

Supplementary Appendix 6. GRADE approach to rate the quality of evidence on the effects of ACEI/ARB on the outcomes of COVID-19 from systematic review and meta-analyses

Outcome	The GRADE domains	Rating the quality of evidence and reasons for judgement
All-cause mortality; Odds ratio (11 studies, 12,601 patients)	Risk of bias	Serious limitations; Although all-cause mortality can be assessed objectively in retrospective studies, we cannot exclude study limitations such as failure to adequately control confounding and selective outcome reporting. These limitations are based on the retrospective study design.
	Imprecision	No serious imprecision; Our results were based on the pooled estimates from 12,601 patients in 11 studies reporting odds ratio. Optimal information size was met. We found satisfactory narrow 95% confidence interval excludes no effect.
	Inconsistency	Serious inconsistency; We found similar trends of pooled estimates in unadjusted and adjusted odds ratios and confidence intervals. However, statistical heterogeneity was found based on the effect size, not the effect direction, of ACEI/ARB use on all-cause mortality.
	Indirectness	No serious indirectness; The effect of ACEI/ARB was directly compared and study outcome (mortality) measurement was identical. All the study subjects were diagnosed with COVID-19 by RT-PCR test using upper respiratory specimen.
	Publication bias	No serious publication bias; We searched and included unpublished studies in our meta-analysis. Egger's and Begg's tests indicated no significant publication bias
	Certainty of evidence	Moderate certainty of evidence (○⊕○⊕⊕)
Severe COVID-19 (13 studies, 12,848 patients)	Risk of bias	Serious limitations; We found several study limitations such as failure to adequately control confounding, selective outcome reporting, and bias in measurement of outcomes. These limitations are based on the retrospective study design.
	Imprecision	No serious imprecision; Our results were based on the pooled estimates from 15,757 patients in 13 studies reporting odds ratio. As 95% confidence interval appears satisfactory narrow and overlaps no effect, we concluded that ACEI/ARB use did not affect severe COVID-19. Therefore, there is no risk of imprecision in our conclusion.
	Inconsistency	Serious inconsistency; Our study showed pooled estimates with statistically heterogeneity in both unadjusted and adjusted odds ratios and confidence intervals.
	Indirectness	Serious indirectness; All the study subjects were diagnosed with COVID-19 by RT-PCR test using upper respiratory specimen, However, different definitions of severe disease were used as study outcome. Although the included COVID-19 patients showed reportedly similar clinical severity across the studies, indirectness still

	cannot be excluded.
Publication bias	No serious publication bias; We searched and included unpublished studies in our meta-analysis. Egger's and Begg's tests indicated no significant publication bias
Certainty of evidence	Low certainty of evidence (○⊕○○⊕)

ACEIs, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; COVID-19, coronavirus disease-19; RT-PCR, real-time reverse transcription-polymerase chain reaction