Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Takotsubo Syndrome in Coronavirus Disease 2019

Around one-fifth of patients with coronavirus disease 2019 (COVID-19) show evidence of acute myocardial injury. The precise etiology remains unclear and the observation that some patients do not show obstructive coronary artery disease on coronary angiography has further complicated our understanding of the pathophysiology.

Takotsubo syndrome (TTS) constitutes an acute heart failure syndrome that may represent a form of acute catecholaminergic myocardial stunning. TTS presents with the typical symptoms of an acute coronary syndrome, like that observed in some patients with COVID-19.

Eleven patients with COVID-19 who were diagnosed with TTS based on current criteria were included and compared to 97 patients with COVID-19 alone and 3,215 patients with TTS to elucidate features of COVID-19 patients who develop TTS and to infer the underlying pathology. Furthermore, we have stratified COVID-19 patients with myocardial injury into 2 groups: those with wall motion abnormalities and those without.

While COVID-19 disproportionately affected men (68.0%), most patients with COVID-19+TTS were women (81.8%). Most COVID-19+TTS patients had either physical (72.7%) or emotional (18.2%) triggers, most likely from infection with the severe acute respiratory syndrome coronavirus 2. Patients with COVID-19+TTS also tended to be older (mean age 72.4 years) compared to patients with COVID-19 alone (mean age 58.5 years) and TTS (mean age 67.8 years). Chest pain was more common among patients with TTS, irrespective of COVID-19, whereas dyspnea was most prevalent among COVID-19 patients who develop TTS. Importantly, patients with COVID-19 who developed TTS had significantly worse outcomes in terms of rates of respiratory therapy or in-hospital death (70.0%) than traditional cases of TTS (18.6%) (Figure 1).

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Troponin and brain natriuretic peptide (BNP) levels were typically elevated at the time of admission in COVID-19 patients with myocardial injury, suggesting that the systemic inflammatory response may be precipitating troponin release in these patients. In contrast, in patients with COVID-19 and TTS, troponin and BNP levels were generally low upon admission but increased during hospitalization. Left ventricular ejection fraction was most significantly reduced in patients COVID-19+TTS among all the groups we analyzed.

Some of these cases of COVID-19-associated myocardial injury had global wall motion impairment, which we postulate may actually be a form of TTS. Although TTS typically presents with regional wall motion abnormalities (e.g., apical ballooning), a "globally" reduced form has also been observed.[1] It is conceivable that the cytokine storm and catecholamine surge in patients with COVID-19 may cause a "global" form of TTS in which the basal myocardium is not able to compensate, leading to global hypokinesia (Figure 1).

Patients with TTS also generally show localized edema in the region of the wall motion abnormality on cardiac magnetic resonance (CMR) images. Meanwhile, a marked biventricular pattern of myocardial edema has been reported in a case of COVID-19-associated myocardial injury.[2] We also observed a COVID-19 patient with TTS who showed marked edema in the region of the wall motion abnormality on CMR in addition to global edema (Figure 1). Indeed, as both TTS and COVID-19 can trigger microcirculatory dysfunction,[3] it is possible they could act jointly resulting in significant cardiac complications. In particular, the cytokine storm that occurs in COVID-19 may work in concert with the exaggerated sympathetic stimulation of TTS to activate similar (albeit currently unknown) pathways, resulting in severe microcirculatory dysfunction, global/regional myocardial edema, and decompensated acute heart failure.

Of note, we observed contraction band necrosis with mononuclear infiltration in four of six patients who died due to COVID-19 and underwent autopsy (Figure 1). In comparison to coagulation necrosis in myocardial ischemia, contraction band necrosis can

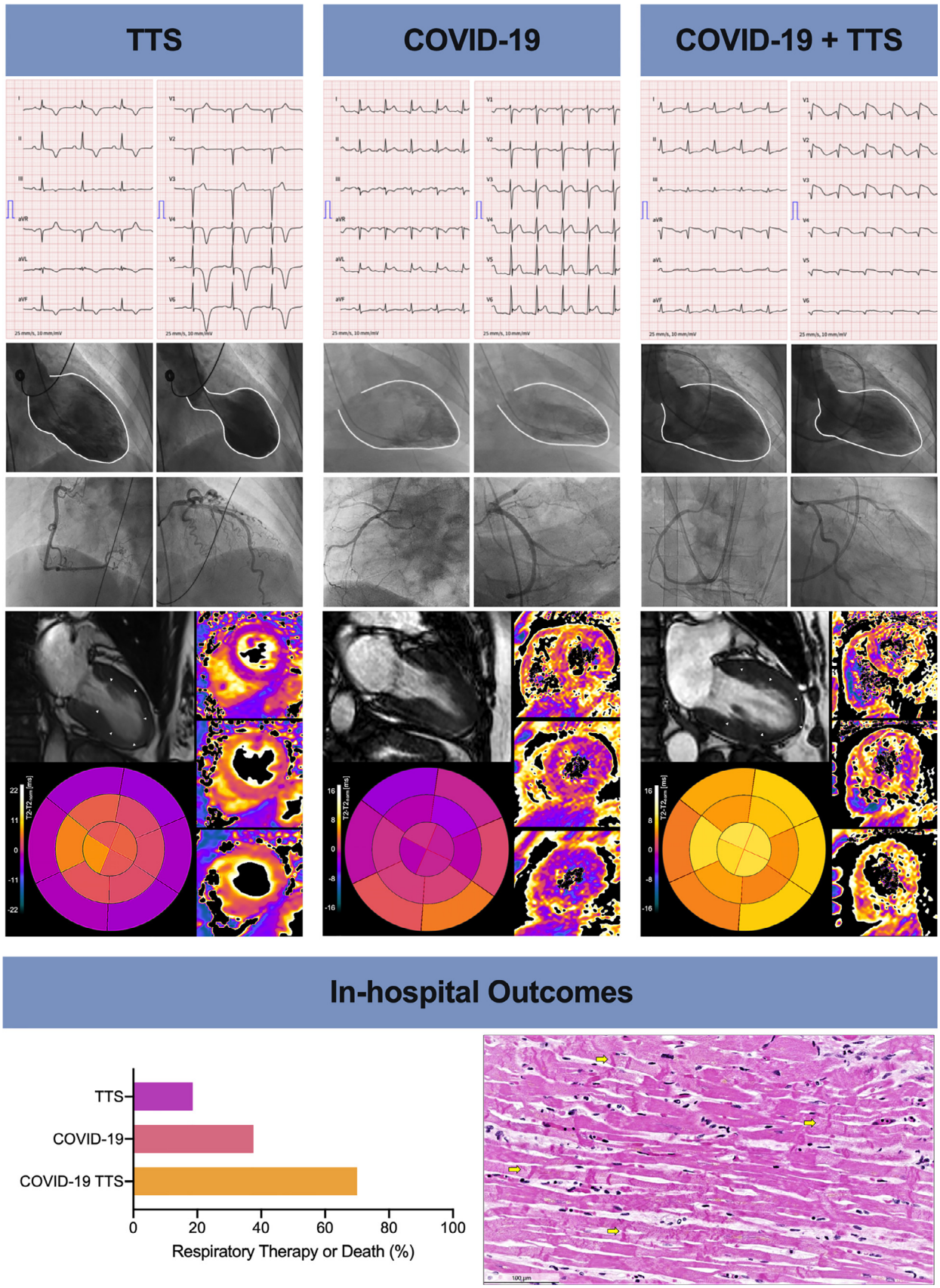

Figure 1. Electrocardiography (ECG; *top row*), left ventriculography (*second row*), and cardiac magnetic resonance images (CMR; *fourth row*) from patients with TTS, COVID-19, and COVID-19+TTS. Coronary angiography (*third row*) showed unobstructed coronary arteries in all 3 patients. The CMR images display the 2-chamber cine frame; the basal, mid-ventricular, and apical T2 maps, and the T2 bulls eye plot. In-hospital outcomes (including death or ventilation) are also summarized (*bottom left*). Routine hematoxylin and eosin (H&E) stained section of the posterior myocardial wall from a COVID-19+TTS patient (autopsy heart specimen; bottom right).

be seen as a result of the biopsy procedure or reflects catecholamine toxicity and sympathetic hyperactivity.[4] Indeed, the presence of contraction band necrosis and mononuclear infiltration has been reported previously in TTS,[5] potentially reflecting sympathetic overdrive. Contraction bands in combination with mononuclear infiltration, argue against artifactual changes and is indicative of the acute phase of severe left ventricular dysfunction. Therefore, an earlier biopsy may reveal the true incidence of contraction band necrosis in cases of COVID-19 myocardial injury with impaired wall motion abnormalities and normal coronary arteries.

In summary, the severe inflammatory response that occurs in COVID-19 may work in concert with the exaggerated sympathetic stimulation of TTS to activate similar pathways, resulting in severe microcirculatory dysfunction, global/regional myocardial edema, and decompensated acute heart failure. We hypothesize the coronary microcirculatory disturbances resulting from the combination of COVID-19+TTS could trigger a sudden calcium influx, culminating in contraction band necrosis. Therefore, patients with a dual diagnosis of TTS and COVID are at increased risk of adverse events.

Disclosures

The authors have no conflict of interest to disclose.

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Impact of Hospital Procedural Volume on Outcomes Following Balloon Aortic Valvuloplasty

Balloon aortic valvuloplasty (BAV) is indicated in patients with acute decompensated heart failure or cardiogenic shock secondary to severe aortic stenosis,[1] either as palliative therapy for patients who are not candidates for valve replacement,[2] or as a bridge to transcatheter (TAVR) or surgical aortic valve replacement (SAVR).[1,3] Given the high morbidity and mortality associated with BAV, especially because it is performed not infrequently in critically ill patients, it is important to understand the effect of hospital procedural volume on outcomes after BAV.

We identified all hospitalizations in patients aged ≥ 60 years who underwent BAV (International Classification of Diseases, Ninth Revision, Clinical Modification procedure code 35.96 and International Classification of Diseases, Tenth Revision, Clinical Modification procedure codes 0ZRF3ZZ, 027F4ZZ, 02NF3ZZ, and 02NF4ZZ) from 2015 to 2017 using the National Inpatient Sample database. The patients who underwent TAVR or SAVR during the same admission were excluded. The procedure was categorized as "urgent" status if the admission was not

First column: TTS patients show deep negative T-waves and prolonged QTc time on ECG. Left ventriculography shows classical apical ballooning with compensatory hypercontractility of the basal segments. CMR with edema sensitive T2-mapping showed normal T2 values in the basal segments and edema of the mid-ventricular and apical segments (T2 z-score mid-ventricular and apical: 4 and 8).
Second column: COVID-19 patient with ST-segment elevation in I, aVL, V5, and V6, with normal QTc time on ECG. Left ventriculography shows mildly-reduced left ventricular ejection fraction with infero- and antero-lateral basal hypokinesia. CMR demonstrates diffusely elevated T2 values that are accentuated in the hypokinetic segments (infero-lateral basal, T2 z-score: 5).
Third column: COVID-19 TTS patients show significant ST-elevations in the septal and anterior chest leads on ECG after 3 weeks of intensive care treatment (including mechanical ventilation for acute respiratory distress syndrome). Left ventriculography shows rapid deterioration of left ventricular function with TTS wall motion pattern. Representative CMR shows excessively high T2 values over the entire myocardium, indicating global edema with peak values in the apical segments (T2 z-score: 9). The myocardial fibers show loss of cross-striations and nuclei are not visible in most areas. Most fibers display several irregularly shaped wavy contractions extending across the myocardial fibers (arrows). Some congested small capillaries can be observed in the interstitial space with increased mononuclear cells.