

EDITORIAL OFFICE'S COMMENTS

The "Article Highlights" section is missing. Please add the "Article Highlights" section at the end of the main text.

Reviewer #1:

Major comments:

- 1. I think it is better to discuss not only marital status (MS) and conventional coronary risk factors but also other previously proposed risk factors of Takotsubo cardiomyopathy (TCM) such as neurological or psychiatric disorders (N Engl J Med 2015;373(10):929). If possible, the authors should additionally adjust neurological or psychiatric disorders as potential confounders. Even if the authors cannot additionally adjust neurological or psychiatric disorders as potential confounders, they should introduce these previously proposed risk factors of TCM in "Background" or the beginning of "Discussion" and note the importance of these potential confounders in "Limitation" paragraph.**

Response

We thank the reviewer for the comments and also for the reference. We have now adjusted for neurological and psychiatric disorders in the multivariable models, and show these results in table 3. We have also updated table 1 with information for the prevalence of neurological and psychiatric disorders. Furthermore, we have expanded the introduction (Page 4, lines 13 and 14 of marked copy) and discussion to include information about neurological and psychiatric disorders in the etiology of takotsubo syndrome (Page 9, lines 1-15 of marked copy).

- 2. Given TCM is common in female, exclusion and differentiation of coronary spastic angina (CSA) is important. How the authors exclude CSA from TCM? Did they perform hyperventilation stress EKG test or acetylcholine stress test during coronary angiography for diagnosis of CSA? If not, the authors should note the possibility of cases with CSA in the participants.**

Response

We agree that exclusion and differentiation of coronary spastic angina is important for a condition such as takotsubo syndrome. However, this information is not available in the National Hospital Discharge Survey. We mention this in the limitation "For TTS, information for confirming the diagnosis such as cardiac enzymes as well as echocardiographic or electrocardiographic readings were not available. Therefore, patients with conditions like coronary spastic angina could not be excluded." (Page 9, lines 26-27 of marked copy).

- 3. It is true that all characteristics are matched, yet I think it is still better to indicate p-value in Table 1 to visually understand the characteristics of each groups.**

Response

Cases were matched to controls by age, sex, year of takotsubo diagnosis and bed size of hospital. We have provided p values for differences in characteristics between cases and controls in Table 1.

Minor comments:

- 1. Please insert a blank line between "Email" and "ABSTRACT".**

Response

Implemented

- 2. ABSTRACT-RESULTS, Line 2: "marched" should be "matched".**

Response

Implemented

- 3. Please insert a blank line above "INTRODUCTION" of the main text.**

Response

Implemented

- 4. "MATERIAL AND METHODS" p.4, 1line 1; "Marital status which was obtained the National Center for Health ..." should be Marital status which was obtained from the National Center for Health ...".**

Response

Implemented

Reviewer #2:

- 1. English: ü Meaning is clearly conveyed, but it needs another revision.**

Response

We thank the reviewer for the comments. We have now corrected all grammatical errors

- 2. What is the purpose of mentioning: bed size of the hospital?**

Response

We matched cases to controls on the bed size of the hospital where they were admitted. Hospital bed size (the number of beds per hospital) was used as a measure of hospital volume. Hospital volumes are often used as a structural measure of quality of care for patients undergoing cardiovascular procedures which can be an important confounder in the diagnosis of a condition like takotsubo cardiomyopathy that was not commonly diagnosed in the time period that this study was conducted compared to now. We have updated the methods to indicate that bed size was used as a measure of hospital volume (Page 5, lines 26-27 of marked copy).

- 3. Check this please "MS who were marched to 295 controls"**

Response

We thank the reviewer for pointing this out to us. We have revised this statement

- 4. Introduction: The introduction was concise, well-structured but it needs to be more informative.**

Response

We have expanded the introduction by adding information on incidence of takotsubo syndrome in the United States, mentioned additional triggers and described characteristics of this syndrome (Page 4, lines 6-12, 17-20 of marked copy).

- 5. Check this please: "MS who were marched to 295 controls" "Marital status information which was obtained the National Center for Health Statistics" "Case was defined as patients"**

Response

We have corrected this and all other grammatical errors in the manuscript.

- 6. What is the purpose of mentioning: bed size of hospital?**

Response

We matched cases to controls on the bed size of the hospital where they were admitted. Hospital bed size (the number of beds per hospital) was used as a measure of hospital volume. Hospital volumes are often used as a structural measure of quality of care for patients undergoing cardiovascular procedures which can be an important confounder in the diagnosis of a condition

like takotsubo cardiomyopathy that was not commonly diagnosed in the time period that this study was conducted compared to now. We have updated the methods to indicate that bed size was used as a measure of hospital volume (Page 5, lines 26-27 of marked copy).

- 7. "A control was defined as any patient without TTS diagnosis during hospitalization." If a control subject is a previous patient with TTS, wouldn't that affect the results?**

Response

We agree that this could influence the results. However, we believe this may not be the case since we used all possible 15 discharge diagnosis to determine takotsubo syndrome. With this algorithm, the possibility of patients with previous takotsubo syndrome being included as controls is minimal.

- 8. Discussion need to be more developed. It is required to add more findings of similar studies (if found). -May the "Type of insurance" reflect the socioeconomic status? If yes, it would be interesting to include it in the discussion. Same for "Health conditions" »!**

Response

We have expanded the discussion to include the few previous studies published on this relation of marital status with takotsubo syndrome (Page 7, lines 24-29; page 8, lines 1-4 of marked copy). We have discussed the influence of health conditions like neurological and psychiatric conditions (Page 9, lines 1-15 of marked copy). The literature is mixed on whether type of insurance is a good surrogate for socioeconomic status. In our efforts to minimize residual confounding, we did not consider types of insurance as a marker for socioeconomic status.

- 9. Table 1: Please check the percentages of participants according to their marital status ü Cases : $39+57.3=96.3$ ü Non-CVD Controls : $42.7+61=103.7$. Also, I think that you need to check all the statistical analyses for cases and Non-CVD Controls if they were calculated using this data.**

Response

We have corrected this mistake of not placing numbers in the appropriate cells in table 1.

- 10. You mentioned, "inability to study the quality of marriage or sex differences on the relation of MS with TTS." Also mentioned, "90% and 88% being women and reporting white race, respectively." It would be interesting if you add the sex and age range in table 1. Then study the sex as a separate factor (table 2). Thank you for your work!**

Response

We have added this information to table 1. Because cases were matched to controls on age and sex, these characteristics are the same among cases and controls. Due to this, effect estimates cannot be calculated for factors that were used in matching cases to controls. We again thank the reviewer for the kind words.