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.
**Introduction**

First described in Japan in 1990, takotsubo syndrome (TTS), also now known as stress cardiomyopathy, is characterized by transient and localized left ventricular (LV) systolic dysfunction with apical ballooning. Takotsubo syndrome often mimics acute coronary syndrome (ACS); 0.7–2.2% of all ACS cases are eventually found to be TTS instead. 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. 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%, \( P = 0.02 \)). 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.

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. 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. 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. 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 \( \chi^2 \) test was used to compare categorical data. The Fisher’s exact test was used in place of the \( \chi^2 \) 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<sup>13</sup> | 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<sup>a</sup>                                            | 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.

<sup>a</sup> 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 dyspnea (70.48%), chest pain (24.76%), and syncope (2.86%). The LV ejection fraction was <35% in 48.83% 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. The Respiratory-TTS cohort had a significantly higher incidence of dyspnea 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. 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%; COPD, 10.1%). 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. The sympathetic responses to hypoxia and hypercapnia, in addition to the exacerbation through peripheral chemoreceptors, further enhance the overall catecholaminergic drive. 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), αminophylline (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 dyspnea (asthma, 76.92%; COPD, 90.00%) rather than chest pain (asthma, 38.46%; COPD, 16.67%) (Tables 2 and 3). 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 dyspnea 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 dyspnea, 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. 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 those without COPD, after adjustments were made for patient and hospital demographics and comorbidities. 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 the nonrecurrent group (57.1% vs. 20.5%, P = 0.04).

**Pneumonia and takotsubo syndrome**

The most common symptoms in patients with pneumonia and TTS were dyspnea (64.10%) and chest pain (28.21%), followed by...
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).
Legionella pneumophila (Supplementary material online, Reference S49), Streptococcus pneumoniae, influenza Type A virus (Supplementary material online, Reference S47), Pseudomonas aeruginosa, 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. Suggested mechanisms include the sensitization of cardiac tissue by bacterial toxins, resulting in increased susceptibility to hypoxia, alterations in calcium transportation, and cellular apoptosis. In an observational study, 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 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.
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%.

In the cases we reviewed, 21.05% of the patients who had pneumonia complicated with TTS died (Table 4).

The ongoing COVID-19 pandemic underscores the importance of recognizing TTS as a potential complication in 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 fully elucidated, the association between COVID-19 and TTS highlights the need for heightened vigilance and prompt intervention to optimize outcomes.

### 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%)  |
| \( \beta \)-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*                                  | 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.

* Includes a case of isolated right ventricular takotsubo syndrome with apical ballooning morphology on TTE.
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%. 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, Reference S41, S42, S45–S47, S49, S53, S55, S58, S60, S63–S65, and S69–S75).

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. In addition, acute PE is a recognized risk factor for secondary TTS, as reported by the European Society of Cardiology Taskforce on TTS, 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, Reference S84). 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,
| 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.
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 pneumothorax44 and pulmonary hypertension.45,46 In addition, TTS has been associated with invasive procedures in patients with lung disease, such as the induction of anesthesia,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 analyzed 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, analyzing 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

Pengyang Li, MD, MSc, earned his medical degree from Xinxiang Medical University and Peking University Health Science Center. He completed his postdoctoral research training at the Texas Heart Institute and internal medicine residency training at Saint Vincent Hospital, and he is currently a first-year cardiology fellow at Virginia Commonwealth University. His research interests include big data-based:

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).
outcomes research, cardiovascular risk factors, and cardiomyopathy, particularly takotsubo syndrome.

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.

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

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