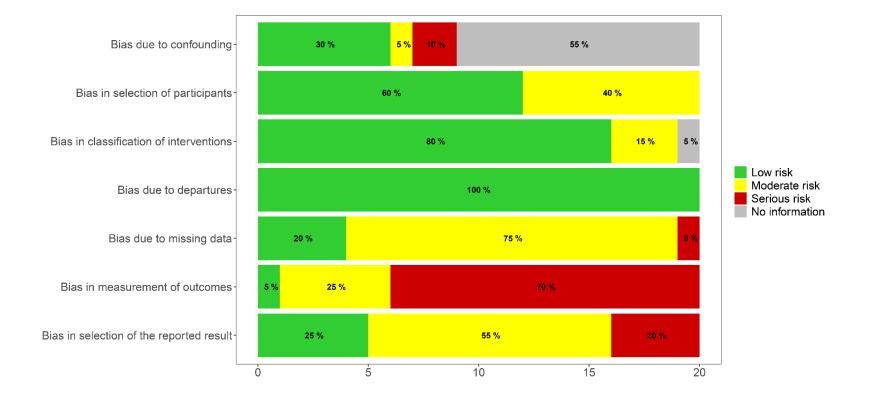
Supplementary Appendix 5. The risk of bias assessment for the included nonrandomized studies and reasons for judgement

| Studies | Bias due to confounding | Bias in selection of participants into the study | Bias in classification of interventions | Bias due to departures from intended interventions | Bias due to missing data | Bias in measurement of outcomes | Bias in selection of the reported result |
|----------------------------|-------------------------|--|---|---|--------------------------|---------------------------------|--|
| Ashraf MA. et al. (2020) | No information | Low | Low | Low | Moderate | Serious | Moderate |
| Bean D. et al. (2020) | Serious | Low | Low | Low | Moderate | Serious | Moderate |
| Benelli G. et al. (2020) | No information | Low | Low | Low | Low | Serious | Serious |
| Caraballo C. et al. (2020) | No information | Low | Low | Low | Moderate | Moderate | Moderate |
| Feng Y. et al. (2020) | Serious | Moderate | Low | Low | Moderate | Serious | Moderate |
| Feng Z. et al. (2020) | Moderate | Low | Moderate | Low | Low | Serious | Moderate |
| lp A. et al. (2020) | No information | Moderate | Low | Low | Moderate | Moderate | Serious |
| Lee H. et al. (2020) | Low | Low | Low | Low | Moderate | Moderate | Moderate |
| Li J. et al. (2020) | Low | Moderate | Low | Low | Moderate | Serious | Low |
| Mancia G. et al. (2020) | No information | Low | Moderate | Low | Moderate | Serious | Moderate |
| Mehra MR. et al. (2020) | No information | Low | Low | Low | Moderate | Moderate | Moderate |
| Meng J. et al. (2020) | Low | Moderate | Low | Low | Moderate | Serious | Low |
| Peng Y. et al. (2020) | No information | Low | Low | Low | Moderate | Serious | Serious |
| Rentsch CT. et al. (2020) | No information | Moderate | Low | Low | Low | Serious | Moderate |
| Reynolds HR. et al. (2020) | Low | Low | Moderate | Low | Moderate | Serious | Moderate |
| Tedeschi S. et al. (2020) | No information | Low | No information | Low | Low | Low | Serious |
| Yan H. et al. (2020) | No information | Low | Low | Low | Serious | Serious | Moderate |
| Yang G. et al. (2020) | Low | Moderate | Low | Low | Moderate | Serious | Low |
| Zeng Z. et al. (2020) | No information | Moderate | Low | Low | Moderate | Serious | Low |
| Zhang P. et al. (2020) | Low | Moderate | Low | Low | Moderate | Moderate | Low |
| | | Interpretation of risk of bias | No information | Low | Moderate | Serious | Critical |



| Author (year) Study name | Domain | Review author's assessment and reason for judgment |
|-----------------------------|--|--|
| Published studies (n=10) | | |
| (2-2) | Bias due to confounding | Serious risk. Underlying chronic diseases were more likely to be found in severe to critical group. These kinds of underlying condition can affect the severity of COVID-19 or mortality risk |
| | Bias in selection of participants into the study | Moderate risk. All the patients newly diagnosed with COVID-19 were included. Medical records were reviewed retrospectively and patients were classified according to disease severity, which was clearly defined in Methods section. However, ACEI or ARB use was analyzed in hypertensive patients, not all the patients. |
| | Bias in classification of interventions | Low risk. As medical records were reviewed retrospectively, there is no misclassification of intervention (ACEI or ARB). Even though misclassification existed, it would be a systematic error. |
| Feng Y. et al. (2020) | Bias due to deviations from intended interventions | Low risk. The use of ACEI or ARB was not intended for antiviral treatment, bur for anti-hypertensive or protective effect on heart, kidney, or other vascular diseases. Therefore, it is difficult to think that there would be a different management according to whether ACEI or ARB was used or not. |
| | Bias due to missing data | Moderate risk. Missing data was not reported in terms of severity and mortality according to use of ACEI or ARB. However, the patient data without information on the use of ACEI or ARB or severity of COVID-19 may be excluded in initial stage of this study. |
| | Bias in measurement of outcomes | Serious risk. This study was conducted retrospectively. Therefore, investigator knew patient data including group and intervention classification before initiation of analysis. The possibility of bias in outcome assessment is strongly suggested. |
| | Bias in selection of the reported result | Moderate risk. Reported results may be prespecified by registered protocol before intervention classification was conducted, but still the possibility of bias in selective reporting cannot be ignored because this study was conducted retrospectively. |
| | Bias due to confounding | Low risk. Underlying chronic diseases and other confounding factors were similar between ACEI/ARB group and non-ACEI/ARB group. |
| | Bias in selection of participants into the study | Moderate risk. Hypertensive patients diagnosed with COVID-19 were included for analysis. Medical records were reviewed retrospectively and patients were classified according to disease severity, which was clearly defined in Methods section. However, there is a still possibility that selection of hypertensive patients may impact on our results. |
| | Bias in classification of interventions | Low risk. As medical records were reviewed retrospectively, there is no misclassification of intervention (ACEI or ARB). Even though misclassification existed, it would be a systematic error. |
| Li J. et al. (2020) | Bias due to deviations from intended interventions | Low risk. The use of ACEI or ARB was not intended for antiviral treatment, bur for anti-hypertensive or protective effect on heart, kidney, or other vascular diseases. Therefore, it is difficult to think that there would be a different management according to whether ACEI or ARB was used or not. |
| | Bias due to missing data | Moderate risk. Missing data was not reported in terms of severity and mortality according to use of ACEI or ARB. However, the patient data without information on the use of ACEI or ARB or severity of COVID-19 may be excluded in initial stage of this study. |
| | Bias in measurement of outcomes | Serious risk. This study was conducted retrospectively. Therefore, investigator knew patient data including group and intervention classification before initiation of analysis. The possibility of bias in outcome assessment is strongly suggested. |
| | Bias in selection of the reported result | Low risk. All the variables were analyzed whether there is any difference between ACEI or ARB user group and non-user group |
| Mancia G. et al. (2020) | Bias due to confounding | No information. Main analysis was conducted to know the risk factors for COVID-19 development. However, it is not possible to know whether there is any difference in underlying diseases between the patients who used ACEI or ARB and those who did not use. |
| | Bias in selection of participants into the study | Low risk. All the patients who received COVID-19 test were included. Medical records were reviewed retrospectively and patients were classified according to COVID-19 positivity. Analysis was conducted to evaluate the risk of severe COVID-19 according to antihypertensive drugs. In the process of inclusion and analysis, selection bias would hardly intervene in this study. |
| | Bias in classification of interventions | Moderate risk. Although claim data were reviewed retrospectively, operational definition was not clearly described (eg. minimum treatment days, when treatment starts and ends). There may be a risk of misclassification of interventions. |

| | Bias due to deviations from intended interventions | Low risk. The use of ACEI or ARB was not intended for antiviral treatment, bur for anti-hypertensive or protective effect on heart, kidney, or other vascular diseases. Therefore, it is difficult to think that there would be a different management according to whether ACEI or ARB was used or not. |
|--------------------------|--|---|
| | Bias due to missing data | Moderate risk. Missing data was not reported in terms of severity and mortality according to use of ACEI or ARB. However, the patient data without information on the use of ACEI or ARB or severity of COVID-19 may be excluded in initial stage of this study. |
| | Bias in measurement of outcomes | Serious risk. This study was conducted retrospectively. Therefore, investigator knew patient data including group and intervention classification before initiation of analysis. The possibility of bias in outcome assessment is strongly suggested. |
| | Bias in selection of the reported result | Moderate risk. Reported results may be prespecified by registered protocol before intervention classification was conducted, but still the possibility of bias in selective reporting cannot be ignored because this study was conducted retrospectively. |
| | Bias due to confounding | No information. Main analysis was conducted to know the risk factors for all-cause mortality. However, it is not possible to know whether there is any difference in underlying diseases between the patients who used ACEI or ARB and those who did not use |
| | Bias in selection of participants into the study | Low risk. Hospitalized COVID-19 patients were included internationally. Medical records were reviewed retrospectively and the patients were classified according to mortality. |
| | Bias in classification of interventions | Low risk. Medical records were reviewed retrospectively, and ACEI or ARB use at the time of hospital admission was identified. |
| Mehra MR. et al. | Bias due to deviations from intended interventions | Low risk. The use of ACEI or ARB was not intended for antiviral treatment, bur for anti-hypertensive or protective effect on heart, kidney, or other vascular diseases. Therefore, it is difficult to think that there would be a different management according to whether ACEI or ARB was used or not. |
| (2020) | Bias due to missing data | Moderate risk. Missing data was not reported in terms of severity and mortality according to use of ACEI or ARB. However, the patient data without information on the use of ACEI or ARB or severity of COVID-19 may be excluded in initial stage of this study. |
| | Bias in measurement of outcomes | Moderate risk. This study was conducted retrospectively. Therefore, investigators knew patient data including group and intervention classification before initiation of analysis. The possibility of bias in outcome assessment can be suggested. However, only mortality was analyzed in this study, that cannot be biased even though the investigators knew the patient data before analysis. |
| | Bias in selection of the reported result | Moderate risk. Reported results may be prespecified by registered protocol before intervention classification was conducted, but still the possibility of bias in selective reporting cannot be ignored because this study was conducted retrospectively. |
| | Bias due to confounding | Low risk. Underlying chronic diseases and other confounding factors were similar between ACEI/ARB group and non-ACEI/ARB group. |
| | Bias in selection of participants into the study | Moderate risk. Hypertensive patients diagnosed with COVID-19 were included for analysis. Medical records were reviewed retrospectively and patients were classified according to disease severity, which was clearly defined in Methods section. However, there is a still possibility that selection of hypertensive patients may impact on our results. |
| Meng J. et al. (2020) | Bias in classification of interventions | Low risk. As medical records were reviewed retrospectively, there is no misclassification of intervention (ACEI or ARB). Even though misclassification existed, it would be a systematic error. |
| | Bias due to deviations from intended interventions | Low risk. The use of ACEI or ARB was not intended for antiviral treatment, bur for anti-hypertensive or protective effect on heart, kidney, or other vascular diseases. Therefore, it is difficult to think that there would be a different management according to whether ACEI or ARB was used or not. |
| | Bias due to missing data | Moderate risk. Missing data was not reported in ACEI or ARB use. However, the patient data without available information on the use of ACEI or ARB may be excluded in initial stage of this study. |
| | Bias in measurement of outcomes | Serious risk. This study was conducted retrospectively. Therefore, investigator knew patient data including group and intervention classification before initiation of analysis. The possibility of bias in outcome assessment is strongly suggested. |
| | Bias in selection of the reported result | Low risk. All the variables were analyzed whether there is any difference between ACEI or ARB user group and non-user group. |
| Peng Y. et al. (2020) | Bias due to confounding | No information. Main analysis was conducted to know the risk factors for mortality in COVID-19 patients upon admission. However, it is |

| | | not possible to know whether there is any difference in underlying diseases between the patients who used ACEI or ARB and those who did not use. |
|----------------------------|--|---|
| | Bias in selection of participants into the study | Low risk. All the hospitalized patients diagnosed with COVID-19 were included. Medical records were reviewed retrospectively and patients were classified according to mortality, which was clearly defined in Methods section. Therefore, selection bias would hardly intervene in this study. |
| | Bias in classification of interventions | Low risk. As medical records were reviewed retrospectively, there is no misclassification of intervention (ACEI or ARB). Even though misclassification existed, it would be a systematic error. |
| | Bias due to deviations from intended interventions | Low risk. The use of ACEI or ARB was not intended for antiviral treatment, bur for anti-hypertensive or protective effect on heart, kidney, or other vascular diseases. Therefore, it is difficult to think that there would be a different management according to whether ACEI or ARB was used or not. |
| | Bias due to missing data | Moderate risk. Missing data was not reported in ACEI or ARB use. However, the patient data without available information on the use of ACEI or ARB may be excluded in initial stage of this study. |
| | Bias in measurement of outcomes | Serious risk. This study was conducted retrospectively. Therefore, investigator knew patient data including group and intervention classification before initiation of analysis. The possibility of bias in outcome assessment is strongly suggested. |
| | Bias in selection of the reported result | Serious risk. Reported results may be prespecified by registered protocol before intervention classification was conducted, but the possibility of bias in selective reporting is strongly suggested because other hypertensive or cardioprotective drugs were not described (eg. beta-blocker) and any other intervention (eg. antibiotics or antiviral agents) which may impact on prognosis were not evaluated at all. |
| | Bias due to confounding | Low risk. Propensity score-matched patients with a positive test for COVID-19 were evaluated according to anti-hypertensive treatments. |
| | Bias in selection of participants into the study | Low risk. Both matched patients with hypertension and all matched patients were evaluated. Medical records were reviewed retrospectively analyzed according to anti-hypertensive treatments. Selection bias would hardly intervene in this study. |
| | Bias in classification of interventions | Moderate risk. Although claim data were reviewed retrospectively, operational definition was not clearly described (eg. minimum treatment days, when treatment starts and ends). There may be a risk of misclassification of interventions. |
| Reynolds HR. et al. (2020) | Bias due to deviations from intended interventions | Low risk. The use of ACEI or ARB was not intended for antiviral treatment, bur for anti-hypertensive or protective effect on heart, kidney, or other vascular diseases. Therefore, it is difficult to think that there would be a different management according to whether ACEI or ARB was used or not. |
| | Bias due to missing data | Moderate risk. Missing data was not reported in ACEI or ARB use. However, the patient data without available information on the use of ACEI or ARB may be excluded in initial stage of this study. |
| | Bias in measurement of outcomes | Serious risk. This study was conducted retrospectively. Therefore, investigator knew patient data including group and intervention classification before initiation of analysis. The possibility of bias in outcome assessment is strongly suggested. |
| | Bias in selection of the reported result | Moderate risk. Reported results may be prespecified by registered protocol before intervention classification was conducted, but still the possibility of bias in selective reporting cannot be ignored because this study was conducted retrospectively. |
| | Bias due to confounding | No information. Main analysis was conducted to know the different mortality according to hypertension or hypertensive drugs in COVID-19 patients. However, it is not possible to know whether there is any difference in underlying diseases between the patients who used ACEI or ARB and those who did not use. |
| | Bias in selection of participants into the study | Low risk. All the hospitalized patients diagnosed with COVID-19 were prospectively enrolled. Patients were classified according to hypertension, which hardly makes selection bias in this study. |
| Tedeschi S. et al. (2020) | Bias in classification of interventions | No information. There was no description how the researchers coded the use of anti-hypertensive drugs when a patient who started or stopped ACEI or ARB during hospitalization. We think there may be a few patients who changed anti-hypertensive medication during hospitalization. However, the information of classification of interventions was not described in the manuscript. |
| | Bias due to deviations from intended interventions | Low risk. The use of ACEI or ARB was not intended for antiviral treatment, bur for anti-hypertensive or protective effect on heart, kidney, or other vascular diseases. Therefore, it is difficult to think that there would be a different management according to whether |

| | | ACEI or ARB was used or not. |
|-----------------------------|--|---|
| | Bias due to missing data | Low risk. There would be no missing data because all the patients were hospitalized and followed up. |
| | Bias in measurement of outcomes | Low risk. As COVID-19 patients were enrolled prospectively in 10 hospitals, investigators independently assessed outcomes and were independent to the researchers who analyzed outcomes. |
| | Bias in selection of the reported result | Serious risk. Reported results may be prespecified by registered protocol before intervention classification was conducted, but the possibility of bias in selective reporting is strongly suggested because other hypertensive or cardioprotective drugs were not described (eg. beta-blocker) and any other intervention (eg. antibiotics or antiviral agents) which may impact on prognosis were not evaluated at all. |
| | Bias due to confounding | Low risk. Underlying chronic diseases and other confounding factors were similar between ACEI/ARB group and non-ACEI/ARB group. |
| | Bias in selection of participants into the study | Moderate risk. Hypertensive patients diagnosed with COVID-19 were included for analysis. Medical records were reviewed retrospectively and patients were classified according to disease severity, which was clearly defined in Methods section. However, there is a still possibility that selection of hypertensive patients may impact on our results. |
| | Bias in classification of interventions | Low risk. As medical records were reviewed retrospectively, there is no misclassification of intervention (ACEI or ARB). Even though misclassification existed, it would be a systematic error. |
| Yang G. et al. (2020) | Bias due to deviations from intended interventions | Low risk. The use of ACEI or ARB was not intended for antiviral treatment, bur for treating hypertension. Therefore, it is difficult to think that there would be a different management according to whether ACEI or ARB was used or not. |
| | Bias due to missing data | Moderate risk. Missing data was not reported in terms of severity and mortality according to use of ACEI or ARB. However, the patient data without information on the use of ACEI or ARB or severity of COVID-19 may be excluded in initial stage of this study. |
| | Bias in measurement of outcomes | Serious risk. This study was conducted retrospectively. Therefore, investigator knew patient data including group and intervention classification before initiation of analysis. The possibility of bias in outcome assessment is strongly suggested. |
| | Bias in selection of the reported result | Low risk. All the variables were analyzed whether there is any difference between ACEI or ARB user group and non-user group. |
| | Bias due to confounding | Low risk. Although underlying chronic diseases and other confounding factors were significantly different between ACEI/ARB group and non-ACEI/ARB group, adjusted effect size was calculated. |
| | Bias in selection of participants into the study | Moderate risk. Hypertensive patients diagnosed with COVID-19 were included for analysis. Medical records were reviewed retrospectively and patients were classified according to disease severity, which was clearly defined in Methods section. However, there is a still possibility that selection of hypertensive patients may impact on our results. |
| | Bias in classification of interventions | Low risk. As medical records were reviewed retrospectively, there is no misclassification of intervention (ACEI or ARB). Even though misclassification existed, it would be a systematic error. |
| Zhang P. et al. (2020) | Bias due to deviations from intended interventions | Low risk. The use of ACEI or ARB was not intended for antiviral treatment, bur for treating hypertension. Therefore, it is difficult to think that there would be a different management according to whether ACEI or ARB was used or not. |
| | Bias due to missing data | Moderate risk. Missing data was not reported according to use of ACEI or ARB. However, the patient data without information on the use of ACEI or ARB may be excluded in initial stage of this study. |
| | Bias in measurement of outcomes | Moderate risk. This study was conducted retrospectively. Therefore, investigators knew patient data including group and intervention classification before initiation of analysis. The possibility of bias in outcome assessment can be suggested. However, only mortality was analyzed in this study, that cannot be biased even though the investigators knew the patient data before analysis. |
| | Bias in selection of the reported result | Low risk. All the variables were analyzed whether there is any difference between ACEI or ARB user group and non-user group. |
| Unpublished study (n=10) | | |
| Ashraf MA. et al. (2020) | Bias due to confounding | No information. Main analysis was conducted according to non- critically ill and critically ill COVID-19 patients. However, it is not possible to know whether there is any difference in underlying diseases between the patients who used ACEI or ARB and those who did not use |

| | Bias in selection of participants into the study | Low risk. All the hospitalized patients diagnosed with COVID-19 were included for analysis. Medical records were reviewed retrospectively and patients were classified according to ACEI/ARB use, which was clearly defined in Methods section. Selection bias was not suspected. |
|-----------------------------|--|--|
| | Bias in classification of interventions | Low risk. As medical records were reviewed retrospectively, there is no misclassification of intervention (ACEI or ARB). Even though misclassification existed, it would be a systematic error. |
| | Bias due to deviations from intended interventions | Low risk. The use of ACEI or ARB was not intended for antiviral treatment, bur for treating hypertension. Therefore, it is difficult to think that there would be a different management according to whether ACEI or ARB was used or not. |
| | Bias due to missing data | Moderate risk. Missing data was not reported according to use of ACEI or ARB. However, the patient data without information on the use of ACEI or ARB may be excluded in initial stage of this study. |
| | Bias in measurement of outcomes | Serious risk. This study was conducted retrospectively. Therefore, investigator knew patient data including group and intervention classification before initiation of analysis. The possibility of bias in outcome assessment is strongly suggested. |
| | Bias in selection of the reported result | Moderate risk. Reported results may be prespecified by registered protocol before intervention classification was conducted, but still the possibility of bias in selective reporting cannot be ignored because this study was conducted retrospectively. |
| | Bias due to confounding | Serious risk. There were significant differences in underlying diseases between ACEI or ARB user group and non-user group. |
| | Bias in selection of participants into the study | Low risk. All the symptomatic and hospitalized patients diagnosed with COVID-19 were included. Medical records were reviewed retrospectively and patients were classified according to recent ACEI or ARB use, which was clearly defined in Methods section. Therefore, selection bias would hardly intervene in this study. |
| | Bias in classification of interventions | Low risk. As medical records were reviewed retrospectively, there is no misclassification of intervention (ACEI or ARB). Even though misclassification existed, it would be a systematic error. |
| Bean D. et al. (2020) | Bias due to deviations from intended interventions | Low risk. The use of ACEI or ARB was not intended for antiviral treatment, bur for anti-hypertensive or protective effect on heart, kidney, or other vascular diseases. Therefore, it is difficult to think that there would be a different management according to whether ACEI or ARB was used or not. |
| | Bias due to missing data | Moderate risk. Missing data was not reported in mortality according to use of ACEI or ARB. However, the patient data without information on the use of ACEI or ARB may be excluded in initial stage of this study. |
| | Bias in measurement of outcomes | Serious risk. This study was conducted retrospectively. Therefore, investigator knew patient data including group and intervention classification before initiation of analysis. The possibility of bias in outcome assessment is strongly suggested. |
| | Bias in selection of the reported result | Moderate risk. Reported results may be prespecified by registered protocol before intervention classification was conducted, but still the possibility of bias in selective reporting cannot be ignored because this study was conducted retrospectively. |
| | Bias due to confounding | No information. Main analysis was conducted to know the risk factors for in-hospital death, ICU admission, and CPAP/NIV use in COVID-19 patients. However, it is not possible to know whether there is any difference in underlying diseases between the patients who used ACEI or ARB and those who did not use |
| Benelli G. et al. (2020) | Bias in selection of participants into the study | Low risk. All the suspected patients admitted to hospital underwent diagnostic SARS-COV-2 real-time polymerase chain reaction assay. Among the COVID-19 positive patients were included. Medical records were reviewed retrospectively and patients were classified according to recent ACEI or ARB use, which was clearly defined in Methods section. Therefore, selection bias would hardly intervene in this study. |
| | Bias in classification of interventions | Low risk. As medical records were reviewed retrospectively, there is no misclassification of intervention (ACEI or ARB). Even though misclassification existed, it would be a systematic error. |
| | Bias due to deviations from intended interventions | Low risk. The use of ACEI or ARB was not intended for antiviral treatment, bur for anti-hypertensive or protective effect on heart, kidney, or other vascular diseases. Therefore, it is difficult to think that there would be a different management according to whether ACEI or ARB was used or not. |
| | Bias due to missing data | Low risk. Researchers reported 8 missing cases. The number of missing data occupied small proportion of total included patients. |

| | Bias in measurement of outcomes | Serious risk. This study was conducted retrospectively. Therefore, investigator knew patient data including group and intervention classification before initiation of analysis. The possibility of bias in outcome assessment is strongly suggested. |
|-------------------------------|--|---|
| | Bias in selection of the reported result | Serious risk. Reported results may be prespecified by registered protocol before intervention classification was conducted, but the possibility of bias in selective reporting is strongly suggested because other hypertensive or cardioprotective drugs were not described (eg. beta-blocker) and any other intervention (eg. antibiotics or antiviral agents) which may impact on prognosis were not evaluated at all. |
| | Bias due to confounding | No information. Main analysis was conducted to know the risk factors for death in COVID-19 patients. However, it is not possible to know whether there is any difference in underlying diseases between the patients who used ACEI or ARB and those who did not use |
| | Bias in selection of participants into the study | Low risk. All the hospitalized patients diagnosed with COVID-19 were included for analysis. Medical records were reviewed retrospectively and patients were classified according to ACEI/ARB use, which was clearly defined in Methods section. Selection bias was not suspected. |
| | Bias in classification of interventions | Low risk. As medical records were reviewed retrospectively, there is no misclassification of intervention (ACEI or ARB). Even though misclassification existed, it would be a systematic error. |
| Caraballo C. et al. (2020) | Bias due to deviations from intended interventions | Low risk. The use of ACEI or ARB was not intended for antiviral treatment, bur for treating hypertension. Therefore, it is difficult to think that there would be a different management according to whether ACEI or ARB was used or not. |
| | Bias due to missing data | Moderate risk. Missing data was not reported according to use of ACEI or ARB. However, the patient data without information on the use of ACEI or ARB may be excluded in initial stage of this study. |
| | Bias in measurement of outcomes | Moderate risk. This study was conducted retrospectively. Therefore, investigators knew patient data including group and intervention classification before initiation of analysis. The possibility of bias in outcome assessment can be suggested. However, only mortality was analyzed in this study, that cannot be biased even though the investigators knew the patient data before analysis. |
| | Bias in selection of the reported result | Moderate risk. Reported results may be prespecified by registered protocol before intervention classification was conducted, but still the possibility of bias in selective reporting cannot be ignored because this study was conducted retrospectively. |
| | Bias due to confounding | Moderate risk. Underlying chronic diseases, medications, and other conditions were not significantly different between ACEI/ARB group and non-ACEI/ARB group, but the small number of included patients may contribute to insufficient statistical power. |
| | Bias in selection of participants into the study | Low risk. Hypertensive patients diagnosed with COVID-19 were included. Medical records were reviewed retrospectively and patients were classified according to disease severity, which was clearly defined in Methods section. Researchers rigorously evaluated medical history of the included patients and selections bias was not suspected. |
| F. 7 | Bias in classification of interventions | Moderate risk. As medical records were reviewed retrospectively, there is no misclassification of intervention (ACEI or ARB). However, 17 patients with available or irregular anti-hypertensive therapy were not classified and excluded from analysis. More clear definition for classification was needed. |
| Feng Z. et al. (2020) | Bias due to deviations from intended interventions | Low risk. The use of ACEI or ARB was not intended for antiviral treatment, bur for anti-hypertensive or protective effect on heart, kidney, or other vascular diseases. Therefore, it is difficult to think that there would be a different management according to whether ACEI or ARB was used or not. |
| | Bias due to missing data | Low risk. Researchers reported missing data in Figure 1. The number of missing data occupied small proportion of total included patients. |
| | Bias in measurement of outcomes | Serious risk. This study was conducted retrospectively. Therefore, investigator knew patient data including group and intervention classification before initiation of analysis. The possibility of bias in outcome assessment is strongly suggested. |
| | Bias in selection of the reported result | Moderate risk. Reported results may be prespecified by registered protocol before intervention classification was conducted, but still the possibility of bias in selective reporting cannot be ignored because this study was conducted retrospectively. |
| Ip A. et al. (2020) | Bias due to confounding | No information. Main analysis was conducted to know the risk factors for death in COVID-19 patients. However, it is not possible to know whether there is any difference in underlying diseases between the patients who used ACEI or ARB and those who did not use |

| | Bias in selection of participants into the study | Moderate risk. Hypertensive patients diagnosed with COVID-19 were included for analysis. Medical records were reviewed retrospectively and patients were classified according to disease severity, which was clearly defined in Methods section. However, there is a still possibility that selection of hypertensive patients may impact on our results. |
|---------------------------|--|---|
| | Bias in classification of interventions | Low risk. As medical records were reviewed retrospectively, there is no misclassification of intervention (ACEI or ARB). Even though misclassification existed, it would be a systematic error. |
| | Bias due to deviations from intended interventions | Low risk. The use of ACEI or ARB was not intended for antiviral treatment, bur for treating hypertension. Therefore, it is difficult to think that there would be a different management according to whether ACEI or ARB was used or not. |
| | Bias due to missing data | Moderate risk. Missing data was not reported according to use of ACEI or ARB. However, the patient data without information on the use of ACEI or ARB may be excluded in initial stage of this study. |
| | Bias in measurement of outcomes | Moderate risk. This study was conducted retrospectively. Therefore, investigators knew patient data including group and intervention classification before initiation of analysis. The possibility of bias in outcome assessment can be suggested. However, only mortality was analyzed in this study, that cannot be biased even though the investigators knew the patient data before analysis. |
| | Bias in selection of the reported result | Serious risk. Reported results may be prespecified by registered protocol before intervention classification was conducted, but the possibility of bias in selective reporting is strongly suggested because other hypertensive or cardioprotective drugs were not described (eg. beta-blocker) and any other intervention (eg. antibiotics or antiviral agents) which may impact on prognosis were not evaluated at all. |
| | Bias due to confounding | Low risk. Although underlying chronic diseases and other confounding factors were significantly different between ACEI/ARB group and non-ACEI/ARB group, adjusted effect size was calculated. |
| | Bias in selection of participants into the study | Low risk. All the COVID-19 patients who were hospitalized or isolated were included in this study. |
| | Bias in classification of interventions | Low risk. As medical records were reviewed retrospectively, there is no misclassification of intervention (ACEI or ARB). Even though misclassification existed, it would be a systematic error. |
| | Bias due to deviations from intended interventions | Low risk. The use of ACEI or ARB was not intended for antiviral treatment, bur for anti-hypertensive or protective effect on heart, kidney, or other vascular diseases. Therefore, it is difficult to think that there would be a different management according to whether ACEI or ARB was used or not. |
| Lee H. et al. (2020) | Bias due to missing data | Moderate risk. Missing data was not reported in mortality according to use of ACEI or ARB. However, the patient data without information on the use of ACEI or ARB may be excluded in initial stage of this study. |
| | Bias in measurement of outcomes | Moderate risk. This study was conducted retrospectively. Therefore, investigators knew patient data including group and intervention classification before initiation of analysis. The possibility of bias in outcome assessment can be suggested. However, only mortality was analyzed in this study, that cannot be biased even though the investigators knew the patient data before analysis. |
| | Bias in selection of the reported result | Moderate risk. Reported results may be prespecified by registered protocol before intervention classification was conducted, but still the possibility of bias in selective reporting cannot be ignored because this study was conducted retrospectively. |
| | Bias due to confounding | No information. Confounding factors were compared between COVID-19 positive and negative patients. However, it is not possible to know whether there is any difference in confounding factors between the patients who used ACEI or ARB and those who did not use. |
| Rentsch CT. et al. (2020) | Bias in selection of participants into the study | Moderate risk. All the patients who were registered in VA Birth cohort and took COVID-19 tests were included. Medical records were reviewed retrospectively and patients were classified according to COVID-19 positivity. There may a selection bias in those who took COVID-19 tests among the VA Birth cohort patients and this may impact on our results. |
| | Bias in classification of interventions | Low risk. As medical records were reviewed retrospectively, there is no misclassification of intervention (ACEI or ARB). Even though misclassification existed, it would be a systematic error. |
| | Bias due to deviations from intended interventions | Low risk. The use of ACEI or ARB was not intended for antiviral treatment, bur for anti-hypertensive or protective effect on heart, kidney, or other vascular diseases. Therefore, it is difficult to think that there would be a different management according to whether |

| | | ACEI or ARB was used or not. |
|----------------------|--|---|
| | Bias due to missing data | Low risk. Missing data on ACEI/ARB use was not found. |
| | Bias in measurement of outcomes | Serious risk. This study was conducted retrospectively. Therefore, investigator knew patient data including group and intervention classification before initiation of analysis. The possibility of bias in outcome assessment is strongly suggested. |
| | Bias in selection of the reported result | Moderate risk. Reported results may be prespecified by registered protocol before intervention classification was conducted, but still the possibility of bias in selective reporting cannot be ignored because this study was conducted retrospectively. |
| | Bias due to confounding | No information. Main analysis was conducted according to severity in COVID-19 patients. However, it is not possible to know whether there is any difference in underlying diseases between the patients who used ACEI or ARB and those who did not use |
| | Bias in selection of participants into the study | Low risk. All the hospitalized patients diagnosed with COVID-19 were included for analysis. Medical records were reviewed retrospectively and patients were classified according to ACEI/ARB use, which was clearly defined in Methods section. Selection bias was not suspected. |
| | Bias in classification of interventions | Low risk. As medical records were reviewed retrospectively, there is no misclassification of intervention (ACEI or ARB). Even though misclassification existed, it would be a systematic error. |
| Yan H. et al. (2020) | Bias due to deviations from intended interventions | Low risk. The use of ACEI or ARB was not intended for antiviral treatment, bur for treating hypertension. Therefore, it is difficult to think that there would be a different management according to whether ACEI or ARB was used or not. |
| | Bias due to missing data | Serious risk. This study was conducted retrospectively. Therefore, investigator knew patient data including group and intervention classification before initiation of analysis. The possibility of bias in outcome assessment is strongly suggested. |
| | Bias in measurement of outcomes | Serious risk. This study was conducted retrospectively. Therefore, investigator knew patient data including group and intervention classification before initiation of analysis. The possibility of bias in outcome assessment is strongly suggested. |
| | Bias in selection of the reported result | Moderate risk. Reported results may be prespecified by registered protocol before intervention classification was conducted, but still the possibility of bias in selective reporting cannot be ignored because this study was conducted retrospectively. |
| | Bias due to confounding | No information. Subgroup analysis was conducted to know the impact of ACEI or ARB on disease severity and all-cause mortality in the patients with hypertension. However, it is not possible to know whether there is any difference in underlying diseases between the patients who used ACEI or ARB and those who did not use. |
| | Bias in selection of participants into the study | Moderate risk. Hypertensive patients diagnosed with COVID-19 were included. Medical records were reviewed retrospectively and patients were classified according to disease severity, which was clearly defined in Methods section. However, there is a still possibility that other hypertensive drug may impact on our results (eg. calcium channel blocker). |
| Zeng Z. et al. | Bias in classification of interventions | Low risk. As medical records were reviewed retrospectively, there is no misclassification of intervention (ACEI or ARB). Even though misclassification existed, it would be a systematic error. |
| (2020) | Bias due to deviations from intended interventions | Low risk. The use of ACEI or ARB was not intended for antiviral treatment, bur for treating hypertension. Therefore, it is difficult to think that there would be a different management according to whether ACEI or ARB was used or not. |
| | Bias due to missing data | Moderate risk. Missing data was not reported in terms of severity and mortality according to use of ACEI or ARB. However, the patient data without information on the use of ACEI or ARB or severity of COVID-19 may be excluded in initial stage of this study. |
| | Bias in measurement of outcomes | Serious risk. This study was conducted retrospectively. Therefore, investigator knew patient data including group and intervention classification before initiation of analysis. The possibility of bias in outcome assessment is strongly suggested. |
| | Bias in selection of the reported result | Low risk. All the variables were analyzed whether there is any difference between ACEI or ARB user group and non-user group. |