

PPI와 코비드 논문에 대한 설명

# Severe clinical outcomes of COVID-19 associated with proton pump inhibitors: a nationwide cohort study with propensity score matching

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Impact  
Factor  
**19.819**



# METHODS

- Korea Centers for Disease Control and Prevention and Ministry of Health and Welfare
- 1 January 2020 and 15 May 2020
- **Cohort database: records of inpatients and outpatients within 3 years** (including healthcare visits, prescriptions, diagnoses and procedures), pharmaceutical visits, COVID-19-related outcomes and death records
- History of underlying diseases: diabetes mellitus, hypertension, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary diseases (COPD), asthma and chronic kidney disease, Charlson Comorbidity Index score - **(ICD-10) code**

# Exposure

- **Current PPI users:** PPIs 1–30 days before the index date.
  - **Past PPI users:** PPIs 31–365 days before the index date
  - **Non users:** never received PPIs within 1 year before the index date
- 
- H2 blocker와 NSAID 는 제외함.
- > **Protopathic bias 고려** : 동반된 상태에 대한 측정오류 또는 질병의 중증도를 포착

# Outcomes

- **The primary outcome:** positive laboratory test result for SARS-CoV-2
- **The secondary outcomes:**
  - ✓ composite endpoint 1 (requirement of oxygen therapy, intensive care unit admission, administration of invasive ventilation or death)
  - ✓ composite endpoint 2 (intensive care unit admission, administration of invasive ventilation or death).

# Statistical analysis

- propensity score matching: balance the baseline characteristics
- logistic regression model: reduce potential confounders
  - > adjustment for the following: age; sex; region of residence (urban or rural); history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, COPD, hypertension or chronic kidney disease; Charlson Comorbidity Index (0, 1 or  $\geq 2$ ); and current use of systemic steroid, metformin or aspirin.

Population  

  234 427

All patients who underwent SARS-CoV-2 testing between January 1, 2020 and May 15, 2020 in South Korea

**Excluded, n = 102,111**

- 1. Age < 18 years, n = 14,467
- 2. H2 blocker prescription within 1 year before the index data, n = 87,784
- 3. NSAID new prescription within 1 month before the index date, n = 2347

  132 316

Patients included in base cohort

  14 163

Current PPI users

  111 911

Non-users

  6242

Past PPI users

13 873  
Current PPI users

in the matched cohort

13 873  
Non-users

6153  
Non-users

in the matched cohort

6153  
Past PPI users

  4785

Who tested positive for SARS-CoV-2

  127 531

Who tested negative for SARS-CoV-2

  364

Current PPI users

  4233

Non-users

  188

Past PPI users

267  
Current PPI users

in the matched cohort

267  
Non-users

148  
Non-users

in the matched cohort

148  
Past PPI users

Identification

Included

Outcomes

# Result

Table 1. Baseline characteristics of all patients who underwent SARS-CoV-2 testing in Korean nationwide cohort (n = 132,316)

Characteristic	Entire cohort	Entire cohort		
		None	Current use of PPI	Past use of PPI
Total, n (%)	132,316	111,911	14,163	6242
Age, years, mean (SD)	48.0 (19.7)	46.7 (19.6)	< 56.3 (18.9)	52.2 (18.7)
Sex, n (%)				
Male	67,480 (51.0)	57,408 (51.3)	7070 (49.9)	3002 (48.1)
Female	64,836 (49.0)	54,503 (48.7)	7093 (50.1)	3240 (51.9)
Region of residence, n (%)				
Rural	59,364 (44.1)	49,760 (44.5)	5927 (41.9)	2677 (42.9)
Urban	73,952 (55.9)	62,151 (55.5)	8236 (58.2)	3565 (57.1)
History of diabetes mellitus, n (%)	20,419 (15.4)	15,235 (13.6)	3840 (27.1)	1344 (21.5)
History of cardiovascular disease, n (%)	17,392 (13.1)	12,667 (11.3)	3621 (25.6)	1104 (17.7)
History of cerebrovascular disease, n (%)	11,986 (9.1)	9183 (8.2)	2145 (15.2)	658 (10.5)
History of COPD, n (%)	8745 (6.6)	6293 (5.6)	1806 (12.8)	646 (10.4)
History of asthma, n (%)	14,531 (11.0)	10,648 (9.5)	2828 (20.0)	1055 (16.9)
History of hypertension, n (%)	36,134 (27.3)	27,699 (24.8)	< 6288 (44.4)	2147 (34.4)
History of chronic kidney disease, n (%)	9046 (6.8)	6947 (6.2)	1570 (11.1)	529 (8.5)
Charlson comorbidity index, n (%)				
0	78,981 (59.7)	70,954 (63.4)	5150 (36.4)	2877 (46.1)
1	13,828 (10.5)	11,042 (9.9)	1890 (13.3)	896 (14.4)
≥2	39,507 (29.9)	29,945 (26.7)	7123 (50.3)	2469 (39.6)
Current use of medication, n (%)				
Systemic steroid	38,237 (28.9)	30,270 (27.1)	5762 (40.7)	2205 (35.3)
Metformin	10,158 (7.7)	7672 (6.9)	1879 (13.3)	607 (9.7)
Aspirin	8049 (6.1)	5769 (5.2)	1787 (12.6)	493 (7.9)



# Result

Table 2. Propensity score-matched baseline characteristics and SARS-CoV-2 infection test-positivity among none versus current use of PPI groups or none versus past use of PPI usage groups in all SARS-CoV2 tested patients.

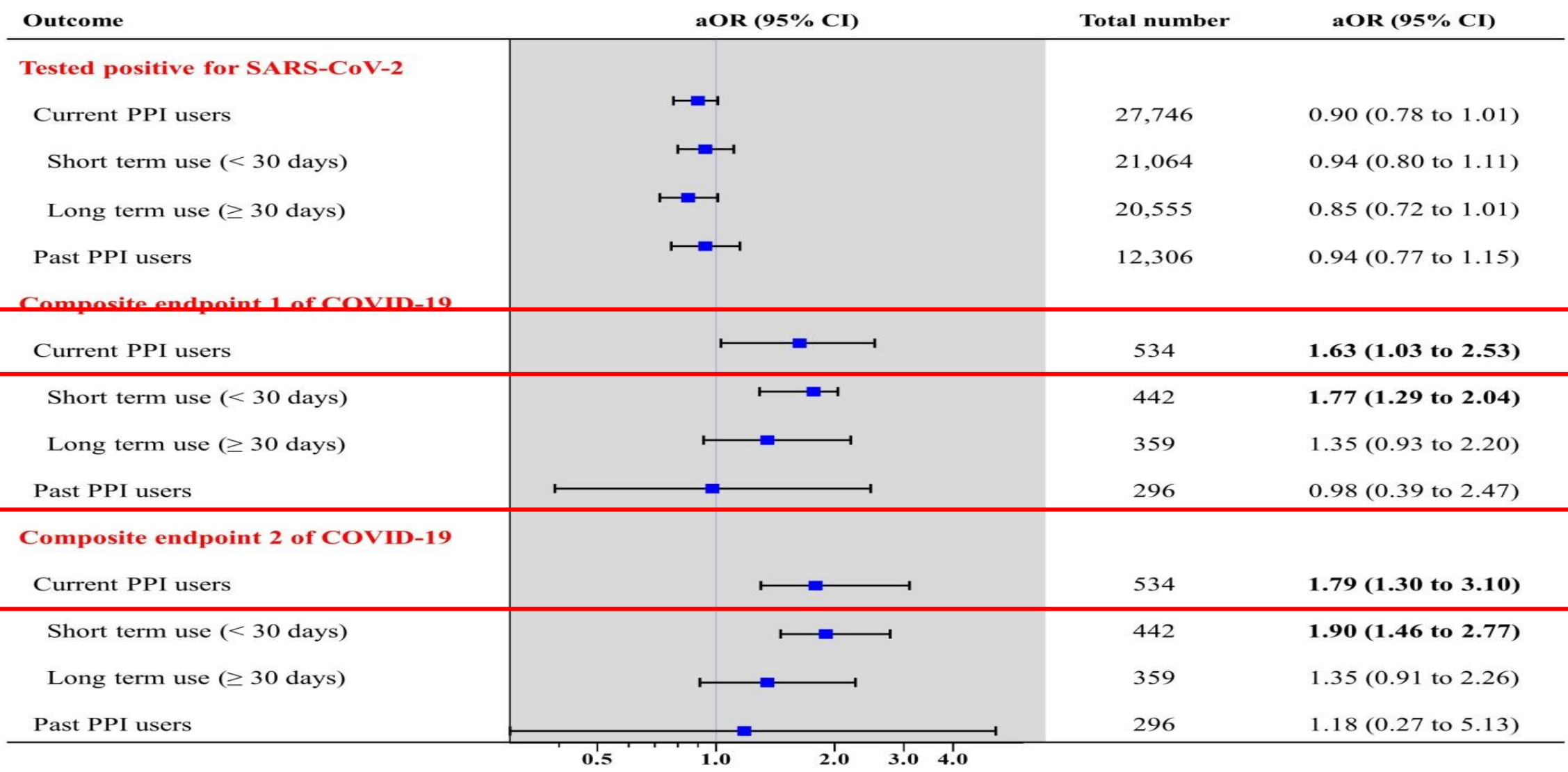
Characteristic	None versus current use of PPI		SMD	None versus past use of PPI		SMD
	None	Current use of PPI		None	Past use of PPI	
Total, n (%)	13873	13873		6153	6153	
Age, years (SD)	56.9 (19.7)	55.9 (18.8)	0.048	52.3 (19.3)	51.9 (18.6)	0.02
Sex, n (%)			0.023			0.008
Male	6754 (48.7)	6915 (49.9)		2979 (48.4)	2953 (48.0)	
Female	7119 (51.3)	6958 (50.2)		3174 (51.6)	3200 (52.0)	
Region of residence, n (%)			0.009			0.003
Rural	5762 (41.5)	5825 (42.0)		2629 (42.7)	2639 (42.9)	
Urban	8111 (58.5)	8048 (58.0)		3524 (57.3)	3514 (57.1)	
History of diabetes mellitus, n (%)	3536 (25.5)	3631 (26.2)	0.017	1262 (20.5)	1282 (20.8)	0.009
History of cardiovascular disease, n (%)	3201 (23.1)	3367 (24.3)	0.031	957 (15.6)	1041 (16.9)	0.039
History of cerebrovascular disease, n (%)	1998 (14.4)	2040 (14.7)	0.009	589 (9.6)	649 (10.6)	0.033
History of COPD, n (%)	1525 (11.0)	1646 (11.9)	0.03	525 (8.5)	592 (9.6)	0.04
History of asthma, n (%)	2544 (18.3)	2612 (18.8)	0.014	972 (15.8)	986 (16.0)	0.007
History of hypertension, n (%)	6116 (44.1)	6018 (43.4)	0.015	2065 (33.6)	2080 (33.8)	0.005
History of chronic kidney disease, n (%)	1423 (10.3)	1503 (10.8)	0.021	470 (7.6)	515 (8.4)	0.028
Charlson comorbidity index, n (%)			0.01			0.002
0	5406 (39.0)	5150 (37.1)		2954 (48.0)	2876 (46.7)	
1	1845 (13.3)	1889 (13.6)		860 (14.0)	893 (14.5)	
≥2	6622 (47.7)	6834 (49.6)		2339 (38.0)	2384 (38.8)	
Current use of medication, n (%)						
Systemic steroid	5351 (38.6)	5503 (39.7)	0.023	2073 (33.7)	2132 (34.7)	0.021
Metformin	1733 (12.5)	1768 (12.7)	0.008	584 (9.5)	595 (9.7)	0.006
Aspirin	1540 (11.1)	1635 (11.8)	0.024	441 (7.2)	471 (7.7)	0.02
COVID-19, n (%)	434 (3.1)	362 (2.6)		201 (3.3)	188 (3.1)	
Minimally adjusted OR	1.00 (reference)	0.88 (0.77 to 1.01)		1.00 (reference)	0.93 (0.76 to 1.14)	
Fully adjusted OR	1.00 (reference)	0.90 (0.78 to 1.01)		1.00 (reference)	0.94 (0.77 to 1.15)	

Table 3. Baseline characteristics of patients with confirmed laboratory COVID-19 in a Korean nationwide cohort (n = 4785)

Characteristic	Entire cohort	Patients with confirmed laboratory COVID-19		
		None	Current use of PPI	Past use of PPI
Total, n (%)	4785	4233	364	188
Age, years, mean (SD)	45.4 (18.8)	44.4 (18.8)	53.8 (16.9)	52.4 (17.6)
Sex, n (%)				
Male	2103 (44.0)	1893 (44.7)	135 (37.1)	75 (39.9)
Female	2682 (56.1)	2340 (55.3)	229 (62.9)	113 (60.1)
Region of residence, n (%)				
Rural	2367 (49.5)	2096 (49.5)	184 (50.6)	87 (46.3)
Urban	2418 (50.5)	2137 (50.5)	180 (49.5)	101 (53.7)
History of diabetes mellitus, n (%)	524 (11.0)	435 (10.3)	57 (15.7)	32 (17.0)
History of cardiovascular disease, n (%)	263 (5.5)	209 (4.9)	35 (9.6)	19 (10.1)
History of cerebrovascular disease, n (%)	272 (5.7)	203 (4.8)	47 (12.9)	22 (11.7)
History of COPD, n (%)	185 (3.9)	142 (3.4)	31 (8.5)	12 (6.4)
History of asthma, n (%)	338 (7.1)	269 (6.4)	44 (12.1)	25 (13.3)
History of hypertension, n (%)	945 (19.8)	771 (18.2)	118 (32.4)	56 (29.8)
History of chronic kidney disease, n (%)	150 (3.1)	113 (2.7)	25 (6.9)	12 (6.4)
Charlson comorbidity index, n (%)				
0	3431 (71.7)	3148 (74.4)	180 (49.5)	103 (54.8)
1	439 (9.2)	356 (8.4)	61 (16.8)	22 (11.7)
≥2	915 (19.1)	729 (17.2)	123 (33.8)	63 (33.5)
Current use of medication, n (%)				
Systemic steroid	1030 (21.5)	848 (20.0)	131 (36.0)	51 (27.1)
Metformin	315 (6.6)	252 (6.0)	48 (13.2)	15 (8.0)
Aspirin	166 (3.5)	122 (2.9)	29 (8.0)	15 (8.0)

Table 4. Propensity score-matched baseline characteristics and clinical outcomes of COVID-19 among none *versus* current use of PPI groups or none *versus* past use of PPI usage groups in patients with confirmed laboratory SARS-CoV-2 infection.

Characteristic	None versus current use of PPI			None versus past use of PPI		
	None	Current use of PPI	SMD	None	Past use of PPI	SMD
Total, n (%)	267	267		148	148	
Age, years (SD)	50.3 (17.9)	50.1 (16.6)	0.009	48.55 (17.1)	49.0 (16.9)	0.025
Sex, n (%)			0.007			0.069
Male	100 (37.5)	101 (37.8)		58 (39.2)	63 (42.6)	
Female	167 (62.6)	166 (62.2)		90 (60.8)	85 (57.4)	
Region of residence, n (%)			0.037			0.027
Rural	150 (56.2)	145 (54.3)		71 (48.0)	73 (49.3)	
Urban	117 (43.8)	122 (45.7)		77 (52.0)	75 (50.7)	
History of diabetes mellitus, n (%)	31 (11.6)	24 (9.0)	0.078	16 (10.8)	20 (13.5)	0.079
History of cardiovascular disease, n (%)	18 (6.7)	18 (6.7)	<0.001	6 (4.1)	8 (5.4)	0.051
History of cerebrovascular disease, n (%)	14 (5.2)	15 (5.6)	0.013	4 (2.7)	6 (4.1)	0.05
History of COPD, n (%)	4 (1.5)	6 (2.2)	0.052	7 (4.7)	5 (3.4)	0.063
History of asthma, n (%)	17 (6.4)	23 (8.6)	0.078	12 (8.1)	13 (8.8)	0.023
History of hypertension, n (%)	62 (23.2)	61 (22.9)	0.009	32 (21.6)	33 (22.3)	0.016
History of chronic kidney disease, n (%)	10 (3.7)	8 (3.0)	0.039	3 (2.0)	2(1.4)	0.033
Charlson comorbidity index, n (%)			0.016			0.134
0	186 (69.7)	166 (62.2)		101 (68.2)	97 (65.5)	
1	29 (10.9)	43 (16.1)		21 (14.2)	16 (10.8)	
≥2	52 (19.5)	58 (21.7)		26 (17.6)	35 (23.7)	
Current use of medication, n (%)						
Systemic steroid	79 (29.6)	79 (29.6)	<0.001	36 (24.3)	30 (20.3)	0.096
Metformin	22 (8.2)	15 (5.6)	0.09	9 (6.1)	12 (8.1)	0.08
Aspirin	10 (3.8)	14 (5.2)	0.067	4 (2.7)	6 (4.1)	0.06
Composite endpoint 1 <sup>+</sup> , n (%)	32 (12.0)	49 (18.4)		13 (8.8)	15 (10.1)	
Minimally adjusted OR	1.00 (reference)	<b>1.69 (1.18 to 2.56)</b>		1.00 (reference)	1.11 (0.46 to 2.64)	
Fully adjusted OR	1.00 (reference)	<b>1.63 (1.03 to 2.53)</b>		1.00 (reference)	0.98 (0.39 to 2.47)	
Composite endpoint 2, n (%)	14 (5.2)	24 (9.0)		5 (3.4)	7 (4.7)	
Minimally adjusted OR	1.00 (reference)	<b>1.82 (1.34 to 2.98)</b>		1.00 (reference)	1.02 (0.29 to 3.65)	
Fully adjusted OR	1.00 (reference)	<b>1.79 (1.30 to 3.10)</b>		1.00 (reference)	1.18 (0.27 to 5.13)	



# What are the new findings

- ✓ PPI usage (current and past use) **did not increase susceptibility to SARS-CoV-2 infection** in a Korean nationwide cohort.
- ✓ **Current PPI** usage was associated with **worse outcomes** of COVID-19.
- ✓ The **short-term current use of PPIs (<1 month)** conferred a significantly increased risk of worse clinical outcomes of COVID-19.

# Possible explanations of our results (severe clinical outcomes of COVID-19 and PPI)

- GI tract expresses higher levels of ACE-2, individuals who use PPIs may be more vulnerable to the effect of high viral loads.  
-> **may be more susceptible to severe courses of COVID19.**
- In a study of Middle East respiratory syndrome coronavirus (MERS-CoV), lethal outcomes were observed in mice treated with PPIs
- Moreover, patients with COVID-19 with other viral or bacterial coinfection are likely to experience a severe form of COVID

# 코로나 관련 분야 최고 경쟁그룹

## 1. Surgisphere 그룹

169 hospitals in Asia, Europe, and North America  
COVID-19 8910명에 대한 병원 EMR 데이터

~~NEJM: Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19~~

~~Lancet: Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis~~

허구.

비화: 우리팀이 쓸려고 했던 논문인데, 같은 주제로 나와서 못씀.

# 코로나 관련 분야 최고 경쟁그룹

## 2. 뉴욕 그룹

New York–Presbyterian Hospital (NYP)–Columbia University Irving Medical Center (CUIMC)

**NEJM:** Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19

**BMJ:** Characterization and clinical course of 1000 patients with coronavirus disease 2019 in New York: retrospective case series

## 3. 뉴욕의 그이외 EMR 합동 모임

Northwell Health COVID-19 Research Consortium

**JAMA:** Prevalence of SARS-CoV-2 Antibodies in Health Care Personnel in the New York City Area

**JAMA:** Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area

-> 전부 차트리뷰. (대구에서 범발했던 코로나 정도의 데이터)



# 코로나 관련 분야 최고 경쟁그룹

## 4. Denmark

**JAMA:** Association of Angiotensin-Converting Enzyme Inhibitor or Angiotensin Receptor Blocker Use With COVID-19 Diagnosis and Mortality

## 5. UK biobank

50만명에 대한 코호트를 예전부터 구축해 놓음.  
COVID-19로 걸려서 죽은 사람은 아는데, 확진자를 모른다.

**JACI:** Association of asthma and its genetic predisposition with the risk of severe COVID-19

## 6. 이탈리아 북부

**JAMA:** Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy

**JAMA:** Risk Factors Associated With Mortality Among Patients With COVID-19 in Intensive Care Units in Lombardy, Italy

# 코로나 관련 분야 최고 경쟁그룹

	소스	장점	단점	현재	
뉴욕팀	EMR	대가가 있다. 빠른 논문화	기저질환이나 약물에 대해서 확인불가	간단한 기저질 환이나 약물에 대한 분석은 가 능하지만, 더 이 상 좋은잡지 가 기는 어려운 상 태	ICU 환자들에 임상특징
이탈리아팀	EMR	대가가 있다.			
덴마크팀	정부	전 국민 대상 자 료 추출이 가능	랩 데이터가 없 다.	<b>계속 나올수있 다.</b>	과거 약물에 대한 영향 생각하기 어려운 질환과의 연관 관 계 (황반변성)
UK biobank	코호트	수많은 N		확진자에 대한 데이터가 없어 서 좋은 잡지를 가기는 어렵다.	
한국팀	정부	전 국민 대상 자 료 추출이 가능	랩 데이터가 없 다.	<b>계속 나올 수 있 다.</b>	
대구팀	EMR		안했다.		

# 코로나 관련 분야 최고 경쟁그룹

nature  
medicine

LETTERS

<https://doi.org/10.1038/s41591-020-1021-2>

Check for updates

## Immune complement and coagulation dysfunction in adverse outcomes of SARS-CoV-2 infection

Vijendra Ramlall<sup>1,2</sup>, Phyllis M. Thangaraj<sup>1,3</sup>, Cem Meydan<sup>4,5</sup>, Jonathan Foox<sup>4,6</sup>, Daniel Butler <sup>4,6</sup>, Jacob Kim<sup>7</sup>, Ben May<sup>5</sup>, Jessica K. De Freitas<sup>8,9</sup>, Benjamin S. Glicksberg <sup>8,9</sup>, Christopher E. Mason <sup>4,6,10,11</sup>, Nicholas P. Tatonetti <sup>1,7</sup>  and Sagi D. Shapira <sup>7</sup> 

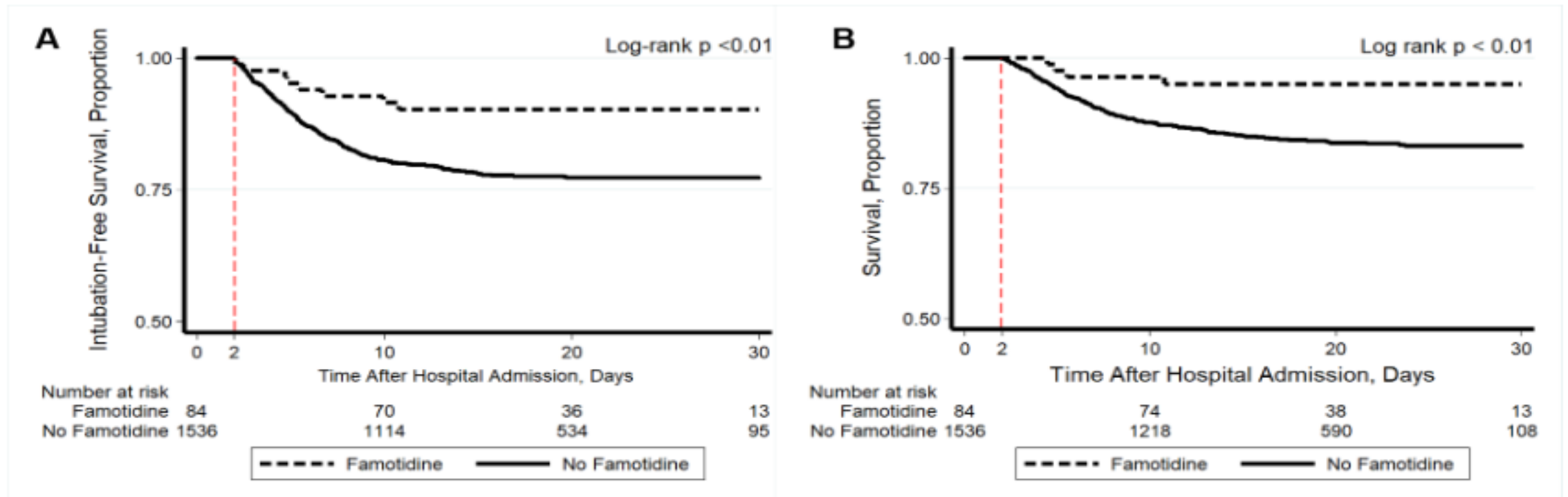
Understanding the pathophysiology of SARS-CoV-2 infection is critical for therapeutic and public health strategies. Viral-host interactions can guide discovery of disease regulators, and protein structure function analysis points to several immune pathways, including complement and coagulation, as targets of coronaviruses. To determine whether conditions associated with dysregulated complement or coagulation systems impact disease, we performed a retrospective observational study and found that history of macular degeneration (a proxy for complement-activation disorders) and history of coagulation disorders (thrombocytopenia, thrombosis and hemorrhage) are risk factors for SARS-CoV-2-associated morbidity and mortality—effects that are independent of age, sex

# Similar research -1

Famotidine Use is Associated with Improved Clinical Outcomes in Hospitalized COVID-19 Patients: A Propensity Score Matched Retrospective Cohort Study

Daniel E. Freedberg, MD, MS,<sup>1</sup> Joseph Conigliaro, MD, MPH,<sup>2</sup> Timothy C. Wang, MD,<sup>1</sup> Kevin J. Tracey, MD,<sup>9</sup> Michael V. Callahan, MD,<sup>10</sup> Julian A. Abrams, MD, MS<sup>1</sup>  
on behalf of the Famotidine Research Group

- 1,620 patients : 84 patients (5.1%) who received famotidine within 24 hours of hospital admission
- Composite outcome 340 (21%) : 42 (8.8%) patients were **intubated** and 238 (15%) **died**
- In patients hospitalized with COVID-19, **famotidine use was associated with a reduced risk of clinical deterioration leading to intubation or death.**  
(no protective association was seen for PPIs)



# Similar research -2

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## Increased Risk of COVID-19 Among Users of Proton Pump Inhibitors

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Brennan M.R. Spiegel, MD, MSHS<sup>1-4,8</sup>

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- 7 Division of Gastroenterology, Michigan Medicine, Ann Arbor, MI
- 8 Department of Health Policy and Management, UCLA Fielding School of Public Health, Los Angeles, CA

## Dose response relationship

**TABLE 2.** Results from the multivariable logistic regression model on reporting a positive COVID-19 test (N=53,130)

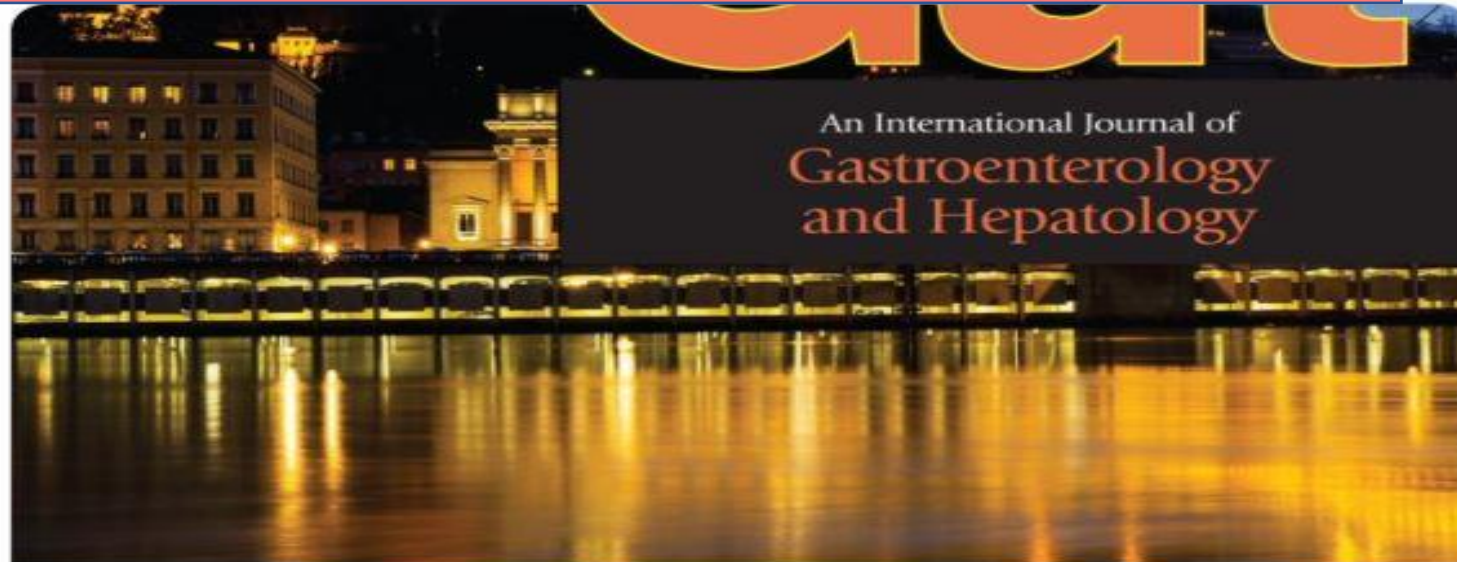
Variable	Positive COVID-19 test (n=3,386)	aOR [95% CI] <sup>a</sup>
<b>PPI exposure:</b>		
No current PPI use	752 (2.1)	Reference
Once daily PPI use or less	2,436 (16.4)	2.15 [1.90–2.44] <sup>b</sup>
Twice daily PPI use	198 (11.7)	3.67 [2.93–4.60] <sup>b</sup>
<b>H2RA exposure:</b>		
No current H2RA use	2,828 (6.3)	Reference
Once daily H2RA use or less	415 (5.6)	0.85 [0.74–0.99] <sup>c</sup>
Twice daily H2RA use	143 (12.4)	0.86 [0.66–1.11]



Brennan Spiegel, MD, MSHS  
@BrennanSpiegel



"Severe outcomes of #COVID19 with proton pump inhibitors": New Korean study reports PPI heartburn meds increase risk of hospitalization, intubation, death by 79%. Did not find link with acquiring the virus, although no data on once vs twice-daily dosage:



Severe clinical outcomes of COVID-19 associated with proton pump inhibitors...  
Objective The adverse effects of proton pump inhibitors (PPIs) have been documented for pneumonia; however, there is no consensus regarding wheth...  
[gut.bmj.com](https://gut.bmj.com)

9:50 AM · Jul 31, 2020 · [Twitter Web App](#)

15 Retweets 17 Likes