

## Letters

## Antibody response to SARS-CoV-2 among individuals with IBD diminishes over time: a serosurveillance cohort study

We read with interest the highly impactful CLARITY IBD study that demonstrated a diminished serological response to SARS-CoV-2 in individuals with IBD receiving infliximab as compared with those receiving vedolizumab.<sup>1</sup> We assessed the prevalence of antibodies to SARS-CoV-2 in patients with IBD and evaluated whether serological response to SARS-CoV-2 wanes over time following infection.

Individuals with IBD from Calgary, Canada, were recruited from October 2020 to April 2021 and stratified into two cohorts: (1) serosurveillance (n=279)

defined as those who were not previously diagnosed with COVID-19; and (2) COVID-19 recovered (n=45), defined as those with a molecular-confirmed diagnosis of SARS-CoV-2 infection via PCR.

Serum was analysed using the Abbott Architect SARS-CoV-2 IgG antibody to the nucleocapsid protein. A positive antibody test was defined as an index signal/cut-off  $\geq 1.4$ . The assay has been validated with 95% sensitivity and >99% specificity 12 days following symptom onset and correlates to neutralising antibodies.<sup>2</sup>

We assessed the proportion, with 95% CIs, of individuals with IBD who mounted an antibody response among those undergoing serosurveillance and following infection with SARS-CoV-2. In those diagnosed with COVID-19, we calculated the days from diagnosis to serological testing and developed a logistic regression model that assessed the effect of time from COVID-19 diagnosis to serology testing

(before vs after 90 days) on nucleocapsid positive versus negative antibody; adjusted for age, sex and anti-tumour necrosis factor (TNF) usage.

The baseline characteristics of the two cohorts are summarised in table 1. Among the serosurveillance cohort, 1.08% (95% CI 0.22 to 3.11) tested positive for nucleocapsid antibody (table 1, figure 1A). Among those who recovered from COVID-19, 53.3% (95% CI 37.9 to 68.3) had a positive nucleocapsid antibody (table 1). The proportion of patients who were nucleocapsid antibody positive was 80.8% (95% CI 60.6 to 93.4) at 0–90 days from diagnosis and 21.7% (95% CI 7.5 to 43.7) after 90 days. Tests performed within 90 days of their diagnosis were associated with nucleocapsid seropositivity (OR: 14.1; 95% CI 3.46 to 57.6) as compared with testing beyond 90 days of COVID-19 diagnosis. An interactive dashboard displaying these data can be

**Table 1** Demographic and clinical characteristics of the serosurveillance and COVID-19 recovered individuals with IBD

Baseline characteristics	Serosurveillance cohort (n=279)*	COVID-19 recovered (n=45)		
		Total COVID-19 recovered (n=45)*	Nucleocapsid positive (n=24)†	Nucleocapsid negative (n=21)†
Age, median (IQR)	48.1 (36.4–59.1)‡	43.1 (32.2–49.8)‡	44.2 (33.6–55.6)	37.9 (30.5–48.8)
Sex, n (%)				
Female	156 (55.9)	27 (60.0)	17 (70.8)	10 (47.6)
Male	123 (44.1)	18 (40.0)	7 (29.2)	11 (52.4)
Disease, n (%)				
Crohn's Disease	226 (81.0)	29 (64.4)	17 (70.8)	12 (57.1)
Ulcerative Colitis	53 (19.0)	16 (35.6)	7 (29.2)	9 (42.9)
Anti-TNF§, n (%)	138 (49.5)	27 (60)	15 (62.5)	12 (57.1)
Ustekinumab, n (%)	89 (32.0)‡	4 (8.9)‡	3 (12.5)	1 (4.8)
Vedolizumab, n (%)	44 (16.1)	6 (13.3)	2 (8.3)	4 (19.1)
Tofacitinib, n (%)	2 (0.72)	1 (2.2)	1 (4.2)	0
Combination therapy¶, n (%)	54 (19.4)	7 (15.6)	3 (12.5)	4 (19.1)
Oral prednisone, n (%)	9 (3.2)	0	0	0
5-ASA alone or no IBD medications, n (%)	5 (1.8)‡	5 (11.1)‡	2 (8.3)	3 (14.3)
Nucleocapsid antibody, n (%)				
Positive ( $\geq 1.4$ S/C index)	3 (1.1)‡	23 (51.1)‡	NA	NA
Days from COVID-19 diagnosis to serology test, median (IQR)*	NA	85 (41.5–122)	51 (25–71)**	123 (93–209)**
COVID-19 severity, n (%)				
Ambulatory	NA	44 (97.8)	23 (95.8)	21 (100)
Hospitalised		1 (2.2)	1 (4.2)	0

Those previously diagnosed with COVID-19 are further stratified by positive versus negative nucleocapsid antibody test based on an S/C index of  $\geq 1.4$ .

\*Two individuals in the serosurveillance cohort were diagnosed with COVID-19 after their serosurveillance serology testing.

†Nucleocapsid positive or negative were based on their first serology test after COVID-19 diagnosis.

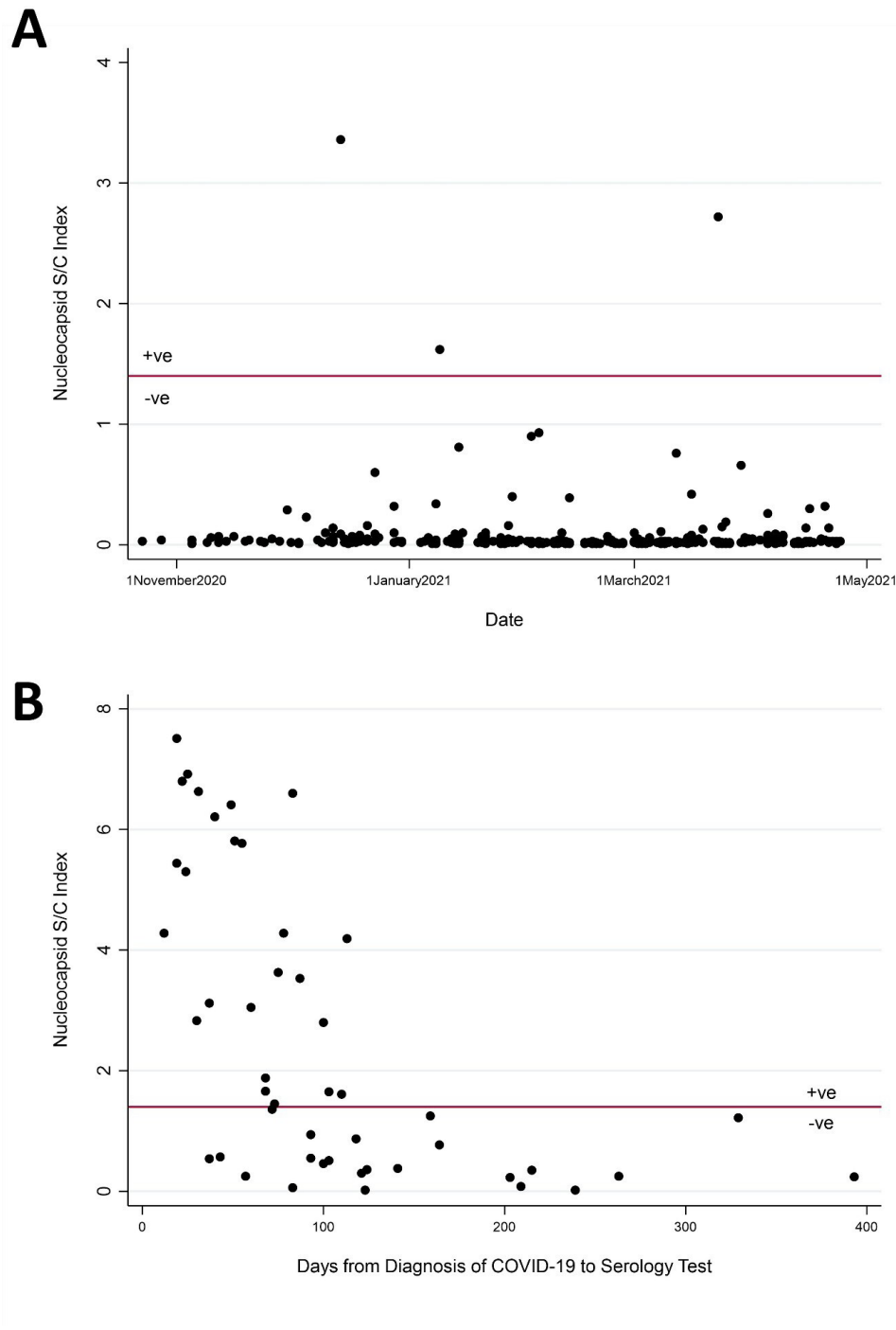
‡Significant p value comparing serosurveillance cohort to COVID-19 recovered cohort. Statistically significant at  $p < 0.05$ ; either defined by two-sample test of proportion (categorical variable) or Wilcoxon rank-sum test (continuous variable).

§Anti-TNF is one of golimumab, adalimumab or infliximab (originator or biosimilar).

¶Any combination of two or more of the following therapies: anti-TNF therapy, vedolizumab, ustekinumab, tofacitinib, azathioprine, 6-mercaptopurine or methotrexate.

\*\*Significant p value comparing COVID-19 recovered nucleocapsid positive to nucleocapsid negative. Statistically significant at  $p < 0.05$ ; either defined by two-sample test of proportion (categorical variable) or Wilcoxon rank-sum test (continuous variable).

Anti-TNF, anti-tumour necrosis factor; NA, not applicable; S/C, signal/cut-off.



**Figure 1** The proportion of individuals with IBD who mounted an antibody response (A) Among those undergoing serosurveillance and (B) following infection with SARS-CoV-2. All clinical and serological data from this study are available open access on an online interactive dashboard: [https://sc-epi.shinyapps.io/COVID\\_Serology/](https://sc-epi.shinyapps.io/COVID_Serology/).

found here: [https://kaplan-gi.shinyapps.io/COVID\\_Serology/](https://kaplan-gi.shinyapps.io/COVID_Serology/).

Seropositivity for SARS-CoV-2 nucleocapsid antibodies was found in 1% of individuals with IBD. In contrast, seropositivity in the general population in Calgary during the same time period was 1.8%, suggesting that patients with IBD were less exposed to SARS-CoV-2 or that

serological response postinfection was not as robust as the general population.<sup>3</sup>

Our seropositivity was lower than prior IBD studies in the USA (3%)<sup>4</sup> and the UK (4.3%).<sup>1</sup> The difference in seropositivity may be explained by the lower prevalence of COVID-19 in the general population in Canada; for example, 5.4% of patients with IBD had antibodies to SARS-CoV-2

in Milan as compared with only 0.4% in regions in Europe with lower rates of infection in their general populations.<sup>5</sup>

In our study, the primary factor associated with seropositivity was the interval from diagnosis to serology testing. Three-quarters were seropositive if tested within 2 months of diagnosis, whereas no one tested after 4 months was seropositive.

Limitations include sample size required to compare across therapies and not testing for neutralising antibodies or immunological memory.<sup>6</sup>

Nonetheless, these data have important clinical implications for individuals with IBD. Serosurveillance studies in IBD may only be reliable for a 3-month window of testing. Moreover, 4 months following COVID-19 diagnosis, patients with IBD may continue to be susceptible to SARS-CoV-2. Our data highlight the importance of studying sustained antibody response over time in order to develop strategies to ensure durable protection and inform public health policy.

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**Contributors** GGK has full access to all data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. GGK, CM, CC, JNK, GT and RP conceived and designed the study. GGK, CM, RP, NS, MH and RJMI were responsible for clinical data. CC, JNK, GT, NS and MH were responsible for serological data. GGK, SC and LH analysed the data. GK drafted the manuscript. All authors interpreted the data and provided critical revisions of the manuscript for important intellectual content. All authors have approved the final draft of the manuscript.

**Competing interests** GGK has received honoraria for speaking or consultancy from Abbvie, Janssen, Pfizer, Amgen and Takeda. He has received research

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### REFERENCES

- Kennedy NA, Goodhand JR, Bewshea C, *et al.* Anti-SARS-CoV-2 antibody responses are attenuated in patients with IBD treated with infliximab. *Gut* 2021;70:865–75.
- Padoan A, Bonfante F, Pagliari M, *et al.* Analytical and clinical performances of five immunoassays for the detection of SARS-CoV-2 antibodies in comparison with neutralization activity. *EBioMedicine* 2020;62:103101.
- Charlton CL, Nguyen L, Bailey A. Pre-Vaccine positivity of SARS-CoV-2 antibodies in Alberta, Canada during the first two waves of the COVID-19 pandemic. *Submitted for Publication. mBio* 2021.
- Gubatan J, Levitte S, Balabanis T, *et al.* SARS-CoV-2 testing, prevalence, and predictors of COVID-19 in patients with inflammatory bowel disease in northern California. *Gastroenterology* 2020;159:1141–4.
- Berte R, Mazza S, Stefanucci MR, *et al.* Seroprevalence of SARS-CoV2 in IBD patients treated with biologic therapy. *J Crohns Colitis* 2021;15:864–8.
- Dan JM, Mateus J, Kato Y, *et al.* Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. *Science* 2021;371. doi:10.1126/science.abf4063. [Epub ahead of print: 05 02 2021].