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Letter

Prognostication in Takotsubo Syndrome

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Matta *et al.* [1] provide a good review of Takotsubo Cardiomyopathy in their recent article published in Reviews in Cardiovascular Medicine (Rev. Cardiovasc. Med.). Although the article is well written and succinctly describes most clinical aspects of Takotsubo syndrome (TTS), the prognosis of TTS has been oversimplified and doesn't touch upon a very important concept of trigger-based prognosis.

With the data available from multiple recent studies, it has become apparent that the prognosis of TTS largely depends on the inciting trigger. There are two forms of TTS: 'primary' and 'secondary'. Primary TTS develops as a result of primary psychiatric or emotional trigger or may have no clear identifiable cause (idiopathic), while secondary TTS is often precipitated by a physical stressor such as a critical illness, sepsis, trauma, post-surgical state, intracranial hemorrhage or cerebrovascular accident [2–5]. Secondary TTS is usually associated with a much higher short- and long-term morbidity and mortality while primary TTS generally has a relatively benign course with a good prognosis, unless primary TTS is complicated by the development of cardiogenic shock. There are a few plausible explanations for these observed differences in the mortality: primary or emotional triggers wax and wane with the emotional state thus inciting a phasic stimulus, whereas physical stimuli often trigger a sustained hyper-catecholamine state that does not minimize without alleviation of the underlying disease. Moreover, clinical conditions that are related to the secondary or physical triggers of TTS may yield variable prognoses influencing the overall survival of patients. For example, prognosis in a previously healthy patient presenting with TTS after an emotional altercation (primary form) would be significantly different from a patient admitted with a stroke or septic shock that later develops TTS, and of course, the prognosis would be largely impacted by the underlying disease state [2,3].

Analysis of RETAKO registry (Spanish National REgistry for TAKOtsubo cardiomyopathy) showed a significantly increased morbidity and mortality in secondary TTS patients compared to primary TTS patients with an otherwise comparable baseline demographic variables [2]. Secondary TTS patients also had higher incidence of cardiogenic shock, cardiac enzyme levels, increased use of inotropes or mechanical circulatory support, mechanical ventilator dependence, increased TTS recurrence rates, and higher number of cardiovascular events resulting in readmissions [2]. Another recent Italian study by Citro and colleagues demonstrated that patients of TTS presenting with severe systolic dysfunction (EF <35%) often have a higher mortality than those with EF >35% at presentation [6,7]. On a further sub-analysis of that study, it was determined that the predominant driver for mortality and significant systolic dysfunction was indeed the secondary forms of TTS as opposed to primary forms of TTS [7,8].

Men generally have worse outcomes compared to their female counterparts in TTS and this can be attributed to generally increased prevalence of acute critical conditions with increased serum catecholamine concentrations in men, resulting in higher inpatient mortality. Furthermore, estrogen hormone exerts a directly protective effect on the sympathetic nervous system and coronary microcirculation through endothelium-dependent and independent pathways and the paucity of estrogen in men may potentially predispose them to more severe adverse effects of TTS [3]. Prior studies showed that the lack of estrogen in postmenopausal women is a major risk factor for the development of TTS. Experimental murine models also have shown the presence of a greater degree of ventricular dysfunction in stress-exposed ovariectomized female rats than in ovariectomized rats receiving estradiol supplementation. It has been hypothesized that since estrogen has a negligible role in men developing TTS, men may potentially develop this condition at any age, due to the effect of an overwhelming surge of plasma catecholamines (usually much higher concentrations than in women), which may potentially result in more serious short-term and long-term direct cardiotoxic effects [3]. In prior large studies, men also have been found to have generally a much higher prevalence of secondary forms of TTS compared to women. These factors are the most likely explanations for a higher mortality in men than women.

In summary, it is thus very important to identify the underlying trigger of TTS and consider a trigger-based prognosis. Patients with secondary forms of TTS and those with significant systolic dysfunction warrant an aggressive clinical management and a close clinical follow-up.

Author contributions

LC drafted, edited, finalized the manuscript.

Ethics approval and consent to participate

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Conflict of interest

The author declares no conflict of interest.

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