The Role of *Helicobacter pylori* Infection in Coronavirus Disease 2019, Cause or Coincidence?

To the Editor: We have read with interest the article by Balamtekin et al (1) suggesting symptoms related to *Helicobacter pylori* (HP) infection in patients with coronavirus disease 2019 (COVID-19) that we praise for innovation.

According to the Maastricht-V Consensus Report (2), the diagnosis of HP should not be based on stool antigen tests and at least confirmed by a second test (^{13}C-urea breath test) performed following a negative COVID-19 test. Moreover, the omission of eradication therapy raises an ethical concern regarding the reason for testing for HP.

Angiotensin-converting enzyme-2 (ACE-2) is expressed in cells of the gastrointestinal tract (3), and several conditions (diabetes, hypertension, obesity and autoimmune diseases) increase the expression of ACE-2 receptors independently from HP (4). The authors state to have evaluated comorbidities, but no mention is given in the results. Concerning the adult age of patients, these conditions should have been considered or patients excluded. Moreover, there was no mention of symptoms before HP or after COVID-19 infection nor a control group of COVID-19 negative patients.

The study misses a power calculation and even considering the relative prevalence of each symptom in HP positive/negative patients as correct, the study would be under-powered; at least 55 patients per arm are needed to have a power of 80% (α-error = 0.05). Finally, other factors related to HP (5) might be responsible for the increased rate of symptoms (6).

Abdominal pain and diarrhea, widespread in the pediatric population, could lead to an overestimation of the suspicion of HP infection during the COVID-19 pandemic that might further overload the health system already at collapse.

Maria Elena Papagni, Viviana Fara Brindicci, Fernanda Cristofori, and Ruggiero Francavilla
Interdisciplinary Department of Medicine – Pediatric Section, University of Bari "Aldo Moro", Giovanni XXIII Children's Hospital of Bari, Bari, Italy

The authors report no conflicts of interest.

REFERENCES

1. Balamtekin N, Artuk C, Arslan M, et al. The effect of *Helicobacter pylori* on the presentation and clinical course of coronavirus disease 2019 infection. *J Pediatr Gastroenterol Nutr* 2021;72:511–3.
2. Malfertheiner P, Megraud F, Morain CAO', et al. Management of *Helicobacter pylori* infection-the Maastricht V/Florence Consensus Report. *Gut* 2017;66:6–30.
3. Parasa S, Desai M, Thoguluva Chandrasekar V, et al. Prevalence of gastrointestinal symptoms and fecal viral shedding in patients with coronavirus disease 2019: a systematic review and meta-analysis. *JAMA Netw Open* 2020;3:e2011335.
4. Gkogkou E, Barnasas G, Vougas K, et al. Expression profiling meta-analysis of ACE2 and TMPRSS2, the putative anti-inflammatory receptor and priming protease of SARS-CoV-2 in human cells, and identification of putative modulators. *Redox Biol* 2020;36:101615. doi: 10.1016/j.redox.2020.101615.
5. Enko D, Kriegshauser G. Functional ^{13}C-urea and glucose hydrogen/methane breath tests reveal significant association of small intestinal bacterial overgrowth in individuals with active Helicobacter pylori infection. *Clin Biochem* 2017;50:46–59.
6. Rao SSC, Bhagatwala J. Small intestinal bacterial overgrowth: clinical features and therapeutic management. *Clin Transl Gastroenterol* 2019;10:e00078.

The Effect of *Helicobacter pylori* on the Presentation and Clinical Course of Coronavirus Disease 2019

Reply: We have read with interest the letter by Papagni et al (1), which includes their praise and views on our article.

In our study, we based the diagnosis of *Helicobacter pylori* on the stool antigen test because it has a high specificity-sensitivity (2) and we believe that is the safest test in terms of transmission risk under extraordinary conditions. We consider that this approach is appropriate for exceptional cases, since every diagnostic procedure to be performed while diagnosing *H pylori* infection will put healthcare workers at greater risk. Eradication treatments were applied to our patients after the coronavirus disease 2019 (COVID-19) infection process finished.

H pylori has been reported to play a role in the pathogenesis of diseases by increasing the expression of angiotensin-converting enzyme-2 receptors in the gastrointestinal tract (3). We found no difference between patients with and without comorbid disease in terms of the course of the disease and the type of symptoms. Therefore, we think that the frequency of diarrhea and abdominal pain complaints is associated with *H pylori*.

We planned our study with 31 experimental subjects and 77 control subjects. Our data indicated that the probability of abdominal pain among *H pylori* negative cases is 2.6%. When the true probability of abdominal pain among *H pylori* positive cases is 19.4%, the null hypothesis is rejected with the probability (power) 0.69. On the other hand, our data also indicated that the probability of diarrhea among *H pylori* negative cases is 9.1%. When the true probability of diarrhea among *H pylori* positive cases is 32.3%, the null hypothesis is rejected with the probability (power) 0.73. The Type I error probability associated with this test of this null hypothesis is 0.05. We used a continuity-corrected chi-squared statistic or Fisher exact test to evaluate this null hypothesis.

This study is very valuable academically because it is the first study to investigate the relationship between the world's most common infectious disease and pandemic, and it pioneers studies in this field; however, as we mentioned in the article, there is a need for more comprehensive studies (where virulent elements of *H pylori* such as VacA can be examined one by one) in which more patients participated. Although our results show that diarrhea and abdominal pain are more common in *H pylori* positive patients during the course of COVID-19, it shows that the presence of *H pylori* does not affect the clinical outcome of COVID-19 infection. In conclusion, considering that the presence of *H pylori* does not affect the course of COVID-19, it is obvious that the presence of *H pylori* will not actually bring an additional burden to hospitals in this critical period.