Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

important, X escape is not uniform across different tissues. In fact, it was shown that approximately 10% of gene escape occurs selectively in specific tissues.[7] These molecular aspects are of medical importance because they could explain sex differences in the natural course of human diseases, including COVID-19.

A recent systematic survey of the landscape of human X-linked genes inactivation using RNA sequencing-based approaches showed that *ACE2* presents remarkable differences in male–female expression levels.[8] Tukiainen et al[8] suggested that tissue differences in X escape can directly translate into tissue-specific sex biases in gene expression.[8] Specifically, the study showed not only that *ACE2* is among the 82 X-escaping genes, but also highlighted that there might be differences in the liver and lung *ACE2* expression levels between males and females.[8] Paradoxically, escape of *ACE2* from X inactivation resulted in low levels of expression in the liver, lung, and visceral adipose tissue of women.[8] Conversely, *ACE2* expression levels in colon transverse and subcutaneous adipose tissue were significantly higher in females than males.[8]

Collectively, these novel observations may have important clinical implications for patients with COVID-19. First, differences between men and women in liver *ACE2* expression levels may help to explain potential clinical differences in the course of COVID-19 in patients with underlying chronic liver disease. Second, differences between men and women in *ACE2* expression levels in gastrointestinal tissues due to escaping from X inactivation, including the colon, could result in different transmission patterns, including fecal–oral transmission. Third, sex-linked differential expression levels in adipose tissue and/or visceral fat might also shed light into potential differences in the odds of presenting severe complications and in-hospital death associated with comorbidities, including severe obesity.

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Most current article

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Fecal–Oral Transmission of SARS-COV-2: Practical Implications

Dear Editors:

We read with great interest the study by Xiao et al[1] on evidence for gastrointestinal infection of coronavirus disease-19 (COVID-19). Testing for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) RNA in stool specimens of 73 hospitalized patients resulted in virus detection in 53.4% of patients, both with and without gastrointestinal manifestations (ie, diarrhea, nausea, vomiting, gastrointestinal bleeding). In addition, COVID-19 nucleic acid was positive in feces of 23.3% of patients in which respiratory samples had already turned negative. Stool positivity after respiratory sample switched negative had already been reported by Tang et al.[2] As the authors stated, these findings support a possible role of fecal–oral transmission and suggest the need of enhanced control measures, especially during the convalescence period of infected patients.

However, the reported data have also other potential consequences that deserve further investigations. First, stool sampling could be a complementary, noninvasive test for initial diagnosis. Currently, real-time reverse transcriptase polymerase chain reaction test for COVID-19 nucleic acid in nasopharyngeal swabs is the recommended modality for etiological diagnosis.[3] However, false-negative results are documented and can be responsible of misdiagnoses or missed isolation of sources of infection.[4,5] Even if the study by Xiao et al[1] evaluated only patients with positive throat swabs, stool sampling could be effective for detecting viral load even in patients with negative nasopharyngeal swabs. Large-scale studies would be useful to determine accuracy of this noninvasive test.

Furthermore, with the growing spread of COVID-19 infection, concerns should raise on how to guarantee safety for Endoscopy operators. Undetected cases (asymptomatic patients or during the latency period) could undergo endoscopy for many indications. Currently, local authorities from a high-incidence area in Italy recommend the use of extraordinary personal protective equipment only for microaerosol-generating procedures, including esophagogastroduodenoscopy. However, unrecognized exposure to potentially infectious biologic samples during endoscopy is well-documented;[5,6] thus, the presence of SARS-CoV-2 RNA in stools, as found in the present study, could lead to a not negligible risk of transmission also for colonoscopy in endemic areas, especially in absence of additional protection measures. Dedicated personal protective equipment should be provided to all clinical staff.

In conclusion, evidence on fecal–oral contagion by SARS-COV-2 is growing. Stepping up infection control measures both among the general population to avoid fecal–oral transmission, and the health care workers operating in the endoscopy room, would be highly desirable.

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Why Does SARS-CoV-2 Invade the Gastrointestinal Epithelium?

Dear Editors:

In patients with coronavirus disease-29 (COVID-19), stool samples may persistently test positive, even when the respiratory sample is negative for the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus. This phenomenon cannot be explained by the temporary gastrointestinal transit of swallowed saliva that contains the virus. Clues to solving this enigma were evident in a study performed by Xiao et al.[1] Gastrointestinal endoscopy was performed on patients who were diagnosed as positive for SARS-CoV-2 in stool samples, and biopsy samples were taken from the esophagus, gastric tissue, duodenum, and colon for histopathologic and immunofluorescent staining. The mucous epithelium of the esophagus, stomach, duodenum, and rectum showed no significant damage with hematoxylin and eosin staining; however, viral host receptor angiotensin-converting enzyme-2 and viral nucleocapsid protein–stained positive, mainly in the cytoplasm of gastrointestinal epithelial cells in the stomach, duodenum, and rectum. These results suggest that the SARS-CoV-2 virus may invade the mucosal cells of the stomach and the small and large intestines, multiply, and produce infectious virions.

There are 2 key findings in this study. The first is the surprising fact that coronaviruses are present in the highly acidic gastric epithelium—the spike protein of SARS-CoV-19 can mediate fusion with the host cell at a neutral pH. SARS-CoV-19 is completely inactivated by highly acidic conditions (pH 1–3) at 37°C, but moderate variations of pH conditions from 5 to 9 had little effect on virus titer, regardless of the temperature (from 4°C to 37°C).[2] In other words, for the SARS-CoV-2 virus to invade epithelial cells without being inactivated in the stomach, the gastric pH must be neutral.

The second important finding is that patients who tested positive on respiratory specimens but tested negative on the stool were, on average, 36 years old [(43 years × 73 cases – 49 years × 39 cases)/(73 – 39 cases) = 36 years]. The average age of the virus-positive population in stool samples was 49 years, suggesting that aging is involved in the ease of virus invasion. Age-related increases in gastric pH can be explained by atrophic gastritis (AG) and gastric intestinal metaplasia owing to *Helicobacter pylori* infection. In China and many other countries, the likelihood of having AG and intestinal metaplasia increases with age.[3] In the stomachs of patients with intestinal metaplasia and/or AG, the pH of the surface of the gastric mucosa increase to $\geq$3,[4] and for elderly AG, the pH found is 5–7.[5] Based on these data, in the stomachs of elderly people with advanced chronic gastritis, it is presumed that the SARS-CoV-2 virus is not inactivated by stomach acid, but instead enters the epithelial cells of the stomach, and further invades the epithelial cells of the small and large intestines.

If this hypothesis is correct, an individual with a history of *H pylori* infection may be susceptible to fecal–oral infection. In the report from China, blood group A had a significantly higher risk for COVID-19 compared with non-A blood groups, whereas blood group O had a significantly lower risk for the infectious disease compared with non-O blood groups.[6] According to >2000 case-control studies in Japan, blood group A is susceptible to *H pylori* infection and AG.[7] Similarly, in Chinese case-control studies, the proportion of *H pylori* infection in blood group A individuals was significantly higher than that of non-A blood groups.[8] These findings indicate that, for individuals with blood group A, the route of viral transmission is likely to include the risk of gastrointestinal infections, in addition to those of the respiratory tract. There are also concerns that users of