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.

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 ($\leq$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 $\geq$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]

Of the 952 patients with COVID-19, 51 (5.4%) had severe disease as defined. Twenty-three (2.4%) and 4 (0.4%) patients were given famotidine and PPIs, respectively. There was no significant association between severe COVID-19 disease and use of famotidine (aOR 1.34; 95% CI, 0.24–6.06; $P = .72$) or PPIs (aOR 0.75; 95% CI, 0.07–6.00; $P = .80$). Leucocyte count $>11 \times 10^9$/L (aOR 5.83; 95% CI, 1.43–2.12; $P = .010$) and lactate dehydrogenase >280 U/L (aOR 3.49; 95% CI, 1.52–7.97; $P = .003$) were independent laboratory parameters associated with severe COVID-19.

Hence, our findings did not support any association between famotidine and COVID-19 severity. Apart from difference in the various statistical adjustments including concurrent medication and laboratory parameters, we speculate that indication or selection bias may also confound the previous positive association, as a clinician's choice of famotidine over PPIs may be influenced by a patient's presentation, particularly on stress ulcer prophylaxis.[6] Because of the discrepant outcomes of the role of famotidine on COVID-19 severity, randomized trials are therefore needed to clarify the uncertain role of famotidine.

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What Underlies the Benefit of Famotidine Formulations Used During COVID-19?

Dear Editors:

This letter is in reference to the study by Freedberg et al[1] recently published in *Gastroenterology*. This retrospective analysis of an inpatient cohort admitted to 2 hospitals in New York found that patients with coronavirus disease 2019 (COVID-19) who were treated with famotidine exhibited a lower risk of death or mechanical ventilation as composite outcomes over a 30-day period. The study was based on computational modelling, which proposed famotidine might inhibit viral replication through direct interaction with the 3-chymotrypsin-like protease,[2] and was also preceded by a small, short-term follow-up, outpatient study suggesting that famotidine use was associated with symptomatic improvement.[3] However, the current study published in *Gastroenterology* provides additional value because the previous cohort was much smaller in number, included patients without a proven COVID-19 diagnosis, and lacked a control group.

The current study by Freedberg et al[1] brings a few questions to mind, which we hope the authors can answer. In the conclusions, the authors stated, "The study was premised on the assumption that use of famotidine represented a continuation of home use." In the Results section, they also say, "Home use of famotidine was documented on admission medication reconciliation in 15% of those who used famotidine while hospitalized." These points bring up a few questions.

1. Does this indicate that the remaining 85% patients given famotidine during hospitalization were using over the counter formulations at home which were not prescribed by a physician?
2. Were these formulations continued in-patient?
3. What were the formulations of famotidine used by the hospital pharmacies?
4. Did some included patients receive concomitant treatment with antacids, particularly calcium-containing compounds?
5. It is also mentioned that 28% hospitalized COVID-19 patients received famotidine intravenously. Was there a difference in outcomes between the intravenously treated group and the orally treated group?

We ask since popular over the counter famotidine formulations such as Pepcid Complete commonly contain 800 mg calcium carbonate per 10 mg famotidine. The answers to these questions are pathophysiologically relevant as we have recently published a report in your journal,[4] suggesting that the hypocalcemia commonly seen in severe COVID-19 disease is prognostically and mechanistically relevant to disease outcomes. We proposed that calcium supplementation early in the disease can, by interacting with fatty acids, decrease the lipotoxicity, which may exacerbate the disease and result in organ failure.

Using in silico molecular docking screens, famotidine has been characterized as potentially being able to bind papain-like protease (PLpro) and 3 chymotrypsin-like protease (Mpro) of SARS-CoV-2.[2,5] To explore this notion further, we downloaded crystal structures of PLpro and Mpro from RCSB.org (PDB IDs 6WX4 and 6LU7, respectively) and imported these to Schrodinger Maestro. The structures were prepared for docking, and famotidine was docked to both