Journal of the American Heart Association

ORIGINAL RESEARCH

Neurological Disorders in Takotsubo Syndrome: Clinical Phenotypes and Outcomes

Francesco Santoro, MD, PhD*; Iván J. Núñez Gil, MD, PhD*; Luca Arcari, MD; Enrica Vitale, MD; Tommaso Martino, MD; Ibrahim El-Battrawy, MD; Federico Guerra, MD; Giuseppina Novo, MD, PhD; Enrica Mariano, MD, PhD; Beatrice Musumeci, MD; Luca Cacciotti, MD, PhD; Pasquale Caldarola, MD; Roberta Montisci, MD; Ilaria Ragnatela, MD; Rosa Cetera, MD; Oscar Vedia, MD; Emilia Blanco, MD; Javier Lopez Pais, MD; Agustin Martin, MD, PhD; Alberto Pérez-Castellanos, MD; Jorge Salamanca, MD; Francesco Bartolomucci, MD, PhD; Ibrahim Akin, MD; Holger Thiele, MD; Ingo Eitel, MD; Thomas Stiermaier, MD* Natale Daniele Brunetti, MD, PhD†

BACKGROUND: Neurological disorders as a risk factor for Takotsubo syndrome (TTS) are not well characterized. The aim of the study was to evaluate TTS-associated neurological phenotypes and outcome.

METHODS AND RESULTS: Patients with TTS enrolled in the international multicenter GEIST (German Italian Spanish Takotsubo) registry were analyzed. Prevalence, clinical characteristics, and short- and long-term outcomes of patients with TTS were recorded. A subgroup analysis of the 5 most represented neurological disorders was performed.

In total, 400 (17%) of 2301 patients had neurological disorders. The most represented neurological conditions were previous cerebrovascular events (39%), followed by neurodegenerative disorders (30.7%), migraine (10%), epilepsy (9.5%), and brain tumors (5%). During hospitalization, patients with neurological disorders had longer in-hospital stay (8 [interquartile range, 5–12] versus 6 [interquartile range, 5–9] days; $P<0.01$) and more often experienced in-hospital complications (27% versus 16%; $P=0.01$) mainly driven by cardiogenic shock and in-hospital death (12% versus 7.6% and 6.5% versus 2.8%, respectively; both $P<0.01$). Survival analysis showed a higher mortality rate in neurological patients both at 60 days and long-term (8.8% versus 3.4% and 23.5% versus 10.1%, respectively; both $P<0.01$). Neurological disorder was an independent predictor of both the 60-day and long-term mortality rate (odds ratio, 1.78 [95% CI, 1.07–2.97]; $P=0.02$; hazard ratio, 1.72 [95% CI, 1.33–2.22]; both $P<0.001$). Patients with neurodegenerative disorders had the worst prognosis among the neurological disease subgroups, whereas patients with TTS with migraine had a favorable prognosis (long-term mortality rates, 29.2% and 9.7%, respectively).

CONCLUSIONS: Neurological disorders identify a high-risk TTS subgroup for enhanced short- and long-term mortality rate. Careful recognition of neurological disorders and phenotype is therefore needed.

Key Words: neurological disease ■ risk stratification ■ Takotsubo syndrome

Takotsubo syndrome (TTS) is a form of reversible acute left ventricular dysfunction, mainly found in women after an episode of emotional or physical stress.[1,2] The underlying mechanisms remain unclear.[3–5] The long-term mortality rate of patients affected by TTS is higher than for patients with ST-segment–elevation

Correspondence to: Natale Daniele Brunetti, MD, PhD, FESC, University of Foggia, Viale Pinto n.1, 71122 Foggia, Italy. Email: natale.brunetti@unifg.it

*F. Santoro and I.J. Núñez Gil contributed equally to this work as co-first authors.

†T. Stiermaier and N.D. Brunetti contributed equally to this work as co-senior authors.

This manuscript was sent to Kolawole W. Wahab, MD, Guest Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.123.032128

For Sources of Funding and Disclosures, see page 9.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- In a European cohort of 2301 patients with Takotsubo syndrome, the prevalence of neurological disorders was 17%.
- The most represented neurological conditions were previous cerebrovascular events (39%), followed by neurodegenerative disorders (30.7%), migraine (10%), epilepsy (9.5%), and brain tumors (5%).

What Are the Clinical Implications?

- Among the neurological phenotypes in Takotsubo syndrome, patients with neurodegenerative disorders or previous cerebrovascular events had the worst prognosis and may require a strict follow-up.

Nonstandard Abbreviations and Acronyms

CVE	cerebral vascular event
GEIST	German Italian Spanish Takotsubo
TTS	Takotsubo syndrome

acute coronary syndrome,[6] and it is mainly driven by noncardiovascular comorbidities.[7,8] There is evidence suggesting a possible link between neurological diseases and TTS.[9] Indeed, acute neurological disorders can trigger this syndrome and are associated with worse outcome at long-term follow-up.[10] Among acute neurological disorders, those more commonly triggering TTS are subarachnoid hemorrhage, status epilepticus and seizures, transient global amnesia, migraine, and cerebrovascular accident.[11] Moreover, a history of neurological disorders (including cerebrovascular events, neurodegenerative disorders, and epilepsy) is a predictor of in-hospital complications during TTS admission.[12] However, a systematic investigation of patients with TTS with neurological disorders and its potential association with outcome has not been conducted yet. The aim of this study was, therefore, to evaluate clinical features and short- and long-term outcome among patients with TTS with neurological disorders.

METHODS

Data are available upon reasonable request.

Study Population Selection

The present study analyzed data from 2301 consecutive patients enrolled in the GEIST (German Italian Spanish Takotsubo) registry. The GEIST registry is a multicenter, international, observational registry of patients with TTS that collects patients from Italy, Germany, and Spain (NCT04361994). Patients' inclusion was performed in accordance with the Heart Failure Association of the European Society of Cardiology TTS diagnostic criteria: (1) transient regional wall motion abnormalities of the left or right ventricle, frequently preceded by a stressful trigger and usually extending beyond a single epicardial coronary artery distribution; (2) absence of culprit coronary artery disease at coronary angiogram; (3) new and reversible electrocardiography abnormalities; (4) elevated cardiac troponin and serum natriuretic peptide levels; and (5) recovery of ventricular systolic function at follow-up in all surviving patients.[13] The evaluation of patients and subsequent inclusion in the registry was performed by the physicians in charge only after all diagnostic criteria were met. All patients underwent coronary angiogram with different timing according to the European Society of Cardiology guidelines on acute coronary syndrome.[14,15] Coronary artery disease was defined as the presence of coronary calcifications, atherosclerosis, plaques, or stenoses, with stenoses >50% of the lumen diameter in arteries with a diameter amenable to percutaneous intervention. Data regarding demographic characteristics, clinical presentation, laboratory measures, electrocardiography/echocardiography/coronary angiography parameters, treatment, and medication were collected. When clearly identifiable, stressors were classified as emotional and physical triggers. Physical triggers were classified into 7 subgroups (infectious, neurological disorders, surgery, physical activity/trauma/pain, hypoxia, anaphylaxis, other).[16] Ballooning patterns were classified as apical (typical), midventricular, basal, and focal,[17] with or without concomitant right ventricular involvement.[18] In-hospital complications and outcome recorded included in-hospital stroke, pulmonary edema, cardiogenic shock, need for invasive ventilation, need for catecholamine therapy, arrhythmias, and in-hospital death. Long-term outcome was verified by outpatient visits, medical records, or phone interviews. Mean follow-up was 2.5 ± 5.8 years.

Underlying neurological disorders were intended as diseases that were present before, or not necessarily related to, the index admission. These were classified into 10 subgroups: cerebrovascular events (CVEs; previous ischemic or hemorrhagic stroke), neurodegenerative disorders (including cognitive disorders and movement disorders), epilepsy, neuroinflammatory/autoimmune diseases, brain tumors, genetic disorders (including muscular dystrophy and tuberous sclerosis), spinal stenosis, peripheral nervous system disorder, migraine, and others. Each medical record was evaluated by a neurologist.

All patients gave a written informed consent for the participation in the registry. The local ethics committee approved this study, complying with the Helsinki guidelines. All local principal investigators reviewed the draft and checked for the accuracy and veracity of data.

Statistical Analysis

Continuous variables were compared using Student's *t*-test for independent samples, while dichotomic with Fisher's exact test and presented as means±SD or median and interquartile range. For the purpose of survival analysis, 5 main subgroups of neurological disorders have been identified: CVE (including ischemic and hemorrhagic stroke), neurodegenerative disorders (including cognitive and movement disorders), epilepsy, migraine, and brain tumors. One-way ANOVA was used to compare variables of interest among these 5 groups. Univariable and multivariable logistic regression analyses were used to calculate estimated odds ratio (OR) and 95% CI for factors associated with the 60-day mortality rate. Univariable and multivariable Cox regression analyses were performed to assess factors independently associated with the long-term mortality rate in the overall cohort. All factors with $P<0.05$ were included in the multivariable model. Kaplan–Meier curves and log-rank test were used to assess survival function at 60 days and long term in both the overall population and subgroups analysis. All data were analyzed with SPSS software version 25.0 (SPSS Inc., Chicago, IL).

RESULTS

Clinical Characteristics

Of 2301 patients included in the GEIST registry, 275 (12%) were men, with a mean age of 71 ± 12 years. Clinical features of the overall population and patients with and without neurological disorders are listed in Table 1.

The prevalence of neurological disorders was 17% (n=400). Patients with neurological disorders were older (74 ± 11 versus 70 ± 11 years; $P<0.001$) and had a higher prevalence of atrial fibrillation (AF; 36% versus 12%; $P<0.01$) and psychiatric comorbidities (16% versus 10%; $P<0.01$), with respect to patients without neurological disorders (Table 1).

At admission, patients with neurological disorders had a lower prevalence of chest pain (43% versus 56%; $P<0.01$), developed TTS more frequently after a physical trigger (46% versus 34%; $P<0.01$), and had lower left ventricular ejection fraction (LVEF) at admission (38 ± 11% versus 41 ± 14%; $P<0.01$; Figure 1). No significant differences were detected regarding admission corrected QT interval (479 ± 50 versus 474 ± 56 ms; $P=0.12$); however, patients with neurological disorders presented a prolonged corrected QT interval at discharge (472 ± 40 versus 452 ± 63 ms; $P=0.02$; Table 1).

Among patients with neurological disorders, the most represented neurological conditions were previous CVE (n=156; 39%) followed by neurodegenerative disorder (n=123; 30.7%), migraine (n=41; 10%), epilepsy (n=38; 9.5%), brain tumors (n=20; 5%), peripheral nervous system disorder (n=15; 3.7%), neuroinflammatory/autoimmune disorders (n=9; 2.2%), spinal stenosis (n=7; 1.7%), and genetic disorders (n=2; 0.5%).

Among brain tumors, the following diseases were found: schwannoma (n=5; 25%), meningioma (n=5; 25%), angioma (n=4; 20%), glioblastoma (n=2; 10%), benign pediatric tumors (n=2; 10%), pituitary adenoma (n=1; 5%), and dermoid cyst in the fourth ventricle (n=1; 5%).

Sepsis (10%), acute neurological trigger (9.5%), and extreme activity/trauma (8.5%) were the more prevalent physical triggers among patients with neurological disorders (Table S1).

In-Hospital Stay

During hospitalization, patients with neurological disorders had longer in-hospital stays (median, 8 [interquartile range, 5–12] versus 6 [5–9] days; $P<0.01$) and higher rate of complications (27% versus 16%; $P<0.01$). In- and out-of-hospital major adverse cardiac events are listed in Table S2.

Patients with neurological disorders more frequently developed cardiogenic shock (12% versus 7.6%; $P<0.01$), pulmonary edema (11.7% versus 7.4%; $P=0.006$), in-hospital stroke (4.5% versus 1.6%; $P<0.01$), and more often required invasive ventilation (10.2% versus 6%; $P<0.01$). Moreover, in-hospital death was significantly higher in the population with neurological disorders (6.5% versus 2.8%; $P<0.01$). Discharge medical therapy is reported in Table S3.

Short- and Long-Term Mortality Rates

Patients with neurological disorders had a higher mortality rate at short- (60 days) and long-term follow-up (8.8% versus 3.4% and 23.5% versus 10.1%, respectively; $P<0.01$; Figure 2). Patients with an acute neurological trigger and a history of neurological disorder had a long-term mortality rate of 25% and, in cases of previous CVE, of 30%.

At multivariable logistic regression analysis for predictors of 60-day mortality rate, including age, male sex, physical triggers, neurological disorder, history of cancer, diabetes, pulmonary disease, AF, and apical ballooning pattern as covariates, neurological disorder was an independent predictor (OR, 1.78 [95% CI, 1.07–2.97]; $P=0.026$) along with age (OR, 1.03 [95%

Table 1. Epidemiological Characteristics and Clinical Features of the General Population, Nonneurological Patients, and Neurological Patients

	General population	Nonneurological patients	Neurological patients	*P* value
Number of patients, n (%)	2301	1901 (82.6)	400 (17.4)	
Age, y (SD)	71±12	70±12	74±11	<0.01
Male sex, n (%)	275 (12)	218 (11)	57 (14)	NS
Risk factors, n (%)				
Hypertension	1566 (68)	1291 (68)	275 (68)	NS
Dyslipidemia	898 (39)	729 (38)	169 (42)	NS
Diabetes	444 (19)	354 (18)	90 (22)	NS
Past medical history, n (%)				
CAD history	228 (9)	196 (10)	32 (8)	NS
Atrial fibrillation	293 (13)	236 (12)	145 (36)	<0.01
Malignancy	303 (13)	259 (13)	41 (10)	NS
Psychiatric disease	252 (11)	185 (9.7)	67 (16)	<0.01
Clinical features				
Chest pain, n (%)	1251 (54)	1076 (56)	175 (43)	<0.01
Dyspnea, n (%)	792 (34)	649 (34)	143 (35)	NS
Admission corrected QT interval, mean (SD)	476±57	474±56	479±50	NS
Discharge corrected QT interval, mean (SD)	455±57	452±63	472±40	0.02
Stressful trigger, n (%)	1561 (68)	1285 (65)	276 (69)	0.59
• Physical	828 (35.9)	643 (33.8)	185 (46.2)	<0.01
• Emotional	821 (35.6)	714 (37.5)	107 (26.7)	<0.01
Ballooning pattern, n (%)				
• Apical	1978 (86)	1623 (85)	355 (88)	NS
• Midventricular	266 (11)	234 (12)	32 (8)	0.01
• Basal	41 (1.7)	29 (1.5)	12 (3)	0.05
• Focal	8 (0.3)	6 (0.3)	2 (0.5)	NS
LVEF at admission, mean (SD)	40±13	41±14	38±11	<0.01
LVEF at follow-up, mean (SD)	57±9	57±10	58±9	NS
RV ballooning, n (%)	67 (2.9)	51 (2.6)	16 (4)	NS

CAD indicates coronary artery disease; LVEF, left ventricular ejection fraction; NS, not significant; and RV, right ventricular.

CI, 1.01–1.06]; *P*=0.006), male sex (OR, 1.84 [95% CI, 1.03–3.28]; *P*=0.039), physical trigger (OR, 1.85 [95% CI, 1.15–2.99]; *P*=0.011), LVEF (OR, 0.97 [95% CI, 0.96–0.98]; *P*<0.001), and history of AF (OR, 2.12 [95% CI, 1.25–3.60]; *P*=0.005; Table S4).

At multivariable Cox regression analysis for predictors of long-term mortality rate, including age, male sex, physical trigger, neurological disorder, history of cancer, diabetes, pulmonary disease, LVEF, AF, apical ballooning pattern, and cardiogenic shock as covariates, neurological disorder was found as an independent predictor of long-term mortality (hazard ratio [HR], 1.72 [95% CI, 1.33–2.22]; *P*<0.001) along with age (HR, 1.06 [95% CI, 1.05–1.08]; *P*<0.001), male sex (HR, 1.56 [95% CI, 1.11–2.14]; *P*=0.005), physical trigger (HR, 1.71 [95% CI, 1.34–2.19]; *P*<0.001), history of cancer (HR, 2.26 [95% CI, 1.71–2.98]; *P*<0.001), diabetes (HR, 2.07 [95% CI, 1.61–2.66]; *P*<0.001), pulmonary disease (HR, 1.39 [95% CI, 1.04–1.85]; *P*=0.025), LVEF (HR, 0.97 [95% CI, 0.96–0.98]; *P*<0.001), and cardiogenic shock (HR, 3.29 [95% CI, 2.49–4.35]; *P*<0.001; Table 2).

Neurological Phenotypes

Patients with neurological phenotypes were stratified into 5 groups: previous CVE (including ischemic and hemorrhagic stroke), neurodegenerative disorders (including cognitive and movement disorders), migraine, epilepsy, and brain tumors. Clinical features, including cardiovascular and noncardiovascular comorbidities, echocardiographic features, and in- and out-of-hospital major adverse cardiac events, were evaluated (Table 3 and Table S5, Figure 3).

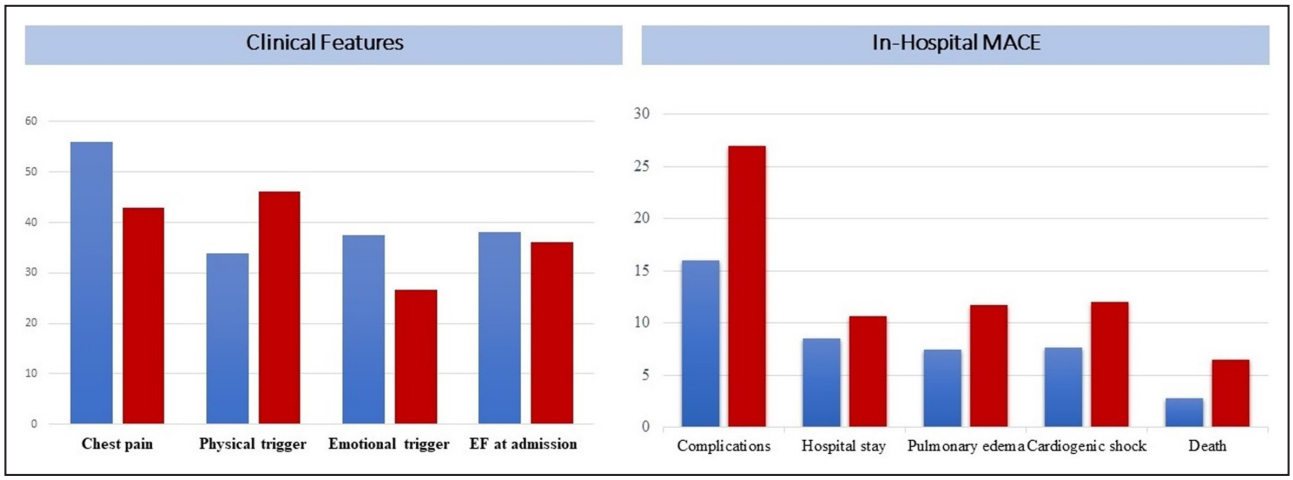


Figure 1. Clinical features and in-hospital MACEs of patients with Takotsubo syndrome and neurological disorders (red columns) or not (blue columns).
EF indicates ejection fraction; and MACE, major adverse cardiac event.

Among the 5 neurological subgroups, neurodegenerative patients had the worse outcome at 60 days, followed by stroke, brain tumors, epilepsy, and migraine. At long-term analysis, the neurodegenerative subgroup had the worst outcome, followed by brain tumors, stroke, epilepsy, and, finally, migraine (Figure 4).

Patients with neurodegenerative disorders were older and had lower admission LVEF (34 ± 14%), and about one-third (32.5%) experienced in-hospital complications such as cardiogenic shock (16.2%) and pulmonary edema (16.2%); further, they have the worst long-term outcome (long-term mortality of 29.2%).

Patients with previous CVE had a higher prevalence of AF, during hospitalization more frequently experienced ischemic stroke (9.6%), and had higher incidence of left ventricular thrombi (3.8%).

Patients with brain tumors had some typical echocardiographic features, with 30% having apical sparing ballooning patterns (midventricular or basal), right ventricular ballooning pattern in 15%, and high risk of in-hospital complications such as cardiogenic shock (10%), pulmonary edema (30%), and in-hospital death (15%).

Patients with epilepsy had a higher prevalence of male sex, smoking habits, and AF and developed TTS more often after an acute neurological trigger (epileptic crisis, 13%; brain trauma, 7%; brain hemorrhage, 2%).

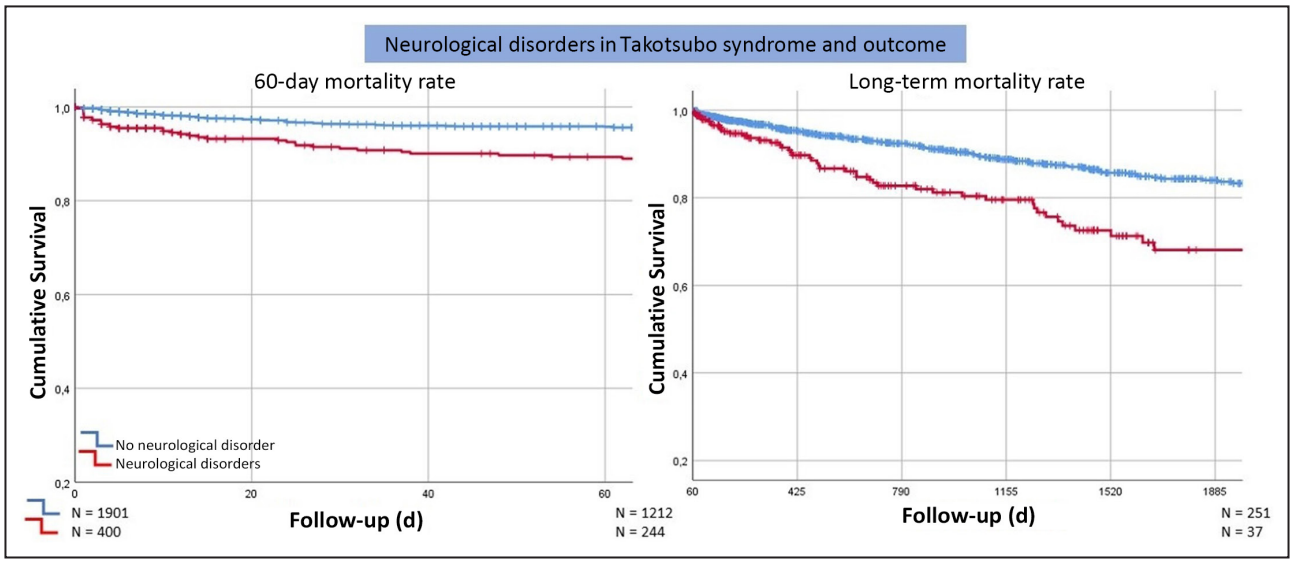


Figure 2. Kaplan–Meier curves for 60 days (left) and long-term (right) mortality rates by neurological comorbidity in the overall population.

Table 2. Univariable and Multivariable Cox Regression Analysis for Factors Associated With Long-Term Mortality Rate

Variable	Univariate		Multivariable	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	1.07 (1.05–1.08)	<0.01	1.06 (1.05–1.08)	<0.01
Male sex	2.08 (1.55–2.79)	<0.01	1.56 (1.11–2.14)	<0.01
Physical trigger	2.47 (1.97–3.11)	<0.01	1.71 (1.34–2.19)	<0.01
Neurological disorders	2.35 (1.84–3.01)	<0.01	1.72 (1.33–2.22)	<0.01
History of cancer	2.62 (2.01–3.42)	<0.01	2.26 (1.71–2.98)	<0.01
Diabetes	2.38 (1.87–3.04)	<0.01	2.07 (1.61–2.66)	<0.01
Pulmonary disease	1.95 (1.48–2.58)	<0.01	1.39 (1.04–1.85)	0.02
LVEF	0.96 (0.95–0.97)	<0.01	0.97 (0.96–0.98)	<0.01
Atrial fibrillation	2.08 (1.58–2.74)	<0.01	NS	NS
Apical ballooning	1.56 (1.09–2.22)	0.01	NS	NS
Cardiogenic shock	4.21 (3.24–5.47)	<0.01	3.29 (2.49–4.35)	<0.01

HR indicates hazard ratio; LVEF, left ventricular ejection fraction; and NS, not significant.

Patients with migraine were younger, mainly female, had a higher prevalence of autoimmune disorders, more often developed TTS after an emotional trigger, experienced fewer in-hospital complications, and had a better long-term prognosis.

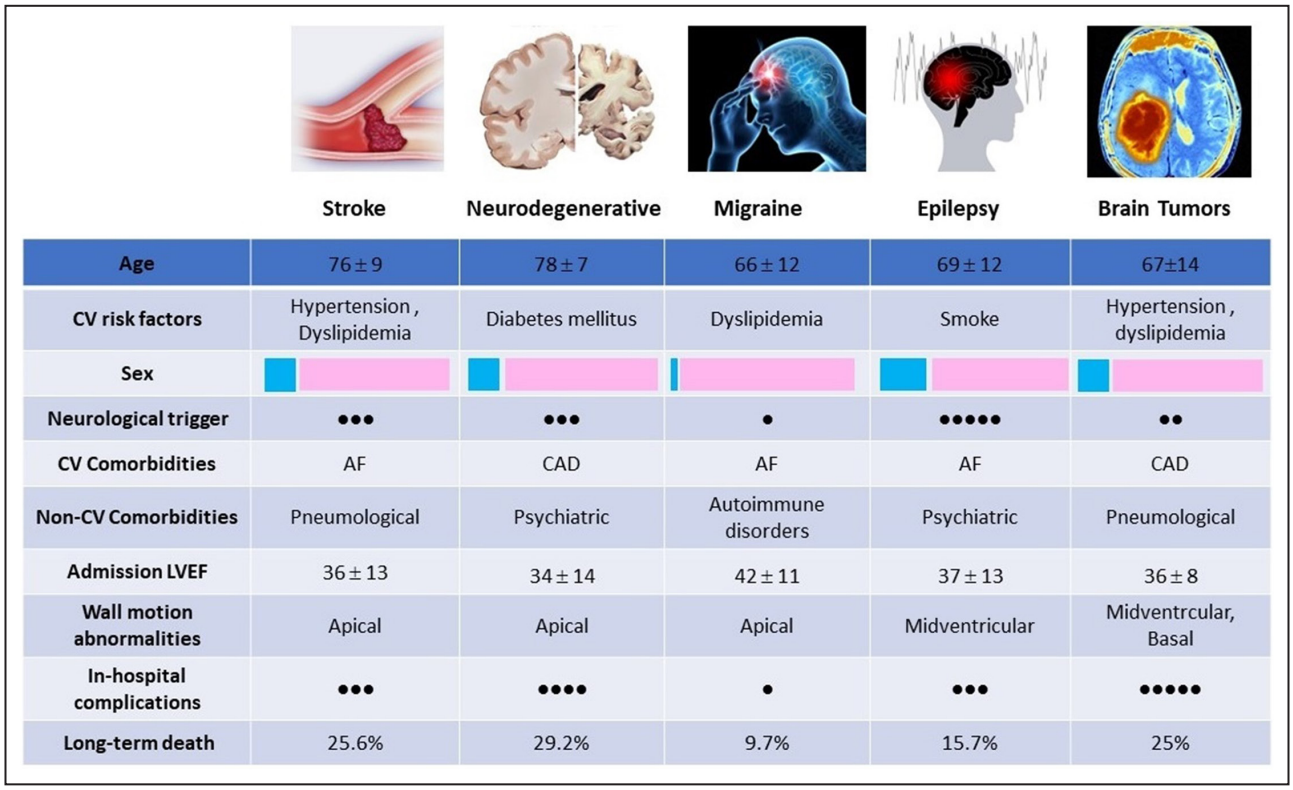
DISCUSSION

To the best of our knowledge, this is the first comprehensive study exploring clinical features and outcomes of patients with TTS with underlying neurological

Table 3. Epidemiological Characteristics, Clinical Features, and In- and Out-of-Hospital Major Adverse Cardiac Events of the 5 Neurological Subgroups

	Previous CVE	Neurodegenerative disorders	Migraine	Epilepsy	Brain tumors	*P* value
Number of patients	156	123	41	38	20	
Age, y (SD)	76±9	78±7	66±12	69±12	67±14	<0.01
Male sex, n (%)	26 (16.6)	21 (17)	1 (2.4)	9 (23.6)	3 (15)	NS
Risk factors, n (%)						
Hypertension	118 (75.6)	81 (65.8)	30 (73.1)	22 (57.8)	12 (60)	NS
Dyslipidemia	76 (48.7)	48 (39)	20 (48.7)	13 (34.2)	5 (41.6)	0.04
Diabetes	36 (23)	39 (31.7)	8 (19.5)	4 (10.5)	2 (10)	NS
Smoking	30 (19.2)	9 (7.3)	4 (9.7)	9 (23.6)	6 (30)	<0.01
Past medical history, n (%)						
CAD history	9 (5.7)	15 (12.1)	1 (2.4)	3 (7.8)	2 (10)	0.03
Atrial fibrillation	30 (19.2)	17 (13.8)	4 (9.7)	7 (18.4)	1 (5)	0.03
Pulmonary disease	26 (16.6)	29 (18.6)	2 (4.8)	7 (18.4)	3 (15)	NS
Malignancy	18 (11.5)	9 (7.3)	4 (9.7)	2 (5.2)	20 (100)	NS
Psychiatric disease	22 (14.1)	26 (21.1)	6 (14.6)	7 (18.4)	1 (5)	NS
Autoimmune disease	9 (5.7)	9 (7.3)	6 (14.6)	3 (7.8)	1 (5)	NS
Echocardiographic features						
Ballooning pattern						
Apical, n (%)	146 (93.5)	111 (90.2)	36 (87.8)	31 (81.5)	14 (70)	0.02
Midventricular, n (%)	7 (4.4)	11 (8.9)	2 (4.8)	4 (10.5)	3 (15)	NS
Basal, n (%)	3 (1.9)	2 (1.6)	2 (4.8)	2 (5.2)	3 (15)	0.01
Admission LVEF, mean (SD)	36±13	34±14	42±11	37±13	36±8	NS
LVEF at follow-up, mean (SD)	55±14	49±21	62±5	55±12	57±4	NS
In-hospital complications, n (%)	40 (25.6)	40 (32.5)	6 (14.6)	9 (23.6)	9 (45)	0.05
Hospital stay, d, median (IQR)	11 (5–12)	4 (5–13)	5 (4–10)	13 (5–12)	13 (6–10)	NS
In-hospital death, n (%)	13 (8.3)	8 (6.5)	0 (0)	1 (2.6)	3 (15)	NS

CAD indicates coronary artery disease; CVE, cerebrovascular events; IQR, interquartile range; LVEF, left ventricular ejection fraction; and NS, not significant.



	Stroke	Neurodegenerative	Migraine	Epilepsy	Brain Tumors
Age	76 ± 9	78 ± 7	66 ± 12	69 ± 12	67±14
CV risk factors	Hypertension, Dyslipidemia	Diabetes mellitus	Dyslipidemia	Smoke	Hypertension, dyslipidemia
Sex					
Neurological trigger	●●●	●●●	●	●●●●●	●●
CV Comorbidities	AF	CAD	AF	AF	CAD
Non-CV Comorbidities	Pneumological	Psychiatric	Autoimmune disorders	Psychiatric	Pneumological
Admission LVEF	36 ± 13	34 ± 14	42 ± 11	37 ± 13	36 ± 8
Wall motion abnormalities	Apical	Apical	Apical	Midventricular	Midventrcular, Basal
In-hospital complications	●●●	●●●●	●	●●●	●●●●●
Long-term death	25.6%	29.2%	9.7%	15.7%	25%

Figure 3. Phenotyping of the 5 neurological subgroups.
AF indicates atrial fibrillation; CAD, coronary artery disease; CV, cardiovascular; and LVEF, left ventricular ejection fraction.

disorders in a multicenter prospective registry. The main findings of our study are as follows: (1) Neurological disorders have a prevalence of ≈17% among a general population with TTS; (2) neurological disorder is an independent predictor of short- and long-term outcomes in patients with TTS; (3) among neurological phenotypes, patients affected by neurodegenerative disorders had worse short- and long-term outcomes, whereas patients with TTS with migraine had a favorable prognosis.

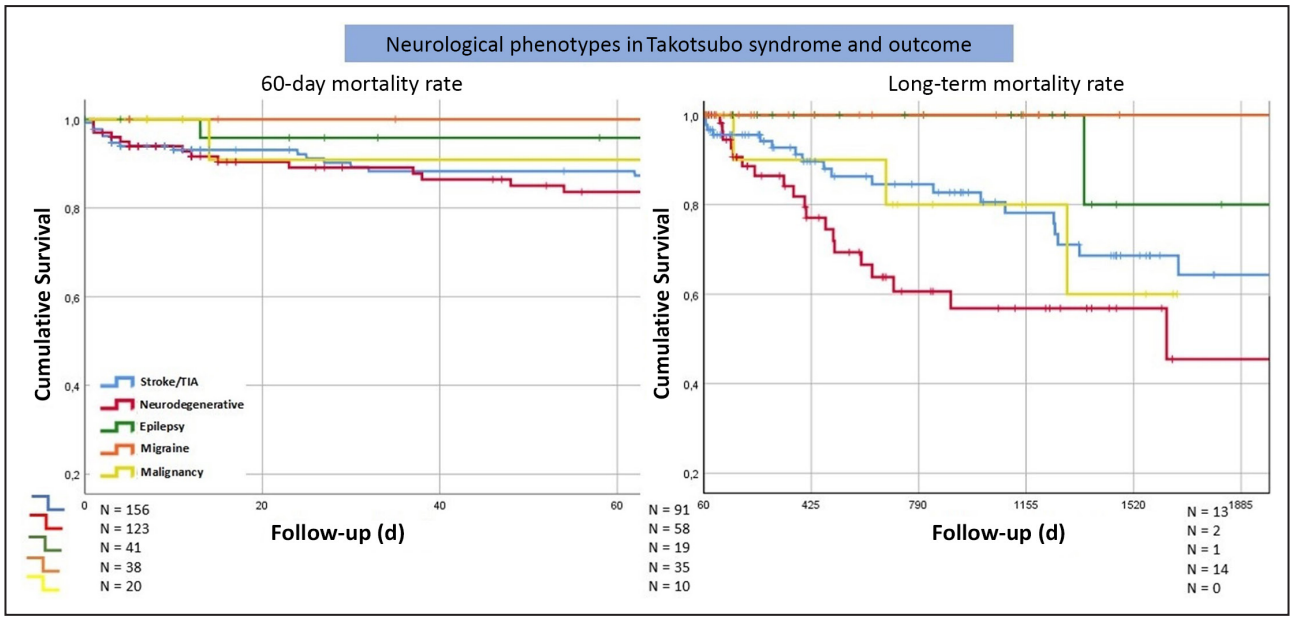


Figure 4. Kaplan–Meier curves for 60 days (left) and long-term (right) among the 5 subgroups of neurological disease.
TIA indicates transient ischemic attack.

Neurological disorders can be associated with structural cardiac changes and several clinical presentations from asymptomatic or mild to life-threatening injury.[19] Indeed, neurological injury and psychological stressors can also involve cardiac structure through development of subendocardial microinfarcts, early coronary calcification, and contraction bands (myocytolysis or myofibrillar degeneration).[20,21] These changes are mainly due to excessive exposure to catecholamines.[22] Myocytolysis can be mainly found around nerve endings with a prevalence of monocytic infiltration.[23]

It is already known that patients with TTS have some typical neurological features. Templin et al[24] evaluated 15 patients with TTS with functional brain magnetic resonance imaging and found that resting-state functional connectivity was reduced in the sympathetic, parasympathetic, and default networks in patients with TTS compared with healthy controls. Moreover, when they analyzed the whole-brain network, hypoconnectivity of the limbic system was found. However, Silva et al[25] reported that patients with TTS showed an increased connectivity in a brain network including the left amygdala and the right insula when stressed by local exposure to cold.

Current literature on neurological disorders and TTS is mainly focused on acute neurological triggers. In an international TTS registry, 161 (6.7%) of 2402 patients were admitted with an acute neurological trigger. Among these triggers, the most common were seizures, intracranial hemorrhage, and ischemic stroke. Patients with TTS with an acute neurological disorder had 3.2-fold increased odds of in-hospital death.[26] These findings were also confirmed on long-term prognosis, where patients with TTS due to acute neurological triggers had a 5.7-fold increased risk of death.[10] In the present study, 38 (9.5%) of 400 patients with neurological disorders had an acute neurological trigger.

History of neurological disorders has been described as a predictor of in-hospital complications among patients with TTS and included in a prediction risk score together with male sex, right ventricular involvement, and LVEF.[12] The present study shows that patients with neurological disorders also have a higher risk of short- and long-term outcome and should be considered as a high-risk TTS subset. Neurological disorders could be associated with worse outcome regardless of TTS episode; therefore, the present study aimed to evaluate potential neurological phenotypes in TTS and outcome.

Based on the most frequent comorbid neurological disorders and associated clinical characteristics in our sample, we identified 5 different phenotypes displaying some typical features. Patients with neurodegenerative conditions have the worst outcome, suggesting the need for a closer follow-up. In this context, catecholamines could act as free radical scavengers in neuronal tissue, and this could result in a systemic increased production.[27] Moreover, in this subset of patients, a dysfunction of the central autonomic network and cell loss in the dorsal motor nucleus of the vagus nerve and hypothalamus (in patients with Parkinson disease) have been reported.[28] The vagus nerve has several roles in the context of physiological homeostasis, including cardiac function regulation[29]; therefore, its dysregulation could be associated with a higher risk of cardiovascular disease.

Patients with history of CVEs may have central autonomic dysfunction due to several mechanisms, including activation of the hypothalamic–pituitary–adrenal axis, sympathetic and parasympathetic regulation, catecholamine surge, gut microbiome dysbiosis, immune responses, and inflammation that could act as a predisposing condition and associate with catecholamine storm.[30–32] Moreover, they have a higher rate of AF (19.5%) and in-hospital left ventricular thrombi (3.8%), suggesting that they could benefit from serial echocardiographic evaluation and prolonged electrocardiographic monitoring during hospitalization.[33–35]

Patients with brain tumors have an increased risk of in-hospital complications and may require a longer stay in the intensive care unit. Indeed, 40% of them experience cardiogenic shock or pulmonary edema. Patients with cancer and TTS are already a well-known high-risk population,[36] and this TTS subset requires a strict oncological and cardiological evaluation.

TTS in epilepsy is mainly associated with different kinds of seizures: tonic–clonic generalized seizures and status epilepticus.[37] Simple focal tonic–clonic seizures could be responsible for increased levels of catecholamines, although their concentrations decline within 30 minutes.[38] Moreover, during a generalized seizure, increases in plasma epinephrine concentration may, in some cases, be large enough to cause cardiac arrhythmias,[39] and it is imputed as a possible mechanism of sudden unexpected death in epilepsy.[40] Patients with epilepsy typically have acute neurological TTS triggers, a higher prevalence of male sex, and high rate of in-hospital complications (23.6%). Male sex in TTS is featured by higher short- and long-term mortality risk.[41] Therefore, this combination could require additional evaluation.

Additionally, patients with neurodegenerative diseases, history of CVEs, and epilepsy could receive antidepressant medication[42] that could increase the risk of sympathetic nerve dysfunction and consequently of CVEs.[43–45]

On the other side, patients with migraine were more often women with concomitant autoimmune disease and displayed a favorable short- and long term-outcome. Similar data on outcome of patients with migraine have recently been published from a large US

registry involving 172 025 patients with TTS.[46] Patients with migraine are known to have an autonomic dysfunction, mainly related to sympathetic impairment.[47] Additionally, these patients have more pronounced microvascular impairment, leading to a higher susceptibility to develop TTS even after small sympathetic activation.[48] Accordingly, they experience TTS mainly due to emotional stressors, an occurrence associated with lower catecholamine levels.[49]

Limitations of the Study

Although including one of the largest TTS populations, this is an observational study and therefore has some limitations, such as the absence of a control group and missing values that could potentially affect the results. The incidence of neurological disease among patients with TTS may be overestimated because the enrolling centers listed could have managed a higher number of complex patients. The enrolling centers used different assays to measure levels of cardiac biomarkers, and no statistical analyses were performed on it. The exact location of cerebrovascular infarction has not been systematically recorded in each center. The length of follow-up was different between patients and participating centers, and the long-term mortality rate was not stratified between cardiovascular versus noncardiovascular death.

CONCLUSIONS

Neurological disorders identify a high-risk TTS subgroup, with an increased short- and long-term risk of death. Careful evaluation of the precise underlying neurological phenotype could assist with an improved risk stratification.

ARTICLE INFORMATION

Received September 2, 2023; accepted December 21, 2023.

Affiliations

Department of Medical and Surgical Sciences, University of Foggia, Foggia, Italy (F.S., E.V., I.R., R.C., N.D.B.); Interventional; Cardiology, Cardiovascular Institute, Hospital Clínico Universitario San Carlos, Madrid, Spain (I.J.N.G., O.V.); Institute of Cardiology, Madre Giuseppina Vannini Hospital, Rome, Italy (L.A., L.C.); Department of Neuroscience, Neurology-Stroke Unit, University Hospital, Foggia, Italy (T.M.); Department of Cardiology, University of Mannheim, Mannheim, Germany (I.E., I.A.); DZHK (German Center for Cardiovascular Research), Partner Site Mannheim, Mannheim, Germany (I.E., I.A.); Department of Cardiology and Angiology, Bergmannsheil University Hospitals, Ruhr University of Bochum, Bochum, Germany (I.E.); Cardiology and Arrhythmology Clinic, Marche Polytechnic University, University Hospital "Umberto I – Lancisi – Salesi", Ancona, Italy (F.G.); Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties, Cardiology Unit, University of Palermo, University Hospital P, Palermo, Italy (G.N.); Division of Cardiology, University of Rome Tor Vergata, Rome, Italy (E.M.); Cardiology, Clinical and Molecular Medicine Department, Faculty of Medicine and Psychology, Sapienza University of Rome, Rome, Italy (B.M.); Department of Cardiology, San Paolo Hospital, Bari, Italy (P.C.); Clinical Cardiology, Department of Medical Science and Public Health, University of Cagliari, Cagliari, Italy (R.M.); Department of Cardiology, University Hospital Arnau de Vilanova, Lleida, Spain (E.B.); Department of Cardiology, Hospital de Orense, Orense, Spain (J.L.P.); Department of Cardiology University hospital, Salamanca, Spain (A.M.); Department of Cardiology, Hospital Son Espases, Palma de Mallorca, Islas Baleares, Spain (A.P.); Department of Cardiology, Hospital de La Princesa, Madrid, Spain (J.S.); Department of Cardiology, Bonomo Hospital, Andria, Italy (F.B.); Department of Internal Medicine/Cardiology, Heart Center Leipzig at University of Leipzig and Leipzig Heart Institute, Leipzig, Germany (H.T.); and University Heart Center Lübeck, Medical Clinic II (Cardiology/Angiology/Intensive Care Medicine) and German Center for Cardiovascular Research (DZHK), partner site Hamburg/Kiel/Lübeck, Lübeck, Germany (I.E., T.S.).

Sources of Funding

None.

Disclosures

None.

Supplemental Material

Table S1
Table S2
Table S3
Table S4
Table S5

REFERENCES

1. Dias A, Núñez Gil IJ, Santoro F, Madias JE, Pelliccia F, Brunetti ND, Salmoirago-Blotcher E, Sharkey SW, Eitel I, Akashi YJ, et al. Takotsubo syndrome: state-of-the-art review by an expert panel – part 1. *Cardiovasc Revasc Med*. 2019;20:70–79. doi: 10.1016/j.carrev.2018.11.015
2. Wittstein IS, Thiemann DR, Lima JA, Baughman KL, Schulman SP, Gerstenblith G, Wu KC, Rade JJ, Bivalacqua TJ, Champion HC. Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med*. 2005;352:539–548. doi: 10.1056/NEJMoa043046
3. Santoro F, Costantino MD, Guastafierro F, Triggiani G, Ferraretti A, Tarantino N, Saguner A, Di Biase M, Brunetti ND. Inflammatory patterns in Takotsubo cardiomyopathy and acute coronary syndrome: a propensity score matched analysis. *Atherosclerosis*. 2018;274:157–161. doi: 10.1016/j.atherosclerosis.2018.05.017
4. Tarantino N, Santoro F, Di Biase L, Di Terlizzi V, Vitale E, Barone R, Della Rocca DG, De Leon De La Cruz NS, Di Biase M, Brunetti ND. Chromogranin-a serum levels in patients with takotsubo syndrome and ST elevation acute myocardial infarction. *Int J Cardiol*. 2020;320:12–17. doi: 10.1016/j.ijcard.2020.07.040
5. Ieva R, Santoro F, Ferraretti A, Spennati G, De Gennaro L, Di Biase M, Brunetti ND. Hyper-acute precipitating mechanism of Tako-Tsubo cardiomyopathy: in the beginning was basal hyperkinesis? *Int J Cardiol*. 2013;167:e55–e57. doi: 10.1016/j.ijcard.2013.03.138
6. Stiermaier T, Moeller C, Oehler K, Desch S, Graf T, Eitel C, Vonthein R, Schuler G, Thiele H, Eitel I. Long-term excess mortality in takotsubo cardiomyopathy: predictors, causes and clinical consequences. *Eur J Heart Fail*. 2016;18:650–656. doi: 10.1002/ejhf.494
7. Santoro F, Ferraretti A, Ieva R, Musaico F, Fanelli M, Tarantino N, Scarcia M, Caldarola P, Di Biase M, Brunetti ND. Renal impairment and outcome in patients with takotsubo cardiomyopathy. *Am J Emerg Med*. 2016;34:548–552. doi: 10.1016/j.ajem.2015.12.065
8. Looi JL, Verryt T, McLeod P, Chan C, Pemberton J, Webster M, To A, Lee M, Kerr AJ. Type of stressor and medium-term outcomes after Takotsubo syndrome: what becomes of the broken hearted? (ANZACS-QI 59). *Heart Lung Circ*. 2022;31:499–507. doi: 10.1016/j.hlc.2021.09.021
9. Santoro F, Carapelle E, Cieza Ortiz SI, Musaico F, Ferraretti A, d'Orsi G, Specchio LM, Di Biase M, Brunetti ND. Potential links between neurological disease and Tako-Tsubo cardiomyopathy: a literature review. *Int J Cardiol*. 2013;168:688–691. doi: 10.1016/j.ijcard.2013.03.093
10. Ghadri JR, Kato K, Cammann VL, Gili S, Jurisic S, Di Vece D, Candreva A, Ding KJ, Micek J, Szawan KA, et al. Long-term prognosis of patients with Takotsubo syndrome. *J Am Coll Cardiol*. 2018;72:874–882. doi: 10.1016/j.jacc.2018.06.016
11. Morris NA, Chatterjee A, Adejumo OL, Chen M, Merkler AE, Murthy SB, Kamel H. The risk of Takotsubo cardiomyopathy in acute

neurological disease. *Neurocrit Care*. 2019;30:171–176. doi: 10.1007/s12028-018-0591-z
12. Santoro F, Núñez Gil IJ, Stiermaier T, El-Battrawy I, Guerra F, Novo G, Guastafierro F, Tarantino N, Novo S, Mariano E, et al. Assessment of the German and Italian stress cardiomyopathy score for risk stratification for in-hospital complications in patients with Takotsubo syndrome. *JAMA Cardiol*. 2019;4:892–899. doi: 10.1001/jamacardio.2019.2597
13. Lyon AR, Bossone E, Schneider B, Sechtem U, Citro R, Underwood SR, Sheppard MN, Figtree GA, Parodi G, Akashi YJ, et al. Current state of knowledge on Takotsubo syndrome: a position statement from the taskforce on Takotsubo syndrome of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2016;18:8–27. doi: 10.1002/ejhf.424
14. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39:119–177. doi: 10.1093/eurheartj/ehx393
15. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, et al. ESC scientific document group. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2021;42:1289–1367. doi: 10.1093/eurheartj/ehaa575
16. Uribarri A, Núñez-Gil IJ, Conty DA, Vedia O, Almendro-Delia M, Duran Cambra A, Martin-Garcia AC, Barrionuevo-Sánchez M, Martínez-Sellés M, Raposeiras-Roubín S, et al. Short- and long-term prognosis of patients with Takotsubo syndrome based on different triggers: importance of the physical nature. *J Am Heart Assoc*. 2019;8:e013701. doi: 10.1161/JAHA.119.013701
17. Templin C, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M, Cammann VL, Sarcon A, Geyer V, Neumann CA, et al. Clinical features and outcomes of Takotsubo (stress) cardiomyopathy. *N Engl J Med*. 2015;373:929–938. doi: 10.1056/NEJMoa1406761
18. El-Battrawy I, Santoro F, Stiermaier T, Möller C, Guastafierro F, Novo G, Novo S, Mariano E, Romeo F, et al. Incidence and clinical impact of right ventricular involvement (biventricular ballooning) in Takotsubo syndrome: results from the GEIST registry. *Chest*. 2021;160:1433–1441. doi: 10.1016/j.chest.2021.04.072
19. Tahsili-Fahadan P, Geocadin RG. Heart-brain Axis: effects of neurologic injury on cardiovascular function. *Circ Res*. 2017;120:559–572. doi: 10.1161/CIRCRESAHA.116.308446
20. Oppenheimer SM, Hachinski VC. The cardiac consequences of stroke. *Neurol Clin*. 1992;10:167–176. doi: 10.1016/S0733-8619(18)30239-1
21. Van der Bilt IA, Vendeville JP, van de Hoef TP, Begieneman MP, Lagrand WK, Kros JM, Wilde AA, Rinkel GJ, Niessen HW. Myocarditis in patients with subarachnoid hemorrhage: a histopathologic study. *J Crit Care*. 2016;32:196–200. doi: 10.1016/j.jcrc.2015.12.005
22. Jacob WA, Van Bogaert A, De Groodt-Lasseel MH. Myocardial ultrastructure and haemodynamic reactions during experimental subarachnoid haemorrhage. *J Mol Cell Cardiol*. 1972;4:287–298. doi: 10.1016/0022-2828(72)90076-4
23. Rona G. Catecholamine cardiotoxicity. *J Mol Cell Cardiol*. 1985;17:291–306. doi: 10.1016/S0022-2828(85)80130-9
24. Templin C, Hänggi J, Klein C, Topka MS, Hiestand T, Levinson RA, Jurisic S, Lüscher TF, Ghadri JR, Jäncke L. Altered limbic and autonomic processing supports brain-heart axis in Takotsubo syndrome. *Eur Heart J*. 2019;40:1183–1187. doi: 10.1093/eurheartj/ehz068
25. Silva AR, Magalhães R, Arantes C, Moreira PS, Rodrigues M, Marques P, Marques J, Sousa N, Pereira VH. Brain functional connectivity is altered in patients with Takotsubo syndrome. *Sci Rep*. 2019;9:4187. doi: 10.1038/s41598-019-40695-3
26. Cammann VL, Scheitz JF, von Rennenberg R, Jäncke L, Nolte CH, Szawan KA, Stengl H, Würdinger M, Endres M, Templin C, et al. Clinical correlates and prognostic impact of neurologic disorders in Takotsubo syndrome. *Sci Rep*. 2021;11:23555. doi: 10.1038/s41598-021-01496-9
27. Jodko K, Litwinienko G. Oxidative stress in the neurodegenerative disease potential antioxidant activity of catecholamines. *Postepy Biochem*. 2010;56:248–259.
28. Chaudhuri KR, Schapira AH. Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. *Lancet Neurol*. 2009;8:464–474. doi: 10.1016/S1474-4422(09)70068-7
29. Capilupi MJ, Kerath SM, Becker LB. Vagus nerve stimulation and the cardiovascular system. *Cold Spring Harb Perspect Med*. 2020;10:a034173. doi: 10.1101/cshperspect.a034173
30. Kato Y, Takeda H, Furuya D, Deguchi I, Tanahashi N. Takotsubo cardiomyopathy and cerebral infarction. *Rinsho Shinkeigaku*. 2009;49:158–166. doi: 10.5692/clinicalneurol.49.158
31. Sander D, Winbeck K, Klingelhöfer J, Etgen T, Conrad B. Prognostic relevance of pathological sympathetic activation after acute thromboembolic stroke. *Neurology*. 2001;57:833–838. doi: 10.1212/WNL.57.5.833
32. Ozdemir O, Hachinski V. Brain lateralization and sudden death: its role in the neurogenic heart syndrome. *J Neurol Sci*. 2008;268:6–11. doi: 10.1016/j.jns.2007.11.009
33. Stiermaier T, Santoro F, Eitel C, Graf T, Möller C, Tarantino N, Guastafierro F, Di Biase M, Thiele H, Brunetti ND, et al. Prevalence and prognostic relevance of atrial fibrillation in patients with Takotsubo syndrome. *Int J Cardiol*. 2017;245:156–161. doi: 10.1016/j.ijcard.2017.07.053
34. Santoro F, Stiermaier T, Tarantino N, De Gennaro L, Moeller C, Guastafierro F, Marchetti MF, Montisci R, Carapelle E, Graf T, et al. Left ventricular thrombi in Takotsubo syndrome: incidence, predictors, and management: results from the GEIST (German Italian stress cardiomyopathy) registry. *J Am Heart Assoc*. 2017;6:e006990. doi: 10.1161/JAHA.117.006990
35. Santoro F, Stiermaier T, Tarantino N, Guastafierro F, Graf T, Möller C, Di Martino LFM, Thiele H, Di Biase M, Eitel I, et al. Impact of persistent ST elevation on outcome in patients with Takotsubo syndrome. Results from the GErman Italian STress cardiomyopathy (GEIST) registry. *Int J Cardiol*. 2018;255:140–144. doi: 10.1016/j.ijcard.2017.11.068
36. Brunetti ND, Tarantino N, Guastafierro F, De Gennaro L, Correale M, Stiermaier T, Möller C, Di Biase M, Eitel I, Santoro F. Malignancies and outcome in Takotsubo syndrome: a meta-analysis study on cancer and stress cardiomyopathy. *Heart Fail Rev*. 2019;24:481–488. doi: 10.1007/s10741-019-09773-6
37. Stöllberger C, Wegner C, Finsterer J. Seizure-associated Takotsubo cardiomyopathy. *Epilepsia*. 2011;52:e160–e167. doi: 10.1111/j.1528-1167.2011.03185.x
38. Simon RP, Aminoff MJ, Benowitz NL. Changes in plasma catecholamines after tonic–clonic seizures. *Neurology*. 1984;34:255–257. doi: 10.1212/WNL.34.2.255
39. Nei M, Sperling MR, Mintzer S, Ho RT. Long-term cardiac rhythm and repolarization abnormalities in refractory focal and generalized epilepsy. *Epilepsia*. 2012;53:e137–e140. doi: 10.1111/j.1528-1167.2012.03561.x
40. Surges R, Thijs RD, Tan HL, Sander JW. Sudden unexpected death in epilepsy: risk factors and potential pathomechanisms. *Nat Rev Neurol*. 2009;5:492–504. doi: 10.1038/nrneurol.2009.118
41. Arcari L, Núñez Gil IJ, Stiermaier T, El-Battrawy I, Guerra F, Novo G, Musumeci B, Cacciotti L, Mariano E, Caldarola P, et al. Gender differences in Takotsubo syndrome. *J Am Coll Cardiol*. 2022;79:2085–2093. doi: 10.1016/j.jacc.2022.03.366
42. Marsh L. Depression and Parkinson's disease: current knowledge. *Curr Neurol Neurosci Rep*. 2013;13:409. doi: 10.1007/s11910-013-0409-5
43. Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146 538 participants in 54 observational studies. *Eur Heart J*. 2006;27:2763–2774. doi: 10.1093/eurheartj/ehl338
44. Dong JY, Zhang YH, Tong J, Qin LQ. Depression and risk of stroke: a meta-analysis of prospective studies. *Stroke*. 2012;43:32–37. doi: 10.1161/STROKEAHA.111.630871
45. Barton DA, Dawood T, Lambert EA, Esler MD, Haikerwal D, Brenchley C, Socratous F, Kaye DM, Schlaich MP, Hickie I, et al. Sympathetic activity in major depressive disorder: identifying those at increased cardiac risk? *J Hypertens*. 2007;25:2117–2124. doi: 10.1097/HJH.0b013e32829baae7
46. Varghese JJ, Yacob O, Frances BS, Garcia-Garcia HM. Impact of migraine headaches on stress-induced 'Takotsubo' cardiomyopathy. *Cardiovasc Revasc Med*. 2022;40:78–81. doi: 10.1016/j.carrev.2022.03.005
47. Miglis MG. Migraine and autonomic dysfunction: which is the horse and which is the jockey? *Curr Pain Headache Rep*. 2018;22:19. doi: 10.1007/s11916-018-0671-y
48. Wittstein IS. Why sex matters in Takotsubo syndrome. *J Am Coll Cardiol*. 2022;79:2094–2096. doi: 10.1016/j.jacc.2022.04.005
49. Sobue Y, Watanabe E, Ichikawa T, Koshikawa M, Yamamoto M, Harada M, Ozaki Y. Physically triggered Takotsubo cardiomyopathy has a higher in-hospital mortality rate. *Int J Cardiol*. 2017;235:87–93. doi: 10.1016/j.ijcard.2017.02.090