
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.

blood-based transcriptomic signature might further improve the LNM predictive efficacy of our risk-assessment model in future studies.

Second, the authors suggested that in addition to receiver operating characteristic curve analysis, inclusion of calibration curves that reflect the agreement between the actual and predicted probabilities might be useful. In such analysis, a perfect calibration would be where the observed versus predicted probability would be equal. Once again, we appreciate this suggestion very much. Accordingly, we performed such calibration analyses in our validation cohort patients using the *RMS* package. The flexible calibration curve was based on local regression. In this regard, when we interrogated the performance of our transcriptomic panel, we noted that patients at high risk tended to get underestimated risk predictions, whereas a good calibration was observed when patients were at low risk. We noticed that compared with the transcriptomic panel, our final risk-stratification model (which included lymphatic and venous invasion, tumor budding grade, and depth of tumor invasion) exhibited a superior calibration performance (data not shown); once again highlighting the clinical significance of our reported risk-assessment model for predicting LNM in patients with T1 CRC.

Third, this correspondence also recommended inclusion of decision curve analysis (DCA), which potentially offers a better measure of net benefit of any predictive biomarkers in clinical settings. The authors are correct in suggestion that DCA is a widely used method to evaluate the alternative diagnostic strategy based on "net benefit" of using any molecular assay, by itself or as an adjunct to other clinicopathological tools used in the clinic.[6] As suggested, we undertook these analyses, and observed that across most of the threshold probabilities, both the transcriptomic panel and risk-stratification model exhibited higher net benefit than the strategy for treating all the patients or none of the patients. Not surprisingly, the risk-assessment model on its own was superior to the transcriptomic panel. The DCA analysis further proved that the risk-assessment model could limit the probability of potential overtreatment in patients with T1 CRC. However, the current calibration analysis and DCA were somewhat limited by number of patients with LNM; hence, future studies with a larger number of such patient populations are needed to better appreciate the clinical significance of such analytical approaches.

Last, this letter proposed enrollment of patients with T1 CRC from multiple centers to further improve the predictive accuracy of our signature. We agree with this important suggestion, because in our published study, all patients had a similar demographic profile and were enrolled at 2 institutions in Japan. Given the importance of this suggestion, we currently have several collaborations under way in which we are prospectively enrolling patients with T1 CRC at different institutions in the United States, Europe, and Asia. We remain optimistic that on completion of such studies, we will have additional evidence to appreciate the clinical significance of our liquid biopsy assay for potential implementation in clinical settings.

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# COVID-19 Vaccination and Inflammatory Bowel Disease: Desired Antibody Responses, Future Directions, and a Note of Caution

Dear Editors:

We have a few thoughts on the important and timely analysis "Serological response to messenger RNA COVID-19 vaccines in inflammatory bowel disease patients receiving biological therapies" by Wong et al.[1] The authors sought to

address the concern of COVID-19 vaccine responsiveness among patients with inflammatory bowel disease (IBD) receiving biologic therapy. The analysis included 48 patients with IBD who had received at least 1 vaccination of either the Pfizer-BioNTech or National Institutes of Health (NIH)–Moderna vaccine and assessed the rates of immunoglobulin response to the receptor binding domain (RBD) of the SARS-CoV-2 S protein (using an in-house enzyme-linked immunosorbent assay [ELISA]), comparing results to those of completely vaccinated health care workers and healthy volunteers. All patients with IBD who received both COVID-19 vaccine doses (n = 26) achieved positive anti-RBD results. However, a quantitative comparison of anti-RBD levels between patients with IBD and health care workers showed that use of anti–tumor necrosis factor was associated with lower anti-RBD total immunoglobulin ($P = .0299$) and that the use of vedolizumab was associated with lower anti-RBD total immunoglobulin, anti-RBD IgG, and anti-S IgG.

The results mirror our own findings using a commercially available ELISA assay for both the COVID-19 nucleocapsid and spike domain antibodies (Roche) among consecutively tested postvaccination patients with IBD on biologic or immunomodulator therapy. The total group included 19 patients, 9 (47%) female, with a mean age of 50 years (range, 27-80 years). Patients' maintenance therapies varied within the cohort, with most patients on biologic therapy, including 7 (37%) on infliximab, 2 (11%) on adalimumab, 1 (5%) on golimumab, 5 (26%) on ustekinumab, 2 (11%) on vedolizumab, 1 (5%) on tofacitinib, and 1 (5%) on methotrexate. Eleven patients received the Pfizer-BioNTech vaccine, and 8 received the NIH-Moderna vaccine. We observed a 95% (18/19) overall response rate. None of the patients with positive results for spike domain antibodies had elevations of nucleocapsid antibodies, suggesting a true vaccine response rather than prior undiagnosed infection. Of the patients with elevated spike domain antibodies, 89% (17/19) had the highest measurable levels, at >250.00 U/mL, with assay reference ranges of ≤0.79 U/mL indicating negative and ≥0.80 U/mL indicating positive results. The only patient negative for spike domain antibodies was a 78-year-old man on adalimumab 40 mg subcutaneously every 14 days, prednisone 5 mg every third day, and sulfasalazine who had received his second NIH-Moderna vaccination 8 weeks prior.

Both the observations by Wong et al[1] and our own provide important and encouraging early data on the effectiveness of SARS-CoV-2 vaccination. Added to these findings are the report by Kennedy et al[2] of 27 patients receiving 2 doses of the Pfizer-BioNTech vaccine, with 85% (17/20) of infliximab-treated patients and 86% (6/7) of vedolizumab-treated patients seroconverting. Although our sample size is also small, the additional numbers, expansion to patients not on biologic therapy, and inclusion of a commercially available ELISA add further support to the findings of Wong et al and Kennedy et al. Still, many more data will be needed to determine the true effectiveness of SARS-CoV-2 vaccination in this high-risk population. Notably, Kennedy also observed the lower vaccine response rates after a single dose of the vaccine in infliximab-treated patients and in those with immunomodulator use. Coupling this with reports showing that combination therapy with tumor necrosis factor antagonists and steroid or thiopurines is associated with severe COVID-19 among patients with IBD suggests that specific vaccine protocols (or the requirement for confirmation of a satisfactory neutralizing antibody response) may need to be developed for this highest-risk population.[3] Also, as information accumulates on the initial antibody response postvaccination, longer-term follow-up will be needed to track the durability of the antibody response and responses to newer vaccines, in both the IBD and general populations.

There is one critical point to note, particularly at a time when many are still waiting for their first SARS-CoV-2 vaccine dose. Previous studies have shown that patients with IBD have lower serologic response rates to hepatitis B virus,[4] pneumococcal,[5] and H1N1 influenza vaccination,[6] with IBD clinicians encouraged to check serologies and revaccinate those with low or absent antibody responses.[7] Although we suspect that time and vaccine availability will lead to the same approach with regard to SARS-CoV-2, there is currently no consensus/recommendations on revaccination after a negative serologic response. As post vaccine testing becomes more widely available and requested, patients and their providers should understand that the proper response to a negative serologic response has yet to be determined.

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