The association between Takotsubo cardiomyopathy and thyrotoxicosis

A systematic review

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Abstract:	Abstract Purpose: This study aims to review all published cases on the association between thyrotoxicosis and Takutsubo Syndrome by describing clinical characteristics, diagnostic work-up, treatment, and outcome. Methods : We searched PubMed and Embase databases from inception to the 17 th of February 2022 for case reports or series reporting the above-mentioned association. We extracted data on demographic characteristics, clinical features, diagnostic work-up, treatment, and clinical outcomes. Cases were stratified into groups based on the presumed cause of the thyrotoxicosis (iatrogenic vs non-iatrogenic and Graves' diseases vs non-Graves' disease, respectively). Results : We identified 25 cases from 24 articles. The mean age was 61.7 years (+/- SD 14.5). Most patients were women (88%). Graves' disease (52%) was the leading cause of thyrotoxicosis. Previous cancer was significantly more common in patients with iatrogenic thyrotoxicosis (P=0.03). The most common symptoms were respiratory symptoms (68%), chest pain (56%), and palpitations (40%). The most common ECG characteristics were T-wave abnormalities (48%) and ST-elevations (36%). Elevated troponin levels were found in 92% of the cases. Patients with Graves's disease and Takutsubo Syndrome had higher plasma levels of serum thyroxine (P=0.03) and were more often treated with beta-blockers (P=0.01) compared to patients with thyrotoxicosis of other origins. Notably, 40% of cases experienced in-hospital complications. No deaths were reported. All patients had improved cardiac function within a median follow-up of 42 days. Conclusion : Evidence based on current case reports suggests an increased risk of

	Takutsubo Syndrome and subsequently increased risk of in-hospital complications in patients with thyrotoxicosis.
Response to Reviewers:	Reply to reviewers' comments: We thank the reviewers for taking the time to assess our article and consider it for publication. We have addressed all the comments point-by-point, as listed below. The changes are highlighted in the manuscript. We hope that our revised paper now is satisfactory, but we are willing to make further changes, if needed. On behalf of all authors Kind regards There are a few errors in English grammar and syntax: 1.Line 30: should be "gold standard" The authors' answer: This is corrected. 2.line 102: should be "hyperthyroidism" instead of "a hyperthyroid disease" The authors' answer: This is corrected. 3.line 114: should be fluid overload The authors' answer: This is corrected. 4.line 151: unclear what you mean by "vital parameters". Do you mean "vital signs"? The authors' answer: This is corrected to "vital signs" Also, while your literature review seems comprehensive, it is unclear why the paper by Aweimer et al. was not cited in your review: Aweimer A, El-Battrawy I, Akin I, Borggrefe M, Mügge A, Patsalis PC, Urban A, Kummer M, Vasileva S, Stachon A, Hering S. Abnormal thyroid function is common in takotsubo syndrome and depends on two distinct mechanisms: results of a multicentre observational study. Journal of Internal Medicine. 2021 May;289(5):675-87. The authors' answer: The above-mentioned study was not classified as a case series and therefore it didn't fulfil the inclusion criteria. However, we've now cited the above-mentioned article in the discussion. We have included the following in the article (from line 62): "Also, a recent multicentre observational study by Aweimer et al. demonstrated that 25% of patients with TTS suffered from subclinical or overt thyrotoxicosis at admission. These findings suggest that thyrotoxicosis is a possible trigger for TTS [38]"

The association between Takotsubo cardiomyopathy and thyrotoxicosis: A systematic review

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Abstract

Purpose: This study aims to review all published cases on the association between thyrotoxicosis and Takutsubo Syndrome by describing clinical characteristics, diagnostic work-up, treatment, and outcome.

Methods: We searched PubMed and Embase databases from inception to the 17th of February 2022 for case reports or series reporting the above-mentioned association. We extracted data on demographic characteristics, clinical features, diagnostic work-up, treatment, and clinical outcomes. Cases were stratified into groups based on the presumed cause of the thyrotoxicosis (iatrogenic vs non-iatrogenic and Graves' diseases vs non-Graves' disease, respectively).

Results: We identified 25 cases from 24 articles. The mean age was 61.7 years (+/- SD 14.5). Most patients were women (88%). Graves' disease (52%) was the leading cause of thyrotoxicosis. Previous cancer was significantly more common in patients with iatrogenic thyrotoxicosis (P=0.03). The most common symptoms were respiratory symptoms (68%), chest pain (56%), and palpitations (40%). The most common ECG characteristics were T-wave abnormalities (48%) and ST-elevations (36%). Elevated troponin levels were found in 92% of the cases. Patients with Graves's disease and Takutsubo Syndrome had higher plasma levels of serum thyroxine (P=0.03) and were more often treated with beta-blockers (P=0.01) compared to patients with thyrotoxicosis of other origins. Notably, 40% of cases experienced in-hospital complications. No deaths were reported. All patients had improved cardiac function within a median follow-up of 42 days.

Conclusion: Evidence based on current case reports suggests an increased risk of Takutsubo Syndrome and subsequently increased risk of in-hospital complications in patients with thyrotoxicosis.

Introduction

Stress-induced cardiomyopathy, also called Takotsubo Syndrome (TTS), represents a syndrome of transient left ventricular dysfunction. TTS was first described in Japanese literature in 1991 and has been increasingly recognized since then [1]. The name was given because left ventriculogram resembles the shape of a Japanese octopus fishing pot (called tako-tsubo) [2]. The clinical presentation of the disease mimics that of acute myocardial infarction but without any evidence of clinically significant coronary artery obstruction [3]. Although numerous causes have been proposed, the pathogenesis of TTS is still not well understood. Currently, the most popular theory focuses on catecholamine-induced microvascular spasms or direct catecholamine-associated myocardial toxicity in acute physical or psychological stress [3]. Although no consensus on the diagnostic criteria for TTS exists, the Revised Mayo Clinic Criteria are widely acknowledged as the gold standard (Table 1) [3, 4].

Thyroid dysfunction is globally one of the leading endocrine disorders. The prevalence of hyperthyroidism is 0.8% in Europe and 1.3% in the USA [5, 6]. Numerous cases presenting the association between thyrotoxicosis and TTS have been reported in recent years, and as the incidence of hyperthyroidism is rising, at least in some populations, TTS will likely become more frequent. In fact, the incidence of TTS might already be underestimated. The pathogenesis behind this association is not yet fully understood. However, thyroid hormones can regulate beta-adrenergic receptor in many tissues, including the heart and this might partly explain the pathophysiology of this association [7–9].

To the best of our knowledge, no systematic review of the association between thyrotoxicosis and TTS exists. Thus, our primary objective was to review all published cases of thyrotoxicosis-related TTS by describing clinical characteristics, diagnostic work-up, treatment, and outcome.

Material and Methods:

The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10]. The predefined review protocol was registered in PROSPERO (International prospective register of systematic reviews) (protocol number: CRD42022308963).

Search strategy for identification of studies

The Cochrane database and PROSPERO database search revealed no similar systematic reviews on this topic. The literature search was supervised by a librarian at Aarhus University Library Service. A systematic electronic search in MEDLINE (via PubMed) and EMBASE electronic databases up to the 17th of December 2021 was conducted to identify case reports and case series describing patients with both thyrotoxicosis and TTS. The search syntax is provided in figure 1. No date or language filters were used. A supplementary citation tracking was performed to identify additional studies. We used reference manager software (covidence.org) to manage the retrieved studies and to identify duplications. Finally, we updated the database search on the 17th of February 2022. Two investigators (AAM and TB) evaluated the studies. Disagreement during the screening process was resolved by a third author (MHO).

Inclusion and exclusion criteria

Studies were included if they met all of the following criteria: Case reports or case series reporting the association between thyrotoxicosis and TTS defined by the Revised Mayo Clinic Criteria [4] (table 1); original article; age ≥ 18 years; written in or reliably translated to English. Commentaries, letters, conference abstracts, and reviews were excluded.

Quality evaluation and data extraction

All selected papers for inclusion were evaluated using the Joanna Briggs Institute (JBI) critical appraisal checklist for case reports [11]. The list consists of eight questions, including patients' demographic characteristics, past medical history, current clinical condition, description of diagnostic test, intervention or treatment, post-intervention clinical condition, adverse event, and mention of takeaway lessons. There are four possible responses for each question: yes, no, unclear, or not applicable. To summarize the results of the JBI checklist, we allocated each answer a score. If the answer to the question was 'yes,' it received a score of 1; if the answer was incomplete or not clear, the score was 0.5; if it was not possible to find any information addressing the question, the score was 0. However, if no adverse event or complication were mentioned in the case, we assumed that there were none, and a score of 1 was given. Thus, the maximum possible score is 8.

Two researchers (AAM and TB) conducted the data extraction. We extracted the following data: 1) first author name, year of publication; 2) age, gender, past medical history, medication prior to admission, main symptoms at admission; 3) objective findings at admission, vital values, findings on chest X-ray, laboratory results, cardiac testing including electrocardiogram (ECG), trans-thoracic echocardiography (TTE) and coronary arteriography; and 4) cause of thyrotoxicosis, medical intervention, follow-up period, and outcome.

Statistics

Cases were stratified into groups based on the presumed cause of the thyrotoxic condition, and all of the above-mentioned extracted data were compared between the groups (iatrogenic vs non-iatrogenic and Graves' disease vs non-Graves' disease, respectively). Different assays for the measurement of thyroid hormones were used, and they also differed on whether total or free hormone levels were measured. To compare the thyrotoxic burden across the reports, we calculated the percent increase of thyroxine (T4) above the upper limit of the reported reference interval. Analysis for triiodothyronine (T3) was not done because this hormone was not measured in most cases. Further, the patients were divided into two groups according to those with the highest relative increase of T4 above the upper reference limit versus those with the lowest increase. This was done to analyze for any association between the severity of thyrotoxicosis and the severity of TTS, the latter defined as the impact on the left ventricular ejection fraction (LVEF) at admission.

Continuous variables are presented as mean ± standard deviation (SD) or median and interquartile range (IQR), and a comparison between groups was performed using student's *t*-test (normal distributed) or Wilcoxon rank-sum test (non-normal distributed). Categorical variables are presented as absolute values and percentages and compared using Fisher's exact test. A two-sided test with a significance level of $P<0.05$ was considered statistically significant for all tests. All analyses were performed using STATA (version 17).

Results

Study selection

The systematic search identified 217 papers, 44 of which were duplicates (figure 2). After reviewing the title and abstract of the remaining 173 papers, we included 55 papers for full-text review. Finally, 24 papers covering 25 patients met the inclusion criteria and were included in the present review [12–36] (table 2). Eleven papers were conference abstracts, and seven papers did not fulfil the Mayo Clinic Criteria for TTS and were therefore excluded.

Study characteristics

The clinical features of the cases are summarized table 3. The mean age was 61.7 years (+/- SD 14.5). The majority of patients were women (88%). Hyperthyroidism prior to hospitalization was known in 24% of the patients. Frequent comorbidities were hypertension (24%), diabetes (16%), and past medical history of cancer (16%), including prostatic cancer, breast cancer, colon cancer, and laryngeal cancer. A possible emotional trigger was reported in 16% of cases.

Graves' disease (52%) and iatrogenic thyrotoxicosis (24%) were the leading causes of thyrotoxicosis (Table 2). Of the six cases with iatrogenic thyrotoxicosis, two were due to levothyroxine overtreatment, one was due to amiodarone, one was due to interferon-alpha, and two were due to recent exposure to radioiodine therapy. Previous cancer was significantly more common in patients with iatrogenic thyrotoxicosis than in non-iatrogenic thyrotoxicosis (P=0.03).

Clinical presentation

Respiratory symptoms (dyspnea, respiratory distress, shortness of breath, tachypnea) were the most common, seen in 68%, followed by chest pain in 56%, and palpitations in 40% of patients (table 4).

Common findings on examination were signs of fluid overload, such as positive lung auscultation (20%) and pulmonary oedema on chest X-ray (12%). On admission, goiter (24%) and high systolic pressure (mean: 152.7; SD: +/- 24.1) were common findings (table 5).

Cardiac testing

All patients showed an abnormal electrocardiogram (ECG) on admission (table 5); ST elevation in 36%, T-wave abnormalities in 48%, and sinus tachycardia in 40%. On echocardiography, 60% of all patients had left ventricular ejection fraction (LVEF) <50%. Twenty-four percent of all cases had LVEF <30%. LVEF was not quantified in 40% of the cases but was described as impaired and with abnormal cardiac wall motion on echocardiography. Elevated cardiac enzymes were reported in 92% (23 of 25 cases) (Table 6). Acute ECG abnormalities were found in the two individuals with normal cardiac enzymes, thus fulfilling TTS criteria. Coronary arteriography was performed in all patients without showing significantly stenotic vessels. However, 40% showed some evidence of coronary atherosclerosis.

Thyroid function tests

Per definition, all patients had elevated plasma levels of thyroid hormones (Table 6). In cases where the reference interval for T4 was reported (i.e., 68%), patients with Graves' disease more often showed an increase of T4 by 50-100% above the upper limit of the reported reference interval than patients with a non-Graves' etiology (P=0.03).

There was no significant difference in the LVEF at admission when comparing the group with highest vs. the lowest relative increase in T4 (P=0.42).

Management

In 64% of cases, antithrombotic or/and anticoagulant agents were given at admission due to suspected acute coronary syndrome. Most patients were treated with beta-blockers (80%), angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (52%), and antithyroid agents (72%) (table 7). When comparing patients with Graves' disease and those without Graves' disease, the former group was significantly more likely to be treated with beta-blockers (P=0.01).

Complication and outcome

All patients showed improvement in the systolic function within a median follow-up of 42 days [16-60]. The median time to euthyroidism, reported in only 6 cases, was 66 days [30-90]. During the hospital stay, arrhythmia developed in four patients (atrial fibrillation (n=3), ventricular tachycardia (n=1)); cardiogenic shock was seen in 12% (n=3) and cardiac arrest in 4% (n=1). After discontinuation of methimazole due to hypothyroidism one patient had a recurrence of thyrotoxicosis and TTS with a similar wall motion abnormality as in the first event. Still, after the resumption of the antithyroid treatment, the symptoms improved along with the normalization of the LVEF [21]. No deaths were reported in any of the cases (Table 7).

Quality assessment

According to the JBI checklist for case reports, the overall mean score was 7.2. Six out of 24 case reports received a maximum score (8/8), while four received the lowest score (6/8). The parameter least reported was a description of the clinical condition due to lack of information about the vital signs. Other reasons for a low score were lack of information about the patient's medication before admission and objective findings at admission. In-hospital complications were reported in only 10 cases. We assume that no complications occurred in the remaining cases, as this issue was not addressed in these papers.

Discussion

The present systematic review provides the first overview of patients with thyrotoxicosis and TTS. To emphasise the relevance of this review, a retrospective study by Aggarwel et al. found that 11.8% of all patients with TTS were hyperthyroid at admission [37]. Also, a recent multicentre observational study by Aweimer et al. demonstrated that 25% of patients with TTS suffered from subclinical or overt thyrotoxicosis at admission. These findings suggest that thyrotoxicosis is a possible trigger for TTS [38].

In summary, our major findings were (1) Graves' disease was the most common cause of thyrotoxicosis among TTS patients; (2) the most frequent subjective symptoms were respiratory, chest pain, and palpitations, while the most frequent objective findings were signs of fluid overload; (3) significantly more patients with Graves's disease and TTS had higher plasma levels of T4 and were treated with beta-blockers compared to TTS patients with thyrotoxicosis of different origin; (4) 40% developed in-hospital complications, however no deaths were reported, and all patients showed improvement of left ventricular function at follow-up.

The exact pathophysiological mechanisms of TTS are not fully understood. In most patients, acute emotional and/or physical stress prior to TTS can be identified[3]. In our study, 84% of cases had no evidence of an emotional trigger. A higher level of catecholamines has been documented in TTS patients[39]. This has led to the suggestion that sympathetic stimulation plays a central role in the pathogenesis of TTS, either by causing multi-vessel microvascular spasm and dysfunction, or by a direct myocardial toxicity with transient myocardial stunning [3]. Clinically, hyperthyroidism resembles a state of catecholamine excess, despite the plasma levels of catecholamines being low-normal[40], as confirmed in several of the cases included in this review [12, 18, 27, 35]. The thyroid hormones enhance the effect of catecholamines by increasing the expression of beta-adrenergic receptors, as demonstrated in animal studies [7, 8, 41, 42]. The apical myocardium contains a higher concentration of adrenoreceptors, leading to increased

sympathetic activity in this region of the heart. Such a distribution of adrenoreceptors provides an explanation why TTS is characterized by focal wall motion abnormalities and apical ballooning [9, 43, 44]. Studies in mice lacking beta-adrenergic receptors have shown preserved cardiovascular responses to thyroid hormones [45]. This suggests that - in addition to increasing beta-receptor expression - thyroid hormones might exert their effects on the myocardium through other pathways. Some authors [46] have speculated that thyroid auto-antibodies may have a direct impact on the myocardium since most cases of TTS are seen in Graves' disease. However, as demonstrated in this review, TTS may occur also in non-Graves' autoimmune thyrotoxicosis. TTS has been reported even in hypothyroidism [47, 48], but the underlying pathophysiology is unclear and the association might be incidental [9].

TTS resembles acute coronary syndrome as both conditions present with similar clinical characteristics. In our study, more than 90% of cases had elevated troponin levels. Nearly as many had signs of acute myocardial infarction on the initial ECG; thus, it is very difficult to differentiate between these two diseases based on the clinical presentation. For this purpose, coronary arteriography is required. This procedure was performed in all reported cases. No patients had a significant coronary disease; however, 40% showed evidence of non-occlusive coronary atherosclerosis, which can influence treatment choice (e.g., prophylactic antithrombotic and lipid-lowering therapy).

Due to the lack of randomized trials, there are no established evidence-based guidelines for TTS management. Treatment is supportive, based on clinical experience and expert consensus [49]. Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and beta-blockers are recommended, while diuretics are indicated only in patients with decompensated heart failure. In our study, 56% of patients received angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, while as many as 76% were treated with beta-blockers. The latter drugs were used more commonly as usually seen in patients with TTS, probably because beta-blockade is widely used to manage severe thyrotoxic symptoms [49–51]. However, beta-blockers should be used with great caution in hemodynamically unstable patients to avoid further worsening of the cardiac output [52]. In fact, patients with thyrotoxicosis and clinical signs of fluid overload should undergo echocardiography to rule out heart failure before beta-blocker treatment is initiated.

Although TTS is a reversible condition, the rates of cardiogenic shock and death are comparable to the risks in acute coronary syndrome [49]. Nearly 20% of all patients with TTS have serious in-hospital complications [53], including cardiac death, cardiogenic shock, cardiac arrhythmias, ventricular thrombus, and pulmonary oedema. Notably, 40% of the included cases in our review experienced pleural effusion, arrhythmias, or cardiogenic shock. Although no deaths were recorded during hospitalization or after long-term follow-up, the high complication rate suggests that thyrotoxicosis *per se* is an additional risk factor in TTS patients. We found no association between the severity of thyrotoxicosis and left ventricular ejection fraction (LVEF), maybe due to the limited number of cases.

Obviously, antithyroid treatment should be initiated in patients with newly diagnosed hyperthyroidism and TTS in order to improve both conditions. Nevertheless, we cannot conclude from this review whether antithyroid treatment leads to faster recovery of the ventricular function. One patient in our study developed recurrent thyrotoxicosis and TTS 20 days after discontinuing antithyroid medication due to the development of hypothyroidism. Whether such recurrence can be attributed to the drug discontinuation is unclear, as the general risk of TTS recurrence is approximately 5%, occurring three weeks to 3.8 years after the first event [49].

Several limitations exist of this systematic review. Firstly, the nature of this paper does not allow us to draw any conclusion about causality between thyrotoxicosis and TTS. Secondly, the relatively few cases included (n=25) limit the generalizability of the study. Thirdly, the papers upon which this systematic review is based may be prone to publication

bias and patient selection bias. Fourthly, differences in measurement, analyses, and the reported data make a comparison between cases difficult. Despite these limitations, we believe our review add important knowledge to the field of TTS and thyroid disorders.

In conclusion, this systematic review suggests an increased risk of TTS and in-hospital complications in patients with thyrotoxicosis. We found that Graves' disease was the most common cause of thyrotoxicosis in TTS patients. The clinical characteristics of patients with TTS were similar as seen in acute coronary syndrome. Importantly, no deaths were reported, and all patients showed improvement in left ventricular function at follow-up. Clinicians who manage thyrotoxic patients should be aware of the risk of TTS. Likewise, thyroid testing should be considered in all patients diagnosed with TTS. The treatment of thyrotoxic patients with TTS follows current guidelines, but beta-blockers should be used with caution. More extensive studies are required to understand the mechanisms behind TTS triggered by thyrotoxicosis.

Figure Captions:

Fig. 1 Search syntax This box shows the search syntax we used to include papers.

Fig. 1 PRISMA flowchart This diagram shows the systematic process we followed to include papers captured by our search
Abbreviations: *TTS: Takutsubo syndrome.*

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Author Contributions:

Abdullahi Mohamed: conceptualization(lead), methodology (lead), investigation (lead), formal analysis (lead), writing-original draft (lead), writing-review and editing (equal), final approval of manuscript (equal), project administration (lead)

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Marwan Othman: writing-review and editing (equal), final approval of manuscript (equal)

Niels Andersen: writing-review and editing (equal), final approval of manuscript (equal)

Steen Bonnema: conceptualization (supporting), writing-review and editing (equal), final approval of manuscript (equal), supervision (lead)

Online Resource materials:

Table 1

Figure 2: PRISMA flowchart

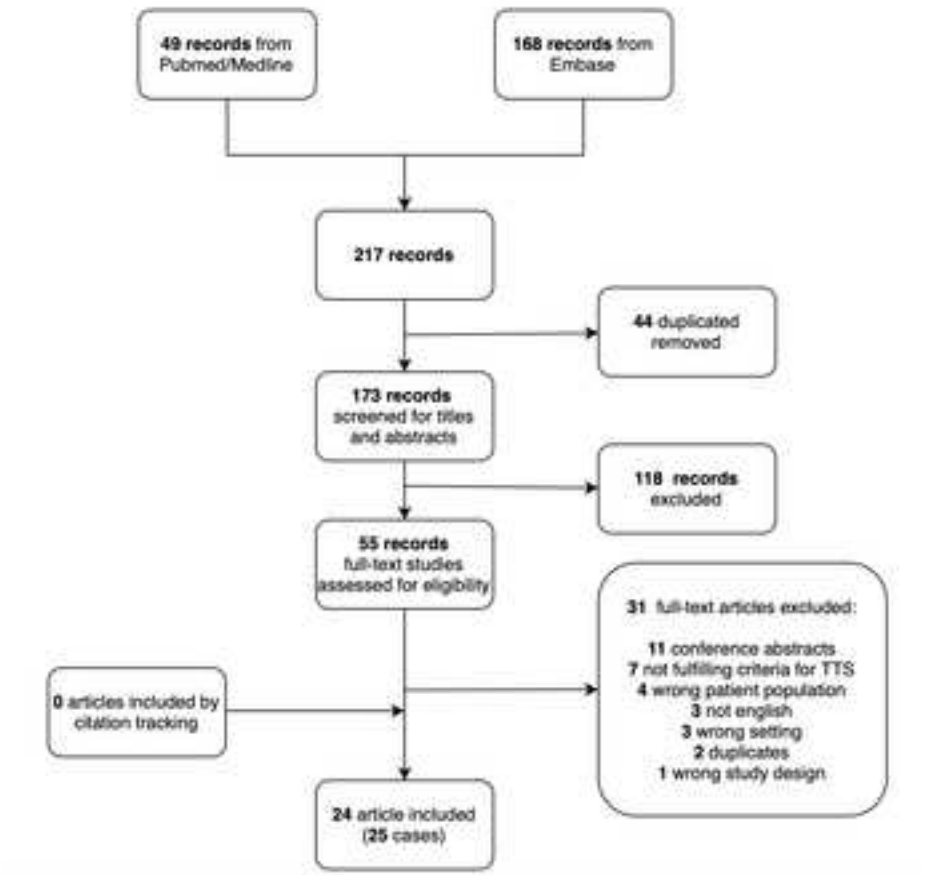

Figure 1: Search syntax

PUBMED:
("Takotsubo Cardiomyopathy"[Mesh] OR "Takotsubo cardiomyopathy" OR "Stress Cardiomyopathy" OR "Tako-tsubo Cardiomyopathy" OR "Tako tsubo Cardiomyopathy" OR "Broken Heart Syndrome" OR "Takotsubo Syndrome" OR "Apical Ballooning Syndrome" OR "Tako-tsubo Syndrome" OR "Tako tsubo Syndromes" OR Takotsubo OR "Takotsubo stress cardiomyopathy") AND ("Hyperthyroidism"[Mesh] OR "Graves' Disease"[Mesh] OR Hyperthyroidism OR Hyperthyroid OR "Primary Hyperthyroidism" OR Hyperthyroidism OR Thyrotoxicosis OR "Graves' disease" OR "Thyroid dysfunction" OR "Thyroid disease")

EMBASE:
("Takotsubo Cardiomyopathy"/exp OR "Takotsubo cardiomyopathy" OR "Stress Cardiomyopathy" OR "Tako-tsubo Cardiomyopathy" OR "Tako tsubo Cardiomyopathy" OR "Broken Heart Syndrome" OR "Takotsubo Syndrome" OR "Apical Ballooning Syndrome" OR "Tako-tsubo Syndrome" OR "Tako tsubo Syndromes" OR Takotsubo OR "Takotsubo stress cardiomyopathy") AND ("Hyperthyroidism"/exp OR Hyperthyroidism OR Hyperthyroid OR "Primary Hyperthyroidism" OR Hyperthyroidism OR Thyrotoxicosis OR "Graves' disease" OR "Thyroid dysfunction" OR "Thyroid disease")

Table 1: Mayo Clinic Criteria for the diagnosis of Takutsubo cardiomyopathy (2014)
1. Transient hypokinesis, akinesis, or dyskinesis in the left ventricular midsegments with or without apical involvement
2. Regional wall motion abnormalities that extend beyond a single epicardial vascular distribution
3. Absence of obstructive coronary artery disease or acute plaque rupture
4. New electrocardiographic abnormalities or modest troponin elevation
5. Absence of pheochromocytoma and myocarditis

Table 2: Case reports of patients with thyrotoxicosis and Takutsubo Syndrome.		
Author	Year of publication	Cause of thyrotoxicosis
Miyazaki et al.[24]	2004	Graves' disease
Rossor et al.[18]	2007	Graves' disease
Radhakrishnan et al.[19]	2009	Graves' disease
Kwon et al.[26]	2009	Iatrogenic thyrotoxicosis (levothyroxine induced)
Van de donk et al.[13]	2009	Iatrogenic thyrotoxicosis (radioiodine induced thyroiditis)
Alidjan et al.[35]	2010	Graves' disease
Kuboyama et al.[27]	2010	Graves' disease
Hutchings et al.[28]	2010	Not specified
Hutchings et al.[28]	2010	Exogenous thyrotoxicosis (desiccated thyroid extract)
Zuhdi et al.[12]	2011	Silent thyroiditis
Bird-Lake [34]	2011	Graves' disease
Gundara et al.[29]	2012	Thyroidectomy due to Graves' disease
Ugurlucan et al.[14]	2013	Not specified
Salameh et al.[36]	2014	Graves' disease
Perkins et al.[20]	2014	Graves' disease
Eliades et al.[30]	2014	Graves' disease
Martin et al.[25]	2014	Iatrogenic thyrotoxicosis (IFN-alpha induced)
Saleh et al.[15]	2015	Not specified
Omar et al.[22]	2015	Graves' disease
Dimakopoulou et al.[31]	2015	Iatrogenic thyrotoxicosis (radioiodine induced thyroiditis)
Murdoch et al.[23]	2016	Toxic multinodular goiter
Patel et al.[21]	2016	Graves' disease
Rueda et al.[17]	2017	Graves' disease
Capel et al.[33]	2017	Iatrogenic thyrotoxicosis (amiodarone induced)
Cervilla-Munoz et al.[32]	2020	Iatrogenic thyrotoxicosis (levothyroxine induced)

Table 3: Clinical features of cases:							
	All cases	*Iatrogenic thyrotoxicosis*	*Non-iatrogenic thyrotoxicosis*	*P-values*	*Graves' disease*	*Patients without Graves' disease*	*P-values*
Total, *n*	25	6 (24)	19 (76)	-	13 (52)	12 (48)	-
Age, y mean ($\pm SD$)	61.7 ($\pm$14.5)	61.5 ($\pm$12.1)	61.8 ($\pm$15.5)	0.97	58.9 ($\pm$16.2)	64.7 ($\pm$12.5)	0.33
Gender *n* (%)							
Female	22 (88)	4 (66.7)	18 (94.7)	0.13	12 (92.3)	10 (83.3)	0.59
Male	3 (12)	2 (33.3)	1 (5.3)	0.13	1 (7.7)	2 (16.6)	0.59
Past medical history, *n* (%)							
Hypertension	6 (24)	1 (16.7)	5 (26.3)	0.64	4 (30.8)	2 (16.7)	0.65
Hyperthyroidism	6 (24)	1 (16.7)	5 (26.3)	1.00	3 (23.1)	3 (25)	1.00
Diabetes	4 (16)	1 (16.7)	3 (15.8)	1.00	2 15.4)	2 (16.7)	1.00
History of cancer	4 (16)	3 (50)	1 (5.3)	**0.03**	1 (7.7)	3 (25)	0.32
Hyperlipidemia	2 (8)	0	2 (10.5)	1.00	1 (7.7)	1 (8.3)	1.00
Ischemic heart disease	2 (8)	1 (16.7)	1 (5.3)	0.43	0	2 (16.7)	0.22
Atrial fibrillation	2 (8)	0	2 (10.5)	1.00	2 (15.4)	0	0.48
Hypothyroidism	2 (8)	2 (33.3)	0	0.05	0	2 (16.7)	0.22
Emotional trigger	4 (16)	1	3	1.00	2	2	1.00
Admission therapy, *n* (%)							
Beta-blockers	2 (8)	1 (16.7)	1 (5.3)	0.43	1 (7.7)	1 (8.3)	1.00
Levothyroxine	2 (8)	2 (33.3)	0	0.05	0	2 (16.7)	0.22
Carbimazole	2 (8)	1 (16.7)	1 (5.3)	0.43	1 (7.7)	1 (8.3)	1.00
Metformin	2 (8)	1 (16.7)	1 (5.3)	0.43	1 (7.7)	1 (8.3)	1.00
ACE-I or ARB	1 (4)	1 (16.7)	0	0.24	0	1 (8.3)	0.48
PTU	1 (4)	0	1 (5.3)	1.00	0	1 (7.7)	0.48
Insulin	1 (4)	0	1 (5.3)	1.00	1 (7.7)	0	1.00

ACE-I: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker, CCB; calcium channel blocker, COPD: chronic obstructive pulmonary disease, PTU: propylthiouracil.

Table 4: Symptoms at admission *n* (%)							
	All cases	*Iatrogenic thyrotoxicosis*	*Non-iatrogenic thyrotoxicosis*	*P-value*	*Graves' disease*	*Patients without Graves' disease*	*P-value*
Total	25	6 (24)	19 (76)	-	13 (52)	12 (48)	-
Respiratory symptoms[a]	17 (68)	4 (66.7)	13 (68.4)	1.00	7 (53.8)	10 (83.3)	0.20
Chest pain	14 (56)	4 (66.7)	10 (52.6)	0.66	6 (46.2)	8 (66.7)	0.43
Palpitations	10 (40)	2 (33.3)	8 (42.1)	1.00	6 (46.2)	4 (33.3)	0.69
Heat intolerance/diaphoresis	5 (20)	1 (16.6)	4 (21.1)	1.00	3 (23.1)	2 (16.7)	1.00
Weight loss	4 (16)	0	4 (21.1)	0.54	4 (30.8)	0	0.09
Restlessness/anxiety	3 (12)	1 (16.6)	2 (10.5)	1.00	2 (15.4)	1 (8.3)	1.00
Nausea/vomiting	3 (12)	0	3 (15.8)	0.55	3 (23.1)	0	0.22
Abdominal pain	3 (12)	0	3 (15.8)	0.55	3 (23.1)	0	0.22
Diarrhea	3 (12)	0	3 (15.8)	0.55	3 (23.1)	0	0.22
Fatigue/lethargy/muscle weakness	2 (8)	0	2 (10.5)	1.00	2 (15.4)	0	0.48
Loss of appetite	1 (4)	0	1 (5.3)	1.00	1 (7.7)	0	1.00

[a]*Respiratory symptoms include dyspnea, respiratory distress, shortness of breath, and tachypneic*

Table 5: Findings on examination:							
	All cases	*Iatrogenic thyrotoxicosis*	*Non-iatrogenic thyrotoxicosis*	*P-values*	*Graves' disease*	*Patients without Graves' disease*	*P-values*
Total, *n*	25	6 (24)	19 (76)	-	13 (52)	12 (48)	-
Objective findings, *n* (%)							
Goitre	6 (24)	0	6 (35.6)	0.29	4 (30.8)	2 (16.7)	0.66
Positive lung auscultation[a]	5 (20)	2 (33.3)	3 (15.8)	0.25	2 (15.4)	3 (25)	0.62
Tremor	4 (16)	1 (16.7)	3 (15.8)	1.00	2 (15.4)	2 (16.7)	1.00
Lower extremity edema	1 (4)	0	1 (5.3)	1.00	0	1 (8.3)	0.44
Normal objective examination	2 (8)	0	2 (10.5)	1.00	2 (15.4)	0	0.48
N/A	11 (44)	2 (33.3)	9 (47.4)	1.00	5 (38.5)	6 (50)	0.44
Vitals, mean (±SD)							
SBP	152.7 (±24.1)	146.7 (±23.4)	154.4 (±25.1)	0.64	154.3 (±26.5)	148.7 (±19.6)	0.71
DBP	90.7 (±17.3)	102.7 (±20.5)	87.5 (±15.9)	0.19	87.8 (±16.7)	98.3 (±18.9)	0.33
Pulse	126.1 (±25.1)	147 (±37.5)	121.3(±20.5)	0.11	120.8 (±21.3)	142 (±32.2)	0.15
Chest X-ray, *n* (%)							
Pulmonary edema	3 (12)	2 (33.3)	1 (5.3)	0.09	1 (7.7)	2 (16.7)	0.57
Cardiomegaly	1 (4)	1 (16.7)	0	0.20	0	1 (8.3)	0.44
Normal	4 (16)	0	4 (21.1)	0.55	3 (23.1)	1 (8.3)	0.60
N/A	18 (72)	3 (50)	15 (78.9)	0.60	10 (76.9)	8 (66.7)	1.00
ECG, *n* (%)							
ST-elevation	9 (36)	1 (16.7)	8 (42.1)	0.62	7 (53.8)	2 (16.7)	0.21
ST-depression	0	0	0	-	0	0	-
T-wave abnormalities	12 (48)	2 (33.3)	10 (52.6)	1.00	6 (46.2)	6 (50)	0.70
Sinus tachycardia	10 (40)	2 (33.3)	8 (42.1)	1.00	6 (46.2)	4(33.3)	1.00
Arrythmia (AFLI, SVT etc.)	2 (8)	1 (16.7)	1 (5.3)	0.37	1 (7.7)	1 (8.3)	0.59
Normal	0	0	0	-	0	0	-
NA	2 (8)	0	2 (10.5)	1.00	1 (7.7)	1 (8.3)	1.00
LVEF, *n* (%)							
≥50%	0	0	0	-	0	0	-
40-49%	3 (12)	0	3 (15.8)	1.00	2 (15.4)	1 (8.3)	1.00
30-39%	6 (24)	2 (33.3)	4 (21.1)	0.56	3 (23.1)	3 (25)	1.00
<30%	6 (24)	1 (16.7)	5 (26.3)	1.00	2 (15.4)	4 (33.3)	0.38
N/A[b]	10 (40)	2 (33.3)	8 (42.1)	1.00	6 (46.2)	4 (33.3)	0.69

[a] *Bibasilar posterior crackles on lung auscultation*

[b] *These patients all had impairment of left ventricular systolic function (LVEF; however, a numerical value for LVEF was not cited in the case reports.*

AFLI: atrial fibrillation, DBP: diastolic blood pressure, LVEF: left ventricular ejection fraction, N/A: not applicable, SBP: systolic blood pressure, SVT: supraventricular tachycardia.

Table 6: Laboratory results, n (%)							
		Iatrogenic thyrotoxicosis	*Non-iatrogenic thyrotoxicosis*	*P-values*	*Graves' disease*	*Patients without Graves's disease*	*P-values*
Total, *n*	25	6 (24)	19 (76)	-	13 (52)	12 (48)	-
Cardiac enzyme elevated	23 (92)	6 (100)	17 (89.5)	1.00	12 (92.3)	11 (100)	1.00
T4 relative increase[a]							
>150% increase	6 (24)	0	6 (31.6)	0.28	4 (30.8)	2 (16.7)	0.65
101-150 increase	3 (12)	2 (33.3)	1 (5.3)	0.13	0	3	0.09
50-100% increase	5 (20)	0	5 (20)	0.29	5 (38.5)	0	0.03
<50%	3 (12)	2 (33.3)	1 (5.3)	0.13	1 (7.7)	2 (16.7)	0.59
N/A	8 (32)	2 (33.3)	6 (31.6)	-	3 (23.1)	5 (41.7)	-

N/A: not applicable, T4: thyroxine,

a Percent increase above the upper limit of the reported reference interval.

Table 7: Treatment, complication, and outcome							
	All cases	*Iatrogenic thyrotoxicosis*	*Non-iatrogenic thyrotoxicosis*	*P-values*	*Graves' disease*	*Patients without Graves' disease*	*P-values*
Total, *n*	25	6 (24)	19 (76)	-	13 (52)	12 (48)	-
Treatment during hospitalization, *n* (%)							
Beta-blockers	20 (80)	3 (50)	17 (89.5)	0.25	13 (100)	7 (58.3)	**0.01**
ACE-inhibitor or ARB	13 (52)	4 (66.7)	9 (47.3)	0.32	8 (61.5)	5 (41.7)	0.43
Antithyroid agents	18 (72)	2 (33.3)	16 (84.2)	0.11	11 (84.6)	7 (58.3)	0.20
Diuretics	11 (44)	2 (33.3)	9 (47.4)	1.00	6 (46.2)	5 (41.7)	1.00
Anticoagulant agent	9 (36)	0	9 (47.3)	0.12	6 (46.2)	3 (25)	0.41
Antithrombotic agent	7 (28)	0	7 (36.8)	0.27	5 (38.5)	2 (16.7)	0.38
Glucocorticoids	7 (28)	2 (33.3)	5 (26.3)	0.60	3 (23.1)	4 (33.3)	0.67
Nitrates	4 (16)	1 (16.7)	3 (15.8)	1.00	3 (23.1)	1 (8.3)	0.59
Statins	3 (12)	0	3 (15.8)	1.00	3 (23.1)	0	0.22
CCB	2 (8)	0	2 (10.5)	1.00	2 (15.4)	0	0.48
Thyroidectomy	2 (8)	0	2 (10.5)	1.00	1 (7.7)	1 (8.3)	1.00
Complications, *n* (%)							
Pleural effusion	6 (24)	1 (16.7)	5 (26.3)	1.00	3 (23.1)	3 (25)	1.00
Arrythmia	4 (16)	2 (33.3)	2 (10.5)	0.17	1 (7.7)	3 (25)	0.32
Cardiogenic shock	3 (12)	0	3 (15.8)	1.00	1 (7.7)	2 (16.7)	0.59
Cardiac arrest	1 (4)	1 (16.7)	0	0.20	0	1 (8.3)	0.48
Outcome, *n* (%)							
Mortality	0	0	0	-	0	0	-
Recurrence	1 (4)	0	1 (5.3)	1.00	1 (7.7)	0	1.00
Time to follow-up:							
Cases presenting with follow-up information, n (%)	25 (100)	7 (100)	19 (100)	-	13 (100)	12 (100)	-
Median (IQR), days	42 [16-60]	45.5 [42-60]	31.5 [9-42]	0.14	30 [7.5-42]	42 [31.5-75]	0.08
LVEF at follow-up							
≥50%	9 (36)	2 (33.3)	7 (36.8)	1.00	5 (38.5)	4 (33.3)	1.00
40-49%	2 (8)	0	2 (10.5)	1.00	1 (7.7)	1 (8.3)	1.00
30-39%	0	0	0	-	0	0	-
<30%	0	0	0	-	0	0	-
N/A[a]	14 (56)	4 (57.9)	10 (52.6)	1.00	8 (61.5)	7 (58.3)	1.00

a These patients all had improvement in left ventricular systolic function (LVEF); however, a numerical value for LVEF was not cited in the case reports.

ACE-I: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker, CCB; calcium channel blocker

Supplementary

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Supplementary Material

Onlineressourcetabel1.xlsx