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REVIEW
Miscellaneous

Takotsubo syndrome and respiratory diseases: a systematic review

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Takotsubo syndrome (TTS) is a rare cardiovascular condition characterized by reversible ventricular dysfunction and a presentation resembling that of acute myocardial infarction. An increasing number of studies has shown the association of respiratory diseases with TTS. Here, we comprehensively reviewed the literature and examined the available evidence for this association. After searching PubMed, EMBASE, and Cochrane Library databases, two investigators independently reviewed 3117 studies published through May 2021. Of these studies, 99 met the inclusion criteria ($n = 108$ patients). In patients with coexisting respiratory disease and TTS, the most common TTS symptom was dyspnoea (70.48%), followed by chest pain (24.76%) and syncope (2.86%). The most common type of TTS was apical, accounting for 81.13% of cases, followed by the midventricular (8.49%), basal (8.49%), and biventricular (1.89%) types. Among the TTS cases, 39.82% were associated with obstructive lung disease and 38.89% were associated with pneumonia. Coronavirus disease 2019 (COVID-19), which has been increasingly reported in patients with TTS, was identified in 29 of 42 (69.05%) patients with pneumonia. The overall mortality rate for patients admitted for respiratory disease complicated by TTS was 12.50%. Obstructive lung disease and pneumonia are the most frequently identified respiratory triggers of TTS. Medications and invasive procedures utilized in managing respiratory diseases may also contribute to the development of TTS. Furthermore, the diagnosis of TTS triggered by these conditions can be challenging due to its atypical presentation. Future prospective studies are needed to establish appropriate guidelines for managing respiratory disease with concurrent TTS.

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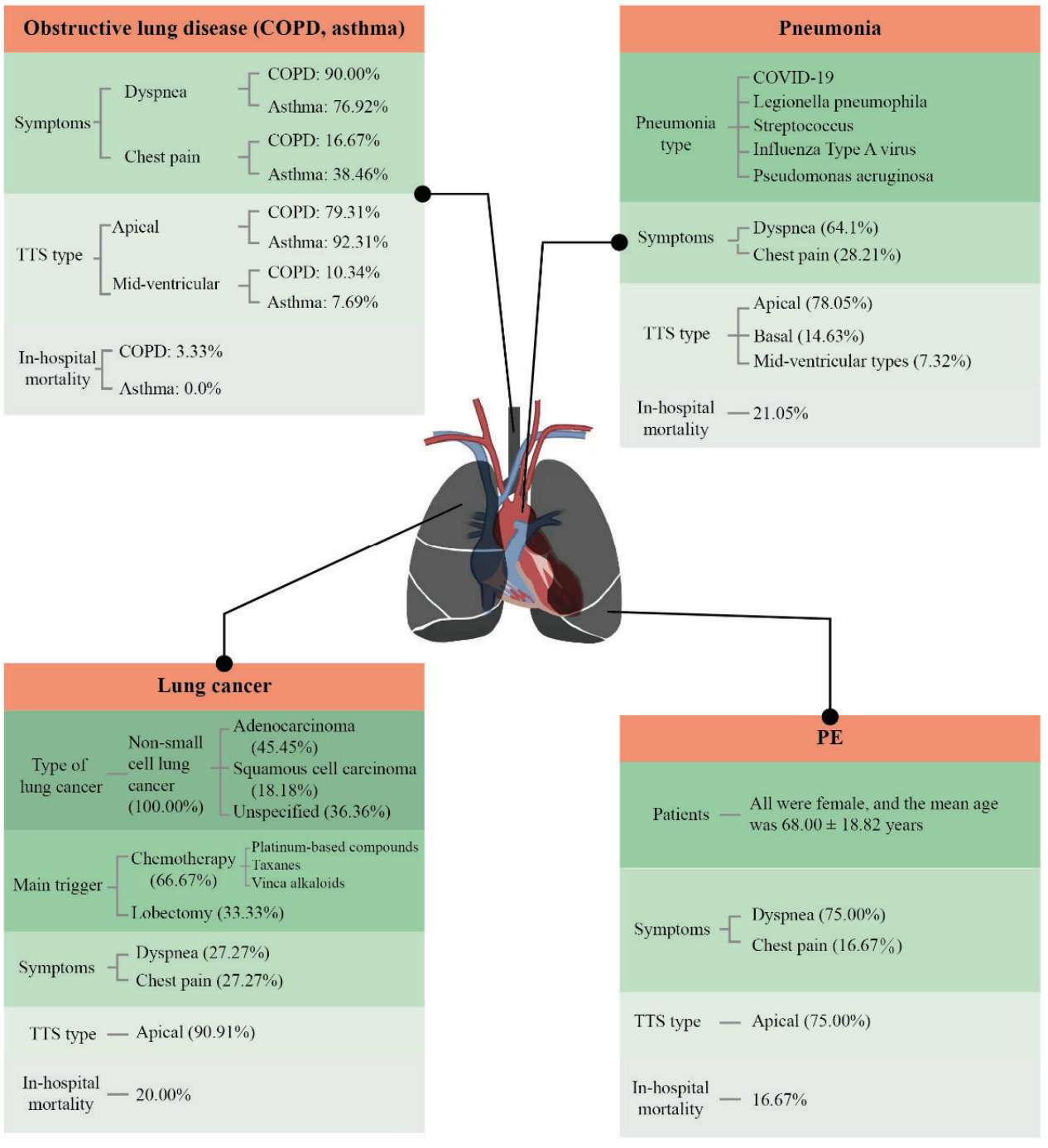
Graphical Abstract

A systematic review of takotsubo syndrome and respiratory diseases



Abbreviations: COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; PE, pulmonary embolism.

Keywords Takotsubo syndrome • Chronic obstructive pulmonary disease • Asthma • Pneumonia • Lung cancer

Introduction

First described in Japan in 1990,[1] takotsubo syndrome (TTS), also now known as stress cardiomyopathy, is characterized by transient and localized left ventricular (LV) systolic dysfunction with apical ballooning.[2] Takotsubo syndrome often mimics acute coronary syndrome (ACS); 0.7–2.2% of all ACS cases are eventually found to be TTS instead.[3–6] In contrast to ACS, patients with TTS may have obstructive coronary artery disease, but the presence of coronary lesions cannot fully explain the observed ventricular dysfunction seen in TTS.[7] Initially considered a reversible disease with an excellent prognosis, TTS is now recognized as having a significant mortality risk. The long-term mortality rate in patients with TTS is even higher than in patients with ST-segment-elevation myocardial infarction (24.7% vs. 15.1%, $P = 0.02$).[8] Furthermore, patients with TTS are at higher risk of developing immediate life-threatening complications such as ventricular rupture, cardiogenic shock, arrhythmias, cardiac arrest, and thrombus formation, as well as long-term complications, such as stroke.[7,9]

Respiratory diseases, such as chronic obstructive pulmonary disease (COPD) and asthma, are highly prevalent, affecting more than 5% and 8% of the general population, respectively.[10,11] Other respiratory illnesses, including pneumonia, pulmonary embolism (PE), and lung cancer, are also common conditions that require hospitalization. Studies have suggested that these respiratory conditions are associated with TTS and may trigger and affect the clinical course of TTS.[12] Furthermore, common therapeutic approaches for managing respiratory disease may influence the treatment of TTS. Overall, the complex relationship between respiratory disease and TTS has not been comprehensively evaluated. Here, we reviewed the literature and summarized the available evidence for the association between TTS and common respiratory illnesses, including COPD, asthma, pneumonia, PE, and lung cancer, to guide further study and raise awareness of special clinical considerations in the management of patients with concurrent respiratory disease and TTS.

Methods

We performed a systematic review of all observational studies reporting an association between respiratory disease and TTS.

Search strategy

We searched the PubMed, EMBASE, and Cochrane Library databases by using the medical subject headings (MeSH) takotsubo syndrome, asthma, chronic obstructive pulmonary disease, pneumonia, PE, and lung cancer. Results were rendered from articles in English published before 8 May 2021. Two researchers independently reviewed the literature (Y.W. and J.L.).

Inclusion and exclusion criteria

Inclusion criteria for studies were as follows: (i) the study was a case report or case series; (ii) study patients were 18 years of age or older; (iii) the study was conducted at an in-patient hospital, and patients were admitted for respiratory conditions including asthma, COPD, pneumonia, PE, or lung cancer; (iv) the study patients were concomitantly diagnosed with TTS during the same admission by performing, at a minimum, echocardiography to confirm transient ventricular akinesis or hypokinesis; (v) obstructive coronary artery disease was excluded as an aetiology; and (vi) the case description included one or more of the following elements: clinical presentation, electrocardiogram (ECG) findings, echocardiography or left ventriculogram findings, outcome, and prognosis. Exclusion criteria included conference abstracts, non-English literature, meta-analyses, reviews, comments, and unrelated studies.

Study selection

Two researchers (Y.W. and J.L.) independently reviewed abstracts and full-text articles in an unblinded manner. Disagreements between the researchers on whether to include a study were resolved by consensus, with adjudication by a third co-author when needed. The literature selection process is illustrated in Supplementary material online, *Figures S1–S5*.

After databases were searched with the keywords mentioned above, a total of 3117 articles were obtained. These articles were then manually screened, and 1968 articles were excluded based on selection criteria. After applying inclusion and exclusion criteria, 99 studies were included for analysis (Supplementary material online, *References S1–S99*). For each article, the year of publication and the patients' gender, age, medical history, clinical presentation, ECG and echocardiography findings, suspected triggers, and clinical outcomes were extracted and summarized (*Tables 1–6* and Supplementary material online, *Tables S1–S5*).

Data analysis

We further compared our results with those of Templin *et al.*[13] in a study that included 1750 patients with TTS of any type (*Table 1*). Continuous variables were presented as the mean and standard deviation, and categorical data were presented as an absolute value and percentage. The χ^2 test was used to compare categorical data. The Fisher's exact test was used in place of the χ^2 test when the expected number was <5. A two-tailed unpaired *t*-test was used for continuous variables. A *P*-value <0.05 was considered statistically significant.

Results

In the 99 studies that met our inclusion criteria, 108 patients were described. Of those, 72.22% were women, and the mean age was 65.34 ± 14.42 years. The most common respiratory diseases for which patients with TTS were admitted were obstructive lung disease (39.82%, including 27.78% COPD and 12.04% asthma) and pneumonia (38.89%, including 26.85% coronavirus disease 2019 (COVID-19) pneumonia and 12.04% other pneumonia), followed by

Table 1 Comparison of clinical characteristics and outcomes between patients with respiratory disease and TTS (Respiratory-TTS) and patients with TTS of all types (TTS-All)

Clinical characteristics	Respiratory-TTS	TTS-All[13]	*P*-value
Number of patients	108	1750	
Age (all), years	65.34 ± 14.42	66.4 ± 13.1	0.46
Age (women), years	65.32 ± 14.01	—	
Age (men), years	65.40 ± 15.44	—	
Women	78 (72.22%)	1571 (89.8%)	<0.001
Coexisting medical condition			
Obstructive lung disease	43/108 (39.82%)	—	
COPD	30/108 (27.78%)	—	
Asthma	13/108 (12.04%)	—	
Pneumonia	42/108 (38.89%)	—	
COVID-19	29/108 (26.85%)	—	
Other pneumonia	13/108 (12.04%)	—	
Lung cancer	11/108 (10.19%)	—	
PE	12/108 (11.11%)	—	
Symptoms			
Chest pain	26/105 (24.76%)	1229/1619 (75.9%)	<0.001
Dizziness	2/105 (1.90%)	—	
Dyspnoea	74/105 (70.48%)	760/1620 (46.9%)	<0.001
Syncope	3/105 (2.86%)	124/1617 (7.7%)	0.10
Ventriculogram/TTE			
LVEF (<35%)	33/68 (48.53%)	—	
Elevated cardiac and inflammatory markers			
CK-MB	20/23 (86.96%)	—	
CRP	31/43 (72.09%)	—	
D-dimer	22/36 (61.11%)	—	
NT-pro-BNP	18/34 (52.94%)	—	
Troponin-I	50/53 (94.34%)	—	
Treatment			
ACEI/ARB	20/84 (23.81%)	532/1405 (37.9%)	0.01
Aspirin	23/84 (27.38%)	459/1372 (33.5%)	0.30
34/84 (40.48%)	456/1405 (32.5%)	0.16	
Diuretics	18/84 (21.43%)	—	
ECG			
ST-segment change			
ST-segment elevation	49/105 (46.67%)	690/1578 (43.7%)	0.63
ST-segment depression	12/105 (11.43%)	121/1578 (7.7%)	0.23
Unspecified	4/105 (3.81%)	—	
T-wave inversion	55/105 (52.38%)	648/1578 (41.1%)	0.03
Prolonged QT interval	19/105 (18.10%)	550/1153 (47.7%)	<0.001
Type of TTS			
Apical[a]	86/106 (81.13%)	1430/1750 (81.7%)	0.98
Midventricular	9/106 (8.49%)	255/1750 (14.6%)	0.11
Basal	9/106 (8.49%)	39/1750 (2.2%)	0.001
Focal	0/106 (0.00%)	26/1750 (1.5%)	0.40
Biventricular	2/106 (1.89%)	—	
In-hospital outcomes			
Death (all)	13/104 (12.50%)	72/1750 (4.1%)	<0.001
Death (women)	8/74 (10.81%)	—	
Death (men)	5/30 (16.67%)	—	

Data are expressed as the mean ± standard deviation or as the number/total number (%).
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CK-MB, creatine kinase-MB; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; PE, pulmonary embolism; TTE, transthoracic echocardiogram; TTS, takotsubo syndrome.
[a] Includes a case of isolated right ventricular takotsubo syndrome with apical ballooning morphology on TTE.

PE (11.11%) and lung cancer (10.19%). The most common symptoms of TTS in patients with respiratory diseases were dyspnoea (70.48%), chest pain (24.76%), and syncope (2.86%). The LV ejection fraction was <35% in 48.53% of patients. In most patients, elevated levels of troponin-I (94.34%), creatine kinase-MB (CK-MB; 86.96%), and C-reactive protein (CRP; 72.09%) were detected. The most common ECG findings were T-wave inversion (52.38%), ST-segment elevation (46.67%), and ST-segment depression (11.43%). Apical TTS was the most common type (81.13%), followed by midventricular (8.49%), basal (8.49%), and biventricular (1.89%) types. The overall in-hospital mortality rate of patients admitted for respiratory disease complicated with TTS was 12.50%.

In addition, we compared data from our patient cohort (i.e. Respiratory-TTS) with those of 1750 patients with TTS of all types (i.e. All-TTS) reported in a study by Templin *et al.*[13] The Respiratory-TTS cohort had a significantly higher incidence of dyspnoea than the All-TTS cohort (70.48% vs. 46.9%; $P < 0.001$) but a lower incidence of chest pain (24.76% vs. 75.9%, $P < 0.001$). Furthermore, basal type TTS was significantly more common in the Respiratory-TTS cohort than in the All-TTS cohort (8.49% vs. 2.2%, $P = 0.001$).

A prolonged QT interval on ECG was less common in the Respiratory-TTS cohort than in the All-TTS cohort (18.10% vs. 47.7%, $P < 0.001$). In addition, patients in the Respiratory-TTS cohort had a higher in-hospital mortality rate than did those in the All-TTS cohort (12.50% vs. 4.1%, $P < 0.001$). The clinical characteristics of patients with respiratory disease and TTS are shown in *Table 1*. In addition, we describe the association between five common respiratory diseases and TTS below.

Obstructive lung disease (chronic obstructive pulmonary disease, asthma) and takotsubo syndrome

Obstructive lung disease, predominantly COPD and asthma, is common yet debilitating and is associated with significant morbidity and mortality.[14] Chronic obstructive pulmonary disease and asthma have both been identified in a high proportion of TTS cases, and their prevalence in patients with TTS is significantly higher than that in the general population (asthma, 25%[15]; COPD, 10.1%[16]). A growing body of evidence supports that asthma and COPD, particularly acute attacks or exacerbations, can be physical triggers of TTS (Supplementary material online, *References S1–S38*). The characteristics of the patients with COPD-TTS and asthma-TTS are summarized in *Tables 2* and *3*, respectively.

In patients with acute exacerbations of obstructive lung disease, the inflammatory cascade results in the release of proinflammatory molecules, such as cytokines and interleukins, mediated by neutrophils, macrophages, and lymphocytes.[17,18] The sympathetic responses to hypoxia and hypercapnia, in addition to the exacerbation through peripheral chemoreceptors, further enhance the overall catecholaminergic drive.[19] In a proinflammatory state, this robust catecholaminergic response may provide the foundation for the development of TTS. In addition, medications used for the treatment of COPD and asthma have been reported to be associated with the development of TTS. In this study, we found that medications were associated with the development of TTS in 31.03% of patients with COPD and 61.54% of patients with asthma (*Tables 2* and *3*). Commonly used medications include anticholinergic agent (Supplementary material online, *References S12* and *S14–S16*), β2-agonists (Supplementary material online, *References S14–S16*, *S19*, *S28*, *S32*, *S33*, *S35*, and *S38*), aminophylline (Supplementary material online, *References S14, S15*, and *S35*), and corticosteroids (Supplementary material online, *References S15*, *S16*, and *S26*), all of which have been reported as triggers of TTS (Supplementary material online, *Tables S1* and *S2*).

The diagnosis of TTS during acute exacerbations of obstructive lung disease can be challenging. In our patient cohort, those with COPD or asthma predominantly presented with atypical symptoms of dyspnoea (asthma, 76.92%; COPD, 90.00%) rather than chest pain (asthma, 38.46%; COPD, 16.67%) (*Tables 2* and *3*, Supplementary material online, *References S1–S10*, *S12–S25*, *S26–S30*, and *S32–S38*). In a case series by Rajwani *et al.* (Supplementary material online, *Reference S15*), patients with COPD were found to have TTS and all presented with increasing dyspnoea and expectoration. One patient presented with unwitnessed syncope, yet none of the patients reported chest pain. In addition, Saito *et al.* (Supplementary material online, *Reference S36*) reviewed 20 cases of acute asthma exacerbations in patients who were found to have TTS, and 75% ($n = 16$) of patients presented with dyspnoea, whereas 25% had chest pain. In contrast, in the general population without acute obstructive lung disease exacerbation, 83.2% of patients with TTS presented with chest pain.[20] Thus, the atypical presentation of TTS can mask underlying cardiac issues, delay prompt TTS diagnosis, and allow unchecked disease progression, leading to poor outcomes.

According to the available data, TTS in patients with COPD is associated with poor in-hospital outcomes (Supplementary material online, *Reference S25*). In the cases we reviewed, 3.33% of patients who were admitted for COPD complicated by TTS died (*Table 2*). Moreover, a retrospective cohort study of 3139 patients with a primary diagnosis of TTS showed that those with a comorbidity of COPD ($n = 678$) had a higher incidence of acute respiratory failure (22.6% vs. 8.2%, $P < 0.001$), cardiogenic shock (5.6% vs. 3.3%, $P = 0.024$), and in-hospital mortality (2.9% vs. 1.0%, $P = 0.005$), as well as higher hospitalization charges ($55 409.23 ± 47 809.13 vs. $46 469.60 ± $42 209.10, $P < 0.001$) and longer lengths of stay (4.02 ± 3.00 days vs. 3.40 ± 3.54 days, $P < 0.001$) than did those without COPD, after adjustments were made for patient and hospital demographics and commodities.[21] It is worth noting that, among the 13 patients with asthma and TTS, no death was reported (*Table 3*).

Chronic obstructive pulmonary disease, in particular, has been associated with recurrent TTS. Of the TTS cases reported in patients with COPD exacerbation, many reoccurred after hospital discharge (Supplementary material online, *References S7*, *S15*, *S18*, *S20*, and *S23*), and one patient had four TTS episodes in 5 years (Supplementary material online, *Reference S23*). A case of TTS recurrence has also been reported in a patient with two different types of morphologic involvement of the left ventricle: both apical and diffuse (Supplementary material online, *Reference S18*). In a prospective study of the TTS recurrence rate in 114 patients, the recurrent group ($n = 7$) was found to have a higher proportion of obstructive lung disease than was the nonrecurrent group (57.1% vs. 20.5%, $P = 0.04$).[22]

Pneumonia and takotsubo syndrome

The most common symptoms in patients with pneumonia and TTS were dyspnoea (64.10%) and chest pain (28.21%), followed by

Table 2 Clinical characteristics and outcome in patients with COPD and TTS β-blockers

Clinical characteristics	COPD-induced TTS (all)	Men	Women
Number of patients	30	7 (23.33%)	23 (76.67%)
Age, years	65.20 ± 10.02	64.57 ± 13.18	65.39 ± 8.83
Symptoms			
Chest pain	5/30 (16.67%)	1/7 (14.29%)	4/23 (17.39%)
Dizziness	0/30 (0.00%)	0/7 (0.00%)	0/23 (0.00%)
Dyspnoea	27/30 (90.00%)	5/7 (71.43%)	22/23 (95.65%)
Syncope	2/30 (6.67%)	0/7 (0.00%)	2/23 (8.70%)
Ventriculogram/TTE			
LVEF (<35%)	9/16 (56.25%)	3/4 (75.00%)	6/12 (50.00%)
Triggering factor			
COPD exacerbations	27/29 (93.10%)	6/7 (85.71%)	21/22 (95.45%)
Medications	9/29 (31.03%)	1/7 (14.29%)	8/22 (36.36%)
Aminophylline	2/9 (22.22%)	0/1 (0.00%)	2/8 (25.00%)
Anticholinergic agent	6/9 (66.67%)	1/1 (100.00%)	5/8 (62.50%)
β2-agonists	8/9 (88.89%)	0/1 (0.00%)	8/8 (100.00%)
Corticosteroids	6/9 (66.67%)	0/1 (0.00%)	6/8 (75.00%)
Elevated cardiac and inflammatory markers			
CK-MB	3/3 (100.00%)	—	3/3 (100.00%)
CRP	8/9 (88.89%)	1/1 (100.00%)	7/8 (87.50%)
D-dimer	1/1 (100.00%)	—	1/1 (100.00%)
NT-pro-BNP	4/6 (66.67%)	1/1 (100.00%)	3/5 (60.00%)
Troponin-I	14/15 (93.33%)	3/3 (100.00%)	11/12 (91.67%)
Treatment			
ACEI/ARB	7/23 (30.43%)	3/7 (42.86%)	4/16 (25.00%)
Aspirin	6/23 (26.09%)	2/7 (28.57%)	4/16 (25.00%)
10/23 (43.48%)	4/7 (57.14%)	6/16 (37.50%)	
Diuretics	6/23 (26.09%)	3/7 (42.86%)	3/16 (18.75%)
ECG			
ST-segment change			
ST-segment elevation	17/30 (56.67%)	3/7 (42.86%)	14/23 (60.87%)
ST-segment depression	4/30 (13.33%)	2/7 (28.57%)	2/23 (8.70%)
Unspecified	1/30 (3.33%)	0/7 (0.00%)	1/23 (4.35%)
T-wave inversion	17/30 (56.67%)	4/7 (57.14%)	13/23 (56.52%)
Prolonged QT interval	7/30 (23.33%)	0/7 (0.00%)	7/23 (30.43%)
Type of TTS			
Apical	23/29 (79.31%)	5/7 (71.43%)	18/22 (81.82%)
Midventricular	3/29 (10.34%)	1/7 (14.29%)	2/22 (9.09%)
Basal	2/29 (6.90%)	0/7 (0.00%)	2/22 (9.09%)
Focal	0/29 (0.00%)	0/7 (0.00%)	0/22 (0.00%)
Biventricular	1/29 (3.45%)	1/7 (14.29%)	0/22 (0.00%)
In-hospital outcomes			
Death (all)	1/30 (3.33%)	1/7 (14.29%)	0/23 (0.00%)

Data are expressed as the mean ± standard deviation or as the number/total number (%).
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CK-MB, creatine kinase-MB; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; TTE, transthoracic echocardiogram; TTS, takotsubo syndrome.

dizziness (2.56%). The most common type of TTS was apical (78.05%), followed by basal (14.63%) and midventricular (7.32%) types. Among the 42 patients with pneumonia and TTS, the mortality rate was 21.05% (22.22% in patients with COVID-19 pneumonia; 18.18% in patients with other pneumonia) (*Table 4*).

In a prospective study of patients admitted primarily for TTS ($n = 101$), the incidence of pneumonia was 20.0%.[20] In a retrospective study of patients with TTS who were admitted for noncardiac issues ($n = 230$), 23.5% presented with pneumonia upon admission.[23] Specific pneumonia-causing pathogens associated with TTS including

Table 3 Clinical characteristics and outcomes in patients with asthma and TTS

Clinical characteristics	Asthma-induced TTS (all)	Men	Women
Number of patients	13	4 (30.77%)	9 (69.23%)
Age, years	57.08 ± 13.71	61.50 ± 7.02	55.11 ± 15.39
Symptoms			
Chest pain	5/13 (38.46%)	1/4 (25.00%)	4/9 (44.44%)
Dizziness	0/13 (0.00%)	0/4 (0.00%)	0/9 (0.00%)
Dyspnoea	10/13 (76.92%)	3/4 (75.00%)	7/9 (77.78%)
Syncope	0/13 (0.00%)	0/4 (0.00%)	0/9 (0.00%)
Ventriculogram/TTE			
LVEF (<35%)	6/13 (46.15%)	1/4 (25.00%)	5/9 (55.56%)
Triggering factor			
Asthma exacerbations	8/13 (61.54%)	4/4 (100.00%)	4/9 (44.44%)
Medications	8/13 (61.54%)	2/4 (50.00%)	6/9 (66.67%)
Anticholinergic agent	0/8 (0.00%)	0/2 (0.00%)	0/6 (0.00%)
Aminophylline	1/8 (12.50%)	0/2 (0.00%)	1/6 (16.67%)
β2-agonists	6/8 (75.00%)	2/2 (100.00%)	4/6 (66.67%)
Corticosteroids	1/8 (12.50%)	0/2 (0.00%)	1/6 (16.67%)
Elevated cardiac and inflammatory markers			
CK-MB	4/4 (100.00%)	—	4/4 (100.00%)
CRP	1/1 (100.00%)	1/1 (100.00%)	0 (0.00%)
D-dimer	—	—	—
NT-pro-BNP	—	—	—
Troponin-I	10/10 (100.00%)	3/3 (100.00%)	7/7 (100.00%)
Treatment			
ACEI/ARB	4/12 (33.33%)	1/3 (33.33%)	3/9 (33.33%)
Aspirin	4/12 (33.33%)	1/3 (33.33%)	3/9 (33.33%)
β-blockers	6/12 (50.00%)	2/3 (66.66%)	4/9 (44.44%)
Diuretics	1/12 (8.33%)	0/3 (0.00%)	1/9 (11.11%)
ECG			
ST-segment change			
ST-segment elevation	6/13 (46.15%)	1/4 (25.00%)	5/9 (55.56%)
ST-segment depression	3/13 (23.08%)	1/4 (25.00%)	2/9 (22.22%)
T-wave inversion	5/13 (38.46%)	2/4 (50.00%)	3/9 (33.33%)
Prolonged QT interval	2/13 (15.38%)	1/4 (25.00%)	1/9 (11.11%)
Type of TTS			
Apical	12/13 (92.31%)	4/4 (100.00%)	8/9 (88.89%)
Midventricular	1/13 (7.69%)	0/4 (0.00%)	1/9 (11.11%)
Basal	0/13 (0.00%)	0/4 (0.00%)	0/9 (0.00%)
Focal	0/13 (0.00%)	0/4 (0.00%)	0/9 (0.00%)
Biventricular	0/13 (0.00%)	0/4 (0.00%)	0/9 (0.00%)
In-hospital outcomes			
Death	0/13 (0.00%)	0/4 (0.00%)	0/9 (0.00%)

Data are expressed as the mean ± standard deviation or as the number/total number (%).
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CK-MB, creatine kinase-MB; CRP, C-reactive protein; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; TTE, transthoracic echocardiogram; TTS, takotsubo syndrome.

Legionella pneumophila (Supplementary material online, *Reference S49*), *Streptococcus pneumonia*,[24] influenza Type A virus (Supplementary material online, *Reference S47*), *Pseudomonas aeruginosa*,[25] and COVID-19 pneumonia (Supplementary material online, *References S50–S53 and S55–S75*) have been reported in previous case reports (Supplementary material online, *Table S3*). Sepsis, both in general and as a result of pulmonary infections, has been associated with the development of apical ballooning.[25–27] Suggested mechanisms include the sensitization of cardiac tissue by bacterial toxins, resulting in increased susceptibility to hypoxia, alterations in calcium transportation, and cellular apoptosis.[28] In an observational study,[29] a group of patients with TTS and pneumonia was found to have a higher in-hospital mortality rate than a group of patients with TTS without pneumonia (odds ratio = 3.07%, 95% confidence

Table 4 Clinical characteristics and outcomes in patients with pneumonia and TTS

Clinical characteristics	Pneumonia-induced TTS (all)	Men	Women
Number of patients	42	15 (35.71%)	27 (64.29%)
Age, years	68.50 ± 15.01	70.00 ± 15.99	67.67 ± 14.37
Pneumonia type			
COVID-19	29/42 (69.05%)	10/29 (34.48%)	19/29 (65.52%)
Other pneumonia	13/42 (30.95%)	5/13 (38.46%)	8/13 (61.54%)
Symptoms			
Chest pain	11/39 (28.21%)	6/14 (42.86%)	5/25 (20.00%)
Dizziness	1/39 (2.56%)	1/14 (7.14%)	0/25 (0.00%)
Dyspnoea	25/39 (64.10%)	8/14 (57.14%)	17/25 (68.00%)
Syncope	0/39 (0.00%)	0/14 (0.00%)	0/25 (0.00%)
Ventriculogram/TTE			
LVEF (<35%)	11/24 (45.83%)	3/8 (37.50%)	8/16 (50.00%)
Elevated cardiac and inflammatory markers			
CK-MB	6/8 (75.00%)	2/2 (100.00%)	4/6 (66.67%)
CRP	22/22 (100.00%)	9/9 (100.00%)	13/13 (100.00%)
D-dimer	15/16 (93.75%)	4/5 (80.00%)	11/11 (100.00%)
NT-pro-BNP	13/14 (92.86%)	4/4 (100.00%)	9/10 (90.00%)
Troponin-I	11/13 (84.62%)	3/4 (75.00%)	8/9 (88.89%)
Treatment			
ACEI/ARB	4/32 (12.50%)	0/11 (0.00%)	4/21 (19.05%)
Aspirin	9/32(28.13%)	2/11 (18.18%)	7/21 (33.33%)
β-blockers	9/32 (28.13%)	3/11 (27.27%)	6/21 (28.57%)
Diuretics	2/32 (6.25%)	1/11 (9.09%)	1/21 (4.76%)
ECG			
ST-segment change			
ST-segment elevation	19/40 (47.50%)	8/14 (57.14%)	11/26 (42.31%)
ST-segment depression	3/40 (7.50%)	0/14 (0.00%)	3/26 (11.54%)
Unspecified	1/40 (2.50%)	1/14 (7.14%)	0/26 (0.00%)
T-wave inversion	22/40 (55.00%)	7/14 (50.00%)	15/26 (57.69%)
Prolonged QT interval	9/40 (22.50%)	4/14 (28.57%)	5/26 (19.23%)
Type of TTS			
Apical[a]	32/41 (78.05%)	12/15 (80.00%)	20/26 (76.92%)
Midventricular	3/41 (7.32%)	0/15 (0.00%)	3/26 (11.54%)
Basal	6/41 (14.63%)	3/15 (20.00%)	3/26 (11.54%)
Focal	0/41 (0.00%)	0/15 (0.00%)	0/26 (0.00%)
Biventricular	0/41 (0.00%)	0/15 (0.00%)	0/26 (0.00%)
In-hospital outcomes			
Death (all)	8/38 (21.05%)	3/14 (21.43%)	5/24 (20.83%)
COVID-19	6/27 (22.22%)	2/10 (20.00%)	4/17 (23.53%)
Other pneumonia	2/11 (18.18%)	1/4 (25.00%)	1/7 (14.29%)

Data are expressed as the mean ± standard deviation or as the number/total number (%).
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CK-MB, creatine kinase-MB; CRP, C-reactive protein; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; TTE, transthoracic echocardiogram; TTS, takotsubo syndrome.
[a] Includes a case of isolated right ventricular takotsubo syndrome with apical ballooning morphology on TTE.

interval = 2.15–4.38; $P < 0.001$). The in-hospital mortality rate among patients with TTS and COVID-19 pneumonia has been reported to be as high as 57%.[30] In the cases we reviewed, 21.05% of the patients who had pneumonia complicated with TTS died (*Table 4*).

Given the ongoing COVID-19 pandemic, it is noteworthy that TTS has increasingly been seen in patients with COVID-19 pneumonia (Supplementary material online, *References S50–S53 and S55–S75*). Addressing this association is of particular importance, and TTS should be considered as a potential complication when managing the care of patients with COVID-19 pneumonia, especially when clinical deterioration occurs with signs of heart failure and shock. Although the exact pathophysiologic mechanisms have yet to be

determined, similar ones to those suggested above have been hypothesized. In a recent observational study, Giustino *et al.*[31] proposed that cytokine-induced damage, direct viral invasion of the myocardium, and microvascular thrombi formation in patients with a catecholaminergic surge may result in the development of TTS. Furthermore, TTS was associated with increased mortality. Of note, all patients in their cohort were men, despite the fact that TTS has been reported predominantly in women. As with other respiratory illnesses, we found that TTS in patients with pneumonia presented largely as dyspnoea (Supplementary material online, *References S41, S42, S45–S47, S49, S53, S55, S58, S60, S63–S65, and S69–S75*).

Lung cancer and takotsubo syndrome

Among the patients with lung cancer and TTS included in this study, 7 out of 11 (63.64%) were women. All of these patients had non-small-cell lung cancers, the most common of which was adenocarcinoma (45.45%), followed by squamous cell carcinoma (18.18%). Chemotherapy (66.67%) and lobectomy (33.33%) were the two main causative factors. In these patients, the most common symptoms were dyspnoea (27.27%) and chest pain (27.27%), and TTS was predominantly the apical type (90.91%) (*Table 5*).

In a meta-analysis in which the prevalence of malignancy in patients with TTS was evaluated, lung cancer was identified as the second most common type of cancer in patients with TTS, with a reported prevalence as high as 17%.[32] Takotsubo syndrome has been reported after patients undergo surgical interventions for lung cancer (i.e. resection of diseased tissue). However, the available evidence is limited to case reports (Supplementary material online, *Table S4* and *References S78, S80, and S85*). Several pathophysiologic mechanisms have been suggested that may explain these findings. Augmented catecholaminergic responses, states of profound physical stress induced by highly morbid surgical procedures, such as thoracotomy, inadequate anaesthesia, tracheal manipulation, exogenous administration of catecholamines during procedures, and haemodynamic and pulmonary compromise that may accompany high-risk procedures have all been implicated in the development of TTS.[33] However, for a causal relationship to be established, these mechanisms require further study.

Other therapeutic interventions used in the treatment of lung malignancy include radiotherapy (Supplementary material online, *Reference S80*) and chemotherapy, such as platinum-based compounds (Supplementary material online, *References S80, S81, S84, and S87*), taxanes (Supplementary material online, *References S80 and S84*), vinca alkaloids (Supplementary material online, *Reference S81*), vascular endothelial growth factor inhibitor (Supplementary material online, *Reference S77*), and tyrosine kinase inhibitor (Supplementary material online, *References S83 and S86*), which have both been associated with TTS (Supplementary material online, *Table S4*). Herrmann *et al.*[34] explored vascular toxicities related to chemotherapeutic agents and described associations between TTS and certain drugs, including 5-fluorouracil, capecitabine, sunitinib, and combretastatin. Monoclonal antibodies, such as bevacizumab and rituximab, were also implicated in the development of TTS. These agents can directly induce vascular stenoses, myocardial ischemia, thrombosis, and coronary vasospasm. Radiation-based therapy is also associated with TTS. Although the exact mechanisms underlying the effects of these therapies on TTS development remain unclear, radiation-induced myocardial fibrosis, capillary endothelial dysfunction, vasculopathy, baroreceptor damage, premature atherosclerosis, and 'coronaritis' have all been implicated to play a role.[35,36]

Other features accompanying lung cancer may also contribute to TTS development, including the stress associated with various diagnostic and therapeutic procedures, cancer-related pain (Supplementary material online, *Reference S81*), and cancer-related symptoms, such as dyspnoea, fever, bleeding, anaemia, and vomiting, causing alterations in preload and afterload.[37] In addition to the chronic state of inflammation in these patients, the psychophysical stress response further enhances TTS risk.

In general, patients who have cancer concurrent with TTS have worse hospitalization outcomes and higher resource utilization, healthcare costs, and mortality than do patients with cancer alone. A retrospective study of data from the National Inpatient Sample showed that patients admitted for TTS with a coexisting malignancy had a significantly higher mortality rate (13.8% vs. 2.9%, $P < 0.0001$), length of stay (7 vs. 4 days, $P < 0.0001$), and total charge ($29 291 vs. $36 231, $P < 0.0001$) than those without malignancy.[38] The data we extracted from case reports showed that the in-hospital mortality rate in patients who had lung cancer complicated with TTS was 20.00% (women, 16.67%; men, 25.00%) (*Table 5*). For the two patients who died, the exact cause of death was not disclosed. One patient had an apical thrombus, possibly resulting from malignancy-associated hypercoagulability and akinetic apex (Supplementary material online, *Reference S79*). For the other patient, autopsy results revealed cancer infiltration in the pericardium and myocardium, as well as cancer cell embolism in small coronary arteries and capillaries (Supplementary material online, *Reference S84*). Currently, there are no clear guidelines for which treatment strategies to adopt in patients with lung cancer and coexisting TTS.[39]

Pulmonary embolism and takotsubo syndrome

Although PE is uncommonly seen in association with TTS, it has also been identified as a risk factor in TTS development.[40] In addition, acute PE is a recognized risk factor for secondary TTS, as reported by the European Society of Cardiology Taskforce on TTS,[41] although this relationship has been shown primarily in case report studies. Patients with concurrent TTS and PE were notably women, had a mean age of 68.00 ± 18.82 years, and were individuals with underlying thrombotic conditions (*Table 6* and Supplementary material online, *Table S6*). However, the underlying mechanisms remain unclear.

Distinguishing between PE alone and PE concurrent with TTS based on clinical symptoms alone is also challenging (Supplementary material online, *References S88–S92 and S95–S99*). Among the cases we reviewed, the most common symptom in patients with PE and TTS was dyspnoea (75.00%), whereas chest pain was present in only 16.67% of these patients. Of note, 8.33% of patients presented with syncope (*Table 6*).

The effect of TTS as a complication on the clinical outcomes of patients with PE remains unclear. In a case review by Jin *et al.* ($n = 7$) (Supplementary material online, *Reference S96*), all patients with coexisting TTS and PE had an uneventful recovery with improved systolic function after treatment. Among the 12 patients with PE and TTS included in our review, the in-hospital mortality rate was 16.67%. Of the two patients who died, one patient died within 24 h due to ineffective thrombolysis (Supplementary material online,

Table 5 Clinical characteristics and outcomes in patients with lung cancer and TTS

Clinical characteristics	Lung cancer-induced TTS (all)	Men	Women
Number of patients	11	4 (36.36%)	7 (63.64%)
Age, years	60.55 ± 12.26	53.50 ± 15.47	64.00 ± 7.87
Type of lung cancer			
Non-small-cell lung cancer	11/11 (100.00%)	4/4 (100.00%)	7/7 (100.00%)
Adenocarcinomas	5/11 (45.45%)	2/4 (50.00%)	3/7 (42.86%)
Squamous cell carcinomas	2/11 (18.18%)	1/4 (25.00%)	1/7 (14.29%)
Unspecified	4/11 (36.36%)	1/4 (25.00%)	3/7 (42.86%)
Small-cell lung cancer	0/11 (0.00%)	0/4 (0.00%)	0/7 (0.00%)
Symptoms			
Chest pain	3/11 (27.27%)	0/4 (0.00%)	3/7 (42.86%)
Dizziness	1/11 (9.09%)	0/4 (0.00%)	1/7 (14.29%)
Dyspnoea	3/11 (27.27%)	1/4 (25.00%)	2/7 (28.57%)
Syncope	0/11 (0.00%)	0/4 (0.00%)	0/7 (0.00%)
Ventriculogram/TTE			
LVEF (<35%)	3/6 (50.00%)	1/1 (100.00%)	2/5 (40.00%)
Triggering factor			
Chemotherapy	6/9 (66.67%)	3/4 (75.00%)	3/5 (60.00%)
Platinum-based compounds	4/9 (44.44%)	2/4 (50.00%)	2/5 (40.00%)
Taxanes	2/9 (22.22%)	2/4 (50.00%)	0/5 (0.00%)
Vinca alkaloids	1/9 (11.11%)	0/4 (0.00%)	1/5 (20.00%)
VEGF inhibitor	1/9 (11.11%)	1/4 (25.00%)	0/5 (0.00%)
Tyrosine kinase inhibitor	2/9 (22.22%)	0/4 (0.00%)	2/5 (40.00%)
Lobectomy	3/9 (33.33%)	2/4 (50.00%)	1/5 (20.00%)
Elevated cardiac and inflammatory markers			
CK-MB	3/4 (75.00%)	2/3 (66.67%)	1/1 (100.00%)
CRP	—	—	—
D-dimer	1/1 (100.00%)	—	1/1 (100.00%)
NT-pro-BNP	—	—	—
Troponin-I	6/6 (100.00%)	2/2 (100.00%)	4/4 (100.00%)
Treatment			
ACEI/ARB	0/6 (0.00%)	—	0/6 (0.00%)
Aspirin	1/6 (16.67%)	—	1/6 (16.67%)
β-blockers	3/6 (50.00%)	—	3/6 (50.00%)
Diuretics	3/6 (50.00%)	—	3/6 (50.00%)
ECG			
ST-segment change			
ST-segment elevation	4/11 (36.36%)	1/4 (25.00%)	3/7 (42.86%)
ST-segment depression	1/11 (9.09%)	1/4 (25.00%)	0/7 (0.00%)
Unspecified	1/11 (9.09%)	0/4 (0.00%)	1/7 (14.29%)
T-wave inversion	4/11 (36.36%)	2/4 (40.00%)	2/7 (28.57%)
Prolonged QT interval	0/11 (0.00%)	0/4 (0.00%)	0/7 (0.00%)
Type of TTS			
Apical	10/11 (90.91%)	4/4 (100.00%)	6/7 (85.71%)
Midventricular	1/11 (9.09%)	0/4 (0.00%)	1/7 (14.29%)
Basal	0/11 (0.00%)	0/4 (0.00%)	0/7 (0.00%)
Focal	0/11 (0.00%)	0/4 (0.00%)	0/7 (0.00%)
Biventricular	0/11 (0.00%)	0/4 (0.00%)	0/7 (0.00%)
In-hospital outcomes			
Death (all)	2/10 (20.00%)	1/4 (25.00%)	1/6 (16.67%)

Data are expressed as the mean ± standard deviation or as the number/total number (%).
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CK-MB, creatine kinase-MB; CRP, C-reactive protein; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; TTE, transthoracic echocardiogram; TTS, takotsubo syndrome; VEGF, vascular endothelial growth factor.

Table 6 Clinical characteristics and outcomes in patients with PE and TTS

Clinical characteristics	PE-induced TTS
Number of patients	12
Age, years	68.00 ± 18.82
Women	12 (100.00%)
Symptoms	
Chest pain	2/12 (16.67%)
Dizziness	0/12 (0.00%)
Dyspnoea	9/12 (75.00%)
Syncope	1/12 (8.33%)
Ventriculogram/TTE	
LVEF (<35%)	4/9 (44.44%)
Elevated cardiac and inflammatory markers	
CK-MB	4/4 (100.00%)
CRP	—
D-dimer	5/5 (100.00%)
NT-pro-BNP	1/1 (100.00%)
Troponin-I	9/9 (100.00%)
Treatment	
ACEI/ARB	5/11 (45.45%)
Aspirin	3/11 (27.27%)
β-blockers	6/11 (54.55%)
Diuretics	6/11 (54.55%)
ECG	
ST-segment change	
ST-segment elevation	3/11 (27.27%)
ST-segment depression	1/11 (9.09%)
Unspecified	1/11 (9.09%)
T-wave inversion	7/11 (63.64%)
Prolonged QT interval	1/11 (9.09%)
Type of TTS	
Apical	9/12 (75.00%)
Midventricular	1/12 (8.33%)
Basal	1/12 (8.33%)
Focal	0/12 (0.00%)
Biventricular	1/12 (8.33%)
In-hospital outcomes	
Death (all)	2/12 (16.67%)

Data are expressed as the mean ± standard deviation or as the number/total number (%).
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CK-MB, creatine phosphokinase-MB; CRP, C-reactive protein; LVEF, left ventricular ejection fraction; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; PE, pulmonary embolism; TTE, transthoracic echocardiogram; TTS, takotsubo syndrome.

Reference S93), and the other autopsy results confirmed the existence of PE and pheochromocytoma (Supplementary material online, *Reference S99*).

Other respiratory conditions and takotsubo syndrome

Other respiratory conditions have also been shown to trigger TTS, although data are limited to case reports, and little is known about the underlying pathophysiologic mechanisms. Other respiratory conditions reportedly associated with TTS include postpartum spontaneous mediastinal emphysema,[42,43] pneumothorax,[44] and pulmonary hypertension.[45,46] In addition, TTS has been associated with invasive procedures in patients with lung disease, such as the induction of anaesthesia,[47] lung transplantation,[48,49] endotracheal intubation,[50] intubation failure,[51] and extubation after mechanical ventilation.[52] However, no reliable estimate of the frequency and causality is available.

Limitations

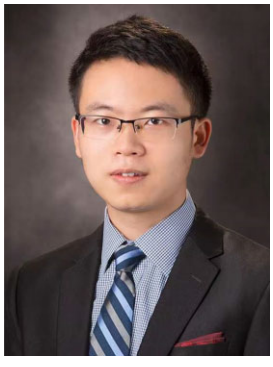
This study had a few limitations. First, only published case reports were included. Thus, reporting bias may have existed, which may have affected our findings. Second, the long-term prognosis of patients with coexisting TTS and respiratory disease could not be analysed because of the lack of follow-up data provided in most case reports. Finally, details attributing to all-cause in-hospital mortality were limited; thus, analysing whether mortality was attributed to respiratory disease or TTS was difficult.

Conclusion

Patients with acute respiratory conditions comprise a large volume of ER visits and hospitalizations in the USA. Concerns about the development of TTS in these patients are important to investigate, given the potential impact on mortality, morbidity, complications, hospitalization, outcomes, and hospital length of stay. Few large-scale studies have evaluated these associations. The data supporting these observations are limited; however, our review of the available literature shows many probable associations between respiratory conditions and TTS.

The development of TTS in patients admitted for respiratory diseases, particularly pneumonia or lung cancer, is associated with increased mortality when compared with patients who have TTS of all types. In patients with respiratory disease, concurrently diagnosing TTS can be challenging and may be delayed because of the atypical presentation of TTS. A high degree of clinical suspicion is required to make an accurate diagnosis and to initiate appropriate therapy. The suggested pathophysiologic mechanisms of TTS in patients vary with respiratory diseases; thus, future prospective studies are needed to investigate the underlying mechanism of TTS development for each respiratory disease. Additionally, studies are required to establish appropriate guidelines for the management of respiratory disease concurrent with TTS.

Lead author biography



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Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

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Conflict of interest: none declared.

Data availability

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

Declaration of Helsinki

The study was conducted according to the guidelines of the Declaration of Helsinki.

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