Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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COVID-19, ACEI/ARBs, and Gastrointestinal Symptoms: The Jury Is Still Out on the Association

Dear Editors:

We read with great interest the article by Tan et al[1] investigating the association between the use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor II Blockers (ARBS), gastrointestinal (GI) involvement, and clinical outcome of coronavirus disease 2019 (COVID-19).[1] The authors concluded that ACEIs/ARBs treatment continuation was associated with a lower rate of GI manifestations (diarrhea, vomiting, nausea, and abdominal pain) and increased mortality. We tried to replicate their analyses in a similar cohort from a single tertiary center in Milan, Italy.

Our cohort included 325 consecutive patients with COVID-19 confirmed by reverse transcriptase polymerase chain reaction who were hospitalized between February 22 and March 30, 2020. The median patient age was 66 years (range, 24–93 years; interquartile range, 55–75), and 68.6% were males. A history of hypertension was reported in 51.3% (167/325) and coronary heart disease in 17.8% (58/325). At admission, a total of 114 patients (35.4%) were taking ACEIs/ARBs.

We observed no difference in terms of the severity of COVID-19 presentation between patients using ACEIs/ARBs or non-ACEIs/ARBs users: among the 2 groups, a similar percentage of patients were breathing in ambient air (34.2% vs 41.8%; $P = .18$), were receiving supplemental oxygen (50% vs 43.27%; $P = .24$) or needed mechanical ventilation (15.8% vs 14.9%; $P = .83$).

Despite our larger cohort, in univariable logistic regression analysis we could not find a statistically significant association between ACEIs/ARBs use and reduced GI involvement at admission (odds ratio [OR], 0.63; 95% confidence interval [CI], 0.37–1.08; $P = .091$). Considering diarrhea alone did not change the results appreciably (OR, 0.63; 95% CI, 0.36–1.11; $P = .107$). Similarly, we found no negative association between use of ACEIs/ARBs and liver injury, using the same cut-offs: aspartate aminotransferase of >40 UI/L, alanine aminotransferase of >40 UI/L, or total bilirubin of >20 mmol/L (OR, 0.94; 95% CI, 0.59–1.48; $P = .782$). We noted that the prevalence of diarrhea at admission in our cohort was higher than reported by Tan et al[1] (23.4% vs 12.0%), whereas prevalence of other GI symptoms was lower (6.5% vs 15.0%). We chose to restrict our analysis to GI symptoms present at admission only to minimize the confounding effect of other hospitalization-related causes of diarrhea, such as antibiotics or antiviral use.

The prognostic interpretation of these findings is not unequivocal and the interplay between sever acute respiratory syndrome coronavirus 2 (SARS-CoV-2) digestive involvement and overall clinical outcome remains unclear. In a previously published analysis of this same cohort, we found an association between GI symptoms and lower rate of clinical deterioration.[2] This finding is in contrast with a meta-analysis of Chinese studies, which concluded that patients with GI involvement tend to develop more severe COVID-19.[3] Further prospective studies are needed to investigate the implications of SARS-CoV-2 digestive involvement.

In the secondary analysis, Tan et al found a protective effect of ACEIs/ARBs use on overall clinical outcome. We could not confirm this result in our cohort. Although in univariable logistic regression analysis the use of ACEIs or ARBs was associated with clinical deterioration, defined as death or intensive care admission (OR, 2.05; 95% CI, 1.28–3.28; $P = .003$), in multivariable analysis, after adjustment for potential confounding factors such as age, coronary artery disease, hypertension and diabetes mellitus, use of ACEIs/ARBs did not remain significantly associated with the outcome (adjusted OR, 0.99; 95% CI, 0.49–1.55; $P = .975$). Although a large retrospective Chinese study found a decreased risk of all-cause mortality among ACEI/ARBs users,[4] the overall quality of evidence is still limited and often conflicting.[5]

Finally, Tan et al interpret their results according to the assumed protective effect of ACEIs/ARBs from endothelial damage, which could lead to less multiorgan involvement with milder GI manifestations and an overall more favorable outcome. This hypothesis lacks a strong biological background because the role of ACEIs/ARBs in the course of COVID-19 infection remains unclear. Moreover, it is in contrast with other studies reporting that multiorgan involvement such as GI or liver involvement is not associated with a more severe COVID-19 disease course.[6,7] Consequently, the GI presentation of COVID-19 should not distract clinicians from giving patients the best level of medical care.

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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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.