

Editorial

Takotsubo syndrome, neurological disorders, and sex: a dangerous liaison?

Rosaria Cappadona^{1,†}, Roberto Manfredini^{1,*†}¹Department of Medical Sciences, University of Ferrara, 44121 Ferrara, Italy***Correspondence:** roberto.manfredini@unife.it (Roberto Manfredini)

† These authors contributed equally.

Keywords

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Takotsubo syndrome (TS) is a poorly recognized heart disease, characterized by a reversible heart failure, initially regarded as a benign condition but recently associated with severe clinical consequences [1]. A growing body of evidence, in fact, seems to indicate that complications and gender, play crucial role in the outcome of TS, and male sex is more likely to show unfavourable outcome [2]. Stiermaier *et al.* [3] evaluated long-term, 28-day and 1-year mortality in 286 TS patients matched for age and gender with 286 STEMI patients, with a mean follow-up of 3.8 ± 2.5 years. In TS patients, long-term mortality was significantly higher compared with the matched STEMI cohort (24.7% vs. 15.1%, hazard ratio [HR] 1.58, 95% confidence interval [CI] 1.07–2.33; $p = 0.02$), whereas no significant difference in the rates of 28-day and 1-year mortality were found [3]. In multivariable regression analysis, male sex was identified as independent predictor of mortality in TS patients, together with high Killip class on admission, and diabetes mellitus [3]. Both United States (US) and European data confirmed significant differences for in-hospital mortality (IHM). Results from the National Inpatient Sample (NIS) database revealed an almost 4-fold higher probability of IHM in males compared to females (3.7% vs. 1.1%; $p < 0.001$) [4]. In particular, males had more complications including cardiogenic shock, ventricular fibrillation/tachycardia, and acute kidney injury [4]. Similarly, data from the Spanish Registry for Takotsubo Cardiomyopathy (RETAKO) reported a higher IHM (4.4% vs. 10.2%; $p < 0.01$), as well as a longer intensive care stay ((4.2 ± 3.7) vs. (3.2 ± 3.2) days; $p = 0.03$) [5]. In a retrospective study of TTS patients in Southern California, followed-up for 5-year, recurrence of TTS and death were observed in 7.5% and 16.2% of cases, respectively. In multivariate analysis,

male sex was associated with a significant risk of recurrence or death (HR 2.52, 95% CI 1.38–4.60), even higher than that of age (HR 1.56 per 10-year increase), pulmonary disease (HR 2.0), diabetes (HR 1.6), and chronic kidney disease (HR 1.58) [6].

According to the National Health and Nutrition Examination Survey (NHANES) 2015–2018 data, the overall stroke prevalence in the US was 2.7% [7]. The prevalence increases with advancing age in both males and females, but each year, ≈ 55000 more females than males have a stroke [7]. Takotsubo syndrome and stroke are linked events. On one hand, they share common temporal frames of higher risk of occurrence, especially during morning hours and Mondays [8–11]. On the other, depending of the temporal profile between the two clinical pictures, they may exhibit reciprocal etiological relationships. Data from the International Takotsubo Registry showed higher rates of neurologic or psychiatric disorders in TS than acute coronary syndrome patients (55.8% vs. 25.7%, respectively, $p < 0.001$) [12]. Moreover, acute neurologic or psychiatric diseases, among others, were independent predictors for in-hospital complications [12]. A systematic review of studies involving patients with spontaneous subarachnoid hemorrhage (SH) found a high incidence of TS (4.4%), as well as a higher risk of IHM (OR 2.6, 95% CI 1.16–5.85, $p = 0.02$) in patients who developed TS [13]. Data from the US National Inpatient Sample, aimed to study the association between TS and neurological diseases, confirmed a strongest associations with SH (odds ratio [OR] 11.7; 95% confidence interval [CI] 10.2–13.4). When a sensitivity analysis included secondary diagnoses of acute neurological diagnoses, an association was found also for intracerebral hemorrhage (OR 1.3; 95% CI

1.1–1.5), and ischemic stroke (OR 1.2; 95% CI 1.1–1.3) [14]. Jung *et al.* [15] observed that stroke patients strictly fulfilling the TS diagnostic had a trend toward a higher mortality rate and prevalence of insular involvement. Since analysis of retrospective data of TS patients reported for stroke an event rate of 2.8% after 30-day and 4.2% after 12-month, it has been hypothesized that rapid improvement in left ventricle (LV) morphology and function may facilitate the formation of cardiac emboli, so increasing stroke risk [16]. Thus, an algorithm based on echocardiographic, electrocardiographic and laboratory data has been proposed, to evaluate when oral anticoagulation should be considered for TS patients [17]. Outcome of TS may depend of LV recovery, that can occur from hours to weeks. Patients without an early LV recovery (cut-off: within 10-day after the acute event) were more often male (12.6% vs. 5.2%; $p = 0.011$), and showed unfavorable 1-year outcome compared with patients with early recovery ($p = 0.003$) [18]. Interestingly, on multiple logistic regression, male sex, left ventricle ejection fraction (LVEF) $<45\%$, and acute neurologic disorders were associated with the absence of early recovery [18].

The combination of male sex and history of neurologic disorder has been chosen as independent predictors of in-hospital complications, together with right ventricular involvement and LVEF, to build up a validation score for TS (German and Italian Stress Cardiomyopathy [GEIST] prognosis score) [19]. This score assigned 20 points each for male sex and history of neurologic disorders, and 30 points for right ventricular involvement, and then subtracting the value in percent of LVEF (decimal values between 0.15 and 0.70) [19]. The validation study included 1007 consecutive patients from the GEIST registry (11% males), compared with 946 patients (13% males) from the RETAKO registry, as the external score validation. An admission risk score was developed using a stepwise multivariable regression analysis from the two registries, and in-hospital complications were defined as death, pulmonary edema, need for invasive ventilation, and cardiogenic shock. Overall rate of in-hospital complications was 23.3% (death, 4.0%; pulmonary edema, 5.8%; invasive ventilation, 6.4%; and cardiogenic shock, 9.1%) [19]. Stratification into three risk groups (<20 , 20–40, and >40 points) classified patients as having low, intermediate or high risk (40.9%, 44.3%, 14.8%, respectively), and the observed in-hospital complication rates in the three risk groups were 12.7%, 23.4%, and 58.8%, respectively) [19]. This risk stratification is important, since after follow-up (2.6-year), patients with in-hospital complications had significantly higher rates of mortality than those without complications (40% vs. 10%, $p = 0.01$) [19]. Thus, in the presence of a combination of male sex and stroke, it is very likely that a patient is classified as high-risk, needing treatment in the intensive care.

Since the dawn of the XX century, some epidemiological observations indicated different patterns among males and females either for health and mortality, as summarized by Judith Lorber and Lisa Jean Moore in the statement “women get sicker, but men die quicker” [20]. Takotsubo syndrome, benign disease for females but life-threatening for males,

is a perfect topic for gender-specific medicine, a novel eye looking at the differences among males and females in terms of prevention, signs and symptoms, therapy, and outcome of different diseases, in the view of a personalized and optimized comprehensive approach.

Abbreviations

CI, confidence intervals; GEIST, German and Italian Stress Cardiomyopathy; HR, hazard ratio; IH, intracerebral hemorrhage; IHM, in-hospital mortality; LV, left ventricle; LVEF, left ventricle ejection fraction; NHANES, National Health and Nutrition Examination Survey; NIS, National Inpatient Sample; OR, odds ratio; RETAKO, Spanish Registry for Takotsubo Cardiomyopathy; SH, subarachnoid hemorrhage; STEMI, ST elevation myocardial infarction; TS, Takotsubo syndrome; US, United States.

Author contributions

RC and RM conceived the idea, analyzed the available literature, wrote the paper.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

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