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Dr Jin-Lei Wang

Associate Editor

World Journal of Cardiology

July 10th, 2018

Dear Dr Wang,

Re: **Manuscript NO: 40110: "Takotsubo Syndrome. Different presentations for a single disease. Case Report Series"**

Thank you for considering our clinical series for potential publication in World Journal of Cardiology. Herein, you will find an itemized response to each of the points raised during the review process.

All authors have participated in the work and have reviewed and agree with the content of the article. No portion of the text has been copied from other material in the literature. I am aware that it is the author's responsibility to obtain permission for any figures or tables reproduced from any prior publications, and to cover fully any costs involved.

We hope that the revised version of the manuscript fulfills the requirements of World Journal of Cardiology.

Kind Regards,

Gonzalo Martínez

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REVIEWER #1 (CODE: 00060493)

The key weakness of this paper lies with the lack or originality. Several papers have already shown these findings.

We agree with the reviewer in that these findings have been reported before. However, TS is still a condition imposing diagnostic challenges and these atypical presentations even more so. Therefore, we strongly believe that this small compendium of atypical TTS cases will add in the recognition of this entity and can be of interest for general cardiologist as those who read World Journal of Cardiology Journal.

REVIEWER #2. (CODE: 02565578)

1. The title of the manuscript is different from the title present in the submission system. It should contain the phrase "case reports".

The manuscript title has been changed accordingly and “case report series” was added.

2. In the introduction, I would suggest to add a statement or build on the sentence We descibe three cases of atypical TTS" to indicate exactly where and when the cases were diagnosed and treated and to indicate that these are indeed the clinical cases encountered in the Authors' medical practice.

A statement clarifying these issues was added (Page 2, para 2).

3. The Authors use the term "tako-tsubo syndrome" throughout the article, however the clinical entity that they describe and discuss is also called differently, "takotsubo cardiomyopathy" being the most common term. Indeed, the Authors used this term as a keyword for the article. Could the authors check whether there is any recommendation for the use of one term rather than the other in cardiology? Also, considering the origin of the word "takotsubo" (it refers to a fishing pot used for trapping octopus and is descriptive of apical ballooning) and its use by the Japanese authors in english, it is better written not hyphenated and must not be written capitalized. In this regard, the use of the acronym TTS is also doubtful, if "takotsubo" is actually one word.

We appreciate this comment from the reviewer. We have changed the nomenclature to “Takotsubo Syndrome” as per the latest European Consensus (European Heart Journal 2018. 39;22:2032-2046). The acronym has been modified to TS.

4. The Authors report the results of the "ultrasensitive troponin assay". Do they mean "high-sensitivity troponin assay" or is it any different? Also, a conventional troponin assay is sufficient for takotsubo cardiomyopathy diagnosis. Did the Authors have a possibility to evaluate B-type natriuretic peptide (BNP) in the serum? While the troponin levels are elevated but still relatively low given the extension of the dysfunctional myocardium, the levels of BNP are significantly elevated in the takotsubo cardiomyopathy.

Indeed, we meant High-sensitivity troponin. This has been corrected. Regarding BNP, unfortunately it was not available, probably reflecting normal clinical practice (it was deemed irrelevant in patients with overt heart failure). Nevertheless, we acknowledge it can have a value in terms of diagnosis and follow-up.

5. Even if the clinical presentation of the takotsubo cardiomyopathy can be different, its diagnosis is based on the specific criteria. To increase the educational value of this publication, I would suggest to summarize the clinical presentation and diagnosis of the describes cases with reference to the diagnostic criteria for the takotsubo cardiomyopathy (2014 European Society of Cardiology (ESC) Takotsubo Syndrome Diagnostic Criteria). The table that is already present in the manuscript could be expanded to include all diagnostic criteria and their presence/absence in the described cases. Then, it could serve as an educational tool for the takotsubo cardiomyopathy diagnosis.

We thank the reviewer for this comment. We have updated the table according to the InterTAK registry Criteria and the ECG findings have been added.

6. The manuscript should be re-read in order to eliminate some minor errors, e.g., corrections to the original version are still present next to the previous version's wording.

These issues have been corrected.

7. Ethical issues: confidentiality is respected, but the Authors did not obtain an informed consent from patients.

At our institution, all patients sign an informed consent, which explains that the data obtained can be potentially used for educational purposes in an anonymous fashion.

PEER-REVIEW REPORT

REVIEWER #3. (CODE: 00257390)

This paper presents a case series of 3 patients presenting with symptoms of Takotsubo cardiomyopathy. The paper is fairly written and presented. Some editing for typos and syntax will be necessary. The authors may want to more clearly highlight the novelty of the 3 cases presented in this paper in comparison to plethora of previous other cases presented with this disease, as mentioned in the current literature. Some echocardiographic images for e.g. demonstrating LVOT obstruction would be useful. In addition, the role of advanced imaging with cardiac MR should be mentioned in this context.

We appreciate the reviewer's comments.
Wording has been corrected.
Unfortunately, no MRI images were available, reflecting normal clinical practice at our institution. It is worth noting, however, that the latest takotsubo Consensus only advice to perform MRI if acute myocarditis (signs or symptoms of viral infection, Elevated CRP or Pericardial Effusion) is suspected.
In case 3 (LVOT obstruction), at the time of cardiac ultrasound the patient had already received intensive volume replacement, thus LVOT was no longer evident and MR was mild to moderate.