Comparative Impacts of ACE (Angiotensin-Converting Enzyme) Inhibitors Versus Angiotensin II Receptor Blockers on the Risk of COVID-19 Mortality

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Treating coronavirus disease 2019 (COVID-19) using ACE (angiotensin-converting enzyme) inhibitors and angiotensin II receptor blockers (ARBs) is a clinical dilemma due to the perceived risk of exacerbating COVID-19 by elevating ACE2 expression.[1] Despite recent studies showing no harm to continue ACE inhibitors/ARBs in the setting of COVID-19,[2,3] it is still unknown whether ACE inhibitors and ARBs have equivalent impacts on COVID-19 mortality among patients preexisting different indications.

To address this critical question, in this multi-centered retrospective study, we enrolled 15 504 participants diagnosed as COVID-19 and admitted to 17 hospitals located at Hubei Province, China, from December 31, 2019 to April 21, 2020. A total of 3572 eligible participants (aged 66 [interquartile range, 58–72] years, 51.1% male sex) with ACE inhibitors/ARBs indications and hospitalized due to COVID-19 were included in our analysis, whereas patients without taking any drugs for treating ACE inhibitors/ARBs indications or recorded hypotension shock within 24 hours after admission were excluded (Figure [A]). Data collection, extraction, and analysis were conducted in a standard procedure by a team of physicians, analysts, and statisticians. The study design and procedures were approved by the central ethics committee and were accepted or approved by the local ethics committees of all participating hospitals. Informed consent forms were waived by each ethics committee. The data that support the findings of this study are available from the corresponding author upon reasonable request.

We analyzed the associations between in-hospital use of ACE inhibitors/ARBs and 28-day all-cause death of COVID-19 compared to the use of non-ACE inhibitors/ARBs agents using propensity score–matched analysis where age, sex, disease severity, comorbidities, and calcium channel blockers medication usage were matched. And 906 ACE inhibitors/ARBs treated subjects were successfully matched with 1812 subjects treated with non-ACE inhibitors/ARBs agents during hospitalization at a ratio of 1:2. After further adjusting for imbalanced variables and in-hospital medications, the in-hospital use of ACE inhibitors/ARBs was significantly associated with lower risk of 28-day all-cause mortality of COVID-19 (adjusted hazard ratio [HR], 0.39 [95% CI, 0.26–0.58]; $P<0.001$) compared with the non-ACE inhibitors/ARBs group. Notably, patients in the ACE inhibitors/ARBs groups had significantly lower risk of 28-day all-cause mortality of COVID-19 among patients with hypertension (adjusted HR, 0.32 [95% CI, 0.15–0.66]; $P=0.002$), hypertension combined with coronary artery disease (adjusted HR, 0.11 [95% CI, 0.04–0.31]; $P<0.001$), and coronary artery disease (adjusted HR, 0.38 [95% CI, 0.16–0.89]; $P=0.03$; Figure [B] and [C]). Thus, patients with hypertension and coronary artery disease might obtain benefits from taking ACE inhibitors/ARBs

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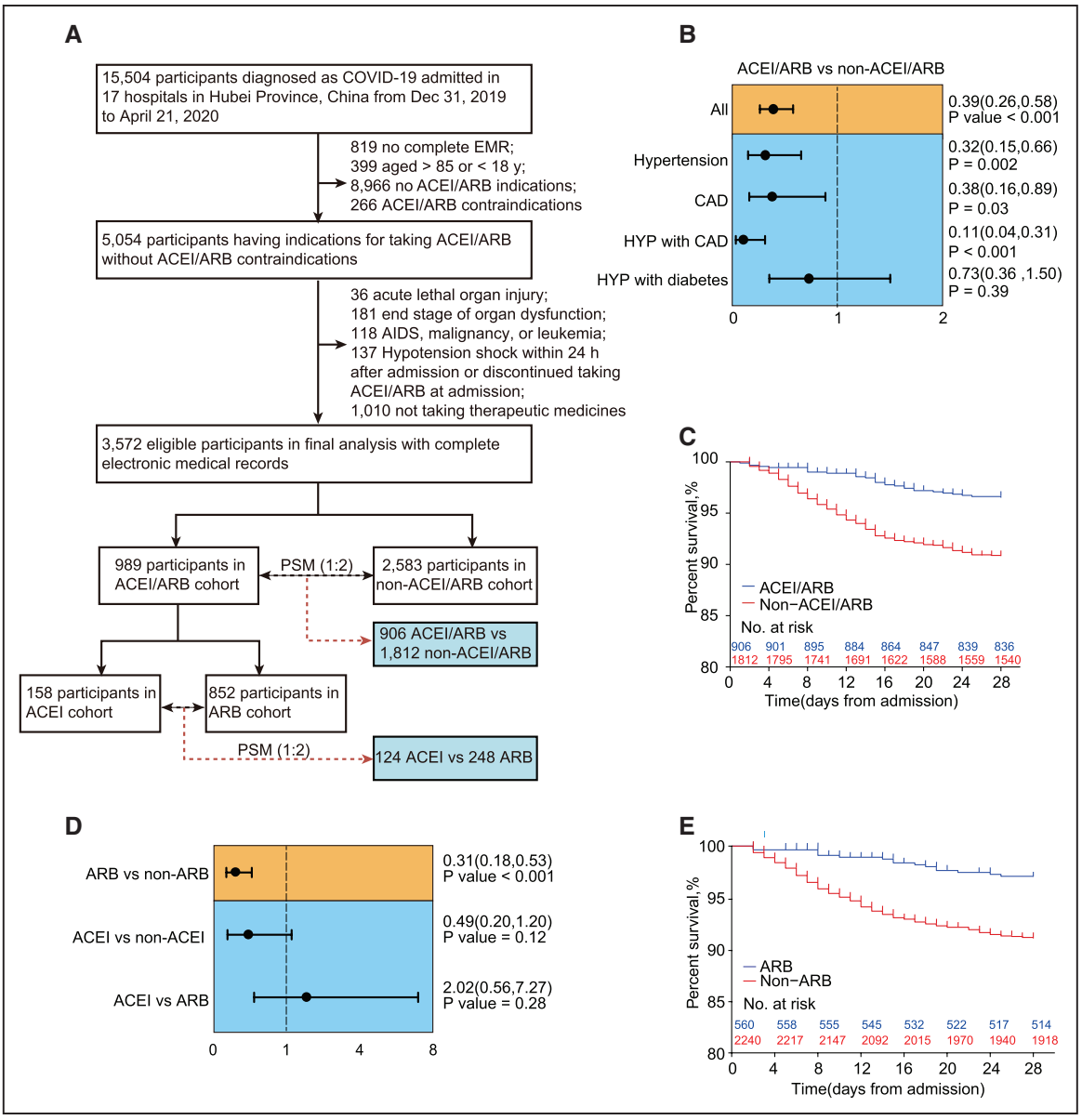

Figure. The flowchart of patient enrollment and the associations of ACE (angiotensin-converting enzyme) inhibitors and angiotensin II receptor blockers (ARBs) with 28-d all-cause death of coronavirus disease 2019 (COVID-19). **A**, Flow chart of enrolling patients in this study. **B**, Forest plots showing the associations of in-hospital use of ACE inhibitors/ARBs vs non-ACE inhibitors/ARBs with 28-d all-cause death of COVID-19 among patients with different indications. **C**, Kaplan-Meier curves showing percent survivals in ACE inhibitors/ARBs and non-ACE inhibitors/ARBs groups among patients with all ACE inhibitors/ARBs indications. The blips indicate censoring. **D**, Forest plots showing the comparative associations of inpatients receiving ACE inhibitors or ARBs or other therapeutic agents with 28-d death of COVID-19 among patients having indications for taking ACE inhibitors/ARBs. **E**, Kaplan-Meier curves showing percent survival among patients in ARBs/ARBs groups during 28 d after admission. The blips indicate censoring. ACEI indicates ACE inhibitors; CAD, coronary artery disease; EMR, electronic medical records; HYP, hypertension; and PSM, propensity score–matched.

compared with the non-ACE inhibitors/ARBs in the setting of COVID-19.

Although ACE inhibitors and ARBs are commonly considered interchangeable in treating hypertension, cardiac diseases, and chronic kidney diseases in clinic application,[4] their risks and benefits must be reconsidered when facing COVID-19 in light of the involvement of pulmonary and multiorgan symptoms.[5] We thus further evaluated ACE inhibitors and ARBs specific associations with the risk of 28-day mortality for COVID-19. A total of 124 participants taking ACE inhibitors (aged 65 [interquartile range, 59–71] years, 62.9% male) were matched with 248 subjects taking ARBs (aged 64 [interquartile range, 56–72] years, 59.7% male) by propensity score matching. Importantly, the risk of 28-day all-cause mortality of COVID-19 was not significantly different between the patients taking ACE inhibitors versus the ones taking ARBs during hospitalization, despite the fact that the risk of death trended higher in the ACE inhibitors group (adjusted HR, 2.02 [95% CI, 0.56–7.27]; P=0.28; Figure [D]).

Notably, in-hospital use of ARBs was associated with a significantly reduced mortality (adjusted HR, 0.31 [95% CI, 0.18–0.53]; P<0.001) compared with non-ARB agents during 28-day follow-up, whereas ACE inhibitors showed no significant association with the 28-day mortality compared to

non-ACE inhibitors drugs (adjusted HR, 0.49 [95% CI, 0.20–1.20]; *P*=0.12; Figure [D] and [E]) among patients with indications for ACE inhibitor/ARBs and infected by severe acute respiratory syndrome coronavirus 2. These data suggested that ARBs medication consistently showed beneficial effects in reducing mortality in COVID-19, but ACE inhibitor specific effects appeared to be less homogenous.

In conclusion, based on the large-scale retrospective study, we demonstrated that in-hospital use of ACE inhibitors/ARBs was associated with a lower risk of 28-day death among hospitalized patients with COVID-19 and coexisting hypertension, coronary artery disease and hypertension combined with coronary artery disease. These data suggested that patients with hypertension and coronary artery disease might obtain benefits from taking ACE inhibitors/ARBs compared to the non-ACE inhibitors/ARBs in the setting of COVID-19. Notably, in-hospital usage of ACE inhibitors tended to have a higher incidence and risk of 28-day COVID-19 mortality than those taking ARBs, but the difference was not statistically significant. Nevertheless, this should be interpreted with caution since the observations were obtained from a retrospective study and might be possibly overcome to null by unmeasured confounders. Despite large-scale and geographically diverse prospective studies and randomized controlled trials are still required, this retrospective study based on a large cohort provides actionable information to clinical physicians for treating patients with ACE inhibitors/ARBs indications and infected with severe acute respiratory syndrome coronavirus 2.

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Disclosures

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