Proton pump inhibitor or famotidine use and severe COVID-19 disease: a propensity score-matched territory-wide study

We read the recent articles published in *Gut* on the relationship between proton pump inhibitor (PPI) use and outcomes in COVID-19 with great interest.[1 2] In the meta-analysis, the authors found that current or regular PPI users were more likely to have severe outcomes of COVID-19 than non-users, but no significant association was observed for previous PPI use.[2] The reason may be reduced secretion of gastric acid that can neutralise the SARS-CoV-2. By contrast, the use of famotidine, another medication for gastric ulcers or gastro-oesophageal reflux disease, was associated with better clinical outcomes in some studies,[3 4] but not others.[5 6]

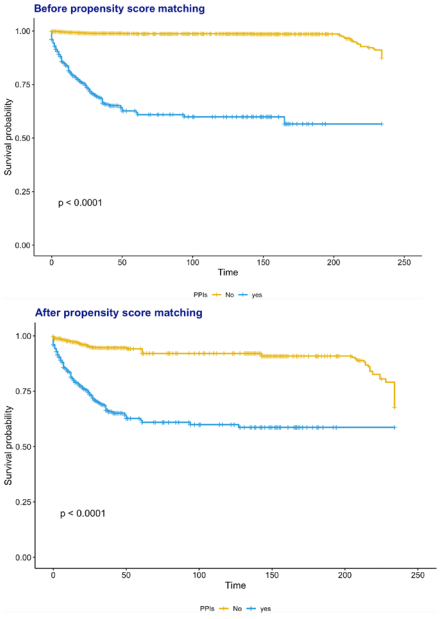

Figure 1 Kaplan-Meier curve stratified by proton pump inhibitor (PPI) use before and after propensity score matching.

Given these conflicting findings, we conducted this territory-wide study to investigate whether PPI or famotidine use was associated with a higher risk of severe disease using propensity score matching. The detailed methodology of the present analyses is shown in the online supplemental appendix. A total of 4445 patients (median age 44.8 years old, 95% CI: (28.9 to 60.8)); 50% male) were diagnosed with the COVID-19 infection between 1 January 2020 and 22 August 2020 in Hong Kong public hospitals or their associated ambulatory/outpatient facilities. On follow-up until 8 September 2020, a total of 212 patients (4.8%) met the primary outcome of need for intensive care unit (ICU) admission or intubation, or death (online supplemental figure 1). The median duration between hospitalisation admission and ICU admission, intubation or death were 35 (95% CI: 24.5 to 50.5), 33 (95% CI: 21.0 to 140.0) and 15 days (95% CI: 7.5 to 24.5), respectively. The baseline clinical characteristics of patients with or without PPI/famotidine use during the inpatient stay are shown in online supplemental table 4. Those for the cohort stratified by PPI or famotidine use before and after propensity score matching for baseline demographics, medical comorbidities and medication history are shown in online supplemental tables 5 and 6, respectively.

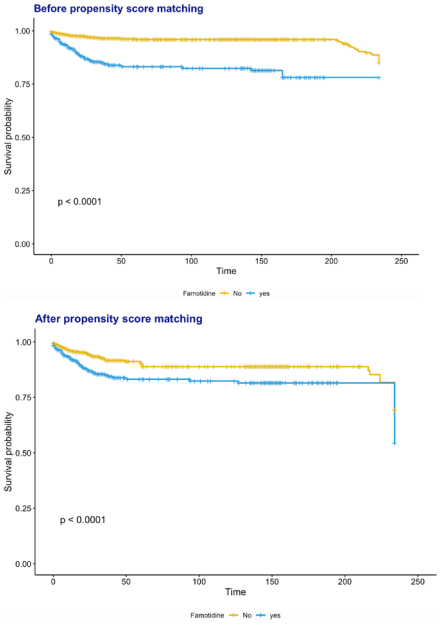

Figure 2 Kaplan-Meier curve stratified by famotidine use before and after propensity score matching.

The percentage of COVID-19 patients meeting the primary outcome was significantly higher in PPI users than in non-users, both before (n=151/524, 28.8% vs n=61/3921, 1.6%; p<0.0001) and after 1:5 propensity score matching for age, sex, medical comorbidities and medication history (n=151/524, 28.8% vs n=173/2620, 6.6%; p<0.0001). Similarly, famotidine users also showed a higher percentage compared with non-users before (n=72/519, 13.9% vs n=140/3926, 3.6%; p<0.0001) and after matching (n=72/519, 13.9% vs n=198/2595, 7.6%; p<0.0001). Kaplan-Meier curves stratified by PPI or famotidine use are shown in figures 1 and 2. Based on the matched cohorts, univariable Cox regression showed that the use of PPI (HR: 6.32, 95%CI: (5.02 to 7.95); p<0.0001) or famotidine (HR: 1.98, 95%CI: (1.47 to 2.66); p<0.0001) was associated with a higher risk of the primary outcome (online supplemental table 7). On multivariable Cox regression adjusting for age, cardiovascular disease, renal disease, stroke, Kaletra, diuretics for heart failure, other anti-hypertensives, PPI/famotidine, neutrophils, lymphocytes, platelets, urea, creatinine, albumin and glucose, the associations remained significant for both PPI (HR: 2.73, 95% CI: (2.05 to 3.64), p<0.0001) and famotidine (HR: 1.81, 95% CI: (1.28 to 2.58), p<0.0001). The Cox analyses were repeated on separate cohorts generated by 1:1 propensity score matching, demonstrating similarly increased risks with PPI (HR: 11.76, 95% CI: (7.77 to 17.79); p<0.0001) or famotidine (HR: 1.81, 95% CI: (1.35 to 2.43); p<0.0001) use. Similarly, on multivariate Cox regression, the associations remained significant for both

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PPI (HR: 2.65, 95% CI: (1.75 to 4.00), p<0.0001) and famotidine (HR: 1.84, 95% CI: (1.16 to 2.92), p<0.0001).

Our data indicate that the use of PPIs or famotidine is associated with a higher risk of severe COVID-19 disease after propensity score matching in a Chinese cohort. Our findings should be validated in future studies.

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