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Objective: To evaluate the relationship between reported coronavirus disease 2019 (COVID-19)-like symptoms and the presence of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) antibodies in patients with an immune-mediated inflammatory disorder or post-solid organ transplantation (IMIDT) with and without immunosuppressive medication (imed) and controls.

Method: The IENIMINI cohort was a prospective cohort study set up in the Netherlands in March 2020, with 2 monthly (paper) or weekly (online) questionnaires about COVID-19-like symptoms. Participants from this cohort who reported these symptoms between March 2020 and November 2020 were approached for this substudy. SARS-CoV-2 antibodies were tested using a total antibody assay.

Results: Of the 1203 participants approached, 629 agreed to participate and were sent a fingerprick test; 565 participants collected a capillary blood sample, of which 562 were usable. Analysis showed that 57/202 (28.2%) of the tested IMIDT group with imed, 48/16 3(29.4%) of the IMIDT group without imed, and 69/197 (35.0%) of the control group tested positive for SARS-CoV-2 antibodies. Seroprevalences of SARS-CoV-2 antibodies between males and females, biological disease-modifying anti-rheumatic drug users and non-users, and those who had had a serious disease period (defined as an episode with dyspnoea and fever) and those who had not, were not statistically different between the three groups.

Conclusions: Approximately 30% of patients who had reported COVID-19-like symptoms had SARS-CoV-2 antibodies. The seroprevalence of SARS-CoV-2 antibodies after reported COVID-19-like symptoms was similar in IMIDT patients with and without imed compared to controls.

During the first wave of the coronavirus disease 2019 (COVID-19) pandemic, there appeared to be no increased risk of COVID-19 disease in patients with autoimmune diseases (1–4). However, as they were generally more aware of infectious risks, these patients may have been more cautious than the general population (5). In addition, in the initial (retrospective) registries, mild infections may have been overlooked. Such bias may have been avoided by the IENIMINI study, a prospective registration of symptoms in both patients with an autoimmune or autoinflammatory disease or who had had an organ transplantation (IMIDT) with or without immunosuppressive medication (imed) and a representative comparative group (1). With the ongoing severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic, there are concerns that patients with IMIDT with or without imed may not develop sufficient protective antibodies after infection or vaccination (6, 7), possibly causing less protection against (severe) illness after reinfection. We compared the seroprevalence of SARS-CoV-2 antibodies between such patients, with or without imed, and controls from the general population.

Method

We included patients and controls from the IENIMINI cohort study who, in that study, reported having had COVID-19-like symptoms (CLS). The IENIMINI cohort was set up in March 2020 with the main objective of prospectively registering CLS in IMIDT patients with or without imed and in controls without such disease or medication. Patient and control selection is described elsewhere (1). Neither the patients nor the general public were involved in the study design. All patients included in this study signed informed consent. The study was approved by the Medical Ethical Committee Leiden-Delft-Den Haag (METC LDD) (NL74902.058.20).

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Participants in the IENIMINI cohort who reported having had CLS at least once between March 2020 and November 2020 were invited by mail to participate in this SARS-CoV-2 antibody substudy. They were instructed that they could not participate if they had already been vaccinated. Those who signed informed consent were sent a fingerprick test kit. Participants conducted the fingerprick test themselves and sent the samples to Sanquin, the analysing partner for this study. Samples were collected between April and June 2021. The serological bridging assay for the detection of antibodies against the receptor-binding domain of the spike protein of SARS-CoV-2 (immunoglobulins IgG, IgA, and IgM) used in this study was developed by Sanquin, and has a sensitivity of 98.1% and a specificity of 99.5% (8). The cut-off for the normalized optical density was 0.10 and samples close to this cut-off were measured twice to confirm the result.

Since the IENIMINI cohort is an explorative cohort, no adjustments on multiple testing were made. Descriptive statistics were used, and chi-squared tests were conducted to test for statistical significance. Statistical analysis was performed using Stata SE version 16 (StataCorp, College Station, TX, USA).

Results

Of the 3172 participants in the IENIMINI cohort, 1203 reported having had at least one disease episode between March 2020 and November 2020. These 1203 participants were approached for this fingerprick substudy. Of these, 629 returned a signed informed consent form, and ultimately, 565 submitted a sample to be tested. Baseline characteristics of the 629 participants who signed informed consent and of the 574 who were approached but did not participate were similar (supplementary Table 1). Three patients were excluded from the analysis because they appeared to be already vaccinated at the time of the fingerprick test. This resulted in 562 samples available for analysis (supplementary Figure 1). Baseline demographic characteristics of the participants were similar between the groups, except for more self-reported heart and lung disease and diabetes mellitus in the IMIDT groups (Table 1).

Of all tested samples, 31.0% were positive for SARS-CoV-2 antibodies. This result was similar across the three groups (35.0% in the controls, 29.4% in the IMIDT group without imed, and 28.2% in the IMIDT group with imed, p = 0.300) (Table 2). Seropositivity was similar in female (31.3%) and male (30.2%) participants, without major differences across the three groups (supplementary Table 2). Also, there was no significant difference in seropositivity between patients who reported more severe symptoms (defined as a disease episode with both dyspnoea and fever) and those who reported milder symptoms (33.9% and 31.2%, respectively, p = 0.681). The small number of hospital admissions (n = 18) did not allow meaningful analysis of this outcome.

Table 1. Baseline characteristics.

	Controls (N = 197)	IMIDT without imed (N = 163)	IMIDT with imed (N = 202)
Age (years)	55.0 ± 12.8	54.4 ± 14.2	54.8 ± 14.0
Gender, female	145 (74)	108 (66)	127 (63)
BMI (kg/m^2)	25.6 (4.1)	25.6 (5.0)	26.1 (5.2)
Daily alcohol use	90 (48.9)	63 (44.0)	81 (40.5)
Current smoker	24 (12.8)	12 (8.2)	12 (6.0)
Self-reported heart disease	25 (13.6)	29 (20.7)	48 (23.9)
Self-reported lung disease	57 (31.0)	73 (52.1)	91 (45.5)
Self-reported diabetes mellitus	8 (4.4)	8 (5.8)	20 (10.1)

Data are shown as mean ± sd or n (%).
BMI, body mass index; imed, immunosuppressive medication; IMIDT, immune-mediated inflammatory disorders or organ transplantation.

Of the 202 IMIDT with imed participants, 72 (35.6%) used glucocorticosteroids (GC), either as monotherapy or in combination with other imed (supplementary Table 3). Furthermore, 31.9% of GC users tested positive for SARS-CoV-2 antibodies compared to 26.2% of non-GC users (p = 0.381). Seropositivity was similar between patients who used or did not use a biological disease-modifying anti-rheumatic drug, either as monotherapy or in combination with other imed (26.8% and 28.8%, respectively, p = 0.779), and more specifically between tumour necrosis factor inhibitor users and patients on other imed (20.0% vs 30.3%, p = 0.197). Only eight patients used either rituximab or cyclophosphamide. Five of these (62.5%) tested positive for SARS-CoV-2 antibodies, compared to 52 (26.8%) of the patients on other imed (p = 0.028).

Discussion

We evaluated the prevalence of SARS-CoV-2 antibodies in patients in our IENIMINI cohort who had reported CLS. We found overall seropositivity in 31.0%, with similar percentages in patients with IMIDT with and without imed and in controls.

The findings in this cohort provide a positive view on antibody formation after experiencing CLS in IMIDT patients with or without imed. The 31.0% seropositivity is much higher than previously reported in similar patient groups and healthy controls. A cohort study in patients with immune-mediated inflammatory diseases treated with cytokine inhibitors showed a lower prevalence of SARS-CoV-2 IgG (0.75%) compared to a combined cohort of healthy participants and firefighters (2.27%) (9). In contrast to our study, they included individuals regardless of

Table 2. Antibody test results.

	IMIDT with imed (N = 202)		IMIDT without imed (N = 163)	Controls (N = 197)
SARS-CoV-2 positive, n (%)	57 (28)		48 (29)	69 (35)
	Yes	No		
	GC use		–	–
n	72	130		
SARS-CoV-2 positive, n (%)	23 (32)	34 (26)	–	–
	bDMARD use		–	–
n	56	146		
SARS-CoV-2 positive, n (%)	15 (27)	42 (29)	–	–
	TNF inhibitor use		–	–
n	40	162		
SARS-CoV-2 positive, n (%)	8 (20)	49 (30)	–	–
	RTX or Cyc use		–	–
n	8	194		
SARS-CoV-2 positive, n (%)	5 (63)	52 (27)	–	–

bDMARD, biological disease-modifying anti-rheumatic drug; Cyc, cyclophosphamide; GC, glucocorticoids (mono or combination therapy); imed, immunosuppressive medication; IMIDT, immune-mediated inflammatory disorders or organ transplantation; RTX, rituximab; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; TNF, tumour necrosis factor.

whether they had had symptoms. Moreover, only IgG was tested, which could have led to missing cases who had been recently ill and in whom IgG had not yet been produced. In addition, that study was conducted earlier (first half-year of 2020) than ours (first quarter of 2021), which could also have led to the difference in seroprevalence.

Among our participants, there appeared to be no association between having had a more severe disease episode(s) and having had only mild complaints. Furthermore, different groups of immunosuppressive medication which can alter antibody production after infection were not associated with differences in antibody prevalence compared to other imed users, except for the rituximab or cyclophosphamide users. Remarkably, despite the B-cell-depleting properties of these medications, in this very small group (eight patients) we found a higher antibody positivity than among users of other imed. Their reported symptoms and number of episodes were comparable to those reported by non-rituximab/cyclophosphamide users (respectively, 16.7% vs 10.8% of symptoms included both dyspnoea and fever, $p = 0.648$, and 6.1% vs 8.3% of patients, respectively, reported at least one episode of CLS, $p = 0.107$). Previous research has shown that patients with IMIDT and/or use of imed are following COVID-19-preventive measures more strictly because they know that they are a risk group for infections (5). This extra caution may have led to these patients staying indoors more compared to healthy controls. However, rituximab and cyclophosphamide are both administered intravenously, which requires hospital visits and potentially more laboratory checks, possibly causing an extra risk of COVID-19 exposure, to which they may also have been more vulnerable.

By using the IENIMINI cohort, this is one of the few studies to date to be able to select IMIDT patients and controls who had prospectively reported CLS, ranging from mild (e.g. resembling a common cold) to more severe (including dyspnoea and fever). The prevalence of SARS-CoV-2 antibodies in our cohort can therefore be seen as a realistic reflection of the SARS-CoV-2 antibody prevalence in controls and patients with IMIDT in the Netherlands who experienced CLS. However, although the antibody screening test has been validated by Sanquin, we cannot completely rule out the possibility of cross-reacting antibodies raised by endemic coronavirus infections, causing false-positive results (10). We also cannot rule out the possibility that more IENIMINI participants were infected but remained asymptomatic and were not selected for this substudy. Nor can we speculate on the percentage of patients who were infected and were asymptomatic, but because of their illness and/or medication did not have (or no longer had) detectable SARS-CoV-2 antibodies. In addition, our test method does not provide antibody titres/levels. With the ongoing pandemic, it is becoming apparent that patients with antibodies can fall ill, although rarely as seriously as patients without antibodies (11). It is possible that antibody titres play a role in susceptibility for (re) infection. Thus, without information on antibody titres, finding a high seroprevalence among our patients is only partly reassuring. As our IENIMINI cohort study period covers the first months of the pandemic with questionnaires, when routine testing was not available, we cannot match symptoms and/or serological outcomes with polymerase chain reaction (PCR) test results or disease episodes, nor can we report on the median time between infection and antibody presence. The cross-sectional design of this study makes it impossible to speculate on how long antibodies against SARS-CoV-2 remain. A review on IgM and IgG response after SARS-CoV-2 infection reports that IgG can last for 6–8 months (12). However, this review was not focused on IMIDT patients and included only one study about patients who had had a kidney transplantation. Further research is needed to learn more about the efficacy and lasting presence of SARS-CoV-2 antibodies in patients with IMIDT after reporting CLS or vaccination.

Conclusion

We found a similar prevalence of SARS-CoV-2 antibodies in patients with IMIDT with or without imed and controls after reporting COVID-19-like symptoms.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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Supplementary material

Supplemental data for this article can be accessed online at https://doi.org/10.1080/03009742.2022.2092269