

# Assessing sex differences in patients with takotsubo syndrome requires homogeneous cohorts

**To the editor** We read with interest the article by Budnik et al<sup>1</sup> about a study of 232 patients with takotsubo syndrome (TTS) from 2 Polish centers of excellence, who were retrospectively evaluated for sex differences in clinical characteristics and in-hospital outcomes. Sex differences were found with regard to the frequency of living alone (higher in men), frequency of physical triggers (higher in men), frequency of emotional triggers (higher in women), frequency of smoking (higher in men), peak level of N-terminal prohormone of brain natriuretic peptide (higher in women), frequency of ST-segment depression (higher in men), and reduced ejection fraction (higher in men), but no sex difference was reported for in-hospital outcomes.<sup>1</sup> Based on that, we have the following comments and concerns.

The main shortcoming of the study is that the group sizes are unequal (211 women vs 21 men).<sup>1</sup> This marked difference makes a comparison between both sexes unreliable. Thus, the conclusions drawn from the study have to be regarded as preliminary. Homogeneity of the groups for size and demographics is necessary to more reliably assess if there are actual sex differences.

Further shortcomings that limit the interpretation of the results are the age difference and the cardiovascular risk profile (median [interquartile range] age in men, 63 [66–72] years; median [interquartile range] age in women, 71 [61–79] years; smokers: men, 57.1%; women, 24.4%).

Moreover, the analysis lacks the results of coronary angiography. We should know if coronary heart disease was truly absent in all included patients as recommended for diagnosing TTS according to the Mayo Clinic criteria.<sup>2</sup> As the prevalence of smokers in both men and women was high, it is crucial to know the frequency of coronary heart disease in the cohorts.

Since it is well known that the clinical appearance of TTS may mimic myocardial infarction and show similar clinical, electrocardiographic, and blood chemical findings, it would be valuable to provide not only the results of instrumental investigations but also the clinical manifestations,

particularly at TTS onset or on admission. We would like to know how many patients in both groups complained of anginal chest pain, exertional dyspnea, leg edema, or palpitations at onset or on admission.

Another shortcoming of the study is that emotional and physical triggers were not further differentiated. Knowing the trigger in each case is essential, as it may strongly determine the outcome of a patient. Outcomes in patients with subarachnoid bleeding may differ from those reported for subjects in whom fear after a raid triggered the signs and symptoms of the disease.

Also, the authors do not report any results of cardiac magnetic resonance imaging (MRI). It would be interesting to know how many patients underwent cardiac MRI and in how many patients TTS was diagnosed based on cardiac MRI but was missed due to uncertain echocardiographic findings, and vice versa.

The lack of a significant difference in mortality (6 cases in women and no cases in men) is not understandable.

If the QTc interval is short, the risk of ventricular tachycardia is low. Thus, patients with a short QTc interval may be at lower risk of developing ventricular arrhythmias than those with a prolonged QTc interval. It is important to determine the propensity for ventricular arrhythmias, as it may influence the outcome and seems to be lower in women compared with men.<sup>3</sup>

Overall, this interesting study has a number of shortcomings that need to be adequately addressed before the final conclusions can be drawn. As long as the sample size and demographic characteristics are disproportional between groups, suspected sex differences in patients with TTS remain vague and uncertain.

## ARTICLE INFORMATION

**AUTHOR NAMES AND AFFILIATIONS** Josef Finsterer, Claudia Stöllberger (Krankenanstalt Rudolfstiftung, Messerli Institute, Vienna, Austria)

**CORRESPONDING AUTHOR** Josef Finsterer, MD, PhD, Krankenanstalt Rudolfstiftung, Messerli Institute, Juchgasse, Postfach 20, 1180 Wien, Austria, phone: +43 1 71165 72085, email: fiffigs1@yahoo.de

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**Authors' reply** We would like to thank Finsterer and Stöllberger for the interesting comment on our article.<sup>1</sup> We fully agree that the main limitation of the study is the small number of men included in the analysis, but this is due to rare occurrence of takotsubo syndrome (TTS) in men in general population. The percentage of men among patients with TTS is only about 10% worldwide.<sup>2</sup> As we mentioned, this may be the reason for underestimating the incidence of complications.

Coronary angiography was performed in all patients except for 2, and in all of them significant coronary artery disease was excluded. However, according to the current International Takotsubo Diagnostic Criteria, even severe coronary artery disease does not exclude the diagnosis of TTS.<sup>3</sup> The majority of experts consider the Mayo Clinic criteria no longer valid.

As shown in Table 2 in our article,<sup>1</sup> chest pain was present in 84.3% of women and 81% of men, whereas dyspnea, in 49.3% and 38.1%, respectively. The difference was not significant. Data on leg edema or palpitations were not collected.

Please note that physical stress triggered TTS in 30 women (14.2%) and 7 men (35%). Because of the small number of men, the difference between TTS classes (I, IIa, IIb, III) in men and women could not be reliably assessed.<sup>4</sup>

We performed cardiac MRI only in the case of clinical doubt. In each such case, we diagnosed TTS only when other conditions were excluded.

Although 6 women and no men died, the difference in mortality was not significant: 2.9% and 0%, respectively.

As far as the QTc interval is concerned, no difference between women and men was reported on days 1, 3, and 5.

To sum up, we agree that there is a need for further multicenter studies to ensure the homogeneity of the groups. However, in our opinion, our analysis based on a population from 2 large Polish cardiology centers is a good starting point for further research.

## ARTICLE INFORMATION

**AUTHOR NAMES AND AFFILIATIONS** Monika Budnik, Grzegorz Opolski (1st Chair and Department of Cardiology, Medical University of Warsaw, Warsaw, Poland)

**CORRESPONDING AUTHOR** Monika Budnik, PhD, 1st Chair and Department of Cardiology, Medical University of Warsaw, ul. Banacha 1a, 02-097 Warszawa, Poland, phone: +48 22 599 29 58, email: moni.budnik@gmail.com

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