

ORIGINAL ARTICLE

The Clinical Course of Takotsubo Syndrome Diagnosed According to the InterTAK Criteria

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Abstract

Background: There has been an increase in the number of cases of Takotsubo syndrome (TTS) and of scientific publications on the theme over the last years. However, little is known about the status of this disease in Brazilian hospitals.

Objective: To assess mortality and major adverse cardiovascular events (MACE) during hospitalization and follow-up of TTS patients seen in a tertiary hospital in Brazil.

Methods: This was a retrospective, observational study on 48 patients. Clinical data, signs and symptoms, complementary tests, MACE and all-cause mortality were assessed on admission and during follow-up. Kaplan-Meier curves were used for analysis of all-cause mortality and risk for MACE at median follow-up. The 95% confidence interval was also calculated for a significance level of 5%.

Results: Mean age of patients was 71 years (SD±13 years), and most patients were women (n=41; 85.4%). During hospitalization, four patients (8.3%) died and five (10.4%) developed MACE. At median follow-up of 354.5 days (IQR of 81.5-896.5 days), the risk of all-cause mortality and MACE was 11.1% (95% CI= 1.8-20.3%) and 12.7% (95% CI= 3.3-22.3%), respectively.

Conclusion: TTS was associated with high morbidity and mortality rates in a tertiary hospital in Brazil, which were comparable to those observed in acute coronary syndrome. Therefore, the severity of TTS should not be underestimated, and new therapeutic strategies are required. (Int J Cardiovasc Sci. 2020; 33(6):637-647)

Keywords: Acute Coronary Syndrome; Takotsubo Cardiomyopathy; Heart Failure; Shock, Cardiogenic; Ventricular Dysfunction.

Introduction

The term “Takotsubo syndrome” (TTS) emerged in the medical literature in the 1990s, in a Japanese book of medicine, to describe a syndrome of symptoms and electrocardiographic changes suggestive of acute myocardial infarction (AMI), but coronary arteries without significant obstructive lesions.^{1,2} The name “takotsubo” comes from the similarity between the cardiac ventriculography in these patients and an old octopus trap used in Japan (in Japanese, “tako” means octopus and “tsubo” means pot/vase).^{1,3}

The pathophysiology of TTS is essentially related to an exacerbated activation of sympathetic autonomic nervous system. However, the mechanism by which catecholamine excess triggers myocardial stunning, with a variety of motion segment dysfunction patterns that characterize this syndrome (dysfunctional apical mid-ventricular, basal or focal segments) is unknown.¹

Despite the significant increase in the number of patients diagnosed with TTS,⁴ and publication of international studies on the theme over the last years,⁵ little is known about current reality of the disease in Brazil.

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The aim of this registry was to assess mortality and major adverse cardiac events (MACE) – composed of stroke/transient ischemic accident (TIA), myocardial revascularization and cardiac mortality – in-hospital and during follow-up, in patients diagnosed with TTS according to InterTAK diagnostic criteria.

Methods

Since the first description of TTS, no widely accepted criteria for the diagnosis of TTS have been established. The most used criteria are the Mayo Clinic criteria, modified in 2008.⁶ According to these criteria, although the presence of

coronary obstructive lesion does not rule out the diagnosis of TTS, this information is not clearly defined and described as very rare.⁷ However, other publications have evidenced that up to 10-29% of the patients diagnosed with TTS have concomitant obstructive coronary disease.⁸⁻¹⁰ Therefore, in attempt to define a new consensus and based on the last available data, a new set of diagnostic criteria (InterTAK criteria) was proposed by experts in TTS in 2018 (Figure 1).¹

Study Population

This was a retrospective observational study, approved by the institutional ethics committee

International Takotsubo Diagnostic Criteria (InterTAK Diagnostic Criteria)

1. Patients with transient^a left ventricular dysfunction (hypokinesia, akinesia, or dyskinesia) presenting as apical ballooning or other left ventricular segmental (midventricular, basal, or focal) wall motion abnormalities. Right ventricular involvement can be present. Besides these regional wall motion patterns, transitions between all types can exist. The regional wall motion abnormality usually extends beyond a single epicardial vascular distribution; however, rare cases can exist where the regional wall motion abnormality is present in the subtended myocardial territory of a single coronary artery (focal TTS).^b
2. An emotional, physical, or combined trigger can precede the Takotsubo syndrome event, but this is not obligatory.
3. Neurologic disorders (e.g. subarachnoid haemorrhage, stroke/transient ischaemic attack, or seizures) as well as pheochromocytoma may serve as triggers for takotsubo syndrome.
4. New ECG abnormalities are present (ST-segment elevation, ST-segment depression, T-wave inversion, and QTc prolongation); however, rare cases exist without any ECG changes.
5. Levels of cardiac biomarkers (troponin and creatine kinase) are moderately elevated in most cases; significant elevation of brain natriuretic peptide is common.
6. Significant coronary artery disease is not a contradiction in takotsubo syndrome.
7. Patients have no evidence of infectious myocarditis.^b
8. Postmenopausal women are predominantly affected.

^a Ventricular contraction abnormalities may remain for a prolonged period of time or documentation of recovery may not be possible. For example, death before evidence of recovery is captured.

^b Cardiac magnetic resonance imaging is recommended to exclude infectious myocarditis and diagnosis confirmation of Takotsubo syndrome.¹

Figure 1 – InterTAK diagnostic criteria

(approval number 3.279.964), conducted following best practices in research.

Electronic data of hospital admissions occurring between January 01, 2013 and December 31, 2018 (six year-period; 75,284 admissions) in the Heart Institute of the University of Sao Paulo (InCor – HCFMUSP) were analyzed. The following terms were searched in the electronic charts: “Takotsubo syndrome”, “Takotsubo cardiomyopathy”, “Broken Heart Syndrome”, “Stress-Induced Cardiomyopathy” and “Adrenergic Cardiomyopathy”.

One hundred and one patients older than 18 years of age were found in the search. Based on the InterTAK diagnostic criteria, TTS was excluded in 53 individuals, and 48 patients were included in the study. Forty-four patients met all diagnostic criteria (including one patient who developed TTS in the postoperative period of cardiac surgery), and four patients, despite fulfilling all the interTAK criteria in the postoperative of cardiac surgery, did not have an anatomical study of coronary artery for the event (all patients underwent preoperative cineangiography, with no evidence of coronary lesions) (Figure 2).

The InterTAK criteria, similar to previous diagnostic criteria for TTS, do not mention the occurrence of the syndrome in the postoperative period of cardiac surgery,¹¹ *i.e.*, do not confirm or exclude the diagnosis of TTS such case. However, due to the increasing number of TTS following cardiac surgery reported in the literature,¹²⁻¹⁵ we decided to include these patients in the analysis.

Data Collection and Variables Analyzed

Data collection was made by review of electronic medical records of the 48 patients selected. When follow-up data after discharge were not available, patients were contacted by telephone to obtain information about new MACE and mortality.

At admission and during hospitalization, information on previous clinical data, signs and symptoms, complementary tests, MACE, all-cause mortality, length of hospital stay, signs of heart failure, signs of renal failure and new arrhythmias was assessed. In the out-of-hospital follow-up, data on MACE, overall mortality and left ventricular

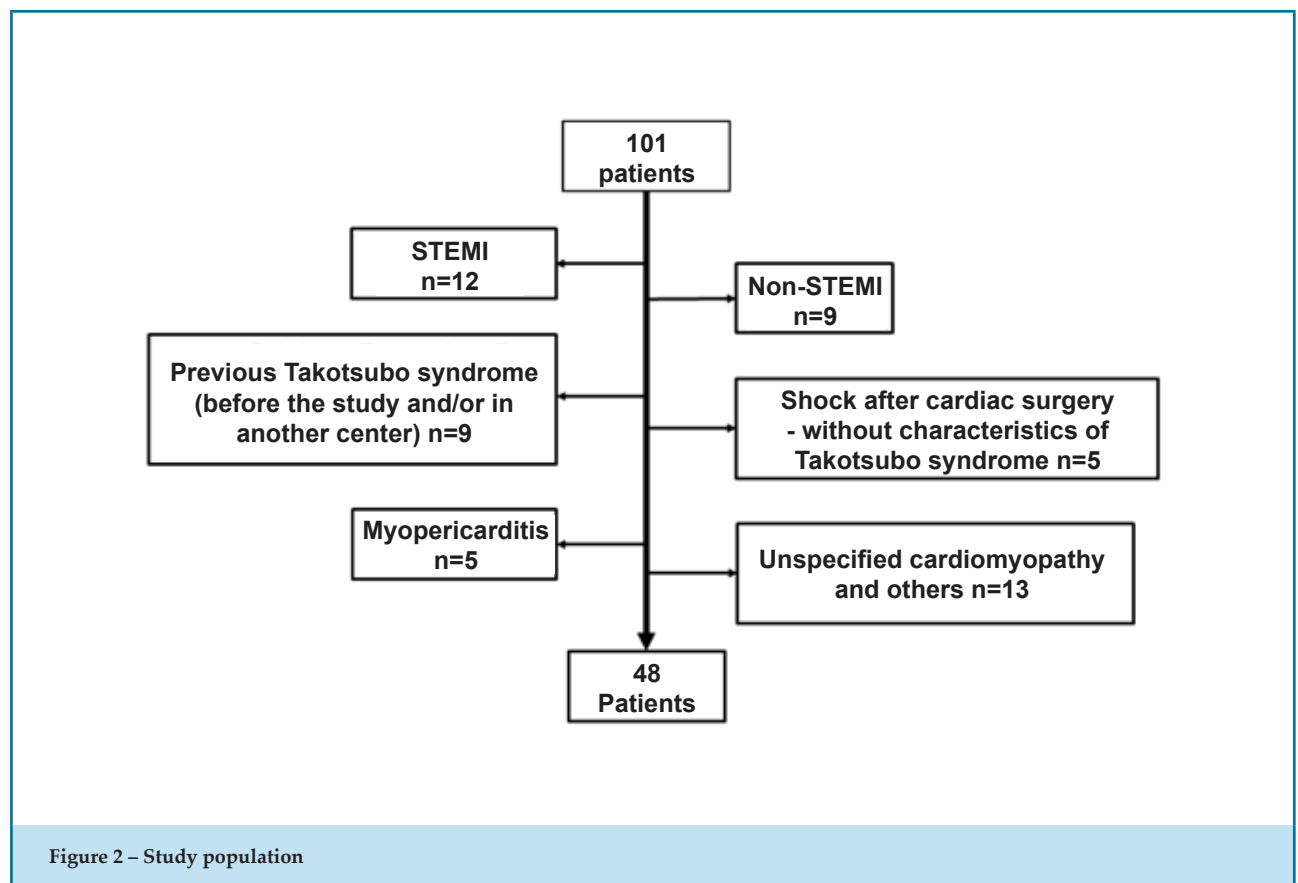


Figure 2 – Study population

ejection fraction values, determined by transthoracic echocardiography, were assessed.

Racial group classifications (white, black or “pardo”) were collected from electronic medical records, which are usually filled with self-declared race.

The diagnosis of acute renal failure (ARF) was made based on the ‘injury’ definition of RIFLE criteria¹⁶, which consider a two-fold increase of serum creatinine from baseline or a decrease of at least 50% in estimated glomerular filtration rate. RIFLE criteria define at least three grades of severity of ARF – ‘risk’, ‘injury’ and ‘failure’ – we adopted the ‘injury’ definition criteria for a balance between sensitivity and specificity for diagnosis of ARF.

Statistical Analysis

All variables were tested for normality using the Shapiro-Francia test. For continuous variables with normal distribution, mean and standard deviation were calculated, and for variables without a normal distribution, median and interquartile range (IQR) were determined. Categorical variables were expressed as absolute numbers and percentages of total population. Data analysis was performed using the IBM SPSS Statistics software package, version 25.0. The Kaplan-Meier survival curves were analyzed using MEDCALC®, version 19.

Kaplan-Meier survival curves were used to estimate the risk of all-cause mortality, and the risk of MACE was defined in the median follow-up time. A 95% confidence interval (95% CI) was calculated with a significance level of 5%.

Results

Table 1 describes the clinical features of patients at admission. Most patients were women (85.4%); 70.8% had systemic arterial hypertension and 14.6% were diabetic.

Most of the cases (75%) manifested with chest pain on presentation, mainly chest pain with anginal characteristics - 47.9% of the study population (Table 2). Regarding the triggering factor, there is a preponderance of physical causes (such as bronchospasm, neoplasia under treatment, surgeries and other concomitant diseases), corresponding to 47.9% of individuals included in the registry.

Regarding complementary tests (Table 2), what draws attention is that almost all patients (97.9%) had

Table 1 – Previous clinical characteristics

Age, years (mean ± SD)	71 ± 13
Sex, n (%)	
Male	7 (14.6)
Female	41 (85.4)
Race, n (%)	
White	35 (72.9)
Black	3 (6.3)
Pardo	10 (20.8)
Systemic arterial hypertension, n (%)	34 (70.8)
Dyslipidemia, n (%)	16 (33.3)
Diabetes, n (%)	7 (14.6)
Smoking, n (%)	
No	33 (68.8)
Yes	10 (20.8)
Ex-smoker	5 (10.4)
Previous atrial fibrillation, n (%)	4 (8.3)
Valvular disease, n (%)	8 (16.7)
Rheumatologic/Autoimmune disease, n (%)	9 (18.8)
Oncologic disease, n (%)	6 (12.5)
Previous stroke, n (%)	2 (4.2)
Previous CAD, n (%)	7 (14.6)
Previous heart failure, n (%)	8 (16.7)
Chronic kidney disease, n (%)	7 (14.6)
Previous pulmonary disease, n (%)	10 (20.8)
Family history of early CAD, n (%)	6 (12.5)
Total, n (%)	48 (100)
<i>CAD: coronary artery disease</i>	

electrocardiographic changes, mainly T-wave inversion (47.9% of the cases). Cineangiography was available during the TTS event for most patients (91.7%), except for four patients (8.3%) who underwent valve replacement surgery and had undergone the test prior to the surgery, and had no evidence of coronary obstructive lesions. In most of TTS patients, there was involvement of the left ventricular apex (87.5%), which is in agreement with the typical presentation of the disease, where apical dysfunction is predominant.

In addition, 10.4% of patients had left ventricular outflow tract obstruction, which increases the severity of the disease due to the increase in the incidence of hypotension and cardiogenic shock.^{17,18}

Table 2 – Clinical presentation and complementary tests

Clinical manifestations	
Chest pain, n (%)	36 (75)
Atypical pain	23 (47.9)
Typical pain	13 (27.1)
Dyspnea, n (%)	10 (20.8)
Syncope, n (%)	2 (4.2)
Triggering factors, n (%)	
Physical triggers	23 (47.9)
Psychological triggers	15 (31.3)
Not reported	10 (20.8)
Heart rate, Mean ± SD	82.16±17.7
Systolic blood pressure, median (IQR)	121.5 (110-139.2)
Complementary tests	
Electrocardiographic changes, n (%)	
ST-elevation	18 (37.5)
Anterior wall	13 (27.1)
Lateral wall	9 (18.8)
Inferior wall	4 (8.3)
ST-depression	4 (8.3)
T-wave inversion	23 (47.9)
Nonspecific changes	5 (10.4)
Normal	1 (2.1)
Cineangiography during the event, n (%)	44 (91.7)
Coronary obstructive lesion ≥ 50%	13 (27)
Type of Takotsubo cardiomyopathy, n (%)	
Apical	42 (87.5)
Mid-ventricular	2 (4.2)
Basal	0
Focal	4 (8.3)
Echocardiography during the event, n (%)	41 (85.4)
LVEF (%), mean ± SD	42.73±9.3
Left atrial diameter (mm), mean ± SD	37.5±5.2
LV diastolic diameter (mm), mean ± SD	47.4±4.3
Left ventricular systolic diameter (mm), mean ± SD	32.1±4.8
Pericardial effusion, n (%)	4 (8.3)
Moderate/severe mitral insufficiency, n (%)	5 (10.4)
LV outflow tract obstruction, n (%)	5 (10.4)
Cardiac nuclear magnetic resonance, n (%)	18 (37.5)
Involvement of the right ventricle at Echo or NMRi, n (%)	2 (4.2)
LV thrombus on Echo or NMRi, n (%)	0
High-sensitivity troponin I* (ng/mL), Median (IQR)	
Baseline	3.41 (1.90-5.78)
Peak	5.38 (3.45-17.44)
CK-MB Mass† (ng/mL), Median (IQR)	
Baseline	11.3 (6.03-20.05)
Peak	16.6 (12.6-26.85)
BNP‡ (pg/mL), Median (IQR)	1788 (501.5-2478.5)
Creatinine (mg/dL), Median (IQR)	
Baseline	0.98 (0.77-1.37)
Peak	1.27 (0.89-2.26)

Reference values: *Troponin I ≤ 0.04 ng/mL / †CK-MB Mass ≤ 4.4 ng/mL / ‡BNP < 100 pg/mL. BNP levels were available for 13 (27%) of the 48 patients included in the study. BNP: brain natriuretic peptide; CKMB: creatine phosphokinase-MB; SD: standard deviation; LVEF: left ventricular ejection fraction; Echo: echocardiogram; IQR: interquartile range; NMRi: nuclear magnetic resonance imaging; LV: left ventricular

Left Ventricular Function

Figure 3A shows left ventricular circumferential dysfunction, and Figure 3B displays a comparative analysis between left ventricular function on admission and on echocardiographic follow-up (in-hospital or out-of-hospital) (n=30). Almost all patients (96.6%) showed recovery of the LVEF, which makes clear the temporary nature of ventricular dysfunction. In this analysis, only one patient did not show improvement of LVEF, which may be explained by the short time from diagnosis to transthoracic echocardiography (four days), *i.e.*, probably, there was not enough time for recovery of the left ventricular function. This patient progressed to death.

Clinical Course

In-hospital outcomes and medications are described in Table 3. A significant proportion of patients (41.7%) developed heart failure during hospitalization, which is the main complication of TTS.¹⁹ High in-hospital mortality (8.3%) and MACE rates (10.4%) were also observed.

Median follow-up was 354.5 days (IQR = 81.5 – 896.5 days), with an all-cause mortality of 11.1% (95% CI: 1.8-20.3%), and prevalence of MACE of 12.7% (95%

CI> 3.3-22.3%) (Figure 4). Interestingly, all MACE occurred during the first three months of follow-up after the diagnosis.

Discussion

The main findings of this study were: (1) the use of the InterTAK diagnostic criteria helped in the establishment of the correct diagnosis of TTC in 47.5% of the 101 patients enrolled in the study; (2) there is a considerable number of TTS patients with concomitant coronary artery disease (CAD); (3) a normalization of ventricular function was detected by echocardiographic follow-up in almost all patients; and (4) there was a high prevalence of clinical events in short-term follow-up.

With respect to diagnosis, the TTS diagnosis was initially considered for 101 patients and, after application of the InterTAK criteria, the diagnosis was confirmed in 48 patients (47.5%). This finding reinforces that a correct diagnosis of STT is not easy and requires a systematic approach to the diagnostic criteria, which have evolved over the years.

Some years ago, little attention was paid to the possibility of a TTS patient having important coronary

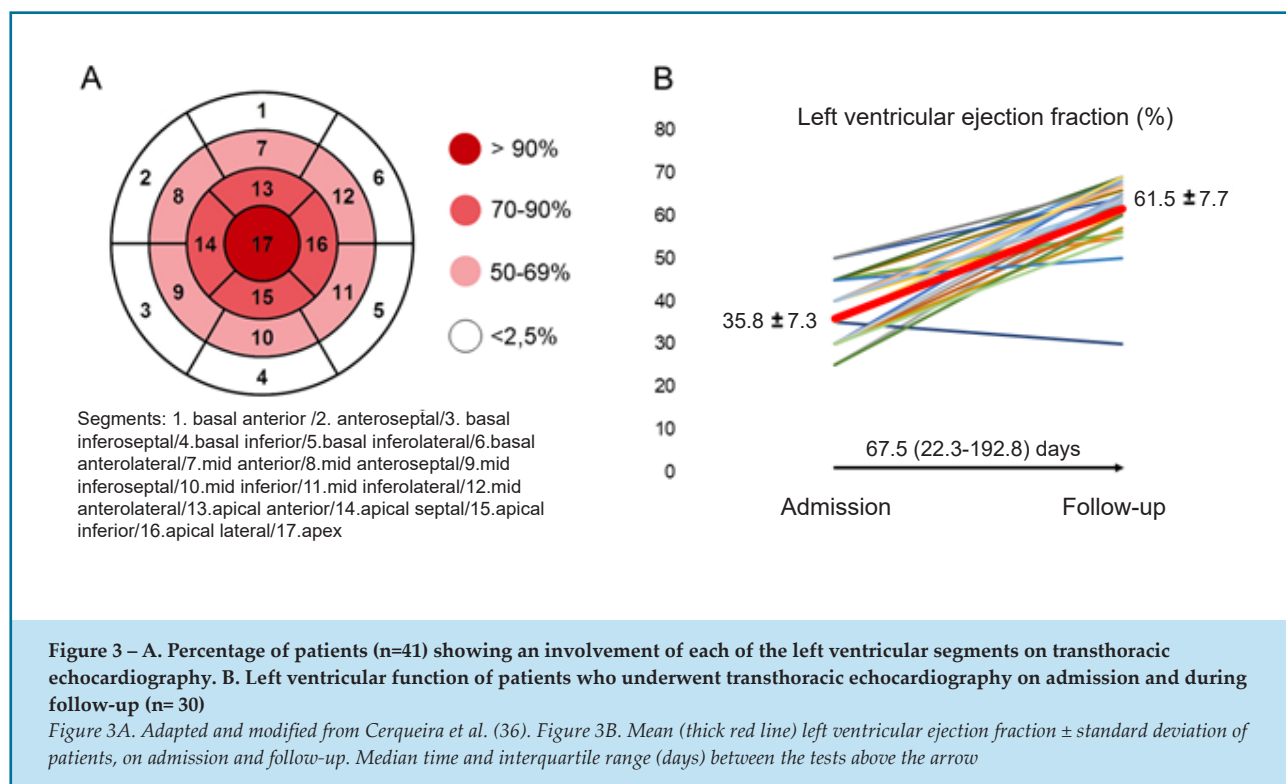


Table 3 - Hospitalization data and medications

Length of hospital stay, days, median (IQR)	5.5 (3.0-12.0)
Acute renal failure, n (%)	11 (22.9)
Acute decompensation of CKD, n (%)	3 (6.3)
All-cause in-hospital mortality, n (%)	4 (8.3)
In-hospital MACE, n (%)	5 (10.4)
Cardiac mortality, n (%)	1 (2.1)
AMI, n (%)	0
Revascularization, n (%)	2 (4.2)
TIA/stroke, n (%)	2 (4.2)
Non-cardiac mortality, n (%)	3 (6.3)
Mechanical ventilation requirement, n (%)	6 (12.5)
Heart failure, n (%)	20 (41.7)
Killip classification, n (%)	
1	28 (58.3)
2	6 (12.5)
3	4 (8.3)
4	10 (20.8)
New arrhythmia, n (%)	8 (16.7)
VF/TV, n (%)	2 (4.2)
Atrial fibrillation, n (%)	3 (6.3)
Medications administered	
Acetylsalicylic acid, n (%)	22 (45.8)
Clopidogrel, n (%)	10 (20.8)
Beta blocker, n (%)	28 (58.3)
Statin, n (%)	31 (64.6)
ACEI, n (%)	30 (62.5)
ARBs, n (%)	3 (6.3)
Spirinolactone, n (%)	14 (29.2)

CKD: chronic kidney disease; MACE: major adverse cardiac events
AMI: acute myocardial infarction; TIA: transient ischemic accident
(TIA), VF: ventricular fibrillation; AF: atrial fibrillation; ACEI:
angiotensin converting enzyme inhibitors; ARBs: angiotensin receptor
blockers; IQR: interquartile range

obstructive disease, which has been corrected by the new criteria proposed (Figure 1). Usually, the association between TTS and CAD is not a cause-effect relationship. Despite the rare cases of TTS patients in whom acute coronary syndrome was the cause of TTS,²⁰⁻²² it is believed that, in most cases, the coronary obstructive lesions found in TTS patients are complementary test findings, since the main

population affected by the syndrome (postmenopausal women) is also a group with a significant prevalence of CAD.²³ In the present study, in line with the complementary tests' results (Table 2), there was a significant prevalence of patients (27% of the study population) with coronary obstructive lesion $\geq 50\%$ of vessel lumen diameter. This is in agreement with more recent literature data, showing a prevalence of 10-29% of TTS patients with concomitant obstructive coronary disease⁸⁻¹⁰

Another important issue is the development of electrocardiographic abnormalities, circumferential dysfunction of ventricular contraction at transthoracic echocardiography, and clinical signs/symptoms (precordial pain and/or hypotension/circulatory shock) in the immediate post-operative period after cardiac surgery. These are possible manifestations of TTS, probably caused by extracorporeal circulation and surgical trauma. In the present study, these patients represented 10.4% of the cases. For the next diagnostic criteria updates, the inclusion of cardiac surgery as trigger for TTS should be considered.

The transient character of left ventricular dysfunction in TTS patients has been consolidated in previous studies and is one of the disease characteristics included in the diagnostic criteria for TTS.^{1,6,24-26} This feature was corroborated by our findings of the analysis of ventricular function (Figure 3 B), which supports the correct diagnosis of TTS in our study group.

Regarding morbidity and mortality of TTS, the mortality rate in previous series was lower – in-hospital mortality of 1-2%,²⁷⁻²⁸ – which generated an erroneous idea of the benign character of the disease. More recent studies, including a greater number of patients and longer follow-up, have shown much higher mortality rates (in-hospital mortality 4-5%), compatible with the mortality rate of acute coronary syndrome treated according to current recommendations.^{8, 29-32}

The largest registry of TTS available, including 1,750 patients, reported an in-hospital mortality rate of 4.1% and overall mortality of up to 5.6% per patient/year and MACE of 9.9% during follow-up.⁸ Similar mortality and MACE rates were found in our study, reinforcing the severity of the disease.

Another finding that deserves attention is the fact that the events occurred within three months after the diagnosis of TTS. Since ventricular dysfunction

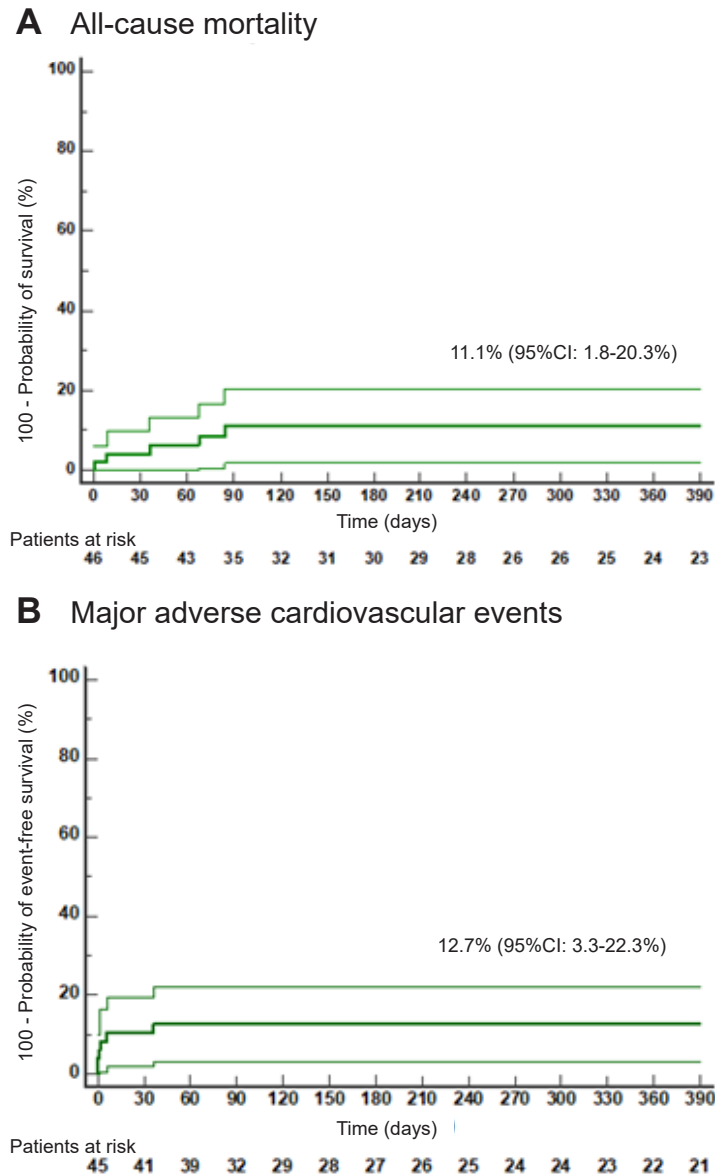


Figure 4 – Kaplan-Meier curves of overall mortality (A) and major adverse cardiovascular events after the diagnosis of Takotsubo syndrome, including both in-hospital and post-discharge events thin lines represent the 95% confidence interval

is potentially reversible in TTS, we may infer that morbidity and mortality of the disease are concentrated in the first months after the event and, if survives the acute phase, with LVEF recovery, the patient will have an excellent prognosis. However, studies with a larger number of patients and longer follow-up have shown that TTS morbidity and mortality are not limited to the first months after diagnosis, and that MACE may occur for years following the first event, at a rate higher than in general population and similar to CAD patients.^{8,29}

³³ The different results obtained in our study may be due to the relatively small number of patients (n=48) and shorter follow-up, of approximately one year.

The reasons why patients with diagnosis of TTS have higher morbidity and mortality compared with the general population and similar to CAD patients, even in acute phase, are not fully understood. First, it was thought that the fact that some of TTS patients also have CAD could have caused this bias. This was explored by Tornvall et al.,²⁹ who compared a group

of patients with TTS and without CAD with further two groups: (a) controls without CAD and TTS; and (b) patients with CAD without TTS. The results were similar to those previously obtained – mortality rate in TTS patients was higher than in controls and similar to the CAD group. Thus, the hypothesis that the concomitance of CAD and TTS would cause higher morbidity and mortality (as compared to healthy controls) became less likely.

Another hypothesis for the high mortality rates after acute phase in TTS patients was based on a population-based study that reported that TTS patients have more comorbidities than patients with previous CAD, including higher rates of past history of stroke/transient ischemic attack, drug abuse, psychiatric disorder, oncologic disease, chronic liver disease and sepsis.³⁴ Therefore, TTS may be seen as a disorder that often affects already ill patients, with higher morbidity and mortality than the general population.

The treatment of TTS is controversial, and based on clinical experience and experts consensus (level of evidence C), since there are no prospective, randomized clinical trials evaluating therapeutic approaches of these patients.¹⁹ Figure 5 summarizes the main recommendations for treatment of the TTS today. In the present registry, most patients received heart failure medications during hospitalization and after discharge, including beta-blockers (58.3%) and angiotensin converting enzyme inhibitors (62.5%).

One of the key issues in TTS treatment is to determine the presence or absence of left ventricular outflow tract obstruction. The presence of this condition changes the therapeutic approach, including the possibility of using short-acting beta-blockers in patients with cardiogenic shock.^{19,35} The detection of left ventricular outflow tract obstruction is usually made by echocardiography or hemodynamic measures during cardiac catheterization.

Limitations

The present study has some limitations that need to be considered. First, the study had a short follow-up period (median 354.5 days) and a small number of patients (n=48) compared with international multicenter registries.⁸ This may explain the occurrence of MACE only in the early phase after the diagnosis, as discussed above. Second, not all patients underwent transthoracic echocardiography

during the syndrome; 41 (85.4%) underwent the test, and seven were assessed by other methods – three underwent ventriculography during cardiac catheterization and cardiac magnetic resonance; three underwent ventriculography only; and one underwent cardiac magnetic resonance only.³⁶ The transthoracic echocardiographic follow-up allows the comparative assessment of ventricular function and of the segments involved, contributing to a better understanding of the syndrome. Also, the test enables the appropriate detection of left ventricular outflow tract obstruction, which is a key point in the TTS treatment. However, despite these limitations, this is the largest registry on the theme conducted in Brazil.

Conclusion

The present study evidenced the high morbidity and mortality of TTS, diagnosed according to the new InterTAK criteria, in a tertiary center in Brazil, especially during hospitalization and within 90 days after the diagnosis. Based on these findings, further research is urgently needed, mainly to establish the most appropriate therapy for this population.

Author Contributions

Conception and design of the research: Fundão NHF, Ribeiro HB, Campos CM. Acquisition of data: Fundão NHF, Seleme VB, Soeiro AM, Vieira MLC, Mathias W, Ribeiro EE. Analysis and interpretation of the data: Fundão NHF, Ribeiro HB, Campos CM. Statistical analysis: Campos CM. Writing of the manuscript: Fundão NHF, Ribeiro HB, Campos CM. Critical revision of the manuscript for intellectual content: Hajjar LA, Filho RK.

Potential Conflict of Interest

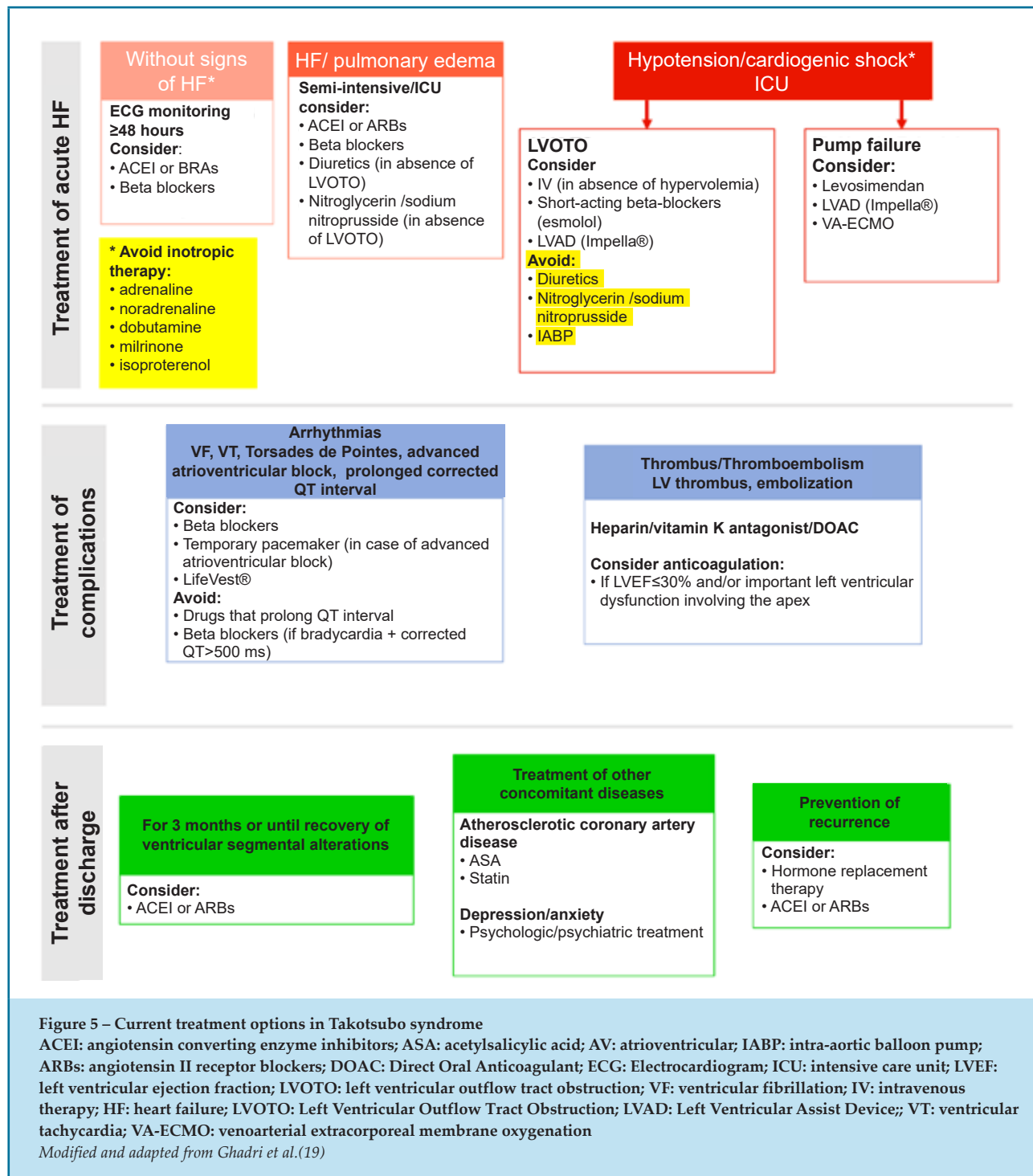
No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.



Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo - USP under the protocol number 3.279.964. All procedures in this study were in accordance with the Helsinki Declaration of 1975, updated in 2013. No consent

form was obtained from the study participants, as it was a retrospective study, only with the collection of secondary data obtained from the analysis of material already collected and review of medical records and without new clinical interventions, the ethics committee waived the need to obtain a free and informed consent form.

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