Clinical Characteristics And Outcomes Of Patients Hospitalised With Takotsubo Syndrome Triggered By Inflammatory Diseases

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Abstract

Background: Inflammatory diseases may have important roles in the development of Takotsubo syndrome (TTS). However, the clinical profile and outcomes of patients with TTS triggered by inflammatory diseases have rarely been studied.

Aim: This study aimed to investigate the prevalences of inflammatory triggers in patients with TTS and describe the clinical characteristics of such patients. Additionally, this study compared the clinical outcomes of patients with TTS triggered by inflammatory diseases to the clinical outcomes of patients with TTS triggered by other mechanisms.

Methods and results: One hundred thirty-two patients were enrolled into the single-centre Takotsubo Registry between October 2013 and May 2021. According to the TTS trigger mechanism, patients were divided into three groups: I (emotional trigger, 34 patients; 31.5%), II (non-inflammatory physical trigger, 36 patients; 33.3%), and III (inflammatory trigger, 38 patients: 35.2%). A clear trigger was not identified in 24 (18.1%) patients.

There were no significant differences among groups in terms of clinical characteristics, electrocardiography (ECG) findings, or imaging results (ejection fraction in echocardiography and type of TTS according to ventriculography). The natriuretic peptide (NT-proBNP) level was higher in group III (11320.3 ± 12538.0 ng/l) than in group I (4641.4 ± 5366.4 ng/l; $p < 0.04$); it did not significantly differ from the level in group II (13366.1 ± 12934.2 ng/l; $p = 0.54$). Patients in group I had the most favourable outcomes in terms of in-hospital survival and an absence of cardiac events. The rates of adverse cardiac events and in-hospital mortality did not significantly differ between groups II and III (22.2% vs. 15.8%; $p = 0.48$).

Conclusion: Almost one-third of all patients with TTS in this study had an inflammatory trigger. The clinical characteristics and outcomes were comparable between patients with TTS caused by inflammatory triggers and patients with other physical triggers. The best clinical outcomes were observed in patients with TTS caused by an emotional trigger.

Introduction

Both physical and emotional stress have important roles as trigger mechanisms in Takotsubo syndrome (TTS). Acute neurological disease, malignancy, and trauma are major physical triggers with a negative impact on patient outcomes [1, 2].

Furthermore, recent studies have shown that inflammatory processes may play important roles in the development of TTS and its outcomes [3, 4]. Nevertheless, a TTS diagnosis in patients admitted to hospital because of an infectious disorder represents a true diagnostic challenge. Patients may have various symptoms caused by either infection or TTS. Moreover, cardiac imaging is often unavailable.

The main pathophysiological mechanism underlying TTS in patients with infectious diseases likely does not differ from other physical triggers because of catecholamines and higher sympathetic activity[5]. However, cytokine storm has additive effects on endothelial function and myocardial tissue in this specific group of patients. These specific conditions have clear impacts on patient status and outcomes [6].

Here, we evaluated the prevalences of inflammatory triggers in TTS patients; we also comprehensively characterised features and outcomes in these patients, compared to patients with TTS triggered by non-inflammatory causes.

Methods

The registry of consecutive patients with TTS hospitalised at the University Hospital Kralovske Vinohrady in Prague is an ongoing prospective observational registry. Included patients must meet the InterTAK diagnostic criteria developed by the Takotsubo International Registry [7] prior to enrolment. For this study, patient records were reviewed; clinical profiles and outcomes data were collected from October 2013 to the last diagnosed patient in May 2021. The study protocol was approved by the local ethics committee.

The following data were evaluated: baseline characteristics, cardiovascular risk factors, comorbidities, electrocardiography (ECG) description, ejection fraction (EF) assessed by echocardiography, laboratory levels of highly sensitive troponin at admission and maximal levels during hospitalisation (highly sensitive Troponin T was initially used; our hospital switched to highly sensitive Troponin I during the study period), maximal natriuretic peptide (NT-proBNP) levels, and other standard laboratory parameters. Furthermore, the type of TTS (apical, midventricular, focal, or basal) was assessed based on ventriculography findings. Finally, medication and clinical status (e.g., need for mechanical ventilation and/or hemodynamic support) were recorded.

Each patient was thoroughly analysed; the trigger factor was determined based on the patient interview, their difficulties, findings at admission, and events related to the onset of difficulties. The patients were then divided into three groups according to the mechanism that triggered TTS.

Group I included patients whose TTS was triggered by an emotional factor (e.g., death of family member, illness in the family, quarrel, or anxiety disorders). Group II consisted of patients whose TTS was triggered by acute physical non-cardiac non-infectious diseases such as trauma (fracture or fall), surgery (osteosynthesis, total hip endoprosthesis implantation, or large abdominal surgery), or neurological disorders (stroke, traumatic brain injury, epilepsy, meningioma brain tumour, or migraine). Finally, Group III included patients whose TTS was triggered by acute inflammatory noncardiac disorders (e.g., exacerbation of chronic obstructive pulmonary disease/asthma, pulmonary infection, urinary tract infection, gastrointestinal infection, or other type of infection).

This study had several goals: 1) assessing the prevalences of trigger mechanisms throughout the cohort, 2) comparing clinical characteristics between groups, 3) comparing laboratory markers between groups,

and 4) evaluating mortality and adverse cardiac events during hospitalisation (e.g., acute heart failure with need for mechanical ventilation and haemodynamic instability requiring levosimendan or other inotropes/vasopressors).

Statistical analysis

Differences among groups were calculated using the Pearson χ^2 test or Fisher's exact test. Laboratory parameters were compared using the Mann-Whitney U test and the Kruskal-Wallis test. The remaining continuous data were compared using unpaired *t*-tests and one-way analysis of variance. A *p-value* < 0.05 (two-sided) was considered statistically significant.

Results

Study population

In total, 132 patients were diagnosed with TTS. A clear trigger mechanism was not identified in 24 patients (18%). The remaining study group consisted of 108 patients aged 37–96 years (mean: 71.6 years), of which 98 (90.7%) were women and 10 were men. An emotional trigger for TTS (group I) was observed in 34 patients (31.5%), while 36 patients (33.3%) had TTS caused by a non-inflammatory physical trigger (group II). An inflammatory mechanism for TTS was present in 38 (35.2%) patients (group III) (Fig. 1).

A detailed analysis of group III revealed that 10 patients presented with exacerbation of chronic obstructive pulmonary disease/asthma, 12 patients presented with pulmonary infection, six patients presented with a urinary tract infection, six patients presented with gastrointestinal infection, and four patients presented with another type of infection (i.e., influenza, shingles, erysipelas, and anaphylactic shock).

There were equal proportions of men and women in all groups. Patient demographics, clinical data, and the results of diagnostic tests performed in this study are shown in Table 1. There were no differences in the incidences of comorbidities such as hypertension, known coronary artery disease, neurologic, and psychiatric disorders. Selected anthropometric data (height, weight, body mass index, body surface area) were also similar among groups. The most common symptom in group III was dyspnoea (68.4%), while the leading symptom in group I was chest pain (76.5%). Chest pain and dyspnoea were present only in 25% and 33% of patients in group II, respectively.

Examination findings

There were no significant differences in ECG – sinus rhythm (group I vs. group III: 85.3% vs. 89.5%; p = 0.6 and group II vs. group III: 77.8% vs. 89.5%; p = 0.17), atrial fibrillation (group I vs. group III: 14.7% vs. 7.9%; p = 0.35 and group II vs. group III: 22.2% vs. 7.9%; p = 0.08), or ischemic changes among groups.

Echocardiographic findings (EF and severity of mitral regurgitation) and the types of TTS according to ventriculography also did not differ among groups (Table 1).

Laboratory values

Levels of natriuretic peptide (NT-proBNP) did not differ between groups II and III (13366.1 ng/l ± 12934.2 vs. 11320.3 ng/l ± 12538.0; p = 0.54). However, NT-proBNP levels were lower in group I (4641.4 ± 5366.4 ng/l) than in group III (p < 0.04); they also differed between group I and group II (p < 0.007).

In contrast, troponin levels on admission and their maximum values did not differ among groups. Levels of C-reactive protein on admission were higher in group III than in group I (49.9 ± 70.4 mg/l vs. 13.4 ± 38.6 mg/l; p = 0.008). However, C-reactive protein levels did not significantly differ between groups I and II or groups II and III (Table 1).

Outcomes

Group I showed the most favourable outcomes in terms of in-hospital survival and no adverse cardiac events. Groups II and III had similar rates of adverse cardiac events in terms of mechanical ventilation (25% [9 of 36] vs. 28.9% [11 of 38]; p = 0.7) and the use of levosimendan/inotropes/vasopressors (38.9% [14 of 36] vs. 42.1% [16 of 38]; p = 0.78). The highest number of in-hospital deaths was observed among patients in group II. However, the in-hospital mortality did not differ between groups II and III (22.2% [8 of 36] vs. 15.8% [6 of 38]; p = 0.48).

Discussion

This study evaluated the clinical manifestations, characteristics, and outcomes of patients who TTS was triggered by different mechanisms; it focused primarily on patients with inflammatory disease triggers. The principal findings were as follows. First, inflammatory mechanisms represented approximately one-third of all TTS trigger mechanisms in this cohort. Second, patients with TTS caused by alternate trigger mechanisms did not differ in terms of clinical characteristics, type of TTS, ECG findings, or echocardiographic results (including EF). However, clinical manifestations did differ among trigger mechanisms, such that dyspnoea was the most common symptom in patients with infectious triggers. Third, there were no differences in troponin levels among groups. Finally, an emotional trigger was associated with excellent in-hospital outcomes. However, in-hospital mortality and the rate of adverse cardiac events in TTS patients with a physical trigger were not negligible; these findings did not differ according to non-inflammatory and inflammatory mechanisms.

Although TTS is generally presumed to affect post-menopausal women because of emotional stress, TTS is more often triggered by a physical stressor with contributions from inflammatory disease. The importance of inflammatory disease in TTS development was recently demonstrated during the coronavirus disease 2019 pandemic. Cytokine release syndrome is accompanied by catecholamine surge; it may predispose patients to TTS during infection with severe acute respiratory syndrome coronavirus.

In addition to infectious pathways, other mechanisms may also be involved in the development of TTS in patients with increased psychological distress, increased sympathetic responses, and microvascular dysfunction. Acute pulmonary disorders are common clinical manifestations that cause TTS in relation to a combination of pathophysiological mechanisms. This subgroup of patients represented 7% of all TTS cases in the InterTAK registry and 21% of cases involving a physical trigger of TTS [8]. A higher rate of pulmonary triggers (16.6%) was observed in our study in the entire cohort; a rate of 29.7% was observed among patients with a physical trigger. The large proportion of TTS patients with physical triggers may be related to close interdisciplinary cooperation in a large university hospital and TTS awareness among physicians.

Similar to previous studies, there were no significant differences among groups in terms of age, sex, comorbidities, anthropometric data, ECG changes, echocardiographic findings, or type of TTS [1, 8]. However, there were higher levels of NT-proBNP in patients with physical triggers than in patients with emotional triggers. Recently, Cammann et al. showed that TTS patients with acute neurological disorders had the highest levels of markers indicative of myocardial injury [2]. Importantly, clinical manifestations differed among groups with different triggers. In patients whose TTS was triggered by an infectious disease, the most common symptom was dyspnoea. This may make TTS diagnosis difficult because dyspnoea is also associated with an infectious trigger. Thus, physicians should be aware of the possibility for TTS development if a patient's clinical status does not improve after initial treatment or if there are ECG changes and higher levels of NT-proBNP. Echocardiography can also help detect this clinical complication.

In this study, we focused on in-hospital outcomes of TTS; the greatest differences were observed in terms of acute complications, including death and adverse cardiac events. A higher number of deaths was observed among patients with physical triggers (both inflammatory and non-inflammatory), but not among patients with emotional triggers. The rate of adverse cardiac events exhibited a similar significant increase in both groups of patients with TTS triggered by physical stress. A more severe physical condition may be involved in the worse prognosis exhibited by patients with TTS triggered by physical stress, compared to patients with TTS caused by emotional stress alone [9]. This is likely because of a similar prognosis between patients with TTS and patients with acute coronary syndrome [6, 10]. Our findings indicate that the clinical outcome of TTS depends on the triggering mechanism.

Limitations

This was a single-centre study with a limited number of patients. Although close cooperation between cardiology and other departments was present in this hospital, some cases of TTS may not have been diagnosed. Additionally, laboratory markers were not collected at specific time intervals; true maximal levels may have differed. Although the data presented suggest that patients with TTS caused by physical stress (both inflammatory and non-inflammatory) have worse outcomes, it is unclear whether this is a causative association or a result of the more severe underlying primarily non-cardiac physical disease.

Conclusion

The registry used in this study involved a wide spectrum of TTS patients with different trigger mechanisms. Almost one-third of all TTS cases were associated with an inflammatory trigger. The clinical characteristics and outcomes were comparable between patients with TTS caused by inflammatory triggers and patients who had a physical trigger. The best clinical outcomes were associated with TTS caused by an emotional trigger. It is important to correctly identify TTS in the context of other severe medical conditions because there are risks of common cardiac complications and poor prognosis. Interdisciplinary cooperation is essential when treating these patients.

Table 1
Characteristics of Takotsubo patients

Parameter Trigger:	Group I Emotional	Group II Other physical	Group III Inflammatory	P-value GI vs. GII	P-value GI vs. GIII	P-value GII vs. GIII
Characteristics	N = 34	N = 36	N = 38			
Demographics						
Female sex	32 (94.1%)	32 (88.9%)	34 (89.5%)	0.43	0.47	0.93
Age, years	72,2 ± 9.9	71.1 ± 12.0	71.7 ± 11.9	0.69	0.86	0.84
Body mass index, kg/m^2	25.8 ± 4.7	25.8 ± 5.6	25.1 ± 4.9	0.96	0.54	0.6
Body surface area, m^2	1.8 ± 0.2	1.8 ± 0.2	1.8 ± 0.2	0.99	0.45	0.45
Cardiovascular history						
Coronary artery disease	9 (26.5%)	5 (13.9%)	4 (10.5%)	0.18	0.08	0.65
Hypertension	27 (79.4%)	21 (58.3%)	24 (63.2%)	0.06	0.13	0.67
Diabetes mellitus	8 (23.5%)	8 (22.2%)	10 (26.3%)	0.89	0.78	0.68
Hypercholesterolemia	12 (35.3%)	12 (33.3%)	15 (39.5%)	0.86	0.71	0.58
Obesity	4 (11.8%)	7 (19.4%)	4 (10.5%)	0.37	0.86	0.28
Current smoking	20 (58.8%)	14 (38.9%)	23 (60.5%)	0.09	0.88	0.06
Coexisting medical condition						
History of neurological disease	11 (32.4%)	15 (41.7%)	8 (21%)	0.42	0.27	0.06
History of psychiatric disease	11 (32.4%)	6 (16.7%)	6 (15.8%)	0.12	0.09	0.92
History of pulmonary disease	6 (17.6%)	9 (25%)	19 (50%)	0.45	0.004	0.027
Menopause	31 (91.2%)	28 (77.8%)	32 (84.2%)	0.12	0.37	0.48
Alcohol consumption	3 (8.8%)	2 (5.6%)	4 (10.5%)	0.59	0.81	0.43
Symptoms on admission						

Parameter Trigger:	Group I Emotional	Group II Other physical	Group III Inflammatory	P-value GI vs. GII	P-value GI vs. GIII	P-value GII vs. GIII
Chest pain	26 (76.5%)	9 (25%)	14 (36.8%)	**0.000**	**0.001**	0.27
Dyspnoea	15 (44.1%)	12 (33.3%)	26 (68.4%)	0.35	**0.04**	**0.002**
ECG on admission						
Heart rate	86.4 ± 22.1	90.4 ± 25.4	89 ± 22.4	0.49	0.62	0.81
Sinus rhythm	29 (85.3%)	28 (77.8%)	34 (89.5%)	0.42	0.6	0.17
Atrial fibrillation	5 (14.7%)	8 (22.2%)	3 (7.9%)	0.42	0.36	0.08
LBBB	4 (11.7%)	4 (11.1%)	1 (2.6%)	0.93	0.13	0.14
RBBB	1 (2.9%)	5 (13.9%)	3 (7.9%)	0.1	0.36	0.41
ST-elevation	9 (26.5%)	10 (27.8%)	11 (28.9%)	0.9	0.81	0.91
ST-depression	0	3 (8.3%)	2 (5.3%)	0.08	0.17	0.6
T-wave inversion	15 (44.1%)	12 (33.3%)	16 (42.1%)	0.35	0.86	0.44
Echocardiography findings						
Ejection fraction (%)	37.4 ± 9.4	36.0 ± 9.1	34.3 ± 9.1	0.56	0.17	0.43
Mitral regurgitation	10 (29.4%)	4 (11.1%)	8 (21.1%)	0.06	0.41	0.24
TTS type						
Apical form	26 (76.5%)	25 (69.4%)	29 (76.3%)	0.51	0.99	0.51
Midventricular form	5 (14.7%)	9 (25%)	8 (21.1%)	0.28	0.48	0.69
Basal form	1 (2.9%)	0	0	0.3	0.29	1.0
Focal form	2 (5.9%)	2 (5.6%)	1 (2.6%)	0.95	0.49	0.52
Laboratory parameters						
Hs-Troponin I, ng/l (on admission)	1288.3 ± 2134.4	546.5 ± 575.2	3040.7 ± 2713.4	0.44	0.25	0.096

Parameter Trigger:	Group I Emotional	Group II Other physical	Group III Inflammatory	P-value GI vs. GII	P-value GI vs. GIII	P-value GII vs. GIII
Hs-Troponin I, ng/l (max value)	4173 ± 3458.5	3394.7 ± 4667.2	4130.1 ± 4648.8	0.76	0.98	0.81
Hs-Troponin T, ng/l (on admission)	310.8 ± 267.3	483.9 ± 416.9	390.6 ± 371.1	0.08	0.38	0.37
Hs-Troponin T, ng/l (on admission)	479.4 ± 454.7	576.6 ± 426.8	615.7 ± 557.8	0.43	0.34	0.76
NT-proBNP, ng/l (mean value)	4641.4 ± 5366.4	13366.1 ± 12934.2	11320.3 ± 12538.0	**0.007**	**0.04**	0.54
C-reactive protein, mg/l (on admission)	13.4 ± 38.6	36.9 ± 61.4	49.9 ± 70.4	0.07	**0.008**	0.42
C-reactive protein, mg/l (max value)	25.1 ± 41.5	69.5 ± 78.5	117.3 ± 99.7	**0.007**	**0.000**	**0.03**
Leucocytosis [x10^3 µmol/l] (on admission)	9.7 ± 2.9	11.7. ± 4.8	21.6 ± 56.2	**0.05**	0.21	0.29
Leucocytosis [x10^3 µmol/l] (max value)	10.4 ± 3	13.5 ± 6.6	24.6 ± 60.5	**0.02**	0.16	0.27
Adverse cardiac events						
Acute heart failure requiring intubation	0	9(25%)	11(28.9%)	**0.002**	**0.000**	0.7
Haemodynamic instability requiring levosimendan/inotropes/ vasopressors	0	14(38.9%)	16(42.1%)	**0.000**	**0.000**	0.78
In-hospital complications						
Cardiopulmonary resuscitation	0	6(16.7%)	5(13.2%)	**0.013**	**0.03**	0.67
Death	0	8(22.2%)	6(15.8%)	**0.003**	**0.016**	0.48

Declarations

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Ethics approval and consent to participate

The protocol for this study was approved by the Ethics Committee of the University Hospital Kralovske Vinohrady.

Consent for publication

All authors gave consent for the publication.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Dr Polednikova had full access to all the data in the study and take responsibility for

the integrity of the data and the accuracy of the data analysis.

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Critical revision of the manuscript for intellectual content: Tousek Petr, Trinh Minh Duc.

All authors read and approved the final manuscript.

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Figures

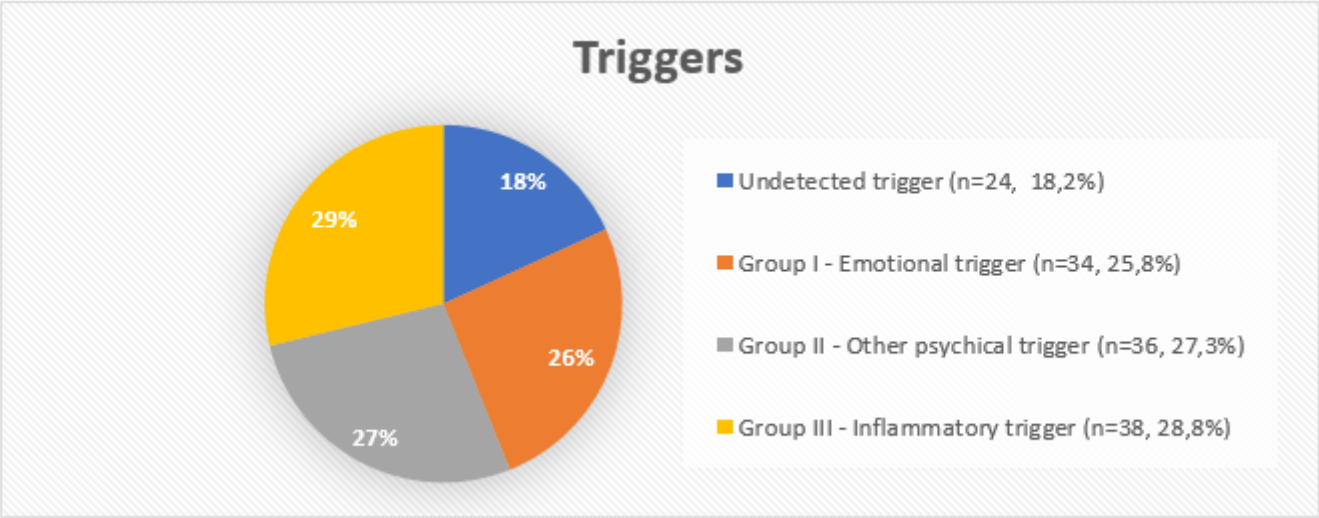

Figure 1

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