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Differential sex-based mortality after cardiac valve surgery: selection bias, confounding, and generalizability

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We thank Windrix and colleagues for their interesting commentary regarding our retrospective cohort study, "Sex Differences in In-Hospital Mortality After Open Cardiac Valve Surgery" where we found that female patients had 1.41 confounder-adjusted increased odds ratio for in-hospital mortality compared to male patients after cardiac valve surgery.[1,2] We would like to acknowledge their important comments concerning our findings and respectfully address them. Specifically, Windrix et al. discuss the temporally associated increase in transcatheter aortic valve replacement (TAVR) use as opposed to surgical aortic valve replacement (SAVR) and how indications for specific procedure type can bias findings, and further issues regarding unmeasured confounding, selection bias, and external validity in administrative database research.

The authors mention that our results may be biased by indication for SAVR as compared to TAVR. During the study period of 2007–2018, numbers of SAVR procedures performed declined in conjunction with the rise of TAVR. TAVR was approved by the FDA in 2012 and subsequent trials demonstrated comparable efficacy to SAVR in treating high, intermediate, and low-risk patients with severe aortic stenosis.[3] The choice between use of SAVR and TAVR is a multidisciplinary, patient centered decision.[4] We agree with the authors' suggestion that sex-based differences in procedure utilization may be potential causes of disparities in access to care (referral bias); however, the relevance and validity of our results that report differences in SAVR mortality between females and males should still hold true. Health care disparities can influence care and assess barriers, quality of health care received, and outcomes. Future studies should evaluate this pre-intervention choice to assess whether it represents a care barrier.

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RSW: The author drafted the initial first draft and subsequent edits as well as help with primary edits to the response.
SLB: This author helped to perform edits, add references, and reviewed final edit.
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We appreciate the authors comment regarding the limitations of the retrospective observation database research and possibility of selection bias and unmeasured granular confounders. As mentioned, referral bias may exist in retrospective observational research as selection bias. Our study sample included data from the State Inpatient Database (SID), Healthcare Cost and Utilization Project (HCUP) databases from Washington, Maryland, Kentucky, and Florida (2007–2018); California (2007–2011); and New York (2007–2016).[1] The SID-HCUP database used for this study represents a near consensus of hospitalizations for open cardiac valve surgery. We believe that the demographic and geographic diversity in the six-state population sampled is a major strength in establishing generalizability of our findings. Other databases, including the Maryland data base mentioned by authors studying racial disparities have similar percentages of Black and Hispanic patients with relative numbers of female and male Black and Hispanic patients.[5] Similarly, the authors suggestion that female patients may be sicker may be true, which is why in our confounder-adjusted analysis, we adjusted for multiple co-morbidities, including the 31 individual Elixhauser comorbidity measures (coded for the presence of each disease and not as an overall composite comorbidity score).

The authors comment that 30-day mortality of SAVR female patients has declined in this time period; with advances in technology and surgical technique and innovation mortality has most likely decreased in both men and women during this time period. Despite these advancements (and the likely overall decrease in mortality), our study reports the relative odds of morality of women versus men and our findings suggests that a significant difference remains in male and female patient in-hospital mortality.

The SID-HCUP does not include all possible perioperative variables and the missing data elements (notably the lack of data on indication for surgery, Body Mass Index, and lab values) precludes calculation of standardized Society of Thoracic Surgeons (STS) risk predictors or euroSCORE risk estimates. Unmeasured or uncontrolled confounding can have an important impact on reported study associations. In our statistical analysis, we calculated an E-value, a sensitivity analysis used in observational research to measure robustness of associations of interest to unmeasured confounding.[6] Considering the limitations of our data source, we calculated the E-value to represent the potential effect of unmeasured confounding. The E-value estimate for the primary outcome was 2.17 (lower limit of the 95% CI: 2.04). This implies that an unmeasured confounder would have to be associated with both sex and in-hospital mortality with a risk ratio ≥ 2.17 for the observed association between female sex and in-hospital mortality to be fully explained away.

Considering these limitations, we welcome future research such as prospective trials focused on women dedicated to understanding of underlying causes for potentially poorer outcomes in women in cardiac surgery and optimizing cardiac surgical care for women.

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