

Letter to the Editor: Proton Pump Inhibitors in Cirrhosis: A Marker of Morbid Conditions or a Cause of Mortality?

TO THE EDITOR:

We read with interest the study by Nardelli et al., which adds to a growing literature on the potential ills of proton pump inhibitors (PPIs) in patients with cirrhosis.⁽¹⁾ Their prospective design allowed for

assessment of minimal hepatic encephalopathy (HE), and they reported that PPI use was independently associated with minimal HE, overt HE, and mortality. While we applaud the authors' efforts, we are concerned about residual confounding that may have led to misinterpretation of mortality results.

The authors outline that decreased gastric acid provides biological plausibility for the association between PPIs and *Clostridium difficile* colitis, spontaneous bacterial peritonitis, and pneumonia, which could explain some increased mortality in PPI users.⁽²⁾ However, infections accounted for just over one third of deaths overall, type of infection was unreported, and cause of death stratified by PPI use was not included. PPI use was weakly associated with overt HE, but this is unlikely to account for the reported mortality, even when considered in combination with infections. This begs the question of whether other explanations may exonerate PPIs.

It is possible that PPI use may merely be a marker of patient comorbidities. Increased health care use, smoking, obesity, nonsteroidal anti-inflammatory drug use, and vascular disease are all potential confounders of PPI use and death.⁽³⁾ These factors were not assessed. Furthermore, 42% of PPI users had “an appropriate” indication, which included recent gastrointestinal bleed and/or endoscopic ligation of varices, both of which may increase mortality independent of Model for End-Stage Liver Disease or Child-Pugh score. It would therefore be worthwhile to examine the mortality among PPI users with strong versus weak indications.

Despite these limitations, this study provides a valuable addition to the literature on PPIs and HE and provides important data arguing for the judicious discontinuance of PPIs in patients with cirrhosis. However, we have a difficult time accepting PPIs as an independent risk factor for all of the deaths observed without knowing more about the causes of death and the comorbidities that come with PPI use.

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Supported in part by the National Institutes of Health (T32 DK007634).

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View this article online at wileyonlinelibrary.com.

DOI 10.1002/hep.30642

Potential conflict of interest: Dr. Barritt consults for Target PharmaSolutions and Dova Pharmaceuticals.

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