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## Short communication

## Takotsubo syndrome in COVID-19 era: Is psychological distress the key?



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## ABSTRACT

Covid-19 pandemic, starting from Wuhan, China spread all over the world and Italy was one of the most affected countries, especially in Lombardy, where, on February 20, the first confirmed case was detected. Italian Government ordered a national lockdown on the 9<sup>th</sup> March 2020, forcing the population to severe restrictive isolation measures. The burden on mental health of the medical emergency related to COVID19 is progressively been revealed. Takotsubo syndrome (TTS), is estimated to represent 1–3% of patients admitted with suspected STEMI, mostly affecting elderly women with emotional stress and/or acute illness preceding the presentation. Comparing patients hospitalised from February to May 2020 with those of the corresponding period in 2019 we observed a significantly increased number of TTS diagnosis in 2020 (11 patients vs 3 in 2019), especially during the first period of lockdown. The only two males were patients with COVID-19 and were the only two who died in hospital. At psychological examination all patients enrolled report to have lived a particularly stressful experience at IES-R in the last year, without presenting the symptoms of a post-traumatic stress disorder. Most patients were positive to the allostatic overload. Only one patient showed a clinical cut-off for HADS and no one for the Fear COVID-19 scale. We finally concluded that subjects with pre-pandemic psychological distress may have experienced additional psychological overload, opening the door to TTS by a series of physiological alterations as the secretion of cortisol and catecholamines, making the subject more vulnerable to the onset of TTS.

## 1. Introduction

Since December 2019 the infection of SARS-CoV-2 (COVID-19), starting from Wuhan, China, spread out all over the world. Italy was one of the most affected countries, especially in Lombardy, where, on February 20 the first confirmed case was detected. The Italian and Regional National Health System instituted several protocols in order to reduce pandemic diffusion and the Italian Government proclaimed a national lockdown on 9<sup>th</sup> March 2020, forcing the entire population to severe restrictive isolation measures. Takotsubo syndrome (TTS), also known as “stress cardiomyopathy” or “apical balloon syndrome” is a poorly recognized heart disease, often identified as a benign condition [1]. The recurrence rate of TTS is estimated to be 1.8% per-patient year [2], mostly affecting women with a mean age of 67–70 years with emotional stress and/or acute illness preceding the presentation [3,4].

The burden on mental health of the medical emergency related to COVID-19 is progressively revealed [5,6]. The clinical observation of the

increasing of TTS patients admitted to our cardiology department during the pandemic (if compared with the same months of previous years) suggests a potential association between TTS onset and COVID-19, both for likely medical and psychological reasons. Some case-reports linked TTS to the psychological impact of COVID-19 [7–9]. To the best of our knowledge, this is the first study that describes a case series of TTS, with a medical and psychological description of patients admitted to the hospital during the Italian peak of pandemic.

## 2. Methods

We retrospectively analyzed consecutive patients hospitalised from February to May 2020 at ASST Santi Paolo e Carlo, Milan, Lombardy, with a diagnosis of TTS. The incidence of TTS has been assessed and compared with that of the corresponding period in 2019. The diagnosis of TTS was based on International TTS Diagnostic Criteria proposed by ESC consensus [1]. The study was performed in accordance to the

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Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of our institution. All data were collected anonymously and all patients signed the informed consent at the moment clinical interview.

The diagnosis of SARS-COV-2 was performed by nasopharyngeal swab test.

An expert psychologist performed the psychological assessment in May 2020 by interviewing patients by phone after the discharge. Allostatic overload, which occurs when environmental demands exceed individual resources [10], was assessed by the specific questionnaire of the Diagnostic Criteria for Psychosomatic Research (DCPR-R) [11]. Clinical criteria used to determination of allostatic overload are based on the presence of an identifiable source of suffering (life events or chronic stress), with clinical manifestations of suffering over the last six months. Current psychological distress was assessed by the Hospital Anxiety and Depression Scale (HADS) [12,13]. It is a 14-item scale that assesses mood and anxiety symptoms in the hospital setting, with a cut-off of 10 for anxiety and depression sub-scales. Traumatic experiences were evaluated by the Impact of Event Scale-Revised (IES-R) [14,15]. It is composed of 22 items that measure the subjective response to a specific traumatic event, especially in the response sets of intrusion, avoidance and hyperarousal. Fear Covid-19 Scale [16,17] was used to assess the fear of COVID-19. The seven items are answered on a 5-point scale with scores ranging from 7 to 35. The higher the score, the greater the fear of COVID-19.

### 3. Results

From February to May 2020, 11 patients have been diagnosed as TTS. During the same months of 2019, only three cases (all females, mean age 72  $\pm$  8 years) of TTS had been admitted in the same hospital.

#### 3.1. Cardiology examination

As reported in literature [18–20], most patients of 2020 were women (72.7%), aged 76  $\pm$  11 years (Table 1). All patients underwent coronary angiography without significant coronary artery disease detection. Moreover, transient cardiac wall motion abnormalities typical for TTS (apical 3/3 in 2019, while apical 8/11, basal 1/11 and atypical 2/11

**Table 1**

Clinical characteristics and timing of hospitalization of Tako-Tsubo patients in 2020.

Clinical characteristics	N = 11
Age (M-SD)	76 $\pm$ 11
Female gender (%)	72.7
Diabetes (%)	18.2
Hypertension (%)	54.5
Active smoke (%)	Na
Previous smoke (%)	18.2
Dyslipidemia (%)	18.2
Current neoplastic disease (%)	na
COPD (%)	18.2
Ejection fraction (M-SD)	41.36 $\pm$ 9.16
Apical Tako tsubo (%)	72.7
Basal Tako tsubo (%)	9
Atypical Tako tsubo (%)	18.2
In-hospital death (%)	18.2
Covid + (%)	18.2
Month of hospitalization	
February (%)	9
March (%)	18.2
April (%)	54.5
May (%)	18.2
Psychological assessment	N = 6
IES-R Traumatic experiences (%)	100
Allostatic Overload (%)	66.6
Hospital Anxiety and Depression Scale (%)	25
Fear Covid-19 Scale (M-SD)	14.2 $\pm$ 0.6

in 2020) were reported in all patients both at trans-thoracic echocardiography and ventricular angiography. COVID-19 diagnosis was confirmed in two patients, who were the only two men, in the other nine cases nasopharyngeal swab test resulted negative. One patient was admitted for COVID-19 pneumonia and developed acute myocardial infarction during hospitalization with ST-segment elevation in inferior leads. The second patient was at home with COVID-19 pneumonia without symptoms requiring hospitalization and was admitted to our emergency department due to an out of hospital cardiac arrest. In the first case, atypical TTS was reported at trans-thoracic echocardiography, while in the second typical apical abnormalities were the main finding. Further investigations such as cardiac magnetic resonance to exclude myocarditis or COVID-19 cardiac manifestation could not be assessed due to early in-hospital death in both cases. Regarding hospitalization time, interestingly, most patients in 2020 (6/11) were admitted in April, at the beginning of the worst period of pandemic, 2/11 on March, 2/11 on May and 1/11 on February.

#### 3.2. Psychological examination

Of eleven patients admitted to the hospital with a diagnosis of TTS during the peak of COVID-19 pandemic, six completed the psychological assessment (three patients refused to be interviewed and two died) (Table 1). At IES-R, all patients (100%) reported to have experienced a particularly stressful experience over the last year, without presenting the symptoms of a post-traumatic stress disorder. Traumatic experiences refer to robbery, death of a family member, hospitalization, restrictions and social isolation related to the lockdown. Most patients (66.6%) were positive to the allostatic overload. Only one patient (25%) showed a clinical cut-off for HADS and no one for the Fear COVID-19 scale.

### 4. Discussion

Our study started by the clinical observation of a greater number of patients with TTS observed during the peak of COVID-19 pandemic (February–May 2020), compared with TTS patients admitted in the same months of the year 2019. The psychological evaluation of TTS patients clearly suggested that all patients experienced a particularly stressful experience over the last year, and 2/3 were positive for allostatic overload. It may be that quarantine and isolation added further negative elements to traditional risk factors for cardiovascular disease. Quarantine has consequences on mental health in terms of anxiety, fear, anger, loneliness [6,21]. Lombardy was the Italian region with the worst situation related to coronavirus pandemic during the period February–April 2020, and we can assume that this represented an additional psychological burden in term of fear and anxiety related to COVID-19. Moreover, several studies have underlined that quarantine and isolation are associated with psychological (anxiety, anger, and stress) and behavioral (unhealthy lifestyle characterized by diet low fresh food, and reduced psychical activity) factors that could increase the risk of developing cardiovascular disease [22]. However, our study suggests that all patients experienced traumatic events in the year preceding the outbreak. In addition, most of the patients showed an allostatic overload condition. After the hospitalization, the patients did not report high levels of anxiety and/or depression or fear of the virus. Several studies suggested a likely relationship between stressful events and TTS [4], evidencing a greater number of traumatic experiences (emotional, physical or sexual abuse) in subjects with TTS compared to healthy people [23]. We hypothesize that patients experienced a difficult psychological condition during the previous year, and that it represented a *milieu* for developing TTS, when further elements of psychological distress (COVID-19 related factors?) occurred in their own life (allostatic overload). It could be that patients had a situation of physical and psychological exhaustion close to the period of the pandemic onset, and the additional burden of COVID-19 contributed to trigger TTS.

In the case of a stressful event, there are physiological responses that

help to maintain homeostasis in the short-term but, over time, the physiological integrity of allostatic mechanisms may be jeopardized, determining the onset of a series of clinical manifestations (e.g. hypertension and metabolic syndrome) [24]. Results of several studies suggest that an allostatic load status is associated with worse health conditions and plays a significant role in the onset, course and outcome of CVD [25]. In the specific case of TTS, although the etiology is still partially unknown, some importance is linked to the effects of catecholamines [26]. In fact, supra-physiological levels of plasma catecholamines have been reported during the acute phase in patients with TTS, underlining a state of hypersensitivity of the sympathetic nervous system [27]. This state of hypersensitivity, linked to an increase in sympathetic activity during post-menopause due to the lack of estrogen, could explain the high incidence of TTS in old women [26]. In addition, it is important to consider the influences of the hypothalamic-pituitary-adrenal axis (HPAA). To protect the body from excessive release of cortisol for a long period, a phase of hyperactivity of the HPAA is followed by a decrease in activity [28]. Hyporesponsiveness (hypocortisolism) of the HPAA has been reported in patients with TTS and other stress-related illnesses [29]. This association could be explained considering that low cortisol level seems to be associated with an increase on the synthesis of catecholamine [30], increase in proinflammatory cytokine levels [29] and an increase on the negative rating of the situation (mood-buffering cortisol effect). The role of Distressed personality is another factor to be analyzed [31,32]. Moreover, some of the most frequently documented physiological changes that accompany negative emotions are jointly implicated in the pathogenesis of CVD and include an alteration of the autonomic, immune and neuroendocrine nervous system [33]. In addition to this framework of greater vulnerability, a greater load of stress related to traumatic experiences in the previous year and the condition of social isolation linked to quarantine could lead to an allostatic overload condition which, with all the physiological consequences previously described, could be the basis of the pathogenesis of Takotsubo syndrome.

## 5. Limitations

The poor number of patients analyzed is the main limitation of our study. Anyway, TTS has been estimated to represent only 1–3% of patients admitted with suspected STEMI [1], with current evidence based only on single case-reports. Moreover, psychological examination was possible only in 6/11 patients in 2020 due to patient's refusal or death. Moreover, we did not realize a lifetime psychiatric evaluation by DSM-5. Another limitation might be that our study not fully captured the degree to which fear of COVID, depression, and anxiety preceded the TTS onset because our psychological evaluation was retrospective. Nevertheless, our findings support more specifically the role of previous life events and allostatic overload as concurrent triggers of TTS.

## 6. Conclusion

Subjects with pre-pandemic psychological distress may have experienced additional psychological overload, opening the door to TTS by a series of physiological alterations as the secretion of cortisol and catecholamines that affect and compromise cardiovascular health, making the subject more vulnerable to the onset of TTS.

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