Reinfection With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in Patients Undergoing Serial Laboratory Testing

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Background. A better understanding of reinfection after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has become one of the healthcare priorities in the current pandemic. We determined the rate of reinfection, associated factors, and mortality during follow-up in a cohort of patients with SARS-CoV-2 infection.

Methods. We analyzed 9119 patients with SARS-CoV-2 infection who received serial tests in total of 62 healthcare facilities in the United States between 1 December 2019 and 13 November 2020. Reinfection was defined by 2 positive tests separated by interval of >90 days and resolution of first infection was confirmed by 2 or more consecutive negative tests. We performed logistic regression analysis to identify demographic and clinical characteristics associated with reinfection.

Results. Reinfection was identified in 0.7% (n = 63, 95% confidence interval [CI]: .5%–.9%) during follow-up of 9119 patients with SARS-CoV-2 infection. The mean period (±standard deviation [SD]) between 2 positive tests was 116 ± 21 days. A logistic regression analysis identified that asthma (odds ratio [OR] 1.9, 95% CI: 1.1–3.2) and nicotine dependence/tobacco use (OR 2.7, 95% CI: 1.6–4.5) were associated with reinfection. There was a significantly lower rate of pneumonia, heart failure, and acute kidney injury observed with reinfection compared with primary infection among the 63 patients with reinfection There were 2 deaths (3.2%) associated with reinfection.

Conclusions. We identified a low rate of reinfection confirmed by laboratory tests in a large cohort of patients with SARS-CoV-2 infection. Although reinfection appeared to be milder than primary infection, there was associated mortality.

Key words. reinfection; coronavirus; SARS-CoV-2; COVID-19; laboratory tests.

By October 2020, 5 cases of reinfection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had been reported from Hong Kong, Belgium, the Netherlands, Ecuador, and the United States [1–5] when over 37 million SARS-CoV-2 infected persons had been reported worldwide [6]. A better understanding of reinfection became one of the priorities for Centers for Disease Control and Prevention to inform public health action [7]. Identification of characteristics and frequency of reinfection was considered crucial by the European Centre for Disease Prevention and Control [8] due to implications for duration of acquired immunity. The results of SARS-CoV-2 Immunity and Reinfection Evaluation (SIREN) [9] were made available in January 2021. Between 18 June and 9 November 2020, 44 reinfections (2 probable, 42 possible) were detected in the baseline positive cohort of 6614 healthcare workers. The study investigators acknowledged that there is paucity of data regarding reinfection limiting our understanding of public health implications. A better understanding of the risk of reinfection is necessary from the public health perspective and may have implications for vaccination strategy.

METHODS

Patients

We analyzed data from the Cerner De-identified Coronavirus Disease 2019 (COVID-19) data set. This is a subset of Cerner Real-World Data extracted from the electronic medical records of healthcare facilities, which have a data use agreement with Cerner Corporation [10, 11]. Patients with a positive laboratory test for SARS-CoV-2 were identified based on Logical Observation Identifiers Names and Codes (LOINC®) 41458-1, 94309-2, 94500–6, 94533–7, 94534–5, and 94646–7. These codes denote detection of SAR-CoV-2 ribonucleic acid in respiratory (nasopharyngeal swabs, bronchoalveolar lavage, sputum) and other specimens or detection of SARS-CoV-2 N gene or RdRp gene in respiratory secretions, all by nucleic acid amplification with probe detection. The Food and Drug Administration has only approved assays for detection of SARS-CoV-2 N gene or RdRp gene in respiratory secretions in the United States.

The methodological aspects of the dataset are available in other publications [12, 13]. The Cerner Real-World Data-COVID-2020 Q3 version of the data included data from 62 contributing Cerner Real-World Data health systems in the United States. The data are based on electronic medical records between 1 December 2019 and 13 November 2020. The data set, as part of the de-identification procedure, does not provide an identifier for the medical institution of a patient's data or its precise location. Our analysis included patients with at least 1 COVID-19 related inpatient or emergency department (ED) encounter who tested positive for COVID-19, had at least 1 medical encounter on record prior to their first COVID-19 related encounter, and who received at least 4 reliable COVID-19 tests that were conclusive.

Reinfection was defined by 2 positive tests separated by interval of > 90 days and resolution of first infection was confirmed by 2 or more consecutive negative tests consistent with definitions used in previous reports [9, 14, 15]. The associated medical diagnoses and outcomes were identified using International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes in the medical records at time of primary infection, and the reinfection. ICD-10-CM codes were used to identify the patients with hypertension (I10, O10.0, O10.9, I16, and I67.4), diabetes mellitus (E08, E09, E10, E11, and E13), atrial fibrillation (I48), hyperlipidemia (E78), stroke (I60, I61, I62.9, I63, I65, I66), heart failure (I50), malignancy (Z85, C80.1), chronic obstructive pulmonary disease (COPD) (J44), asthma (J45), chronic kidney disease (CKD)/end-stage renal disease (ESRD) (N18), nicotine dependence/tobacco use (F17, Z72.0), pneumonia (J12-J18), urinary tract infection (N30.9), acute kidney injury (N17), septic shock (R65.21), hepatic failure (K72, K74.3–K74.6), respiratory failure (J96), cardiac arrest (I46), thrombosis/pulmonary embolism (I26, I74, I75, I82.40–I82.44, I82.49, I82.4Y, I82.4Z), encephalopathy (G93.4), ST-elevated myocardial infarction (STEMI) (I21.0–I21.3), and non-ST elevated myocardial infarction (NSTEMI) (I21.4). Intubation and mechanical ventilation were identified by ICD-10-CM codes 0BJ17EZ and Z9911 or current procedural terminology codes 31500, 94656, and 94657 (for intubation) or 94002 to 94005 (for mechanical ventilation).

Discharge destination was categorized as home or nonroutine discharge (acute rehabilitation, intermediate care, skilled nursing facility, or nursing home) during a SARS-CoV-2 infection related encounter.

Statistical Analysis

A large proportion of patients in the data set were excluded from the analysis due to lack of serial tests performed for detection of SARS-CoV-2. To better understand the selection bias, we compared patients' age, sex, race/ethnicity, cardiovascular risk factors, and medical complications between included and excluded patients.

We provided the rate of reinfection with 95% confidence interval (CI) without continuity correction [16]. We compared patients' age, sex, race/ethnicity, cardiovascular risk factors, medical complications, and discharge status (categorized into nonroutine discharge or expired in medical facility) for patients in strata based on presence or absence of reinfection during follow-up among patients with SARS-CoV-2 infection. We used the χ^2 test for categorical data, and analysis of variance (ANOVA) test for continuous variables. We performed logistic regression analysis including all patients with SARS-CoV-2 infection to identify the associations between various demographic and clinical characteristics and odds of reinfection. Stepwise feature selection was used to select variables. All the hypothesis tests were 2 sided, with $P < .05$ considered statistically significant, and all the analyses were done using R software (version 3.6.1). We also provided estimates for rates of reinfection defined using different cutoff periods for time interval between first and second positive tests (>45 days, >60 days, >75 days, >90 days, and >105 days).

RESULTS

A total of 9119 patients with SARS-CoV-2 infection met our inclusion criteria among 110 754 patients with positive SARS-CoV-2 tests in the data. Compared with patients who were excluded, patients who were included in the analysis were more likely to aged >65 years, African-American or Hispanic, and have higher proportion of those with hypertension, diabetes mellitus, atrial fibrillation, nicotine dependence, hyperlipidemia, prior stroke, COPD, asthma, and chronic kidney disease. Included patients also had a higher proportion of patients with new stroke, heart failure, cardiac arrest, pneumonia, respiratory failure, and acute kidney injury. The proportion of patients who required intubation/mechanical ventilation was higher in included patients.

Reinfection was identified in 0.7% (n = 63, 95% CI: .5%–.9%) of the patients (see Table 1). The mean period (± standard deviation [SD]) between 2 positive tests was 116 ± 21 days. There were no significant differences based on age or sex among patients with and without reinfection. The proportion of patients categorized under other race/ethnicity was higher in those with reinfection. The proportion of patients with nicotine dependence/tobacco use, asthma, and COPD were higher in patients with reinfection. The proportion of patients with nonroutine discharge were similar between reinfection and without reinfection groups. In the logistic regression analysis, patients with asthma (odds ratio [OR] 1.9, 95% CI: 1.1–3.2), and nicotine dependence/tobacco use (OR 2.7, 95% CI: 1.6–4.5) were at higher risk for reinfection. Furthermore, compared with White patients, the patients categorized as other race/ethnicity (OR 2.3, 95% CI: 1.2–4.5) were associated with higher risk for reinfection.

Table 1. Baseline, Clinical Characteristics, and Outcomes of Patients With or Without Reinfection With SARS-CoV-2

Characteristics	Patients With Reinfection no.(%)	Patients Without Reinfection no.(%)	P value
Total	63	9056	…
Demographics			
Age, y			.11
<35	11 (17)	1682 (18.6)	
35–49	15 (24)	1578 (17.4)	
50–65	24 (38)	2737 (30.2)	
>65	13 (21)	3059 (33.8)	
Sex			.66
Men	28 (44)	4257 (47)	
Women	35 (56)	4754 (52.5)	
Race/ethnicity			.03
White, Non-Hispanic	23 (37)	3269 (36.1)	
African American	10 (16)	1599 (17.7)	
Asian or Pacific Islander	0 (0)	161 (1.8)	
Hispanic	16 (25)	3110 (34.3)	
Other	14 (22)	917 (10.1)	
Preexisting medical conditions			
Hypertension	44 (70)	5901 (65.2)	.44
Diabetes mellitus	31 (49)	3932 (43.4)	.36
Atrial fibrillation	13 (21)	1674 (18.5)	.66
Hyperlipidemia	33 (52)	4338 (47.9)	.48
Malignancy	6 (10)	1256 (13.9)	.32
COPD	22 (35)	1659 (18.3)	<.001
Asthma	22 (35)	1647 (18.2)	<.001
CKD ESRD	15 (24)	2458 (27.1)	.55
Nicotine dependence/tobacco use	34 (54)	2325 (25.7)	<.001
Previous cardiac arrest	1 (2)	78 (0.9)	.54
Previous stroke	7 (11)	777 (8.6)	.48
Previous heart failure	17 (27)	1761 (19.4)	.13
Previous STEMI	2 (3)	92 (1.0)	.09
Previous NSTEMI	4 (6)	408 (4.5)	.48
New events			
Pneumonia	21 (33)	4087 (45.1)	.06
Respiratory failure	20 (32)	3313 (36.6)	.43
Urinary tract infection	6 (10)	1238 (13.7)	.34
Acute kidney injury	17 (27)	2299 (25.4)	.78
Septic shock	5 (8)	774 (8.5)	.86
Hepatic failure	4 (6)	397 (4.4)	.45
Stroke	1 (2)	349 (3.9)	.35
Encephalopathy	5 (8)	1356 (15)	.12
Thrombosis/pulmonary embolism	3 (5)	455 (5)	.92
Cardiac arrest	0 (0)	190 (2.1)	.25
STEMI	0 (0)	29 (0.3)	.65
NSTEMI	0 (0)	223 (2.5)	.21
Heart failure	12 (19)	1679 (18.5)	.92
Received intubation/mechanical ventilation	3 (5)	762 (8.4)	.46
Outcome[a]			
Nonroutine discharge	28 (44)	4412 (48.7)	.50
Expired in medical facility	2 (3)	504 (5.6)	.41

Abbreviations: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; NSTEMI, non-ST elevated myocardial infarction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; STEMI, ST-elevated myocardial infarction.
[a]Determined by medical encounter in proximity to fourth laboratory test.

There were 2 deaths (3%) associated with reinfection. There was a significantly lower rate of pneumonia, heart failure, and acute kidney injury observed with reinfection compared with primary infection among the 63 patients with reinfection (see Table 2). There was a trend toward lower rates of respiratory failure and hepatic failure during reinfection. Intubation/

Table 2. Medical Diagnoses in Primary Infection and Reinfection Among Patients With Reinfection

Diagnoses	Diagnosis Rate During First Infection no. (%)	Diagnosis Rate During Second Infection no. (%)	P value
Total	63	63	…
Stroke	0 (0)	1 (2)	.32
Heart failure	10 (16)	3 (5)	.04
Pneumonia	17 (27)	7 (11)	.02
Urinary tract infection	3 (5)	4 (6)	.70
Acute kidney injury	11 (17)	3 (5)	.02
Septic shock	1 (2)	1 (2)	1
Hepatic failure	3 (5)	0 (0)	.08
Respiratory failure	13 (21)	6 (10)	.08
Cardiac arrest	0 (0)	0 (0)	1
Thrombosis/pulmonary embolism	0 (0)	2 (3)	.15
Encephalopathy	1 (2)	1 (2)	1
STEMI	0 (0)	0 (0)	1
NSTEMI	0 (0)	0 (0)	1
Received intubation/mechanical ventilation	2 (3)	0 (0)	.15

Abbreviations: NSTEMI, non-ST elevated myocardial infarction; STEMI, ST-elevated myocardial infarction.

mechanical ventilation was required in 2 (3%) patients during primary infection but in none of the patients during reinfection.

The rates of reinfection ranged from 0.4% to 2.2% using different cutoffs for time intervals between first and second positive tests for definition with decrease in rates observed with increase in time intervals (see Figure 1).

DISCUSSION

We found a low rate of reinfection (0.7%) with SARS-CoV-2 confirmed by laboratory tests based on the analysis of large cohort of patients in the Cerner Real-World data. The rate of reinfection was similar to the 0.66% rate reported in previous SIREN [9] study. SIREN study defined possible reinfection with 2 reverse transcription polymerase chain reaction (RT-PCR) positive samples 90 or more days apart (based on national surveillance analysis) [17] or an antibody positive participant with a new positive RT-PCR at least 4 weeks after the first antibody positive result. The rate of reinfection was 0.65% (95% CI: .51–.82) in an individual-level data analysis from the Danish Microbiology Database [15] The study used 2 positive RT-PCR tests, one performed before 1 June 2020 and the second performed from 1 September to 31 December 2020 (minimum of 90 day interval) as evidence of reinfection. Other authors [14] have also recommended a time interval of 90 days to differentiate reinfection from relapse or re-positivity. The European Centre for Disease Prevention and Control [8] recognizes that longer time-interval between 2 RT-PCR positive samples increases the likelihood of reinfection as it relates to waning immunity and lower antibody levels. Redetection of the primary episode is more likely the cause than a true reinfection with shorter period of time interval between 2 RT-PCR positive samples. We acknowledge that reinfection is possible
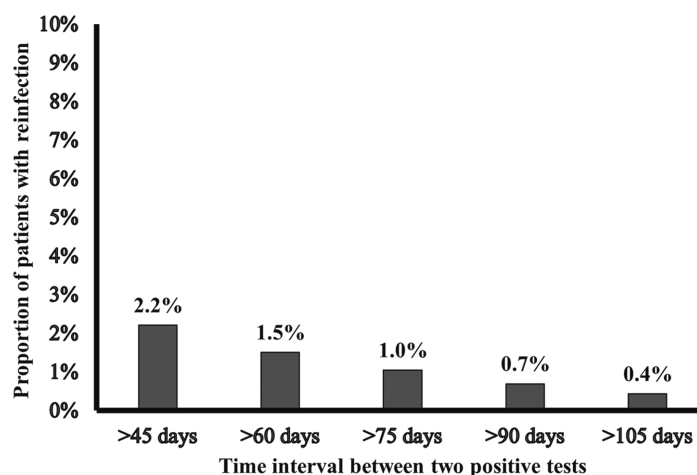
Figure 1. Rates of reinfection defined using different cutoff periods for time interval between first and second positive tests.

within a time interval <90 days and therefore have also presented the rates based on various time intervals used to define reinfection. The rates of reinfection ranged from 0.4% to 2.2% in our analysis using different cutoffs for time intervals between first and second positive tests (see Figure 1). Another analysis of national surveillance database in Qatar reported a reinfection rate of 0.01% (95% CI: .01–.02%) [18] when reinfection was defined by ≥45 days interval between 2 RT-PCR positive tests. The longitudinal study of healthcare workers in Oxford University Hospitals [19] reported a rate of 0.2% when using a time interval of ≥60 days between detection of serum antibodies against SARS-CoV-2 and subsequent positive RT-PCR test to define reinfection and exclude patients with persistent viral shedding from initial infection. One of the 3 patients with reinfection had 2 positive RT-PCR tests separated by an interval of 190 days (5 negative tests in the interim period).

In our analysis, age of the patient at the time of initial infection was not associated with reinfection either in the univariate or stepwise logistic regression analysis. We compared occurrence of medical events reflective of multi-organ involvement or requirement of mechanical ventilation during initial SARS-CoV-2 infection between patients with or without reinfection (see Table 1) but did not identify any differences in surrogate markers of severity of infection between the 2 groups. Reinfection was associated with preexisting asthma and nicotine dependence/tobacco use. Patients with asthma are at higher risk for respiratory viral infections [20] and an increased risk of H1N1 infection has been reported in children with asthma [21]. Cigarette smokers are also at high risk for viral infection including SARS-CoV-2.because of deficits in mucociliary clearance mechanisms and cell-mediated immunity in the lung alveolus [22]. Additional evidence of immunosuppression such as depressed migration and chemotaxis of leukocytes, reduced natural killer cell activity, and lower levels of circulating serum immunoglobulin levels have been reported in cigarette smokers [22]. Cessation of cigarette smoking can result in recovery of immune function within 6–12 weeks [23, 24].

In our analysis, reinfection appeared to have less severe manifestations than the primary infection with lower rates of pneumonia, heart failure, and acute kidney injury. However, there were 2 deaths (3.2%) associated with reinfection. There seems to be some controversy whether reinfection is a less severe or more severe disease compared with the primary infection [25–28]. Selvaraj et al [29] reviewed 34 patients reported in the literature with reinfection and found variable severity of clinical manifestations. Patients with reinfection have antibodies against SARS-CoV-2 identified in serum at time of reinfection [25–28]. Therefore, persistent immunity may result in less severe manifestations of infection. However, antibody-dependent enhancement may facilitate viral entry during reinfection or exaggerated immune response may result in more severe manifestations [30] We have to consider that survival in

patients with SARS-CoV-2 infection has been improving over time [31], and appearance of less severe manifestations during reinfection may be partly due to more effective medical management in subsequent months. There is also another bias with patients with mild manifestations during initial SARS-CoV-2 infection being more likely to be more exposed to reinfection due to higher survival and shorter time in isolation.

Reinfection was initially attributed to heterogeneity in response and decline in immunity over time among patients with SARS-CoV-2 infection. Long et al [32] and Muecksch et al [33] reported a decline in immunoglobulin G (IgG) antibodies and neutralizing antibody against SARS-CoV-2 spike (S) or nucleocapsid (N) within the first 3 months after infection. However, Wajnberg et al [34] and Ogega et al [35] reported persistent neutralizing antibodies and memory B cells capable of providing humoral immunity against SARS-CoV-2 for a longer period of time. Persistent T cells specific to SARS-CoV-2 provide immunity even in absence of antibodies [36]. However, patients who have antibodies to SARS-CoV-2 are not completely immune to reinfection during follow-up [9, 37]. Boyton and Altmann [38] pointed out that the exact immunological correlates of protection from SARS-CoV-2 infection are not well understood, but the quality, quantity, and durability of protective immunity elicited by natural infection with SARS-CoV-2 are poor relative to the much higher levels of virus-neutralizing antibodies and T cells induced by the vaccines [39]. European Centre for Disease Prevention and Control [8] also recommended the need for further studies to elaborate the role of cellular immunity in the prevention of reinfection with SARS-CoV-2. Phylogenetically distinct variants of SARS-CoV-2 have been implicated in reinfections [1–5]. Mutations in the SARS-CoV-2 receptor-binding domain (RBD) of the viral spike protein that escape antibody binding are also implicated in reinfection [40].

Our study is based on the Cerner Real-World data, which lacks the design strengths such as patient selection and systematic ascertainment methodologies seen in prospective studies. There is heterogeneity in timing, assays used, and indications for repeat testing. Mandatory serial testing for all patients was not possible or justified. A total of 9119 patients with SARS-CoV-2 infection met our inclusion criteria of serial testing among 110 754 patients with positive SARS-CoV-2 tests. We noted that patients who were included based on performance of serial testing appeared to have more medical comorbidities and severe disease manifestations compared with those who were excluded. Thus, there is perhaps an underrepresentation of patients with minimal comorbidities and mild disease manifestations in our analysis. However, such data are more representative of broader population and provide large unselected cohorts. We acknowledge that a positive test after being considered infection free based on serial negative laboratory test may be due to other reasons in addition to reinfection. There may be a relapse or recrudescent of infection with the "first" SARS-CoV-2 inoculum, or prolonged shedding of remnant

ribonucleic acid (RNA) fragments of the "first" SARS-CoV-2 infection [41] confounded by laboratory errors, or technical limits of RT-PCR assays. The mean time between initial positive RT-PCR testing and subsequent negative change was 6.9 days with a range of 4–15 days and a median of 7 days in a previous study [42] suggesting that it is uncommon to have to have persistent infection beyond 15 days, and persistent positive status by RT-PCR for up to 80 days is perhaps the longest period reported in rare cases [43, 44]. Therefore, using a time interval of >90 days should eliminate those with persistence of primary infection. RT-PCR tests have an estimated false negative rate of 13% (95% CI: 9–19%) for detection of SARS-CoV-2 [45, 46]. Therefore, the possibility that some patients classified as reinfection were those with persistent viral shedding and interim RT-PCR test was falsely negative [47]. However, the rate of false negative tests decreases if two false negative tests are used like in ours and other studies [1–5, 48]. We did not have access to any genomic characterization of SARS-CoV-2 detected in reinfected patients and are unable to comment upon the role of phylogenetically distinct variants of SARS-CoV-2 in reinfection. We could not identify the role of any specific therapeutic interventions used during primary infection in preventing reinfection due to lack of data and small number of reinfections. We were also unable to identify immunodeficiency by laboratory tests or use of immunosuppressive medication which precluded a more detailed analysis.

The exact prevalence of reinfection may be confounded by the selection criteria of our analysis, which only included those with serial laboratory tests. This approach eliminates those patients who may have undetected SARS-CoV-2 reinfection because follow-up laboratory tests were not performed. We also included those patients who had at least 1 qualifying ED or inpatient encounter, which was considered related to SARS-CoV-2 infection. ED and inpatient encounters are more reliable due to completeness of data recorded in electronic medical records [13] but may exclude some patients with mild disease who were not seen in ED or hospitalized. We acknowledge the effect of variability in hospitalization criteria over time and between institutions on our analysis is not known. We also cannot exclude the possibility that in a certain proportion of patients, some tests may be performed in centers not included in the Cerner Real-World data and thus not available for analysis. The possibility of such occurrence is very low as all included patients had serial tests performed within centers in Cerner Real-World data. The vulnerability for reinfection may be underestimated due to implementation of social distancing policies (March 2020) and universal face mask use (July 2020) recommended by Centers for Disease Control and Prevention [49, 50]. Reinfection may be additionally reduced due to behavioral changes among SARS-CoV-2 infection survivors [51] that may result in high compliance with social distancing measures [52], thus reducing the chance of a reinfection.

Our observations strongly suggest that survivors from SARS-CoV-2 infection must not relax compliance with proven interventions in prevention of SARS-CoV-2 transmission such as social distancing [53] and universal face mask use [50]. Our study supports the position taken by European Centre for Disease Prevention and Control [8] and Centers for Disease Control and Prevention [54] that individuals that have been infected once with SARS-CoV-2 are not always immune, and infection prevention/control and contact principles should be followed even after infection. Due to concerns for reinfection, the Centers for Disease Control and Prevention [54] currently recommends vaccination for patients who had SARS-CoV-2 infection after 90 days but acknowledges that limited data available to support the recommendation.

Notes

Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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