Clinical Infectious Diseases

BRIEF REPORT

Association Between Duration of SARS-CoV-2 Positivity and Long COVID

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In an observational study, we analyzed 1293 healthcare workers previously infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), of which 34.1% developed postacute sequelae of SARS-CoV-2 infection (also known as long COVID). Using a multivariate logistic regression model, we demonstrate that the likelihood of developing long COVID in infected individuals rises with the increasing of duration of infection and that 3 doses of the BNT162b2 vaccine are protective, even during the Omicron wave.

Keywords. long COVID; COVID-19; SARS-CoV-2 infection; vaccine.

Long COVID (also known as post-COVID conditions) refers to a condition in which individuals continue to experience symptoms after recovering from acute severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [1]. These symptoms can persist for weeks to months and can be severe and debilitating, affecting a person's physical and mental well-being [1–3]. Studies have found that several factors may influence the onset of long COVID [2, 4]. Furthermore, a meta-analysis and systematic review reported that female sex and preexisting asthma were associated with a higher probability of long COVID [5], even though women are less susceptible to severe disease [2, 6–8]. Additionally, recent evidence from our and other groups has shown that individuals who have received full vaccination against coronavirus disease 2019 (COVID-19) are less likely to develop long COVID compared to those who have not been vaccinated [9, 10]. However, the mechanism underlying the protective effects of vaccination against long COVID remains elusive, and further investigation is needed. To our knowledge, the potential relationship between the duration of SARS-CoV-2 positivity and the development of long COVID has yet to be explored.

METHODS

Clinical Study

We excluded from the analysis participants with missing epidemiological data and individuals who completed the survey <28 days after their infection date as for time-restrain it was impossible to determine if they would develop long COVID. No exclusion was made based on the participants' working role or hospitalization status.

All the analyzed individuals were vaccinated with 3 doses of BNT162b2 vaccine received in the same periods: first and second doses between January and February 2021 and the third dose in November–December 2021.

The observational period consisted of wave 1 (wild-type variant), ranging from the beginning of the pandemic till 30 September 2020; wave 2 (Alpha variant), ranging from 1 October 2020 to 31 July 2021; and wave 3 (Delta and Omicron variants), ranging from 1 August 2021 to April 2022.

Self-reported SARS-CoV-2 positivity duration was categorized into 4 groups: ≤10 days, 11–14 days, 15–21 days, and >21 days.

Statistical Analysis

All continuous variables were tested for normality distribution with the Shapiro-Wilk test.

Univariate statistical analyses were performed with *t* test (2-sided) or Mann–Whitney test (2-sided) according to the feature's distribution (normal and nonnormal, respectively). Categorical variables were tested using χ^2 test. A multivariate logistic regression model was used to identify variables that could correlate with the long COVID status, including self-reported positivity duration. To check our findings, we also performed a sensitivity analysis using a similar logistic regression model on the subset of individuals with known exact positivity duration (n = 479). Statistical significance was set at $P < .05$. Analyses were done using Python, version 3.8.3.

RESULTS AND DISCUSSION

In this observational study, approved by the Institutional Review Board of Humanitas Research Hospital, we recruited 4354 individuals working in Humanitas healthcare facilities

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from March 2020 to April 2022 [10]. All participants provided written informed consent, and at the end of the study (February–April 2022) they completed a survey including demographics, comorbidities, vaccination status, and questions about their SARS-CoV-2 history (date of infection, positivity duration, and SARS-CoV-2–related symptoms at the time of infection and their duration). We defined long COVID as at least 1 symptom lasting for >4 weeks following the first SARS-CoV-2 infection. Of 3883 participants with a complete survey, we analyzed 1293 healthcare workers previously infected with SARS-CoV-2, of whom 441 (34.1% [95% confidence interval {CI}: 31.5%–36.8%]) had long COVID. All of the analyzed individuals received 3 doses of BNT162b2 vaccine. We considered only the first COVID-19 infection during the observational period consisting of wave 1 (wild-type variant), wave 2 (Alpha variant), and wave 3 (Delta and Omicron variants). Univariate analysis revealed significant associations between long COVID and factors such as female sex ($P = .01$), older age ($P < .001$), high body mass index (BMI) ($P = .01$), the presence of allergies ($P = .001$), COVID-19 wave ($P < .001$), number of vaccine doses received prior to infection ($P < .001$), higher number of comorbidities ($P < .001$), and self-reported longer positivity duration ($P < .001$) (Supplementary Table 1). In a multivariate logistic regression model that controlled for multiple factors (Table 1), with a reference group of males with no allergy, infected during wave 1, unvaccinated, and with a positivity duration of ≤10 days, we found that vaccination with 3 doses and infection in wave 3 (odds ratio [OR], 0.42 [95% CI: .29–.61]; $P < .001$) correlated with a lower probability of long COVID. By contrast, a higher probability of long COVID was associated with the self-reported positivity duration (11–14 days: OR, 2.30 [95% CI: 1.53–3.46], $P < .001$; 15–21 days: OR, 4.10 [95% CI: 2.84–5.91], $P < .001$; >21 days: OR, 5.39 [95% CI: 3.74–7.77]; $P < .001$), female sex (OR, 1.78 [95% CI: 1.30–2.44]; $P < .001$), high BMI (OR, 1.17 [95% CI: 1.02–1.34]; $P = .02$), and the presence of allergies (OR, 1.51 [95% CI: 1.16–1.96]; $P = .002$). Interestingly, the probability of developing long COVID increased as the duration of the infection increased. Indeed, only 14.5% of individuals with a positivity duration of ≤10 days developed long COVID, but this percentage reached 42.5% for individuals infected for 15–21 days and 56.2% for those positive for >21 days (Supplementary Table 1). To assess the reliability of the self-reported positivity duration, we conducted a sensitivity analysis that included a subcohort of 479 healthcare workers with a known record of positivity duration provided by the occupational medicine of Humanitas hospital (using the exact dates of the initial positive and subsequent negative polymerase chain reaction [PCR] test for SARS-CoV-2). Confirming the analysis on the large cohort, we found a positive correlation between long COVID and the number of days of COVID-19 positivity with an OR of 1.47 (95% CI: 1.17–1.85; $P = .001$), after adjusting for the same confounders mentioned above (Supplementary Table 2). On the contrary, vaccination with 3 doses and infection in wave 3 were associated with a lower probability of long COVID (OR, 0.32 [95% CI: .13–.78]; $P = .01$). In addition, female sex (OR, 1.73 [95% CI: 1.02–2.95]; $P = .04$) and older age (OR, 1.28 [95% CI: 1.02–1.6]; $P = .03$), but not BMI, were associated with a higher probability of long COVID.

Table 1. Multivariable Logistic Regression Analysis of the Association of Long COVID (N = 1293) With Patient Characteristics

Characteristic	OR (95% CI)	*P* Value
Female sex	1.78 (1.30–2.44)	**<.001**
Age[a]	1.09 (.95–1.25)	.24
BMI[a]	1.17 (1.02–1.34)	**.02**
No. of comorbidities[b]	1.17 (.97–1.40)	.10
Allergies	1.51 (1.16–1.96)	**.002**
COVID-19 wave and No. of vaccine doses[c]		
Wave 2 and no doses	0.77 (.55–1.07)	.12
Wave 2 and 1 dose	0.70 (.24–1.99)	.50
Wave 2 and 2 doses	0.62 (.28–1.37)	.24
Wave 3 and 2 doses	0.55 (.27–1.12)	.10
Wave 3 and 3 doses	0.42 (.29–.61)	**<.001**
Positivity duration		
11–14 d	2.30 (1.53–3.46)	**<.001**
15–21 d	4.10 (2.84–5.91)	**<.001**
>21 d	5.39 (3.74–7.77)	**<.001**

Reference model: males with no allergies, infected in COVID-19 wave 1, unvaccinated, and with a positivity duration of ≤10 days. Significant characteristics are highlighted in bold.

Abbreviations: BMI, body mass index; CI, confidence interval; COVID-19, coronavirus disease 2019; OR, odds ratio.

[a]Age and BMI have been standardized: mean, 0 (standard deviation [SD], 1). Age: SD, 12.1 years; BMI: SD, 4.1.

[b]No. of comorbidities is a discrete variable ranging from 0 to 4, where 4 represents ≥4 different comorbidities. Individuals with ≥4 comorbidities were classified as value 4.

[c]The number of vaccine doses received prior to infection were only considered if at least 14 days had passed between the vaccine dose and the infection date. Fourteen is a number of days sufficient for the immune system to respond to the vaccination dose.

One point of strength of this study is the large population analyzed and the subcohort with confirmed positivity by the occupational medicine records. We showed that the higher the SARS-CoV-2 positivity duration, the higher the chances of long COVID development. Indeed, as the number of days of infection increased, the likelihood of contracting long COVID increased. This suggests that long COVID is related to the persistence of viral infection, which likely chronicizes the inflammatory response and prolongs symptom duration. Moreover, we confirmed our previous work that COVID-19 vaccination is associated with protection [10]; by combining COVID-19 waves and BNT162b2 vaccine doses, we observed that 3 vaccine doses and infection in wave 3 were associated with a lower probability of long COVID, suggesting that vaccination by reducing the duration of infection impacts long COVID establishment. Finally, in agreement with the literature and our previous work, female sex and preexisting allergies were associated with a higher probability of long COVID

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[5, 10]. Our study has some limitations: SARS-CoV-2 positivity duration and COVID-19–related symptoms and their duration were self-reported, which may introduce bias. However, our sensitivity analysis performed on 479 individuals with a known record of the exact positivity duration confirmed the analysis on the larger cohort. In summary, this observational study conducted among healthcare workers reveals that the likelihood of developing long COVID in infected individuals rises with the increased duration of SARS-CoV-2 positivity, and 3 doses of BNT162b2 vaccine are protective even during the Omicron wave.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. C. P.: data curation, project administration, writing—original draft. R. S.: data curation, formal analysis, methodology. R. L. and M. M.: formal analysis, methodology. E. A.: data collection, project administration. R. B.: supervision, methodology. A. M.: conceptualization, supervision. M. R.: conceptualization, supervision, funding acquisition, writing—original draft.

Data availability. Patient informed consent does not allow for the deposition of clinical data in public access repositories. Interested researchers should contact biblioteca@humanitas.it to inquire about access; requests for noncommercial academic use will be considered and require ethics review.

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Potential conflicts of interest. M. R. reports payment or honoraria for speaking engagements from Fondazione Internazionale Menarini. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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