Proton pump inhibitors and the risk of severe COVID-19: a post-hoc analysis from the Korean nationwide cohort

We appreciate the comment and discussion from Dr Roulet[1] on our original article.[2] The author criticised that (1) our study did not consider the dose-dependent exposure to proton pump inhibitors (PPIs); (2) our study did not investigate the relationship of PPI use in hospitalised patients with COVID-19 during treatment for COVID-19 and (3) although our study accounted for protopathic bias by excluding new non-steroidal anti-inflammatory drug users, protopathic bias occurred in patients who responded to the early digestive symptoms of COVID-19. We acknowledge that plausible academic concerns have been raised, which might improve the original discussion and extend the insight into the association between PPI usage and COVID-19.[1] We have performed a post-hoc analysis from the Korean nationwide cohort, addressing these concern.

Data were obtained from the Korean nationwide cohort study, which includes patients (≥18 years) who underwent SARS-CoV-2 testing between 1 January and 15 May 2020.[2–4] We performed propensity score matching between current PPI users (prehospitalisation PPI usage) and non-users among patients with laboratory-confirmed COVID-19 (n=4785), as previously described.[2] Post-hospitalisation PPI usage was defined as in-hospital PPI use in general wards, not intensive care units. The outcomes were a composite endpoint 1 (requirement of oxygen therapy, intensive care unit admission, administration of invasive ventilation or death) and a composite endpoint 2 (intensive care unit admission, administration of invasive ventilation or death). The study protocol was approved by the institutional review board of Sejong University (SJU-HR-E-2020-003).

In the propensity score-matched cohort, we matched 267 COVID-19 patients currently using PPIs and 267 COVID-19 patients not using PPIs. First, the risk of the composite endpoint 1 (fully adjusted OR (aOR): 2.39; 95%CI: 1.08 to 5.10) and the risk of composite endpoint 2 (fully aOR: 3.30; 95%CI: 1.22 to 8.73) were significantly higher in patients who took twice daily or more PPI than patients who have never taken PPIs (table 1). Second, prehospitalisation and posthospitalisation PPI usage had an increased risk of severe COVID-19 (composite endpoint 1; fully aOR: 4.60; 95%CI: 2.03 to 10.38), compared with patients who have never taken PPIs (table 1). Finally, patients with early digestive symptoms of COVID-19 may have started PPI therapy before SARS-CoV-2 testing, so we excluded new PPI users (0–6 days; n=26). Patients taking PPIs for 7–30 days had an increased risk of severe COVID-19

Table 1 Propensity score-matched additional analysis for the association of the risk on clinical outcomes with PPI usage among patients with laboratory-confirmed SARS-CoV-2 infection (none vs current use of PPI among patients with laboratory-confirmed SARS-CoV-2 infection (n=534))

			Dose of PPI usage	
Event	**Variable**	**None**	**Once-daily PPI use**	**Twice-daily PPI use or more**
Composite endpoint 1*	Event number/total number (%)	32/267 (12.0)	38/222 (17.1)	11/45 (24.4)
	Minimally adjusted OR† (95% CI)	1 (reference)	1.54 (0.93 to 2.55)	**2.39 (1.11 to 5.17)**
	Fully adjusted OR‡ (95% CI)	1 (reference)	1.49 (0.87 to 2.50)	**2.36 (1.08 to 5.10)**
Composite endpoint 2§	Event number/total number (%)	14/267 (5.2)	17/222 (7.7)	7/45 (15.6)
	Minimally adjusted OR† (95% CI)	1 (reference)	1.51 (0.74 to 3.14)	**3.35 (1.27 to 8.80)**
	Fully adjusted OR‡ (95% CI)	1 (reference)	1.49 (0.71 to 3.10)	**3.30 (1.22 to 8.73)**
			Duration of PPI usage	
		None	**7–30 days**	**≥30 days**
Composite endpoint 1*	Event number/total number (%)	32/267 (12.0)	29/149 (19.5)	15/92 (16.3)
	Minimally adjusted OR† (95% CI)	1 (reference)	**1.78 (1.04 to 3.08)**	1.40 (0.94 to 2.32)
	Fully adjusted OR‡ (95% CI)	1 (reference)	**1.76 (1.01 to 3.05)**	1.35 (0.93 to 2.20)
Composite endpoint 2§	Event number/total number (%)	14/267 (5.2)	16/149 (10.7)	6/92 (6.5)
	Minimally adjusted OR† (95% CI)	1 (reference)	**2.18 (1.04 to 4.61)**	1.29 (0.90 to 2.05)
	Fully adjusted OR‡ (95% CI)	1 (reference)	**2.16 (1.02 to 4.58)**	1.35 (0.91 to 2.26)
			Current PPI users (prehospitalisation PPI usage)	
		None	**Without posthospitalisation PPI usage**	**With posthospitalisation PPI usage¶**
Composite endpoint 1*	Event number/total number (%)	32/267 (12.0)	37/236 (15.7)	12/31 (38.7)
	Minimally adjusted OR† (95% CI)	1 (reference)	1.38 (0.83 to 2.28)	**4.65 (2.06 to 10.45)**
	Fully adjusted OR‡ (95% CI)	1 (reference)	1.34 (0.80 to 2.25)	**4.60 (2.03 to 10.38)**
Composite endpoint 2§	Event number/total number (%)	14/267 (5.2)	20/236 (8.5)	4/31 (12.9)
	Minimally adjusted OR† (95% CI)	1 (reference)	1.68 (0.84 to 3.42)	2.69 (0.84 to 8.72)
	Fully adjusted OR‡ (95% CI)	1 (reference)	1.66 (0.81 to 3.35)	2.65 (0.80 to 8.68)

Number in bold indicate significant differences (p<0.05).
*Composite endpoint 1 consisted of requirement of oxygen therapy, admission to the intensive care unit, invasive ventilation or death.
†Minimally adjusted: adjustment for age and sex.
‡Fully adjusted: adjustment for age; sex; region of residence (urban or rural); history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, COPD, hypertension and chronic kidney disease; Charlson comorbidity index (0, 1 or ≥2); and current use of systemic steroid, metformin and aspirin.
§Composite endpoint 2 consisted of admission to the intensive care unit, invasive ventilation or death.
¶Posthospitalisation PPI usage was defined as in-hospital PPI use in general wards, not intensive care units.
COPD, chronic obstructive pulmonary disease; PPI, proton pump inhibitor; ;**SARS-CoV-2**, **severe acute respiratory syndrome coronavirus 2**.

(composite endpoint 1, fully aOR: 1.76; 95% CI: 1.01 to 3.05; and composite endpoint 2, fully aOR: 2.16; 95% CI: 1.02 to 4.58), compared with patients who have never taken PPIs (table 1).

Our results of the post-hoc analysis found the first potential association of severe clinical outcomes of COVID-19 with dose-dependent exposure to PPI and prehospitalisation and posthospitalisation PPI usage among COVID-19 patients currently using PPIs (figure 1). Higher-dose PPI and posthospitalisation PPI usage among prehospitalisation PPI users (current PPI users) was significantly associated with increased likelihood of severe COVID-19 outcomes. Also, we found that short-term PPI usage was still associated with the increased risk of severe COVID-19 outcomes. This was accounted for by protopathic bias since new PPI users were excluded.

A previous study reported the dose-dependent relationship between PPI usage and SARS-CoV-2 infection,[5] and several previous studies described that prehospitalisation PPI users had a higher risk of severity from COVID-19.[6 7] But the dose-dependent association and the relationship of prehospitalisation and posthospitalisation with PPI usage and severity of COVID-19 is unknown. Our data suggest that PPIs affect the natural course of COVID-19, and the subset of patients with PPI use should be monitored with caution.[2 5–7] We agree that our data must be interpreted with caution since our cohort was made up only of Asian patients and since Asians have a higher prevalence of *Helicobacter pylori* infection, which might have influenced the effect of PPIs as well as the susceptibility to virus infection.[7–9] Further international collaborative studies with multiethnicities are warranted to clarify this issue.

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Contributors Dr DKY had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the final version before submission. Conception and design: SWL and DKY; analysis and interpretation of the data: SWL, JMY and DKY; drafting of the article: JMY, IKY, AÖY and DKY; critical revision of the article for important intellectual content: SWL, JMY, IKY, EKH, JYC, MSK, JIS and DKY; final approval of the article: all authors; statistical expertise: SYM, SWL and DKY; administrative, technical or logistic support: SWL and DKY; collection and assembly of data: DKY.

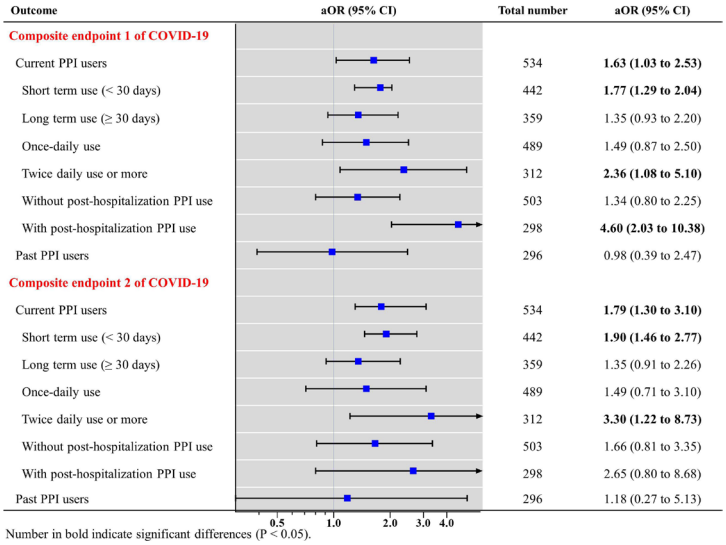

Figure 1 Summary of propensity score-matched association of the risk on clinical outcomes with PPI usage among patients with laboratory-confirmed SARS-CoV-2 infection (summary of an original and a post-hoc analysis). Composite endpoint 1 consisted of requiring oxygen therapy, admission to the intensive care unit, invasive ventilation or death. Composite endpoint 2 consisted of admission to the intensive care unit, invasive ventilation or death. Risk factors were adjusted for age; sex; region of residence (urban or rural); history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, hypertension and chronic kidney disease; Charlson Comorbidity Index (0, 1 or ≥2); and current use of systemic steroid, metformin and aspirin. aOR, adjusted OR; PPI, proton pump inhibitor.

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