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Association between famotidine use and COVID-19 severity in Hong Kong: a territory-wide study

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To the editor: We read with interest the study by Freedberg et al[1] which showed the improved clinical outcome in hospitalized COVID-19 patients 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 non-structural proteins essential for replication of virus. However, there were certain limitations of this study despite the use of propensity score matching to adjust for difference in patient's baseline characteristics. First, concomitant medication usages were not considered including angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and statin, 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 COVID-19 patients 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 1 January 2020 and 10 May 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 non-invasive], (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 (ACEIs, ARBs, 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 [LDH]). We used 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 COVID-19 patients, 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=0.72) or PPIs (aOR:0.75, 95% CI:0.07–6.00; p=0.80). Leucocyte count >11 x 10^9/L (aOR:5.83, 95% CI:1.43–2.12; p=0.010) and LDH >280 U/L (aOR:3.49, 95% CI:1.52–7.97; p=0.003) 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 clinician's

choice of famotidine over PPIs may be influenced by patient's presentation, particularly on stress ulcer prophylaxis.[6] Due to 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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