

RESEARCH LETTER

Sex- and Age-Based Temporal Trends in Takotsubo Syndrome Incidence in the United States

Varun K. Pattisapu, MD,* Hua Hao , PhD,* Yunxian Liu , PhD; Trevor-Trung Nguyen, BS; Amy Hoang, MBS; C. Noel Bairey Merz , MD; Susan Cheng , MD, MPH

Takotsubo syndrome (TTS) is an uncommon but important cause of myocardial infarction that has been increasingly recognized in the United States.^{1,2} The extent to which documented TTS incidence in the United States may have changed over time, across age groups as well as by sex, is not well understood.

All data supporting the findings are publicly available through the National Inpatient Sample (NIS) database provided by the Healthcare Cost and Utilization Project.

We investigated age- and sex-based temporal trends in TTS incidence, using NIS³ data from years 2006 to 2017. We included patients aged ≥ 18 years with a primary or secondary TTS diagnosis (*International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 429.83 or International Classification of Diseases, Tenth Revision, Clinical Modification [ICD-10-CM] code I51.81*). We excluded those without coronary angiography or with coronary angiography and subsequent percutaneous coronary intervention. Per Healthcare Cost and Utilization Project analysis guidelines, we applied “trend weights” and estimated incidence (and SEs) using PROC SURVEYMEANS. We used generalized linear regression to test for differences in temporal trends across sex-stratified age groups. All analyses were performed

using SAS v9.4 and R v3.6.3. All study protocols were approved by the Cedars-Sinai Institutional Review Board, with the requirement for individual informed consent waived.

Over the total study period, we identified 135 463 documented cases of TTS. The annual incidence increased steadily in both sexes, with women contributing most cases (88.3%), especially those aged ≥ 50 years (Figure). In particular, we observed a significantly greater increase in TTS incidence among middle-aged (128 cases per million per year) and older (96 cases per million per year) women compared with younger (15 cases per million per year) women ($P < 0.001$). Increase in TTS incidence among middle-aged (20 cases per million per year) men was also significant compared with younger (10 cases per million per year) men ($P < 0.001$), but not significant for older (16 cases per million per year) men ($P = 0.082$). In more granular analyses of TTS incidence by quarter year periods, we observed no appreciable difference in temporal trends across the quarters of year 2015 (ie, the transition from *ICD-9* to *ICD-10* coding). In addition, we observed that the average age of the NIS source sample remained stable for women, with a slight increase for men (0.7 year older per year) over the entire study period (Figure). Accordingly, we also observed relatively stable proportions of sex-based age groups

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Correspondence to: Susan Cheng, MD, MPH, Department of Cardiology, Smidt Heart Institute, Cedars-Sinai Medical Center, 127 San Vicente Blvd, Suite A-3100, Los Angeles, CA 90048. E-mail susan.cheng@cshs.org

*V.K. Pattisapu and H. Hao contributed equally.

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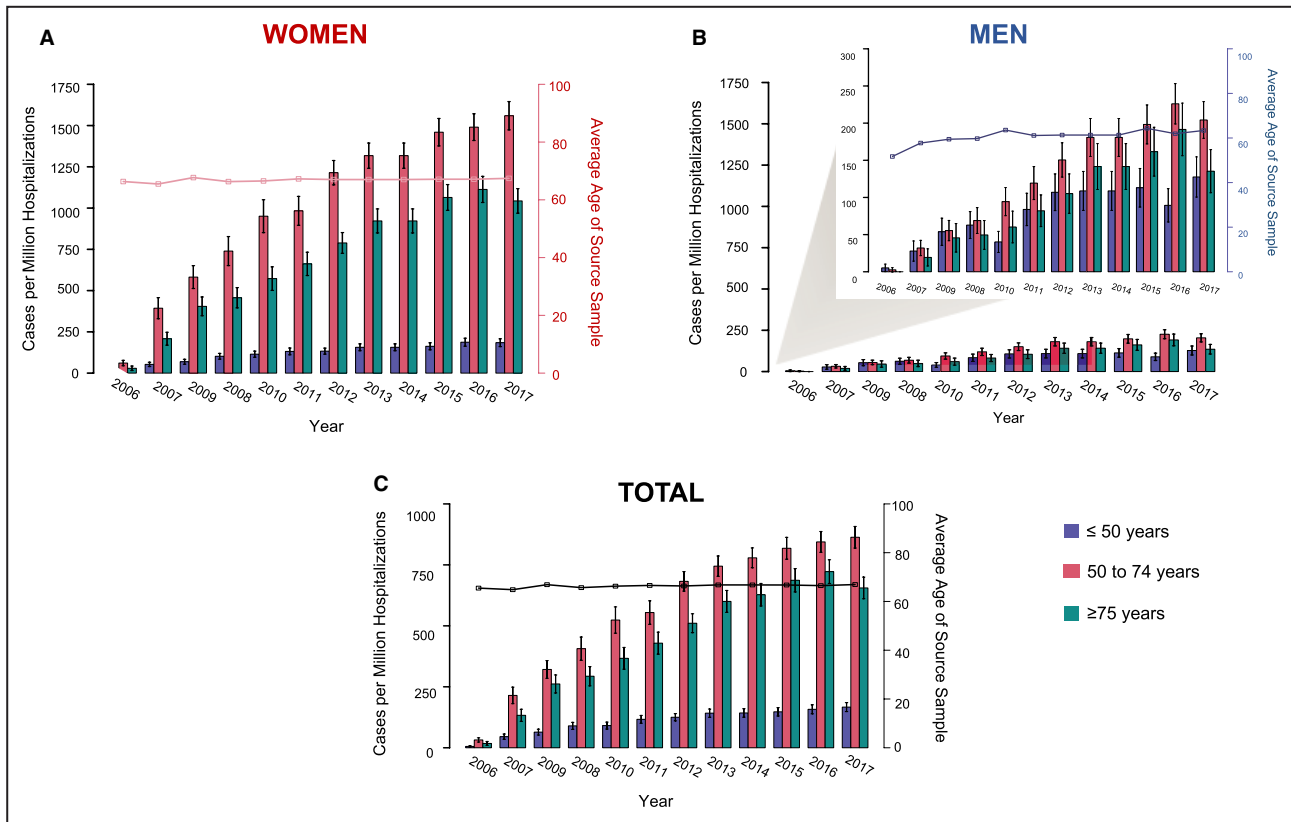


Figure. Two decades of temporal trends in Takotsubo syndrome in the United States.

Age- and sex-specific temporal trends in Takotsubo syndrome hospitalizations in the United States are shown from years 2006 through 2017, in women (A) and men (B) as well as in both sexes combined (C).

comprising the larger US population at risk over the entire study period (data not shown).

Consistent with reports from national and international cohorts, women have continued to contribute the vast majority of TTS diagnoses over time.^{2,4} Although TTS case diagnoses have steadily increased in both sexes, and across all age groups, the increase over time has been especially pronounced among women aged ≥ 50 years. Notwithstanding the importance of increased recognition, advancing diagnostic techniques, and improved documentation of the TTS diagnosis, additional factors contributing to the observed temporal trends may include the following: (1) continued increase in size of the at-risk population, which includes aging adults and aging women in particular; (2) secular changes in socioeconomic and environmental stressors that may be particularly relevant to susceptible middle-aged and particularly older-aged individuals; and (3) potential evolution in the nature of TTS as a disease entity, which is known to be heterogeneous in cause as well as presentation.⁵ Notably, potential drivers appear more relevant to older women than older men at risk, for reasons that are currently unclear. Intriguingly, the most prominent at-risk group was

women aged 50 to 74 years. This finding could be caused by the greater propensity for excess sympathetic activation in younger age, combined with a greater susceptibility to cardiac stress and injury in older age, converging in middle-aged people at risk and particularly women.⁵

Our analyses using NIS data were limited by dependence on appropriate ICD-9 or ICD-10 coding of diagnoses, procedures, and other in-hospital measures. Notwithstanding uniform labeling of TTS codes over time and consistent results observed for temporal trends, data from before and after the ICD-9 to ICD-10 coding transition should be interpreted with caution. In addition, NIS data do not include biomarkers, echocardiographic measures, and angiographic measures typically used to evaluate TTS cases. Thus, follow-up studies that can more comprehensively differentiate between TTS and alternate or overlapping diagnoses (eg, myocarditis, pericarditis, or coronary vasospasm) are warranted. Nonetheless, the availability of diagnosis data on >135 000 cases documented over a span of almost 2 decades offered ample statistical power to detect not only increasing incidence of TTS in the United States, but a steep increase among especially middle-aged to older women. This overall trend was disproportionate

to that seen in other subgroups and appears not completely explained by improvements in clinical recognition. Future studies are needed to validate and extend from our results as part of efforts to clarify the susceptibility, pathophysiological features, and outcomes related to TTS for those individuals at the highest risk.

ARTICLE INFORMATION

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Affiliations

Barbra Streisand Women's Heart Center, Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, CA (V.K.P., C.N.B.M., S.C.); University of Southern California Keck School of Medicine, Los Angeles, CA (H.H.); and Department of Cardiology, Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, CA (Y.L., T.N., A.H., C.N.B.M., S.C.).

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