

Reviewer 1 v.1

Comments to the Author

This paper by Li et al reports a meta-analysis of studies which have evaluated levels of Angiotensin-2 (Ang-2), a ligand of the Tie-2 endothelial receptor, as a biomarker conferring risk of mortality in patients with acute respiratory distress syndrome (ARDS), a link that has remained unclear. Their systematic review from 10 cohort studies showed that the pooled OR suggested that high Ang-2 level contributed to ARDS mortality (OR = 1.49) which increased to an OR of 1.68 if analyzed only in the high-quality-scored studies. Importantly, no significant mortality risk was identified in the low-quality studies (OR = 1.00). Overall this is a well done analysis that concluded that higher circulating Ang-2 level may independently predict the risk of mortality in patients with ARDS. The authors discuss the limitations of the analysis and potential bias and the need for further large-scale prospective cohorts or interventional studies to fully evaluate the diagnostic power of Ang-2 and its causative role in ARDS outcomes. Minor comments include:

- Please include the issues/divergences whereby the senior consultant provided input into the analyses
- What was the range in timing of the day1 samples for analysis? In the ER, at time of diagnosis, at time of ICU admission, at time of enrollment?
- Is the analysis differ if children studies are excluded?
- The authors found a difference in mortality risk based upon compliance. This should be further discussed.
- Was there a difference in results that was dependent on the platform used for Ang-2 measurements?