Are Proton Pump Inhibitors Contributing to SARS-COV-2 Infection?

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We read with interest the recent article by Almario et al (1) examining the association between proton pump inhibitor (PPI) use and odds of a positive COVID-19 test. We are writing to express concerns about the validity of the data set, possible confounding, and discrepancy with our own institutional experience. We initially wrote on July 11, then reviewed the updated manuscript and author statement in depth, and we continue to have the same concerns. First, the authors used the research firm Cint to acquire internet-based survey responses from 53,130 adult respondents. The population testing positive for COVID-19 was highly unusual and is not an accurate representation of the US population, typical PPI users, or other COVID-19 positive cohorts as the authors suggested. For example, among patients who tested positive for COVID-19, the authors report that 74.5% aged 30–39 years, 81% were married, and 63.5% had a household annual income exceeding $200,000 per year, although 69% had a high school degree or less. An unusually high 73.1% were every day smokers and 68.5% were from the South. Most strikingly, only 3.2% reported gastroesophageal reflux disease; however, 71.9% were reportedly taking PPI daily. The unusual distribution of these demographic data raises the question of underlying data integrity and raises broader questions about unaudited commercially generated data used to study COVID-19 (2). The added sensitivity analyses in the revision do not address concerns about data authenticity (3).

Second, the association, if true, replicates the confounding problems of multiple previous studies on PPI associations with chronic diseases (4). COVID-19 testing has been limited by a severe shortage of tests, resulting in underdiagnosis of COVID infections and testing of select populations. Thus, comorbidities, which are highly correlated with PPI use (4), could have influenced the physician's decision to order the test. Reporting of negative tests would provide a better description of the true odds and address testing availability bias. Third, because approximately one third of patients with COVID-19 develop gastroenterologic symptoms before presentation or testing (2), recent PPI use may be a response to new symptoms of COVID-19. Almario et al do not specify the temporal relation of PPI use to COVID-19 diagnosis.

To consider these possibilities, we independently examined the association between PPI use and COVID-19 testing through the Stanford STARR database of approximately 83,735 patients tested for SARS-COV-2 RNA, of whom 2,890 tested positive (3.4%) that we used previously (2,5). This unadjusted analysis showed 355 of 18,240 patients with documented PPI use tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) compared with 2,535 of 66,085 not on PPI (odds ratio [OR] of SARS-COV-2 with PPI 0.48, 95% confidence interval (CI), 0.39–0.58, $P < 0.0001$). Similar odds were seen with sensitivity analyses limiting to PPI initiation 6 months before infection (OR 0.50, 95% CI, 0.49–0.56) or with any H2 blocker use (OR 0.60, 95% CI, 0.53–0.68). Although these preliminary data are not adjusted for known confounders, they are inconsistent with the increased odds of COVID-19 with PPI use (OR of 2.15–3.67), as reported by Almario et al. We note that the American College of Gastroenterology released an information sheet to counsel gastroenterologists and patients on changes in practice based on this study. We believe that greater scrutiny of this study and independent validation of these associations in more robust nonsurvey-based medical databases with auditable source data are needed before practices changes are considered.

CONFLICTS OF INTEREST

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