Proton pump inhibitors (PPI) use and outcomes in COVID-19

A Multicenter Global Research Network Study

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Introduction

- Proton pump inhibitors (PPIs) are one of the top 5 prescribed medications in the clinical practice today.
- Previous studies on long-term use of PPI showed an increased risk of infections such as pneumonia, clostridium difficile, and all-cause mortality.
- SARS-CoV-2 might escape the gastric acid inactivation due to PPI-induced hypochlorhydria and cause increased gastrointestinal (GI) symptoms and severity.
- Smaller studies has shown that COVID-19 patients on PPI may be at higher risk of developing GI symptoms which could be due to a higher expression of angiotensin-converting enzyme-2 (ACE-2).

Methods

- All patients with COVID-19 were identified from January 20, 2020, to July 19, 2020, using a federated cloud-based network (TriNetX).
- TriNetX provides access to EHR from multiple healthcare organizations from the US and Europe with a mix of hospitals, primary care, and specialty treatment providers.
- Patients were divided into two groups depending on the exposure to PPIs within 90-days before the diagnosis: PPI-group and non-PPI-group.
- The outcomes of our study included the need for hospitalization, mechanical ventilation, and mortality within 30 days of the COVID-19 diagnosis.
- All statistical analyses were performed on the TriNetX online platform.
- A priori defined 2-sided alpha value of <.05 was used for statistical significance.
- After propensity matching, groups were relatively matched in terms of comorbidities.

Results

- A total of 92,412 COVID-19 patients were analyzed from 37 healthcare organizations.
- The PPI-group comprised of 12,893 patients, and the non-PPI group included 79,519 patients.
- Mean age of the PPI-group was 55 years (SD 23 years), with 50.7% whites and 17.9% blacks.
- The point prevalence of the GI symptoms were higher in the PPI-group.
- The results of the study are depicted in the Table 1 below:

30-day Clinical Outcomes	Before propensity matching			After propensity matching		
	PPI Exposure Group N=12,893 (%)	Non-PPI Exposure Group N=79,519 (%)	Odds Ratio (95% CI)	PPI Exposure Group N= 11,990 (%)	Non-PPI Exposure Group N= 11,990 (%)	Odds Ratio (95% CI)
Mortality	989 (7.67)	1812 (2.32)	3.5 (3.231, 3.79)	906 (7.56)	606 (5.05)	1.54 (1.38, 1.71)
Mechanical Ventilation	603 (4.677)	1231 (1.58)	3.07 (2.78, 3.39)	540 (4.50)	358 (2.99)	1.53 (1.34, 1.76)
Hospitalization	3512 (27.24)	9945 (12.73)	2.57 (2.46, 2.68)	3166 (26.41)	2221 (18.52)	1.58 (1.48, 1.68)

Table 1: 30-day clinical outcomes in COVID-19 patients based on PPI-exposure before and after propensity matching

Strengths

- Large sample size with a multicentric database
- Use of propensity-matched analysis and inclusion of large number of variables between PPI users and non-users.
- Availability of extensive sociodemographic, clinical, laboratory, and outcomes.

Weaknesses

- Presence of potential unrecognized confounding variables
- Use of ICD-10 codes to find patients with COVID-19

Discussion

- Our study shows that COVID-19 patients who were exposed to any PPI within the last 90-days of diagnosis were at:
  - Increased odds of mortality (OR:1.54),
  - Higher odds of needing mechanical ventilation (OR:1.53),
  - Higher odds of being hospitalized (OR:1.58)
- These findings persisted even after adjusting for potential confounding variables.
- *Possible mechanisms:*
  - Profound hypochlorhydria caused by irreversible inhibition of proton pump by PPIs can result in increased GI SARS-CoV-2 viral load.
  - PPI-induced altered gut microbiome.
  - Modulation of immune response by effecting neutrophilic function,
  - Worsening of the cytokine storm by PPIs.

Conclusion

- Our results are inline with other smaller studies which have shown that PPI use might be associated with severe COVID-19 and poorer outcomes.
- Physicians should be aware and vigilant about the side effects of the PPIs which are one of the most prescribed medications in the United States

References

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