Proton-pump inhibitor use is not associated with severe COVID-19-related outcomes: a propensity score-weighted analysis of a national veteran cohort

We read with interest the study by Lee *et al*.[1] The authors conducted a propensity score (PS)-matched analysis of a national South Korean cohort evaluating the association between proton pump inhibitor (PPI) use and SARS-CoV-2 susceptibility (primary outcome) and COVID-19 clinical severity (secondary outcome). Between January and May 2020, 4785 patients tested positive for SARS-CoV-2 (3.6% positivity); 267 current PPI users and 148 former PPI users were 1:1 PS-matched to non-users for the secondary outcomes. The authors reported current PPI use versus non-use was associated with a statistically significant increased risk of the composite endpoints: (1) oxygen therapy, intensive care unit (ICU) admission, mechanical ventilation use or death (composite OR 1.63; 95% CI, 1.03–2.53); and (2) ICU admission, mechanical ventilation or death (composite OR 1.79; 95% CI, 1.30 to 3.10).

We assembled a national retrospective cohort of US veterans who tested positive for SARS-CoV-2 (index date). Current outpatient PPI use up to and including the index date (primary exposure) was compared with non-use, defined as no PPI prescription fill in the 365 days prior to the index date (online supplemental figure 1). The primary composite outcome was mechanical ventilation use or death within 60 days; the secondary composite outcome also included hospital or ICU admission. In contrast to PS matching, PS weighting allowed inclusion of all patients. Weighted logistic regression models evaluated severe COVID-19 outcomes between current PPI users versus non-users.

Our analytic cohort included 97 674 veterans with SARS-CoV-2 testing, of whom 14 958 (15.3%) tested positive (6262 (41.9%) current PPI users, 8696 (58.1%) non-users). In the unweighted cohort, current PPI users were older, more often current or former smokers, and had more comorbidities than non-users. After weighting, all covariates were balanced (table 1, online supplemental figure 2). In the unweighted cohort, we observed higher odds of the primary (9.3% vs 7.5%; OR 1.27; 95% CI, 1.13-1.43) and secondary (25.8% vs 21.4%; OR 1.27; 95% CI, 1.18-1.37) composite outcomes among PPI users versus non-users (figure 1, online supplemental table 1). After PS weighting,

Table 1 Characteristics of veterans with positive SARS-CoV-2 testing, stratified by current PPI user versus PPI non-user

	Unweighted cohort of veterans with positive SARS-CoV-2 test		Weighted cohort of veterans with positive SARS-CoV-2 test		
Covariates	PPI non-users (n=8696)	Current PPI users (n=6262)	PPI non-users (n=8696)	Current PPI users (n=6262)	SMD†
VHA facility‡	‡	‡	‡	‡	0.070
Age, mean years (SD)	60.46 (15.77)	64.37 (13.42)	61.94 (15.14)	62.15 (14.52)	0.014
Male sex, n (%)	7382 (84.9)	5578 (89.1)	7529 (86.6)	5441 (86.9)	0.009
Race/ethnicity, n (%)					0.033
Non-Hispanic white	4437 (51.0)	3885 (62.0)	4757 (54.7)	3527 (56.3)	
Non-Hispanic black	2243 (25.8)	1315 (21.0)	2125 (24.4)	1477 (23.6)	
Non-Hispanic other or unknown	794 (9.1)	515 (8.2)	764 (8.8)	540 (8.6)	
Hispanic	1222 (14.1)	547 (8.7)	1049 (12.1)	717 (11.5)	
Days from 1 January 2020 to index date, mean (SD)*	282 (82.8)	289 (78.7)	285 (81.5)	285 (81.2)	0.005
Smoking status, n (%)					0.067
Current smoker	1030 (11.8)	754 (12.0)	1047 (12.0)	762 (12.2)	
Former smoker	3441 (39.6)	3085 (49.3)	3773 (43.4)	2780 (44.4)	
Never smoker	3430 (39.4)	2180 (34.8)	3260 (37.5)	2376 (37.9)	
Unknown	795 (9.1)	243 (3.9)	616 (7.1)	344 (5.5)	
Comorbidities, n (%)					
Asthma	629 (7.2)	685 (10.9)	747 (8.6)	571 (9.1)	0.018
Coronary artery disease	1645 (18.9)	1911 (30.5)	2034 (23.4)	1500 (24.0)	0.013
Cancer	1770 (20.4)	1750 (27.9)	2020 (23.2)	1508 (24.1)	0.020
Cardiomyopathy	255 (2.9)	279 (4.5)	309 (3.5)	228 (3.6)	0.005
Charlson comorbidity index, mean (SD)	1.82 (2.22)	2.55 (2.54)	2.12 (2.38)	2.17 (2.40)	0.022
Congestive heart failure	621 (7.1)	746 (11.9)	791 (9.1)	582 (9.3)	0.007
Chronic lung disease	2652 (30.5)	2757 (44.0)	3129 (36.0)	2315 (37.0)	0.020
Chronic neuromuscular disease	394 (4.5)	323 (5.2)	420 (4.8)	308 (4.9)	0.004
Chronic kidney disease	1161 (13.4)	1219 (19.5)	1390 (16.0)	1026 (16.4)	0.011
Chronic kidney failure	153 (1.8)	151 (2.4)	180 (2.1)	130 (2.1)	0.001
Chronic obstructive pulmonary disease	1316 (15.1)	1646 (26.3)	1694 (19.5)	1270 (20.3)	0.020
Cerebrovascular disease	2800 (32.2)	2966 (47.4)	3320 (38.2)	2453 (39.2)	0.021
Diabetes	3070 (35.3)	2815 (45.0)	3415 (39.3)	2469 (39.4)	0.003
Drug dependency	379 (4.4)	345 (5.5)	416 (4.8)	311 (5.0)	0.008
Emphysema	126 (1.4)	170 (2.7)	171 (2.0)	126 (2.0)	0.003
Heart disease	2093 (24.1)	2281 (36.4)	2533 (29.1)	1846 (29.5)	0.008
Heart failure (non-congestive)	790 (9.1)	898 (14.3)	988 (11.4)	709 (11.3)	0.001
Helicobacter pylori positive	1841 (21.2)	1138 (18.2)	1746 (20.1)	1232 (19.7)	0.022
HIV	120 (1.4)	51 (0.8)	105 (1.2)	78 (1.2)	0.003
Hypertension	5075 (58.4)	4620 (73.8)	5616 (64.6)	4149 (66.3)	0.035
Lower respiratory infection	1010 (11.6)	855 (13.7)	1076 (12.4)	796 (12.7)	0.010
Obstructive sleep apnea	2884 (33.2)	2773 (44.3)	3254 (37.4)	2454 (39.2)	0.037
Medications, n (%)					
ACE inhibitors	2233 (25.7)	2152 (34.4)	2549 (29.3)	1887 (30.1)	0.018
ARBs	1170 (13.5)	1239 (19.8)	1378 (15.8)	1036 (16.6)	0.019
H2RAs	626 (7.2)	423 (6.8)	638 (7.3)	459 (7.3)	0.001
NSAIDs	5359 (61.6)	4745 (75.8)	5812 (66.8)	4358 (69.6)	0.059
Statins	4176 (48.0)	4249 (67.9)	4832 (55.6)	3656 (58.4)	0.057

*This variable represents the days from 1 January 2020 to the index date of SARS-CoV-2 testing to account for temporal differences.
†Only SMDs for the weighted cohort are provided in this table. Please refer to online supplemental figure 1 for the SMD plots for both the unweighted and weighted cohorts.
‡All of the 127 VHA facilities were included as covariates in this analysis; however, the proportion of patients at each station for each group is not listed here due to space considerations. The SMD between PPI users and non-users in the unweighted cohort was 0.36, with balance achieved after weighting (SMD: 0.07).
ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; H2Ras, histamine-2 receptor antagonists; NSAIDs, non-steroidal anti-inflammatory agents; PPI, proton-pump inhibitor; SMD, standardised mean difference; VHA, Veterans Health Administration.

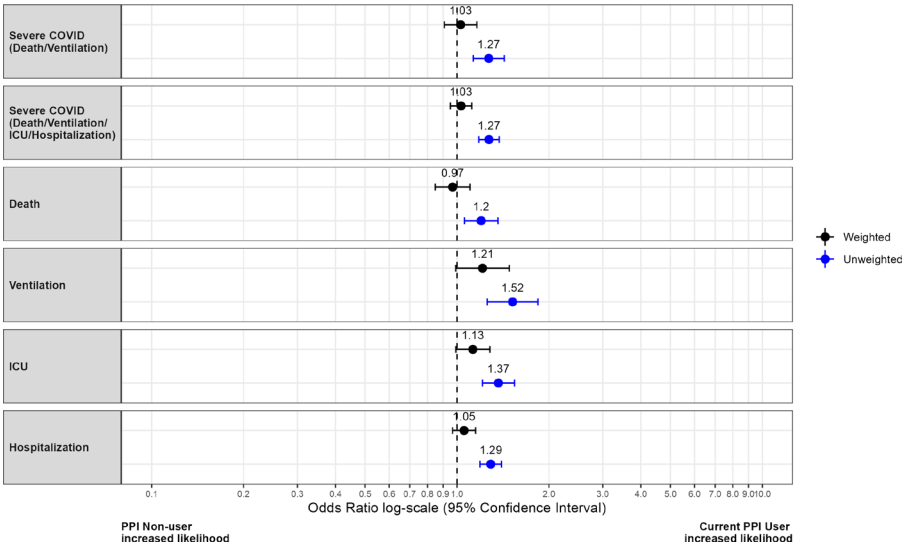

Figure 1 Forest plot of primary and secondary COVID-19 outcomes within 60 days of the index date, weighted and unweighted cohorts (semi-log scale, range 0.1 to 10). In the unweighted cohort, current outpatient PPI use compared with PPI non-use was associated with increased odds of severe COVID-19 outcomes, defined based on composite (primary: death or mechanical ventilation; secondary: death, mechanical ventilation, ICU admission or hospitalisation) and individual component outcomes. Each of these associations were statistically non-significant after more fully accounting for covariates in the propensity-weighted cohort, including date of SARS-CoV-2 testing and VHA facility location. Of note, there was no significant interaction between age group and PPI use on these outcomes. ICU, intensive care unit; PPI, proton pump inhibitor.

PPI use versus non-use was not associated with the primary (8.2% vs 8.0%; OR 1.03; 95% CI, 0.911.16) or secondary (23.4% vs 22.9%; OR 1.03; 95% CI, 0.95-1.12) composite outcomes. There were no significant interactions between age and PPI use on composite or individual outcomes.

Disparate results are reported in studies analysing COVID-19-related outcomes among PPI users versus non-users[2–6] due to varied PPI exposure definitions; COVID-19 severity outcomes; covariate assessment and adjustment; study design and populations; contemporaneous treatments; and healthcare infrastructure. In our unweighted analysis, we also observed an association between PPI use and severe COVID-19 outcomes (separately and as composites) which was not demonstrated in the PS-weighted cohort, suggesting that the associations in previous studies might reflect incomplete covariate adjustment.[7] Indeed, the low E-values (all <2.0) for the weak associations between PPI exposure and COVID-19 severity outcomes (although variably defined) that are demonstrated in previous studies suggest incomplete covariate adjustment and residual confounding (see online supplemental material).[8] Similar to the Lee *et al* study, prior studies also include data from the first months of the COVID-19 pandemic, when management and available treatments were rapidly evolving. Lee *et al*'s outcome definition also included oxygen therapy. Oxygen administration may not correlate with COVID-19 severity and may be considered routine protocol, especially early in the pandemic. Similarly, ICU admission may be influenced by health system factors, such as bed availability. Our study was designed to avoid immortal time, lag time and protopathic biases, which have been present in some PPI studies (see online supplemental material).[9] We further accounted for the pandemic timeframe and clinical management evolution by considering COVID-19 prevalence and US geography.

In conclusion, with respect to COVID-19, our robust PS-weighted analysis provides patients and providers with further evidence for PPI safety.

Shailja Shah ,[1,2] **Alese Halvorson,**[3] **Brandon McBay,**[4] **Chad Dorn,**[5] **Otis Wilson,**[6,7] **Sony Tuteja,**[8,9] **Kyong-Mi Chang,**[8,9] **Kelly Cho,**[10,11] **Richard Hauger,**[12,13] **Ayako Suzuki,**[14,15] **Christine Hunt,**[14,15] **Edward Siew,**[7,16] **Michael Matheny,**[5,7,16] **Adriana Hung** ,[6,16] **Robert Greevy,**[3,6] **Christianne Roumie**[6,17,18]

[1]Gastroenterology Section, VA San Diego Healthcare System, San Diego, California, USA
[2]Division of Gastroenterology, University of California, San Diego, California, USA
[3]Department of Biostatistics, Vanderbilt University Medical Center, Nashville, Tennessee, USA
[4]Department of Public Health, Harvard University T H Chan School of Public Health, Boston, Massachusetts, USA
[5]Department of Biomedical Informatics, Vanderbilt University Medical Center, Nashville, Tennessee, USA
[6]Clinical Services Research and Development, VA Tennessee Valley, Nashville, TN, USA
[7]Health Services Research and Development, VA Tennessee Valley, Nashville, Tennessee, USA
[8]The Corporal Michael J. Crescenz VA Medical Center, Philadelphia, Pennsylvania, USA
[9]University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA
[10]VA Boston Healthcare System, Boston, Massachusetts, USA
[11]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
[12]Department of Psychiatry, University of California San Diego, La Jolla, California, USA
[13]Center of Excellence for Stress & Mental Health, VA San Diego Healthcare System, San Diego, California, USA
[14]Division of Gastroenterology, Duke University Medical Center, Durham, North Carolina, USA
[15]Gastroenterology Section, Durham VA Health Care System, Durham, North Carolina, USA
[16]Division of Nephrology & Hypertension, Vanderbilt University Medical Center, Nashville, Tennessee, USA
[17]Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA
[18]VA Geriatrics Research Education and Clinical Center (GRECC), VA Tennessee Valley Health System, Nashville, Tennessee, USA

Correspondence to Dr Shailja Shah, Gastroenterology, VA San Diego Healthcare System, La Jolla, CA 92161, USA; s6shah@health.ucsd.edu

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ORCID iDs
Shailja Shah http://orcid.org/0000-0002-2049-9959
Adriana Hung http://orcid.org/0000-0002-3203-1608

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