs. 28/95 (29.5) 0.083 |
| History of AF                                                | 30 (14.0) vs. 19 (16.0) vs. 11 (11.5) 0.343          |
| Permanent AF                                                 | 10 (4.7) vs. 5 (4.2) vs. 5 (5.2) 0.755               |
| Stroke                                                       | 19 (8.8) vs. 12 (10.1) vs. 7 (7.3) 0.630             |
| Prior TTS                                                    | 3 (1.4) vs. 1 (0.8) vs. 2 (2.1) 0.587               |
| β-blocker prior to admission                                 | 51/201 (25.4) vs. 31/112 (27.7) vs. 20/89 (22.5) 0.399 |
| Clinical characteristics at admission                       |                                                          |
| Dyspnea                                                      | 106 (49.3) vs. 43 (36.1) vs. 63 (65.6) <0.001        |
| Syncope                                                      | 9 (4.2) vs. 4 (3.4) vs. 5 (5.2) 0.517                |
| Heart rate (beats/min)                                      | 93±24 vs. 78±16 vs. 11±20 <0.001                     |
| Temperature (°C)                                            | 36.7±0.47 vs. 36.6±0.5 vs. 36.8±0.4 0.420            |
| SBP (mmHg)                                                   | 126±28 vs. 135±27 vs. 116±25 <0.001                   |
| DBP (mmHg)                                                   | 70±14 vs. 72±14 vs. 68±15 0.069                      |
| Trigger                                                      |                                                          |
| Physical                                                     | 107 (49.8) vs. 42 (35.3) vs. 65 (67.7) <0.001       |
| Emotional                                                    | 56 (26.0) vs. 39 (32.8) vs. 17 (17.7) <0.001         |
| Unknown                                                      | 52 (24.2) vs. 38 (31.9) vs. 14 (14.6) <0.001         |

Data given as n (%) or mean±SD. AF, atrial fibrillation; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; PAD, peripheral artery disease; SBP, systolic blood pressure; SIRS, systemic inflammatory response syndrome; TTS, takotsubo syndrome.
Demographics

A total of 241 TTS patients were identified and enrolled in the ATAK registry. A total of 215 met the study criteria and were further stratified according to SIRS occurrence (Supplementary Figure). SIRS was documented in 96 TTS patients (44.7%). Patients who developed SIRS were more likely to be men, of younger age and to have a history of cancer (P<0.001). Physical trigger was significantly associated with SIRS (P<0.001). Higher heart rate was evidenced in this subset of patients (111±20 vs. 78±16 beats/min; P<0.001).
Mid- and Long-Term Outcomes

Mid- and long-term outcomes were available for 178 patients (82.8%) with a median follow-up of 518 days (IQR, 128–1,004 days). The 30-day (12.6% vs. 3.4%; P=0.017) and 1-year mortality were higher in SIRS patients (29.4% vs. 10.8%; P=0.002), despite similar LVEF at discharge and at follow-up. Kaplan-Meier curves stratified according to SIRS showed higher survival from cardiovascular death (P=0.015; log-rank test) and non-cardiovascular death (P=0.002; log-rank test) for the non-SIRS group compared with the SIRS patients (Figure). Conversely, neoplasia-related death, TTS recurrence or re-hospitalization for heart failure were not significantly different between the 2 groups.

Predictors of SIRS

On logistic regression analysis, history of cancer, physical trigger, LVEF impairment (<40%) on admission, high BNP (>400ng/L), hypertension, and dyslipidemia were significant predictors of SIRS. On multiple logistic regression analysis, LVEF <40% (OR, 2.31; 95% CI: 1.16–4.58; P=0.017) and history of cancer (OR, 3.36; 95% CI: 1.54–7.31; P=0.02) remained as independent predictors of SIRS (Table 4).

In-Hospital Outcomes

In-hospital death (14.6% vs. 5.0%; P=0.019), cardiacogenic shock (26.0% vs. 5.0%; P<0.001) and supraventricular arrhythmia (33.3% vs. 16.0%; P=0.003) occurred more frequently in SIRS patients. Likewise, in-hospital composite endpoint (acute heart failure, cardiacogenic shock, death) was more frequently observed in the SIRS group (69.8% vs. 32.8%; P<0.001). In contrast, no significant differences in life-threatening arrhythmias or in infections during hospitalization were seen between the 2 groups. In-hospital complications are listed in Table 3. Causes of in-hospital death are given in Supplementary Table.

Table 3. TTS Patient In-Hospital and Follow-up Outcomes vs. SIRS Status

| In-hospital endpoints | Total TTS (n=215) | Non-SIRS (n=119) | SIRS (n=96) | P-value |
|-----------------------|------------------|-----------------|-------------|---------|
| Arrhythmia            |                  |                 |             |         |
| Supraventricular arrhythmia | 51 (23.7) | 19 (16.0) | 32 (33.3) | 0.003   |
| Sinus dysfunction     | 4 (1.9)          | 4 (3.4)         | 0 (0)       | 0.130   |
| Third-degree AV block | 2 (0.9)          | 2 (1.7)         | 0 (0)       | 0.503   |
| Sustained VT          | 1 (0.5)          | 0 (0)           | 1 (1.0)     | 0.447   |
| Torsade de pointe     | 1 (0.5)          | 1 (0.8)         | 0 (0)       | 1.000   |
| VF                    | 2 (0.9)          | 0 (0)           | 2 (2.1)     | 0.198   |
| Acute HF              | 72 (33.5)        | 31 (26.1)       | 41 (42.7)   | 0.010   |
| Cardiogenic shock     | 31 (14.4)        | 6 (5.0)         | 25 (26.0)   | <0.001  |
| Mechanical assistance |                  |                 |             |         |
| IABP                  | 12 (5.6)         | 2 (1.7)         | 10 (10.4)   | 0.007   |
| ECLS                  | 2 (0.9)          | 0 (0)           | 2 (2.1)     | 0.198   |
| Cardiac arrest        | 10 (4.70)        | 3 (2.50)        | 7 (7.3)     | 0.115   |
| Infection             | 96 (44.7)        | 49 (41.2)       | 47 (49.0)   | 0.254   |
| Composite endpoint (death, HF, cardiacogenic shock) | 106 (49.3) | 39 (32.8) | 67 (69.8) | <0.001 |
| Length of stay (days) | 12.2±20          | 8.7±7.9         | 16.5±39     | 0.037   |

Follow-up endpoints

|                  | Total TTS (n=215) | Non-SIRS (n=119) | SIRS (n=96) | P-value |
|------------------|------------------|-----------------|-------------|---------|
| LVEF (%)         | 58.3±11.7        | 59.4±11.1       | 57.0±12.4   | 0.150   |
| TTS recurrence   | 5 (2.3)          | 4 (3.4)         | 1 (1.0)     | 0.384   |
| Acute HF re-hospitalization | 18/211 (8.5) | 8/118 (6.8) | 10/93 (10.8) | 0.330   |
| Other cardiovascular re-hospitalization | 28/214 (13.1) | 18 (15.1) | 10/95 (10.5) | 0.322   |

Mortality

|                  | Total TTS (n=215) | Non-SIRS (n=119) | SIRS (n=96) | P-value |
|------------------|------------------|-----------------|-------------|---------|
| In-hospital      | 20 (9.3)         | 6 (5.0)         | 14 (14.6)   | 0.019   |
| 30-day           | 16/211 (7.6)     | 4/116 (3.4)     | 12/95 (12.6) | 0.017   |
| 1-year           | 35/178 (19.7)    | 10/93 (10.8)    | 25/85 (29.4) | 0.002   |
| Cardiovascular causes | 11/181 (6.1) | 2/96 (2.1) | 9/85 (10.6) | 0.026   |
| Neoplasia-related death | 6/181 (3.3) | 2/96 (2.1) | 4/85 (4.7) | 0.422   |
| Other causes     | 27/181 (14.9)    | 7/96 (7.3)      | 20/85 (23.5) | 0.003   |

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| 30-day           | 16/211 (7.6)     | 4/116 (3.4)     | 12/95 (12.6) | 0.017   |
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| Other causes     | 27/181 (14.9)    | 7/96 (7.3)      | 20/85 (23.5) | 0.003   |

Data given as n (%) or mean±SD. AV, atrioventricular; ECLS, extra-corporeal life support; HF, heart failure; IABP, intra-aortic balloon pump; VF, ventricular fibrillation; VT, ventricular tachycardia. Other abbreviations as in Tables 1,2.
Predictors of Cardiac Mortality

On univariate Cox analysis, age, concomitant significant coronary artery disease (>50% stenosis on a main coronary artery), SIRS and LVEF <40% at discharge were associated with higher rates of cardiac mortality at maximum follow-up. On multivariate Cox regression analysis, age (HR, 1.09; 95% CI: 1.02–1.16; P=0.010), SIRS (HR, 12.8; 95% CI: 1.58–104; P=0.017) and LVEF impairment at discharge (HR, 9.88; 95% CI: 2.54–38.4; P=0.001) remained as independent predictors of cardiac mortality (Table 5).

Figure. (A) Kaplan-Meier analysis of the probability of (A) cardiac survival and (B) survival from non-cardiovascular death according to the presence of systemic inflammatory response syndrome (SIRS) in patients with takotsubo syndrome.
SIRS as a Prognostic Factor in TTS

Table 4. Predictors of SIRS in TTS Patients

|                     | Univariate | | | | Multivariate | | | |
|---------------------|------------|---|---|---|------------|---|---|---|
|                     | OR         | 95% CI     | P-value  | OR         | 95% CI     | P-value  |
| Male                | 2.00       | 1.00–3.99  | 0.049    |            |            |          |
| Age                 | 0.978      | 0.957–1.00 | 0.051    |            |            |          |
| Comorbidities       |            |            |          |            |            |          |
| Psychiatric disorders | 1.32      | 0.741–2.34 | 0.349    |            |            |          |
| Dementia            | 1.07       | 0.346–3.29 | 0.910    |            |            |          |
| Cancer              | 3.16       | 1.66–6.00  | <0.001   | 3.36       | 1.54–7.31  | 0.002    |
| Cardiovascular risk factors | | | | | | |
| Hypertension        | 0.556      | 0.322–0.959| 0.035    | 0.586      | 0.290–1.16 | 0.124    |
| Diabetes mellitus   | 0.732      | 0.382–1.40 | 0.732    |            |            |          |
| Dyslipidemia        | 0.513      | 0.290–0.906| 0.022    | 0.519      | 0.250–1.07 | 0.074    |
| Current smoking     | 1.39       | 0.701–2.74 | 0.348    |            |            |          |
| Prior smoking       | 1.475      | 0.800–2.72 | 0.213    |            |            |          |
| Cardiovascular history |         |            |          |            |            |          |
| CAD or PAD          | 1.74       | 0.926–3.29 | 0.085    |            |            |          |
| History of AF       | 0.681      | 0.307–1.51 | 0.345    |            |            |          |
| Permanent AF        | 1.25       | 0.352–4.46 | 0.728    |            |            |          |
| Stroke              | 0.701      | 0.265–1.86 | 0.475    |            |            |          |
| Prior TTS           | 2.51       | 0.224–28.1 | 0.455    |            |            |          |
| Regional variant of TTS |       |            |          |            |            |          |
| Apical              | 0.860      | 0.480–1.54 | 0.612    |            |            |          |
| Midventricular      | 0.953      | 0.526–1.73 | 0.874    |            |            |          |
| Significant concomitant CAD | 1.24  | 0.700–2.20 | 0.464    |            |            |          |
| Physical trigger    | 3.84       | 2.175–6.794| <0.001   | 1.51       | 0.739–3.07 | 0.259    |
| Infections          | 1.37       | 0.797–2.36 | 0.254    |            |            |          |
| LVEF on admission <40% | 3.54       | 1.98–6.33 | <0.001   | 2.31       | 1.16–4.58  | 0.017    |
| Troponin on admission | 1.01       | 0.971–1.05 | 0.587    |            |            |          |
| BNP on admission    | 1.00       | 1.00–1.00  | 0.001    | 1.00       | 1.00–1.00  | 0.110    |

CI, confidence interval; OR, odds ratio. Other abbreviations as in Tables 1,2.

Discussion

The current report drawn from a cohort of 215 TTS patients is the first study to specifically evaluate the impact of SIRS on in-hospital and late outcomes. The salient results of the present study are as follows: (1) at the acute phase, SIRS was observed in a large proportion of the cohort and was associated with enhanced myocardial damage and LVEF impairment; (2) predictive factors of SIRS are LVEF impairment and a history of cancer; (3) SIRS was associated with sustained inflammatory response and neurohormonal activation at hospital discharge; and (4) SIRS had a dramatic impact on in-hospital mortality and on late outcomes, such as higher cardiovascular mortality. Altogether, these findings suggest that the occurrence of SIRS could identify a subset of vulnerable patients after TTS onset.

In cardiovascular disease, previous studies have underlined that SIRS could occur in a variety of non-infectious major systemic injuries, including acute coronary syndrome (ACS), cardiogenic shock or, more recently, transcatheter valve replacement. SIRS has been identified in 18–40% of cases of myocardial infarction and has been associated with LVEF impairment, leukocytosis and enhanced myocardial damage, evidenced by increased troponin. In ACS, the restoration of blood flow is thought to be the main trigger of cytokine release and widespread systemic inflammation. During SIRS, previous studies have emphasized a key role of the release of inflammatory mediators and the expression of inducible nitric oxide, possibly leading to a decreased myocardial contractility. The proportion of SIRS observed in the present study (44.7% of TTS patients) appears to be in the upper range compared with that reported in ACS. The deleterious impact of SIRS on the myocardium during TTS is reflected in the more pronounced LVEF impairment at the acute phase, together with the higher levels of troponin and BNP. In the present study, recovery of LVEF, however, was greater in SIRS patients, and LVEF at hospital discharge was equivalent between the groups. In contrast, inflammatory response and neurohormonal activation (reflected by BNP level) were still higher at hospital discharge, suggesting an ongoing process of myocardial infiltration, consistent with recent MRI reports. Although the description of the mechanisms relating adrenergic surge and inflammation are far beyond the scope of the present study, several possible physiopathological pathways should be considered. Studies based on animal models and human endomyocardial biopsy have described the time course of inflammation in the myocardium during TTS, consisting of a mononuclear cells infiltrate, contraction band necrosis and myocardial inflammation-mediated edema. Interestingly, similar histological patterns could be seen during septic shock, and a correlation between epinephrine dose and monocyte infiltration has been reported in this setting. The presence of intramyocardial inflammatory activation in patients with...
TTS has also been documented indirectly on technetium pyrophosphate imaging18 and on cardiac MRI.19 Recent insights have emphasized that activation of adrenergic signaling pathways contributes to enhanced cytokadehesis expression by bone marrow cells and also by cardiac endothelial cells (intercellular adhesion molecule-1), which may favor diapedesis and development of sterile inflammation and remodeling of the failing heart.20 According to this view, specific patterns of cytokine release have been described in TTS with respect to those observed in ACS, and controversies are still open concerning the respective importance of anti-inflammatory21 or pro-inflammatory cytokines.3 Among the various mechanisms involved in the induction of cytokine release and cytokadehesis expression by endothelial cells, a key role of p53 has been established. In heart failure, several animal models have highlighted the importance of the catecholamine/β-2-adrenergic/reactive oxygen species (ROS) p53 signaling pathway in the induction of cardiac dysfunction. The primordial importance of this pathway is highlighted by the fact that catecholamine/β-2 stimulation regulates p53 in endothelial cells and macrophages and induces cardiac inflammation, while monocyte infiltration catecholamine/β-2 cardiac dysfunction could be blunted in p53 endothelial cell knockout mice.20 Cytokines and ROS released by activated inflammatory cells could contribute directly to myocardial damage.21 In rats, immobilization stress induces the production of heat shock protein 70 by the myocardium, a potent activator of the inflammatory response,23 and enhances atrial and BNP expression.24 Other hypotheses are based on an adaptive immune response triggered by cardiomyocyte necrosis. Representing an essential mechanism of wound healing, immune cell infiltration into the damaged myocardium could also trigger a process named sterile inflammation, given that the immune system is activated despite the lack of any discernible infectious insult. This mechanism could lead to ongoing inflammation.1 The clinical relevance of this paradigm was recently demonstrated in TTS. Using ultra-small supermagnetic particles of iron oxide to monitor inflammatory macrophage infiltration in the myocardium, Scally et al showed that TTS is 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.3 In line with this observation, other recent cardiac MRI data show that TTS is characterized by a state of intramyocardial edema secondary to a global left ventricular inflammatory response, which is detectable early on after the index event, and persists well beyond the resolution of segmental left ventricular contractile dysfunction.15 Beyond the scope of TTS, the interplay between SIRS and cancer has been extensively investigated in observational studies and a recent metanalysis.25 In the present report, both physical stress and cancer were evidenced as independent predictors of SIRS. In the context of TTS, in line with the present findings, some authors have recently reported that cancer and/or physical stress were associated

### Table 5. Predictors of Cardiac Death in TTS Patients

|                        | Univariate | | | | Multivariate | | | |
|------------------------|------------|---|---|---|------------|---|---|---|
|                        | HR         | 95% CI    | P-value | HR          | 95% CI    | P-value |
| Male                   | 2.29       | 0.668–7.84 | 0.188   | 1.09        | 1.02–1.16 | 0.010   |
| Age                    | 1.09       | 1.02–1.16  | 0.032   | 1.09        | 1.02–1.16 | 0.010   |
| Comorbidities          |            |            |         |             |            |         |
| Psychiatric disorders  | 0.429      | 0.093–1.99 | 0.279   |             |            |         |
| Dementia               | 2.94       | 0.633–13.6 | 0.169   |             |            |         |
| Cancer                 | 1.73       | 0.503–5.92 | 0.385   |             |            |         |
| COPD/asthma            | 0.682      | 0.062–7.52 | 0.754   |             |            |         |
| Cardiovascular risk factors |         |            |         |             |            |         |
| Hypertension           | 1.92       | 0.508–7.23 | 1.92    |             |            |         |
| Diabetes mellitus      | 2.69       | 0.821–8.81 | 0.102   |             |            |         |
| Dyslipidemia           | 0.515      | 0.136–1.95 | 0.328   |             |            |         |
| Current smoking        | 0.035      | 0.001–20.9 | 0.305   |             |            |         |
| Prior smoking          | 0.976      | 0.259–3.68 | 0.971   |             |            |         |
| Cardiovascular history |            |            |         |             |            |         |
| CAD or PAD             | 3.14       | 0.948–10.389 | 0.061  |             |            |         |
| AF                     | 1.56       | 0.336–7.21 | 0.571   |             |            |         |
| Stroke                 | 1.59       | 0.544–4.66 | 0.395   |             |            |         |
| Physical trigger       | 2.96       | 0.782–11.2 | 0.110   |             |            |         |
| Wall motion            |            |            |         |             |            |         |
| Apical                 | 1.67       | 0.355–7.89 | 0.515   |             |            |         |
| Midventricular         | 0.627      | 0.133–2.95 | 0.555   |             |            |         |
| Concomitant CAD        | 5.07       | 1.30–19.7  | 0.019   | 3.88        | 0.933–16.1 | 0.062  |
| SIRS                   | 5.41       | 1.17–25.0  | 0.031   | 12.8        | 1.58–104  | 0.017  |
| BNP >400ng/L on admission | 4.28     | 0.908–20.2 | 0.066   |             |            |         |
| LVEF <40% on admission | 1.67       | 0.444–6.31 | 0.447   |             |            |         |
| LVEF <40% at discharge | 10.4       | 3.02–35.7  | <0.001  | 9.88        | 2.54–38.4 | 0.001  |

HR, hazard ratio. Other abbreviations as in Tables 1–3.
with adverse outcome in the acute phase but also at longer follow-up.\textsuperscript{27} We have previously established that a diagnosis of malignancy is associated with ongoing inflammatory response in TTS. Moreover, because higher CRP and leukocyte levels were also seen at baseline, we hypothesized that the sustained inflammatory status associated with malignancy may promote the onset of TTS.\textsuperscript{27} Altogether, these data underline the complex interplay between cancer and physical stress in the induction of acute inflammatory response associated with TTS. In the present study, the paramount importance of SIRS during the early phase is underlined by the higher rates of adverse events seen in the SIRS patients.

To clarify a possible role of the effect of SIRS and ongoing inflammatory response on the cardiovascular compartment, late follow-up was focused on cardiac events. Despite a similar recovery of LVEF, SIRS patients were characterized by ongoing inflammation and neurohumoral activation, consistent with persistent myocardial infiltration by leukocytes. Consistent with the negative impact of ongoing chronic low-grade inflammation, higher rates of cardiovascular mortality were noted in the SIRS group. On multivariable analysis, advanced age, SIRS and LVEF impairment at hospital discharge were the sole independent predictors of cardiovascular death. Other reports have suggested that systemic inflammation could be associated with adverse events in TTS.\textsuperscript{27} Besides the negative role of inflammation in athero-thrombotic burden, systemic inflammation could also pave the way to arrhythmias as observed in the early phase, possibly causing fatal events.\textsuperscript{29, 32} Altogether, the present data identify SIRS patients as a vulnerable high-risk subgroup requiring close follow-up. Along these lines, therapies to attenuate SIRS in TTS represent an appealing subject for future research.

Study Limitations
Owing to the retrospective nature of this study, there were inherent limitations related to cofounding known or unknown factors. The time points of heart rate, temperature and WBC count measurement varied. This was a large study, however, and to our knowledge, the only study to specifically focus on SIRS in TTS. Inflammation evaluation was restricted to SIRS. Other parameters, such as pro- and anti-inflammatory cytokines, may have been helpful in detecting the inflammatory responses in TTS.

Conclusions
SIRS was noted in a large proportion of TTS patients and was associated with enhanced myocardial damage and adverse outcome at the acute phase. At long-term follow-up, SIRS remained an independent factor of cardiac death. SIRS patients are therefore a high-risk subgroup that should be targeted in future clinical trials with therapies to attenuate SIRS.

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Disclosures
The authors declare no conflicts of interest.

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Supplementary Files

Please find supplementary file(s):
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