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Clinical Characteristics and Outcomes of Patients With SARS-CoV-2 Reinfection

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Abstract

Objective: To examine the clinical characteristics, risk of hospitalization, and mortality of patients diagnosed with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reinfection.

Patients and Methods: We retrospectively reviewed all patients with SARS-CoV-2 reinfection at all Mayo Clinic sites between May 23, 2020, and June 30, 2021 (the period before the emergence of the Delta variant in the United States). The reinfection was defined as a positive SARS-CoV-2 test more than or equal to 90 days after initial infection or 45-89 days after with symptomatic second episode. Vaccination status was classified as fully vaccinated, first dose, and unvaccinated. Comparative analysis of baseline characteristics and comorbidities was performed by hospitalization and vaccination status. The survival analysis of the hospitalized patients was performed using Cox proportional hazard regression.

Results: Among the 554 patients reinfected with SARS-CoV-2, 59 (10.6%) were pediatric, and 495 (89.4%) were adults. The median age was 13.9 years (interquartile range, 8.5-16.5 years) for the pediatric and 50.2 years (interquartile range, 28.4-65.6 years) for the adult population. Among the adult patients, the majority were unvaccinated (83.4%, n=413), and the duration to reinfection from initial infection was the longest in the fully vaccinated group ($P<.001$). Forty-two (75%) out of 56 patients were seropositive within 7 days of reinfection. In hospitalized adult patients, Charlson Comorbidity Index was an independent risk factor for mortality (adjusted hazard ratio, 0.35; 95% CI, 0.19-0.51).

Conclusion: In this study, most adult patients with SARS-CoV-2 reinfection were unvaccinated. Furthermore, the duration to reinfection was longest in fully vaccinated individuals. Seropositivity was common among adult patients.

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Coronavirus disease 2019 (COVID-19) continues to be a threat, totaling over 260 million infections since declared a pandemic by the World Health Organization on March 11, 2020.[1] Since then, our understanding of diagnosing and treating active infection has grown exponentially. Since the rollout of vaccination, critical illness from COVID-19 is rare in those who are vaccinated but continues to be a danger in the unvaccinated population. The natural history of the disease remains poorly understood, and newer variants posing a threat to the population are even less understood.[2,3]

During the initial phases of the pandemic, it was thought that natural immunity from a previous infection would protect against reinfection.[4] Despite the addition of live attenuated vaccines, we have learned that reinfection is still possible, primarily driven by mutated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) strains. During the current study period, there were 3 main SARS-CoV-2 variants that are associated with increased transmissibility and virulence.[5,6] These variants were mainly N501Y.V1 (Alpha), 501Y.V2 (Beta), and P.1 (Gamma).[7,8] Alpha and Gamma variants carry clinically significant sequence variations in the spike protein, whereas the Beta variant has an escape sequence variation thought to neutralize antibodies produced by the body against the

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SARS-CoV-2 virus.[8] The emergence of new variants poses essential questions regarding reinfection, active and passive immunity against them, the patient population at risk, and the severity of reinfection.[4]

The risk of reinfection after a prior COVID-19 episode in the vaccinated and unvaccinated population is not well established, and it is challenging to differentiate reinfection from persistent viral shedding. Previous studies have found that there can be prolonged viral shedding of up to 82 days leading to a persistent initial infection with waxing and waning symptoms as well as persistent reverse transcriptase-polymerase chain reaction positivity.[2,9,10] Reinfection may occur as early as 2 weeks to more than 8 months after the initial infection because of waning antibodies or escape sequence variation of the virus.[2] Therefore, it is challenging to determine if a positive reverse transcriptase-polymerase chain reaction represents an ongoing shedding from a previous infection or a true reinfection. Genomic evidence is not always feasible in resource-constrained settings, and it is imperative to understand who is at risk for reinfection and its implications in both vaccinated and unvaccinated individuals. This study aims to detail the clinical characteristics of patients diagnosed with SARS-CoV-2 reinfection due to strains before the emergence of the Delta variant in the United States and to examine the risk of hospitalization and mortality in both vaccinated and unvaccinated individuals.

PATIENTS AND METHODS

Study Design and Patient Population

We performed a retrospective cohort study of patients with SARS-CoV-2 reinfection at all Mayo Clinic sites between May 23, 2020, and June 30, 2021. Adult (≥18 years) and pediatric (<18 years) patients were analyzed separately. Patients were identified using an electronic health record (EHR) built-in registry that flagged patient charts with active COVID-19. Patients who had an active infection on more than one occasion at least 45 days apart were identified. Three infectious disease clinicians (P.S., J.C.O., and I.Y.C.) reviewed the charts and determined the symptom status, date of symptom onset, and clinical significance of the repeat positive SARS-CoV-2 test. Only the patients who authorized research were included. The Mayo Clinic Institutional Review Board reviewed and exempted this study.

Definitions

The initial COVID-19 episode was defined as the first positive SARS-CoV-2 test. COVID-19 reinfection investigative criteria were adapted from the Centers for Disease Control and Prevention.[11] We defined reinfection as the detection of SARS-CoV-2 greater than or equal to 90 days after the initial infection or detection of SARS-CoV-2; 45-89 days after the initial infection only in the presence of a symptomatic second episode. The date of the repeat positive SARS-CoV-2 test was accepted as the reinfection date.

We have classified COVID-19 vaccination status as fully vaccinated, first dose, and unvaccinated. Patients were considered fully vaccinated 2 weeks after they had completed the 2-dose mRNA COVID-19 live attenuated vaccine series (BNT162b2 [Pfizer-BioNTech], mRNA-1273 [Moderna]), or a single-dose viral vector live attenuated vaccine (Ad26.COV2.S [Janssen]).[12] The first dose group included the patients who received only the first dose of the 2-dose live attenuated vaccine series, and the unvaccinated group included patients who did not receive any of the available COVID-19 live attenuated vaccines at least 2 weeks before the reinfection date. Immunocompromised status was considered as one of the following: human immunodeficiency virus infection, receipt of chemotherapy, or other immunosuppressive medications.

Data Collection

We reviewed and extracted the demographic characteristics, clinical, and laboratory data from the EHR built-in registry. Clinical variables included comorbidities, COVID-19 severity risk scores, vaccination, and hospitalization status. For classification and standardization of comorbidities, we used Charlson Comorbidity Index (CCI) scores,[13] which were extracted from the EHR system and Mayo Clinic Unified Data Platform.[14] Body mass index (BMI; calculated as the weight in kilograms divided by the height in meters

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squared) percentile for the pediatric population was generated using automated medical calculators. In previous studies, the median seroconversion time was approximately 10-15 days from illness onset.[15-17] Therefore, we took the period from 1 week after the initial positive test date to 1 week after the reinfection date to capture the COVID-19 serology results. Serology status was deemed positive if a patient had positive results for SARS-CoV-2 IgG, anti-nucleocapsid, or anti-spike antibodies during the predefined period. We also reported the serology status for each antibody within 7 days before and after and on the day of COVID-19 reinfection.

Hospitalization events within the 1 month after the reinfection were determined by manual chart review and automated extraction from EHR. To capture the community-acquired COVID-19 cases, patients who had positive retest on admission day or the next day were included in the hospitalized group. Medical records, autopsy, and postmortem documents were reviewed to identify the cause of death. Death was deemed attributable if COVID-19 is indicated as the cause of death or contributing factor on autopsy or expiration notes by medical examiners. It directly caused or resulted in events leading to the demise within 100 days.

Statistical Analyses

We reported descriptive statistics using frequencies and proportions for categorical variables and medians and interquartile range (IQR) for continuous variables. Kruskal–Wallis rank sum test, Wilcoxon–Mann–Whitney test, Pearson chi-square test, Fisher exact test, log-rank test, and Cox proportional hazard regression were used to compute P values whenever appropriate. A $P<.05$ was accepted for statistical significance. The follow-up period for survival analysis was determined as 100 days after reinfection. Descriptive, comparative statistics and survival analysis were performed using Python 3 (NumPy [version 1.20.1], pandas [version 1.2.4], lifelines [version 0.26.3]), and IBM SPSS Statistics for Windows (version 27.0. Armonk, NY: IBM Corp.). Figures were generated using seaborn (version 0.11.1) and matplotlib (version 3.3.4) packages in Python 3 environment.[18,19]

RESULTS

The baseline characteristics of the patient population are summarized in Table 1. We identified a total of 554 patients who met the criteria for COVID-19 reinfection during the study period; 59 (10.6%) were pediatric and 495 (89.4%) were adults. Majority were from Minnesota (46.8%, n=259) followed by Wisconsin (33.9%, n=188), Arizona (8.8%, n=49), Florida (5.8%, n=32), and other states (4.7%, n=26; Figure 1).

Pediatric Population

In this cohort, there were a total of 59 pediatric patients with COVID-19 reinfection. The median age was 13.9 years (IQR, 8.5-16.5 years) and ranged from 8 months to 17.9 years. There were 3 (5.1%) patients aged below 1 year; 6 patients (10.2%) aged between 1 and 2 years; 4 (6.8%) aged between 3 and 5 years; 11 (18.6%) aged between 6 and 11 years; and 35 (59.3%) aged between 12 and 17 years. The majority were female (54.2%, n=32) and non-Hispanic White (71.2%, n=42). We calculated the BMI percentile for pediatric patients older than 2 years on the basis of their age and sex. Of patients with available BMI, 1 (2.2%) patient was underweight (<5th percentile); 24 (52.2%) were normal-weight (5th-84th percentile); 3 (6.5%) were overweight (85th-94th percentile); 18 (39.1%) patients were obese (≥95th percentile). None of the patients were vaccinated for COVID-19 or had any comorbidities from CCI scoring. One patient had heart and renal transplant; therefore, was immunosuppressed with concomitant medications. The median duration to reinfection was 114 days (IQR, 77-128 days). A total of 3 patients were hospitalized within 1 month after reinfection, and there were no deaths. The following analysis did not include pediatric patients because of the low rate of comorbidities and differences in outcome.

Baseline Characteristics

The median age of the 495 adult patients was 50.2 years (IQR, 28.4-65.6 years). Of 495 patients, 267 (53.9%) were women and 405 (81.8%) were White. Two hundred and eight

TABLE 1. Baseline Characteristics of Patients With COVID-19 Reinfection by Hospitalization Status (May 2020 to June 2021)

Characteristic	Adult (n=495)	Pediatric (n=59)
Age (y), median (IQR)	50.2 (28.4-65.6)	13.9 (8.5-16.5)
Women, n (%)	267 (53.9)	32 (54.2)
Race/ethnicity, n (%)		
Hispanic (all races)	38 (7.7)	10 (16.9)
White, non-Hispanic	405 (81.8)	42 (71.2)
Black or African American, non-Hispanic	25 (5.1)	2 (3.4)
Asian, non-Hispanic	9 (1.8)	2 (3.4)
All others/missing	18 (3.6)	3 (5.1)
BMI (kg/m^2), n (%)		
<15	0 (—)	1 (1.7)
15.0-18.4	8 (1.6)	14 (23.7)
18.5-24.9	106 (21.4)	24 (40.7)
25.0-29.9	126 (25.5)	4 (6.8)
≥30	208 (42.0)	9 (15.3)
Missing	47 (9.5)	7 (11.9)
Vaccination status, n (%)		
Unvaccinated	413 (83.4)	59 (100.0)
Received only first dose	30 (6.1)	—
Fully vaccinated	52 (10.5)	—
Immunocompromised, n (%)	54 (10.9)	1 (1.7)
Congenital heart disease, no. (%)	4 (0.8)	1 (1.7)
Time to reinfection from initial infection, median (IQR), d	114 (95-154)	114 (77-128)

BMI, body mass index; COVID-19, coronavirus disease 2019; IQR, interquartile range.

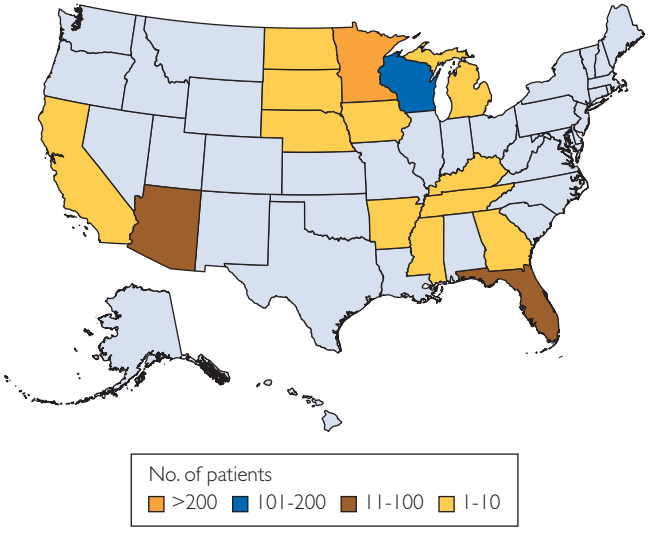

FIGURE 1. Geographic distribution of the patient population with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reinfection, Mayo Clinic, May 2020 to June 2021.

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TABLE 2. Baseline Comorbidities of Adult Patients With COVID-19 Reinfection by Hospitalization Status (May 2020-June 2021)[a]

	Hospitalized (n=153)	Not hospitalized (n=342)	*P* value
CCI score, median (IQR)	4 (1-6)	1 (0-3)	**<.001**[b]
CCI score, n (%)			**<.001**[c]
<2	40 (26.1)	204 (59.6)	
2–4	41 (26.8)	85 (24.9)	
≥5	72 (47.1)	53 (15.5)	
CCI DM without complications, n (%)			**<.001**[c]
No	114 (74.5)	308 (90.1)	
Yes	39 (25.5)	34 (9.9)	
CCI DM with complications, n (%)			**.001**[c]
No	136 (88.9)	330 (96.5)	
Yes	17 (11.1)	12 (3.5)	
CCI CHF, n (%)			**<.001**[c]
No	120 (78.4)	321 (93.9)	
Yes	33 (21.6)	21 (6.1)	
CCI PVD, n (%)			**<.001**[c]
No	124 (81.0)	326 (95.3)	
Yes	29 (19.0)	16 (4.7)	
CCI chronic obstructive pulmonary disease, n (%)			**.002**[c]
No	113 (73.9)	293 (85.7)	
Yes	40 (26.1)	49 (14.3)	
CCI malignancy, n (%)			**<.001**[c]
No	113 (73.9)	304 (88.9)	
Yes	40 (26.1)	38 (11.1)	
CCI mild liver disease, n (%)			.226[c]
No	144 (94.1)	330 (96.5)	
Yes	9 (5.9)	12 (3.5)	
CCI renal, n (%)			**.001**[c]
No	134 (87.6)	327 (95.6)	
Yes	19 (12.4)	15 (3.0)	
CCI CVA or TIA, n (%)			**<.001**[c]
No	140 (91.5)	337 (98.5)	
Yes	13 (8.5)	5 (1.5)	

[a]CCI, Charlson Comorbidity Index; CHF, congestive heart failure; COVID-19, coronavirus disease 2019; CVA, cerebrovascular accident; DM, diabetes mellitus; PVD, peripheral vascular disease; TIA, transient ischemic attack.
[b]Mann–Whitney U test,
[c]Chi-square test were used to generate *P* values.

(42%) patients were obese (BMI ≥30 kg/m^2) and 8 (1.6%) were underweight (BMI <18.4 kg/m^2). The time interval to reinfection from initial infection ranged from 45 to 372 days with a median of 114 days (IQR, 95-154 days). Four hundred and thirteen patients were unvaccinated. Thirty patients received only the first dose of the 2-dose series, and 52 were fully vaccinated for COVID-19. The age of patients with COVID-19 reinfection significantly differed on the basis of vaccination status (*P*<.001).

Hospitalization

A summary of the comorbidities and severe SARS-CoV-2 infection risk factors of adult patients is reported in Table 2. Of 495 adult patients, 153 (30.9%) were hospitalized within the first month of reinfection. Overall, hospitalized patients were older (*P*<.001; Figure 2A) and had significantly higher CCI scores (*P*<.001) compared with patients not needing hospitalization. In subgroup analysis, the difference in CCI score was most notable in unvaccinated patients (Figure 2B).

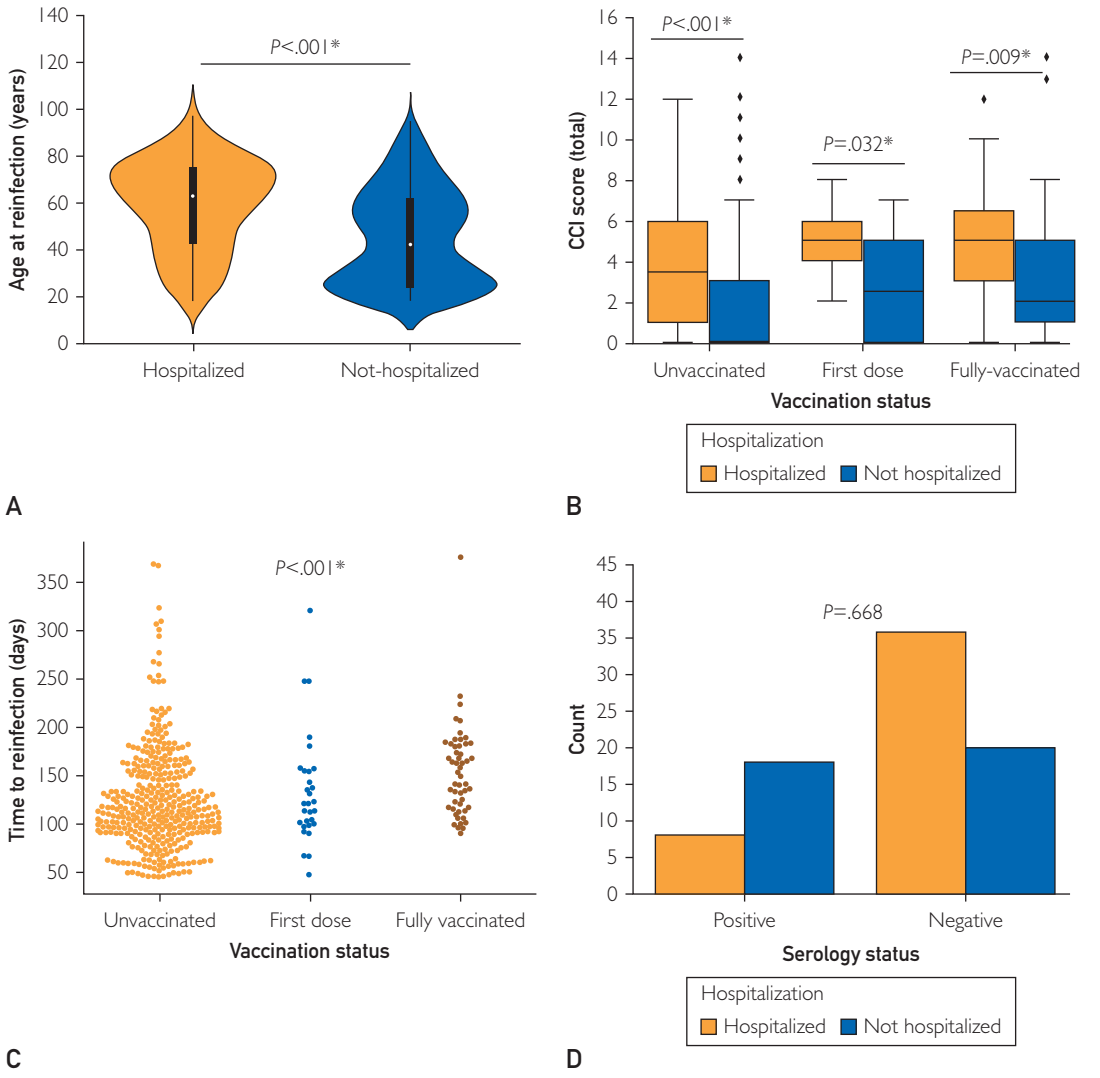

FIGURE 2. Overview of the clinical characteristics of adult study population. A, Comparison of age distribution between hospitalized vs not hospitalized patients using swarm plot. Hospitalization status is given on x-axis. B, Comparison of Charlson Comorbidity Index (CCI) scores between hospitalized and not hospitalized patients in fully vaccinated, first dose, and unvaccinated groups. Overall, hospitalized patients had a higher CCI scores within all groups. C, Swarm plot of time elapsed to reinfection in days by vaccination status. Fully vaccinated patients took longer to develop reinfection in group comparison. No statistically significant differences in (D) hospitalization status between seropositive and seronegative patients.

The common comorbidities in hospitalized patients included hypertension (54.9%, n=84), chronic obstructive pulmonary disease (26.1%, n=40), diabetes mellitus (26.1%, n=40), malignancies (26.1%, n=40), and congestive heart failure (21.6%, n=33). In terms of the risk factors for severe COVID-19, hospitalized patients had an overall higher number of risk scores. Notably, hospitalized patients had higher rates of hypertension, coronary artery disease, and end-stage kidney disease. Time to reinfection did not significantly differ by hospitalization status (*P*=.129).

Vaccination and Serology

The clinical characteristics of the adult patients by vaccination status are summarized in Table 3. Overall, fully vaccinated patients

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TABLE 3. Baseline Comorbidities and Severe COVID-19 Risk Factors of Adult Patients With COVID-19 Reinfection by Vaccination Status (May 2020 to June 2021)[a]

	Unvaccinated (n=413)	First dose (n=30)	Fully vaccinated (n=52)	*P* value
CCI score, median (IQR)	1 (0-4)	3.5 (1.5-6)	3 (2-6)	<.001[b]
CCI score, n (%)				<.001[c]
<2	225 (54.5)	7 (23.3)	12 (23.1)	
2-4	98 (23.7)	11 (36.7)	17 (32.7)	
≥6	90 (23.7)	12 (40.0)	23 (44.2)	
CCI DM without complications, n (%)				.385[c]
No	355 (86.0)	26 (86.7)	41 (78.8)	
Yes	58 (14.0)	4 (13.3)	11 (21.2)	
CCI CHF, n (%)				<.001[c]
No	379 (91.8)	24 (80.0)	38 (73.1)	
Yes	34 (8.2)	6 (20.0)	14 (26.9)	
CCI PVD, n (%)				.002[d]
No	384 (93.0)	25 (83.3)	41 (78.8)	
Yes	29 (7.0)	5 (16.7)	11 (21.2)	
CCI chronic obstructive pulmonary disease, n (%)				.187[c]
No	344 (84.7)	24 (80.0)	38 (73.1)	
Yes	69 (16.7)	6 (20.0)	14 (26.9)	
CCI malignancy, n (%)				.731[c]
No	349 (84.5)	26 (86.7)	42 (80.8)	
Yes	64 (15.5)	4 (13.3)	10 (19.2)	
CCI mild liver disease, n (%)				.222[d]
No	396 (95.9)	27 (90.0)	51 (98.1)	
Yes	17 (4.1)	3 (10.0)	1 (1.9)	
CCI renal, n (%)				.619[d]
No	386 (93.5)	28 (93.3)	47 (90.4)	
Yes	27 (6.5)	2 (6.7)	5 (9.6)	
CCI CVA or TIA, n (%)				.600[d]
No	399 (96.6)	29 (96.7)	49 (94.2)	
Yes	14 (3.4)	1 (3.3)	3 (5.8)	
Coronary artery disease, n (%)				.026[b]
No	371 (89.8)	24 (80.0)	41 (78.8)	
Yes	42 (10.2)	6 (20.0)	11 (21.2)	
End-stage liver disease, n (%)				.127[d]
No	392 (94.9)	26 (86.7)	48 (92.3)	
Yes	21 (5.1)	4 (13.3)	4 (7.7)	
End-stage kidney disease, n (%)				.757[d]
No	393 (95.2)	28 (93.3)	49 (94.2)	
Yes	20 (4.8)	2 (6.7)	3 (5.8)	
Hypertension, n (%)				<.001[c]
No	279 (67.6)	21 (70.0)	21 (40.4)	
Yes	134 (32.4)	9 (30.0)	31 (59.6)	
Immunocompromised, n (%)				.448[c]
No	371 (89.8)	25 (83.3)	45 (86.5)	
Yes	42 (10.2)	5 (16.7)	7 (13.5)	
Nursing home resident, n (%)				.166[d]
No	409 (99.0)	30 (100.0)	50 (96.2)	
Yes	4 (4.0)	0	2 (3.8)	

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TABLE 3. Continued

	Unvaccinated (n=413)	First dose (n=30)	Fully vaccinated (n=52)	*P* value
Pregnant, n (%)				1.000[d]
No	409 (99.0)	30 (100.0)	51 (98.1)	
Yes	4 (4.0)	0	1 (1.9)	

[a]CCI, Charlson Comorbidity Index; CHF, congestive heart failure; COVID-19, coronavirus disease 2019; CVA, cerebrovascular accident; DM, diabetes mellitus; PVD, peripheral vascular disease; TIA, transient ischemic attack.
[b]Kruskal–Wallis test,
[c]chi-square test, and
[d]Fischer exact test were used to generate *P* values.

were older than other groups (*P*<.001). Notably, overall CCI and COVID-19 risk scores were higher in patients in the first dose and fully vaccinated groups. Correspondingly, these patients had a higher rate of comorbidities, including congestive heart failure, peripheral vascular disease, coronary artery disease, and hypertension. Fully vaccinated patients had a higher rate of hospitalization compared with unvaccinated ones (26 [7.9%] vs 26 [19.4%], *P*<.001). Time to reinfection differed by vaccination status and was longest in the fully vaccinated group (*P*<.001; Figure 2C). We had 85 patients with COVID-19 serology available with 59 positives and 26 negatives during the predefined period. A total of 25 patients tested for an anti-spike antibody with 24 positives and 1 negative; 62 patients had anti-nucleocapsid antibody tested with 39 positives and 23 negatives; and 17 patients were tested for SARS-CoV-2 IgG with 7 positives and 10 negatives. Serology results between episodes did not differ significantly by hospitalization (*P*=.67), immunosuppression (*P*=1.00), or vaccination status (*P*=.40; Figure 2D). There was no statistically significant difference in the time interval to reinfection by serology status. There were 56 patients who had serology within 7 days of reinfection; 42 (75%) were positive and 14 were negative (25%). Of 42 positive patients, 16 were tested on the reinfection date.

Survival

A summary of the survival analysis for hospitalized patients is presented in Table 4 and Figure 3. In this cohort, a total of 17 patients died during a 100-day follow-up period after reinfection. The median duration from reinfection to demise was 35.5 days (IQR, 12.7-64.5 days). The majority were above 65 years old (88%, n=15), and the median age of patients who died was 75.2 years (IQR, 70-79 years). Among 11 patients with the cause of death identified, 7 deaths were attributable to

TABLE 4. Cox Proportional Hazard Regression for Survival Analysis of Hospitalized Patients

Covariates	Univariate (unadjusted)		Multivariate (adjusted)	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age, ≥65 y	1.62 (0.36 to 2.89)	**.01**	0.53 (−0.84 to 1.90)	.45
Men	0.75 (−0.32 to 1.83)	.17	0.52 (−0.65 to 1.70)	.38
BMI ≥35 kg/m^2	−1.56 (−3.58 to 0.47)	.13	−1.39 (−3.43 to 0.65)	.18
Fully vaccinated	1.02 (−0.05 to 2.10)	.06	0.65 (−0.53 to 1.84)	.28
CCI score, median	0.35 (0.19 to 0.51)	**<.005**	0.36 (0.16 to 0.55)	**<.005**
Immunosuppressed	−0.10 (−1.59 to 1.38)	.89	−0.57 (−2.23 to 1.10)	.50
Time to reinfection ≥90 d	0.42 (−1.61 to 2.45)	.69	0.16 (−1.96 to 2.27)	.88

BMI, body mass index; CCI, Charlson Comorbidity Index; HR, hazard ratio.

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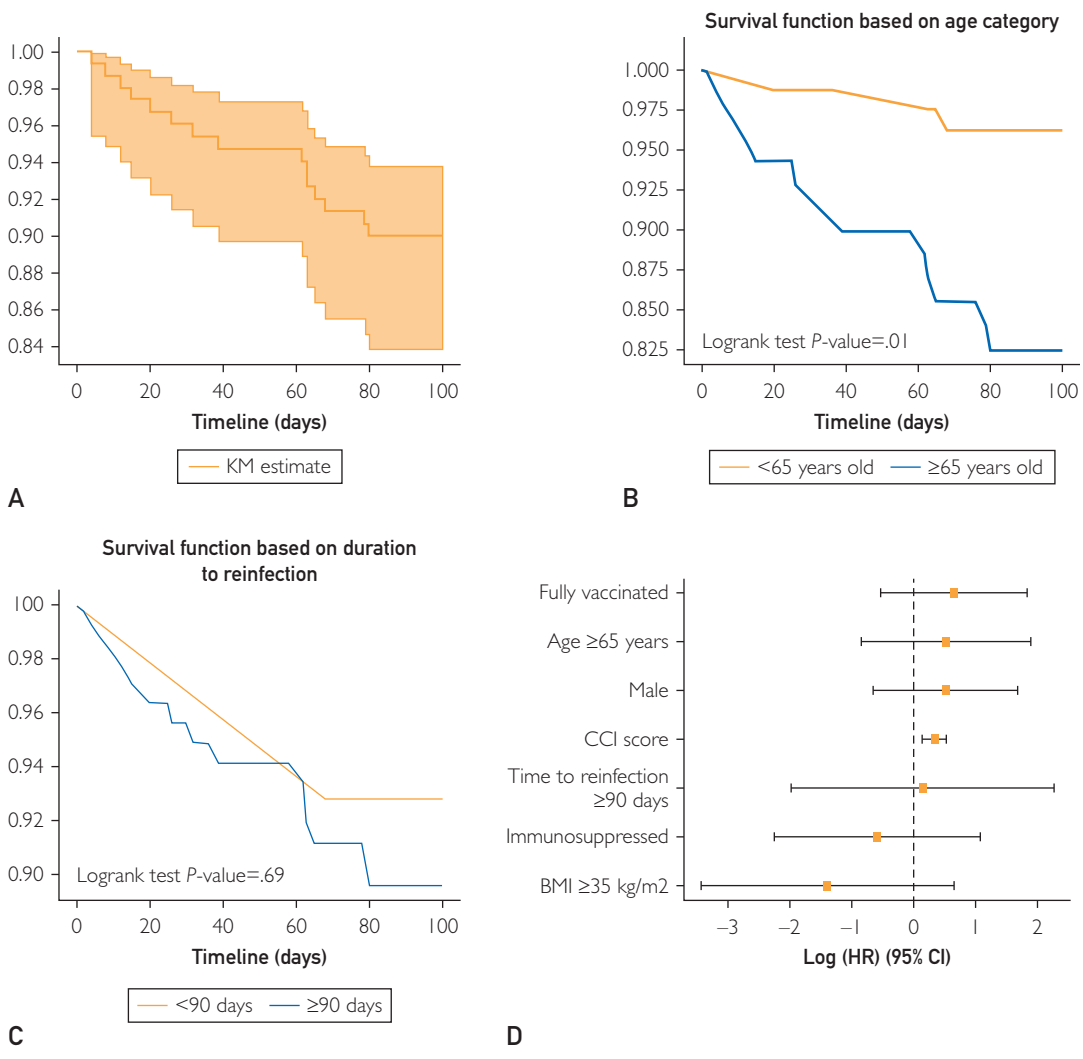

FIGURE 3. Survival analysis of adult hospitalized patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reinfection. A, Kaplan–Meier (KM) curve of adult study population. x-axis represents days elapsed. KM curves and log-rank test results on the basis of (B) age category and (C) time elapsed from initial infection to reinfection (d). D, Multivariate Cox proportional hazard regression model for survival analysis of adult hospitalized patients. CCI, Comparison of Carlson comorbidity index; BMI, body mass index; HR, hazard ratio.

COVID-19. We have performed survival analysis for hospitalized patients and looked at the effect of age, sex, BMI, CCI score, time interval to reinfection, immunosuppression, and vaccination status. In univariate analysis, men (HR, 0.75; 95% CI, −0.32 to 1.83), BMI ≥35 kg/m^2 (HR, −1.56; 95% CI, −3.58 to 0.47), immunosuppression (HR, −0.10; 95% CI, −1.59 to 1.38), fully vaccinated status (HR, 1.02; 95% CI, −0.05 to 2.10), and time interval to reinfection greater than or equal to 90 days (HR, 0.42; 95% CI, −1.61 to 1.38) were not significant variables predicting survival, whereas CCI score (HR, 0.35; 95% CI, 0.19-0.51) and age greater than or equal to 65 years (HR, 1.62; 95% CI, 0.36-2.89) were significant covariates. The only significant covariate predicting survival in multivariate analysis was a lower CCI score (HR, 0.35; 95% CI, 0.16-0.54).

DISCUSSION

The current study aimed to report the contemporary experience of patients with SARS-CoV-2 reinfection over a relatively long study period that captures the pre-Delta period. The rising number of studies about laboratory-confirmed SARS-CoV-2 reinfection has raised multiple questions.[20-24] First, the exact incidence of SARS-CoV-2 reinfection is unknown, and reinfection is still considered a rare phenomenon. In a meta-analysis, the incidence of recurrent SARS-CoV-2 positivity after disease recovery was as high as 14.8%,[25] whereas the reinfection rates were around 1%-5% in other studies.[26-28] Longer follow-up duration over the course of the pandemic and the emergence of phylogenetically distinct variants warrants a focus on this entity. Second, the data on the demographic spectrum, clinical characteristics, and the outcomes of these patients are limited, which makes the identification of patients at risk of severe reinfection challenging.[21] Third, previous studies using genomic analysis have found that despite herd immunity, there is a risk of reinfection as the virus continues to circulate among populations.[20] Correspondingly, the current evidence regarding the duration and level of protection with primary infection and vaccination from reinfection is limited.[21] Previous studies suggested that protection from a prior infection was more than 80%.[26,27]

In this study, a total of 554 patients were identified to have COVID-19 reinfection between May 23, 2020, and June 30, 2021. Among 495 adult patients, 153 (30.9%) were hospitalized within a month after reinfection. The hospitalization rate was overall higher than those seen in other studies,[26,29] likely because of differences among study cohorts and definitive criteria of reinfection used between studies. A recent retrospective cohort study reported 1304 patients with reinfection, 4 had severe disease, and none had a critical disease. At reinfection, the odds of severe disease were 0.12 times that of primary infection.[29] In another retrospective study, among 62 patients with identified reinfection, 18 were hospitalized within 30 days of a positive test and 31 were symptomatic.[26]

The median time interval to reinfection was 114 days in adult and pediatric patients in this study and did not differ between age groups. The time interval was longer in fully vaccinated patients than in unvaccinated ones, although it was not associated with survival in univariate and multivariate analysis. A meta-analysis of 123 patients with repeated SARS-COV-2 positivity suggested that patients with shorter positivity intervals (<60 days) had more severe disease courses.[30] In another study, the reinfection risk was the highest just after 90 days from initial infection and decreased afterward, which suggested an increase in protection over time from primary infection.[26] We did not see any differences in the 100-day survival between adult patients with a time interval to reinfection greater than or equal to 90 days vs less than 90 days. These findings could be related to the different outcome parameters applied between studies.

SARS-COV-2 serology has been one of the benchmarks to study the protection from natural infection or vaccination.[21] For example, Akinbami et al[31] looked at the serostatus (spike antibody) of 40 patients with reinfection out of 1572 previously infected health care workers. The reinfection rate was significantly higher in seronegative compared with seropositive patients.[31] We did not see any differences in serology status by the time interval to reinfection, hospitalization, vaccination, and immunosuppression status in adults. Similar to a recent study, we have seen seropositivity in patients with reinfection.[32]

In our cohort, the hospitalization rate was higher in fully vaccinated patients compared with unvaccinated ones. However, given that fully vaccinated patients were older and had a significantly higher number of comorbidities, we considered that the comparison was confounded by these factors. Not surprisingly, a higher CCI score was an independent risk factor for mortality. We did not see any significant differences in survival by immunosuppression, fully vaccinated status, male status, and BMI of greater than or equal to 35 kg/m^2.

Because of the descriptive nature of this study, we acknowledge that the timing of antibody tests was at the provider's discern and did not have a standardized protocol. Although previous studies reported stable neutralizing antibody titers at different time

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points after disease recovery, testing times largely varied in this study population between initial and reinfection dates. To mitigate differences, we reported the serology status of patients within 7 days of the reinfection date and on the reinfection date. The definitive identification of reinfection requires viral genomic testing of paired respiratory specimens from initial and subsequent infections.[33] Because of logistic limitations (inability to preserve initial samples, limited laboratory resources, cost issues), this approach is less likely to be pursued in clinical practice.[32,33] Therefore, we adapted investigative criteria of the Centers for Disease Control and Prevention to define the reinfected population.[11] This approach allows us to capture a larger cohort of patients but at the risk of possible overestimation of the reinfected patients as prolonged viral shedding can occur for weeks to months after the initial infection.[7,33] Therefore, prospective studies are needed to identify the exact incidence of reinfection. Additionally, determining more clinically applicable and feasible criteria for reinfection definition might allow the clinicians to identify the individuals with reinfection and enhance our understanding of this entity.

CONCLUSION

We analyzed 554 patients with SARS-CoV-2 reinfection due to strains preceding the emergence of the Delta variant in the United States. About 75% of patients who were tested within 7 days of the reinfection date were seropositive. The duration to reinfection was longest in fully vaccinated individuals. A higher comorbidity score was an independent risk factor for mortality, whereas immunosuppression, vaccination status, and the time interval to reinfection were not significant predictors for survival in hospitalized patients.

POTENTIAL COMPETING INTERESTS

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Abbreviations and Acronyms: **BMI,** body mass index; **CCI,** Charlson Comorbidity Index; **COVID-19,** coronavirus disease 2019; **EHR,** electronic health record; **HR,** hazard ratio; **IQR,** interquartile range; **SARS-CoV-2,** severe acute respiratory syndrome coronavirus 2

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