A nationwide cohort study with propensity score matching

Lee and colleagues recently published the first large-scale study to investigate the association between proton pump inhibitor (PPI) use and the infectious disease caused by COVID-19.[1] Using a nationwide cohort sample with propensity score matching, they concluded that short-term current—but neither long-term current nor past—PPI usage was associated with worse outcomes of COVID-19. These results deserve some comments.

By decreasing the barrier effect of gastric acidity and thus promoting the survival of ingested pathogens, PPIs are a known risk factor for some enteric bacterial and virus infections.[2 3] Based on the evidence for a fecal–oral transmission in COVID-19, the authors made the hypothesis that PPI use might influence the susceptibility to COVID-19. Nevertheless, criteria other than biological plausibility should be taken into account when considering retrospective observational studies, in which information is not collected with a specific hypothesis in mind; level of exposure to PPIs is unknown; and confounders and biases persist even after adjustments.[4]

One of these criteria is strength of association. In the study by Lee and colleagues, all adjusted ORs are below 2. Because weaker associations are less likely to be causal, some authors recommend that results of risk estimates (OR or RR) between 0.5 and 2.0 (also referred to as the 'zone of potential bias') should be rejected and considered non-informative.[5] Applying this criterion to the present study leads to questioning the clinical relevance of its findings.

In their discussion, Lee and colleagues reported that their study accounted for protopathic bias by excluding new nonsteroidal anti-inflammatory drugs users and designing propensity score matching. However, their results are very suggestive of protopathic bias since the increase in risk of worse clinical outcomes of COVID-19 only occurred in patients newly exposed to PPIs, this risk disappearing in patients exposed for 1 month or more. It can therefore be hypothesised that a PPI was introduced in some of these patients in response to the early digestive symptoms of COVID-19, before the infection was diagnosed. As noted by the authors, the same concerns about protopathic bias have been raised about the association between PPI use and risk of pneumonia.[6]

Lastly, a statistically significant association was found between PPI use and worse outcomes of COVID-19, but not between PPI use and the infection rates of COVID-19 among tested patients, which suggests that confounding by indication seems very likely. Stress ulcer prophylaxis is actually recommended to be administered to critically ill patients who are assessed as high risk for GI bleeding, including those requiring mechanical ventilation or high-dose corticosteroids.[7] Given the criteria used to construct the composite endpoints 1 and 2 (ie, requirement of oxygen therapy, intensive care unit admission, administration of invasive ventilation, severe clinical outcomes of COVID-19 or death), the study was designed to select patients with both PPI prescription and worse outcomes of COVID-19. Baseline characteristics of included patients (see table 1) support this hypothesis, with patients in the 'current PPI use group' being older and having more comorbidities than in the other groups. The use of propensity score matching was a valuable but probably insufficient effort to fully balance these major differences in baseline characteristics.

For all these reasons, these results should be interpreted with caution. In the patients most severely affected by COVID-19 who require intensive care management, the proven benefits of PPIs should not be outweighed by a risk that remains hypothetical to date.

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