

COVID-19 in heart transplant patients: is there a cause for concern?

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In a recent meta-analysis, Ahmed *et al.*¹ reported that the risk of Coronavirus Disease 2019 (COVID-19) infection was significantly higher in the heart transplant (HT) population compared with the general population (OR 5.47; 95% CI 3.03–9.89, $I^2 = 90.6\%$, $P < 0.001$). The pooled mortality rate in HT recipients due to COVID-19 was 27.6% (95% CI 23.2–32.2%) and the pooled hospitalization rate was 82.9% (95% CI 77.1–87.9%). COVID-19 also significantly increased the mortality rate in HT population as compared to the general population (OR 3.37; 95% CI 2.25–5.05, $I^2 = 64.5\%$, $P < 0.001$).

We have several issues regarding this meta-analysis. Ahmed *et al.* stated that they conducted their study in accordance with the Cochrane Handbook for Systematic Reviews of Interventions,² but we find several methodological weaknesses in their review that challenge their claim. The Cochrane guidelines emphasize that the risk of bias assessment should be undertaken for every study included in a systematic review. The grave omission of quality assessment by Ahmed *et al.* leaves us with no way to ascertain the internal validity of their results, particularly considering that their meta-analysis is based on observational studies, which are inherently at a higher risk of bias, especially confounding and selection biases, as compared to randomized trials. Studies judged to be at a high risk of bias have substantially lesser reliable results.² In the light of this, a critical appraisal of the included studies would greatly improve our interpretation of the results. The Joanna Briggs Institute (JBI) critical appraisal tool for case series and the Newcastle–Ottawa Scale for cohort studies are two examples of validated and widely used tools which the authors could have used.³

Moreover, the outcomes comparing the risk of COVID-19 infection and mortality between the HT population and the general population suffered from considerable and substantial heterogeneity, respectively. An appropriate investigation of heterogeneity serves to increase the clinical and scientific interpretation of the results of a meta-analysis.⁴ In their limitations, the authors acknowledge that 'differences in COVID-19 infection rate, management protocols, differences in heart transplantation protocols and immunosuppressive treatments between countries may limit the interpretation of our

findings'¹ but an attempt should have been made to provide a plausible explanation for the heterogeneity observed for example by running subgroup or sensitivity analyses on the basis of the location of the studies. This combined with the substantial imprecision in their results, as evidenced by the wide confidence intervals, may lead to a 'low' or 'very low' certainty of evidence in a GRADE (Grading of Recommendations, Assessment, Development and Evaluations) assessment of the outcomes.² The inclusion of a GRADE assessment would be invaluable in determining, with more confidence, the implications for practice this meta-analysis could provide.

Another issue we find is that Ahmed *et al.* pooled the hospitalization and mortality rates in their study using the arcsine transformation. However, the arcsine-based transformations may provide seriously misleading results unless applied with certain safeguards in place which are described by Doi and Xu⁵ in their paper. The correct execution of the arcsine transformation with these safeguards can be implemented by using Stata module *metan* or MetaXL.⁵ In addition, the Freeman–Tukey double-arcsine transformation may stabilize variances better in general⁶ as compared with the arcsine-square-root transformation, which Ahmed *et al.* used in their meta-analysis.

Lastly, we would like to point out that Ahmed *et al.* provided no references to any of the included studies or to the sources they used to calculate the COVID-19 infection and mortality rates in the general population, which they used as comparators in their meta-analyses. The supplementary file enclosed does not have the information they have claimed it does in their study. All of these issues raise concerns over the validity and integrity of their results and, while their conclusions may be accurate, we would like to have better certainty and confidence in them as to better inform clinicians and researchers in the concerned fields.

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