IJID Regions 3 (2022) 21–23

Contents lists available at ScienceDirect

IJID Regions

journal homepage: www.elsevier.com/locate/ijregi

Short Communication

SARS-CoV-2 seropositivity and subsequent infection risk: a prospective cohort study

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ARTICLE INFO

Key words:
COVID-19
SARS-CoV-2
infectious diseases
public health
epidemiology

ABSTRACT

Objectives: This aim of this study was to examine the relationship between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) seropositivity and subsequent infection.
Design: A cohort study design was employed.
Methods: Stratified random sampling was undertaken to identify individuals aged 10 years and above registered with Qatar's largest primary healthcare provider. A questionnaire was administered, and blood samples were collected and analyzed for immunoglobulin G antibodies against SARS-CoV-2 at baseline. Participants were followed up until March 31, 2021 (a 34-week follow-up period) for vaccination status and a positive polymerase chain reaction (PCR) test for SARS-CoV-2.
Results: A total of 2044 individuals participated in the study (97.2% of the planned sample). Of these, 185 (9%) were found to be seropositive at baseline. 450 individuals were vaccinated during the follow-up period — 246 with one dose and 204 with two doses. 86 (4.2%) individuals had a positive PCR test during the follow-up period, of which 80 (3.9%) were seronegative and six (0.3%) were seropositive (five undiluted and one with a titer ≥ 1:8).
Conclusions: Overall, the findings suggest that reinfections are uncommon. Antibody concentrations potentially influence the risk of subsequent infection. Therefore, it might not be necessary to subject seropositive individuals to vaccination and the quarantine policies that apply to seronegative individuals.

As of September 28, 2021, over 18 months since the first cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection were reported, 231 416 660 cases and 4 741 330 deaths had been reported globally (World Health Organization, 2021). Continued community transmission of SARS-CoV-2 has been observed in many countries. While reinfection is uncommon, it is a possibility. Currently, there is limited evidence on the role of antibodies (due to previous infection) with regard to subsequent infection. Several serological studies have reported on the risk of reinfection in seropositive individuals in various contexts (Kohler et al., 2021; Kurtikov et al., 2021; Hall et al., 2021; Leidi et al., 2021; Leidi et al., 2022). These included healthcare workers, residents of long-term care facilities, and essential workers. Follow-up durations for these study cohorts ranged from 5 weeks to 10 months. The findings indicated that SARS-CoV-2 antibodies provide between 80% and 94% protection against reinfection. Some studies have compared reinfections between symptomatic and asymptomatic initial infections and between different age groups. However, these studies did not report findings in relation to antibody titers prior to subsequent infection.

Our study examined the relationship between seropositivity and subsequent infection, specifically with regard to the role of antibody titer concentration in relation to the risk of subsequent infection.

Individuals aged 10 years and above, registered with the Primary Health Care Corporation (PHCC), Qatar's largest primary healthcare provider, were eligible for inclusion. Approximately 70% of Qatar's population is registered with the PHCC across 27 primary healthcare centres. A stratified random sampling by age, gender, and nationality strata was used to identify a representative sample (N = 2012) of the total PHCC-registered population (N = 1 063 243) (Figure 1).

Randomly identified individuals were invited to a PHCC health centre in July 2020. A questionnaire was administered, and blood samples were collected and analyzed for immunoglobulin G antibodies against SARS-CoV-2 at baseline. 150 µL of plasma was used for detection of anti-SARS-CoV-2 immunoglobulin G (IgG) using the CL-900i Chemiluminescence Immunoassay System (Mindray Bio-Medical Electronics Co, Shenzen, China), according to the manufacturer's instructions. Immunoglobulins were directed against the spike protein (S subunit).

Participants were followed up until March 31, 2021 (a 34-week follow-up period) for vaccination status and a positive polymerase chain

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https://doi.org/10.1016/j.ijregi.2022.02.005
Received 31 October 2021; Received in revised form 9 February 2022; Accepted 10 February 2022

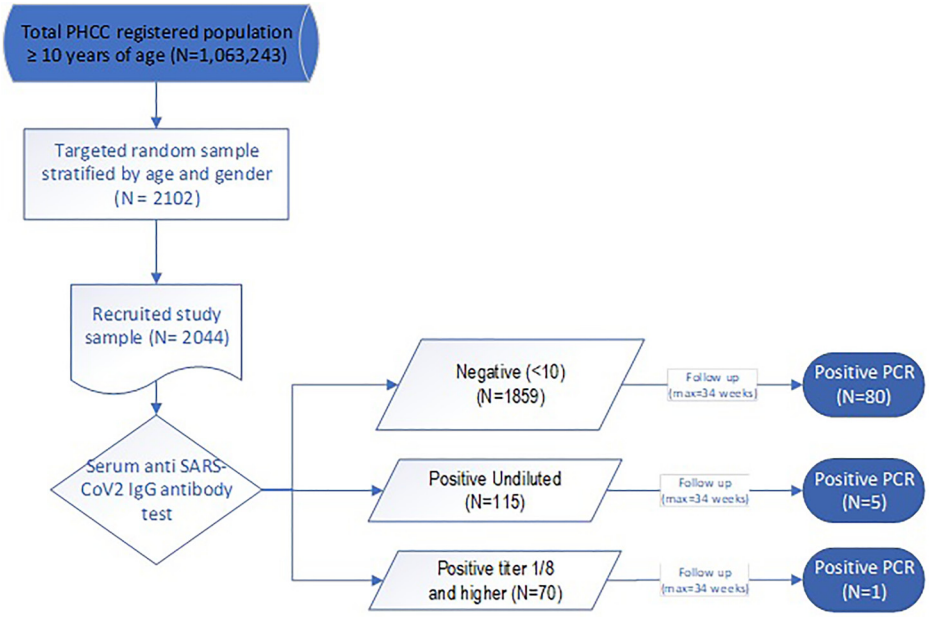

Table 1
Risk of a positive PCR test by age, gender, comorbidity, and serology status

	Adjusted hazard ratio	*p*-value
Age		0.089 [NS]
18–39 years compared with 10–17 years	2.22	0.032 [NS]
40–59 years compared with 10–17 years	2.20	0.053 [NS]
60+ years compared with 10–17 years	0.81	0.796 [NS]
Gender		
Male gender compared with female gender	1.45	0.117 [NS]
Comorbidities		
Arthritis	2.04	0.49 [NS]
Cardiovascular disease	0.35	0.31 [NS]
Diabetes mellitus	1.21	0.59 [NS]
Dyslipidemia	1.63	0.13 [NS]
Hypertension	0.50	0.09 [NS]
Cerebrovascular disease	7.11	0.06 [NS]
Thyroid disorder	0.64	0.35 [NS]
Serology status		0.49 [NS]
Seropositive (undiluted) compared with seronegative	0.91	0.84 [NS]
Seropositive (titre ≥ 1:8) compared with seronegative	0.31	0.24 [NS]

p (model) = 0.045
NS = not significant

reaction (PCR) test for SARS-CoV-2. For the PCR tests, RNA was extracted and isolated prior to amplification on various platforms. Extracted nucleic acid underwent thermal cycling on ABI 7500 Thermal Cyclers (ThermoFischer, USA) using a range of thermal mixes. PCR tests were conducted if participants reported contact with a suspected or confirmed case, or if they had COVID-19 symptoms during the follow-up period. 'Subsequent infection' was defined as a positive PCR test in seropositive participants during the follow-up period.

Cox-regression was undertaken to assess the risk (hazard ratio [HR]) of a positive PCR test during the follow-up period. The analysis was adjusted for age, gender, comorbidities, and serology status. Survival analysis was also undertaken. The analyses took into account vaccination status and excluded individuals 2 weeks from the date of receiving the first dose.

A total of 2044 individuals participated in the study (97.2% of the planned sample). Of these, 185 (9%) were found to be seropositive at baseline. 450 individuals were vaccinated during the follow-up period — 246 with one dose and 204 with two doses. 86 (4.2%) individuals had a positive PCR test during the follow-up period. Of these, 80 (3.9%) were seronegative and six (0.3%) were seropositive (five undiluted and one with a titer ≥ 1:8).

Individuals aged 18–39 years (HR 2.22) and 40–59 years (HR 2.20) were at a higher risk of a positive PCR test compared with those aged 10–17 years (Table 1). Males were at a higher risk (HR 1.45) compared with females. Diagnoses of cerebrovascular disease (HR 7.11), arthritis (HR 2.04), dyslipidemia (HR 1.63), and diabetes mellitus (HR 1.21) were found to increase the risk of a positive PCR test. Seropositive individuals with an undiluted titer (HR 0.91) had a lower risk of subsequent infection compared with seronegative individuals. Those with a higher antibody titer (≥ 1:8) had an even lower risk (HR 0.31). The overall mean survival time to a positive PCR test was 33.22 weeks.

Only 3.2% of seropositive individuals had a subsequent infection during the follow-up period. This figure was higher than that reported by Vitale et al. for a cohort of seropositive individuals followed up for a period of 1 year, with a reported reinfection rate of 0.31% (Vitale et al., 2021).

Older adults (60+ years) had a lower risk of a subsequent infection compared with younger individuals. In contrast, Leidi et al. (2021) reported a higher risk in participants aged 60+. The majority of comorbidities (cerebrovascular disease, arthritis, dyslipidemia, diabetes) included in our study showed a higher risk of subsequent infection. However, Leidi et al. (2021) reported a lower risk in individuals with comorbidi-

ties. These different findings must be compared and interpreted with caution, due to differences in the study populations and the low numbers of subsequent infections.

While no differences in risk over time were observed between seropositive and seronegative individuals, antibody titer concentration appeared to play a role in defining the risk of subsequent infection. Those with a titer ≥ 1:8 has a lower risk by one-third. A recent study reported that seropositive individuals had about one-fifth the risk of subsequent infection compared with seronegative individuals (Letizia et al., 2021). However, this only included healthy 18–20 year-olds, with a follow-up of 6 weeks.

The key strengths of our study were the random selection of participants from the PHCC-registered population and the long follow-up duration. A limitation of the study was the lack of statistically significant results due to the small number of subsequent infections in the cohort that was followed up. However, this limitation is unlikely to have impacted the results of the study.

Overall, the findings suggest that reinfections are uncommon. Antibody concentrations potentially influence the risk of subsequent infection. Therefore, it might not be necessary to subject seropositive individuals to vaccination and the quarantine policies that apply to seronegative individuals.

Funding Source

Funding for the study was approved by the Primary Health Care Corporation's Research Budget Working Group (ref. PHCCDCR202103016).

Ethical Approval

This study was conducted with integrity according to generally accepted ethical principles and was approved by the Primary Health Care Corporation's Research Sub-committee (ref. PHCCDCR202103016). Informed consent was waived due to the retrospective nature of the study.

Declaration of Competing Interest

All authors declare no conflicts of interest.

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