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In conclusion, our findings are in contrast with those presented by Tan et al and suggest caution when interpreting clinical associations between outcome ad concomitant medications. Since ACEIs/ARBs are commonly prescribed in elderly and comorbid patients, any analysis of related outcomes must account for the potential confounders often found in this subset of patients.

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Most current article

**Reply.** We thank Parigi et al, who tried to replicate our analyses of the association between the use of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARBs), gastrointestinal (GI) symptoms, and mortality in patients with COVID-19 in a cohort from a single tertiary center in Milan, Italy.[1] Indeed, the protective role of ACEI/ARBs demonstrated in our study was confirmed by several previous studies.[2,3] A large case-control study showed improved survival in patients with coronavirus disease 2019 (COVID-19) taking ACEI.[2] By showing a significantly lower risk of mortality in the continuation group, another subsequent large cohort study support continuation of ACEI/ARBs therapy during COVID-19 hospitalization.[3] Potential mechanisms of an ACEI/ARB-mediated protective effect include reduced severity of COVID-19 pneumonia, preserved hypoxic vasoconstriction, limited deterioration of renal function, and protection against myocardial injury.[4]

The discrepancy between our study and study by Parigi et al[1] may be explained by several reasons. First, their cohort differed from ours; we included only patients with hypertension, whereas the cohort used by Parigi et al[1] recruited all consecutive patients, including those with and without history of hypertension. A systematic review[5] showed that ACEI/ARBs exposure was not associated with a lower risk of COVID-19 severity or mortality; however, when limited to patients using an ACEI/ARBs indicated for hypertension, a significantly lower risk of mortality was observed among those who used ACEI/ARBs. Another meta-analysis with the largest sample size to date (n = 28,872) used deaths and critical events, including intensive care admission as a primary end point, and demonstrated a beneficial effect of ACEI/ARBs especially in the hypertensive cohort with COVID-19.[6] The cohort of Parigi et al included patients without hypertension in the non-ACEI/ARBs group, which may underestimate the protective elect of ACEI/ARBs.

Another possible explanation may lay in the significant geographical disparities as evident by previous studies.[7] Patoulias et al[7] conducted a meta-analysis that included 25 observational studies, and found in Asian countries, the use of ACEI/ARBs decreased the odds for severe or critical illness and death, whereas ACEI/ARBs increased the odds for intensive care admission in North America and death in Europe.

Third, the preferred use of ACEI over ARBs in our study may partly account for the positive role. As evident by previous study, risk of in-hospital death was found to be associated with the use of ACEI (odds ratio [OR], 0.33; 95% confidence interval [CI], 0.20–0.54), but not the use of ARBs (OR, 1.23; 95% CI, 0.87–1.74).[2] Additionally, the use of ARBs, as opposed to ACEIs, may augment the risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in younger patients.[8] However, these associations should be considered with caution because of potential unmeasured confounding given the observational design of included studies. Results from ongoing phase IV clinical trials that aim to assess the effects of losartan and valsartan on progression of acute respiratory distress syndrome with SARS-CoV-2 infection (NCT04340557 and NCT04335786) may provide further evidence in this setting.

So far, a conclusive role of ACEI/ARBs on GI symptoms and liver function is still lacking. Our study found a negative association between ACEI/ARB use and GI symptoms/liver injury at admission or throughout the disease course, whereas Parigi et al[1] and another retrospective study from Wuhan found no significant association between ACEI/ARBs use and liver dysfunction.[4] However, owing to the small sample size, selection bias, and lack of a general validated definition for liver dysfunction, further evidence is necessary.

The pooled prevalence of digestive symptoms was 12%–15%,[9,10] with nausea or vomiting, diarrhea, and loss of appetite being the 3 most common symptoms. The geographical disparities also exist for the prevalence of GI symptoms and liver injury as reported by the American Gastroenterological Association Institute publication that digestive involvement was more prevalent outside China.[5,11] As for the association between GI involvement and the severity of COVID-19, according to our meta-analysis,[9] patients with GI involvement tended to have a poorer disease course. Our preliminary finding has been confirmed by subsequent studies.[12,13] This might be ascribed to the fact that even after the virus has been cleared from the respiratory system, it can persist in the gut of some patients for several days (≤47 days), which leads to a high level of virus and longer lasting disease.[9]

In conclusion, current evidence supports continued use of ACEI/ARBs in COVID-19 patients with hypertension. As an important clinical feature in patients with COVID-19, digestive symptoms should be treated with caution in the early stage of COVID-19, and dynamic monitoring of liver function is imperative during clinical practice to reduce the complications and mortality of COVID-19.

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# Association Between Famotidine Use and COVID-19 Severity in Hong Kong: A Territory-wide Study

Dear Editors:

We read with interest the study by Freedberg et al,[1] which showed the improved clinical outcome in hospitalized patients with Coronavirus Disease 2019 (COVID-19) with the use of famotidine, but not proton pump inhibitors (PPIs). The results corroborate the computer modeling analysis that famotidine is one of the drugs predicted to bind 3Cl$^{pro}$,[2] a protease that generates nonstructural proteins essential for replication of virus. However, there were certain limitations of this study despite the use of propensity score matching to adjust for differences in patient's baseline characteristics. First, concomitant medication usages were not considered, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and statins, which had been shown to be associated with a lower risk of severe disease.[3,4] Second, laboratory parameters, which could serve as surrogate markers for disease severity, were not adjusted for in their analysis.

Herein, we reported the results of our territory-wide retrospective cohort study in all patients with COVID-19 from Hong Kong to investigate the association between famotidine use and severity of COVID-19. Data were retrieved from the territory-wide electronic healthcare database (Clinical Data Analysis and Reporting System) of the Hong Kong Hospital Authority. We identified all adult patients aged ≥18 years with the diagnosis code of "COVID-19" between January 1, 2020, and May 10, 2020. The primary outcome was severe disease, which was defined as the presence of (1) critical complication (respiratory failure, septic shock, and/or multiple organ dysfunction), (2) ventilatory support (invasive or noninvasive), (4) intensive care unit admission, and/or (5) death. Drug exposure, including famotidine and PPIs, was defined as exposure on the day of admission. There were 26 covariates in the logistic regression model, which included age, sex, comorbidities (diabetes mellitus, hypertension, ischemic heart disease, stroke, and atrial fibrillation), other medications (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aspirin, statins, and prednisolone), and laboratory parameters (leukocyte, platelet, C-reactive protein, urea, creatinine, sodium, potassium, bilirubin, alkaline phosphatase, alanine aminotransferase, albumin, globulin, and lactate dehydrogenase). We used a multivariable logistic regression model to derive the adjusted odds ratio (aOR) of severe COVID-19 disease with famotidine. Similar analysis was performed for PPIs. To deal with missing data in the regression model, multiple imputation was used to construct 50 complete datasets by imputing the missing variables. All variables were included into the multivariable analysis, as negative confounding can mask a potential association between the outcome and variable.[5]