

# Reviewer's queries and authors responses: MS. ID: 47807, "Takotsubo syndrome: The Past, the Present, and the Future"

## *Reviewer 1:*

*Dear author, the paper is essentially an Editorial letter which is focused on the up-to-date vision of Takotsubo syndrome. The manuscript is written with the good English-speaking adduction of the arguments. The article is sufficiently novel and very interesting to warrant publication. All the key elements are presented and described clearly. The most discussable options in the article are: Would you please kindly briefly provide a reader with the info regarding the main types of the syndrome and what is important - atypical manifestation. Which criteria are the most critical for diagnosis in routine clinical practice? Please, underline it. What are about the microvascular dysfunction? Can we trust Echo? What kind of Echo - TTE is preferable? Please generally harmonize your paper with more transparent info for clinical practice.*

The most common form is the typical apical ballooning which occurs in 75-80% of patients; its easily recognized and is associated with typical complications including thrombus formation due to apical akinesis and left ventricular outflow tract obstruction due to basal hyperkinesis. This has been added to the manuscript (page 2, paragraph 2). Other less common types include midventricular, basal or inverted, biventricular, right ventricular, or with focal dysfunction. This was already discussed in the manuscript (page 2, paragraph 2).

The most commonly applied diagnostic criteria include the Revised Mayo Clinic Criteria, InterTAK (International Takotsubo Diagnostic Criteria), and the Heart Failure Association-European Society of Cardiology Criteria. These have been added in the manuscript (page 2, paragraph 3).

Microvascular dysfunction is one of the postulated mechanisms in the pathophysiologic basis of Takotsubo syndrome and can be assessed by Thrombolysis in Myocardial Infarction (TIMI) Frame Count or TIMI perfusion grade. This has been highlighted on our manuscript (page 2, paragraph 2).

Transthoracic echocardiography with color and tissue Doppler is the preferred noninvasive imaging modality for patients suspected of Takotsubo syndrome but most of these patients undergo emergent coronary angiography to rule out acute coronary syndrome. This has been added in our manuscript (page 2, paragraph 3).

*Reviewer 2: The Authors present an editorial about the history of takotsubo syndrome and future prospects. I agree with authors that further research is needed to clarify the pathophysiology to help guide clinical decision-making and development of novel therapeutic strategies for those at risk of mortality, acute complications or chronic cardiac symptoms. Current knowledge may help for precise diagnosis of TTS and to optimize clinical management during both the acute and chronic phase. However, large-scale randomized controlled trials are needed to obtain more robust evidence for optimal treatment of TTS. In parallel with these clinical approaches, it is necessary to clarify the exact pathophysiology, which can rapidly facilitate systematic management strategies for TTS. I suggest to add a comment about a recent editorial by Sattler S, Couch LS, Harding SE. Takotsubo Syndrome: Latest Addition to the Expanding Family of Immune-Mediated Diseases? JACC Basic Transl Sci. 2018 Dec 31;3(6):779-781. doi: 10.1016/j.jacbts.2018.11.003. eCollection 2018 Dec. PubMed PMID: 30623137; PubMed Central PMCID: PMC6314959.*

We appreciate the comments made by the reviewer and for their excellent suggestion. Accordingly, we have implemented the suggested paper in our manuscript (page 2, paragraph 2) and is copied below

*A possible autoimmune and/or autoinflammatory component has also been hypothesized for TTS, akin to myocardial infarction, thereby providing an impetus to explore long-term immunological effects of TTS.*

*Reviewer 3:*

*This is the educative editorial for takotsubo syndrome (TTS). The authors had better add any figures or pictures of TTS.*

We thank the reviewer for their comments and we have now added a figure in our manuscript (page 4)

*Reviewer 4:*

*This is an excellent editorial about Takotsubo syndrome. This manuscript is nicely structured and well written. However, I have one minor comment about this manuscript. Please consider the following comments. (Comment) References [16] seemed to be found nowhere in the text.*

We thank the reviewer for their encouraging comments and for pointing out the error. This has now been corrected in the manuscript.