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Outcomes associated with SARS-CoV-2 reinfection in individuals with natural and hybrid immunity

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ABSTRACT

Background: Studies comparing SARS-CoV-2 reinfection outcomes among individuals with previous infection (natural immunity) and previous infection plus vaccination (hybrid immunity) are limited.
Methods: Retrospective cohort study comparing SARS-CoV-2 reinfection among patients with hybrid immunity (cases) and natural immunity (controls) from March 2020 to February 2022. Reinfection was defined as positive PCR > 90 days after initial laboratory-confirmed SARS-CoV-2 infection. Outcomes included time to reinfection, symptom severity, COVID-19-related hospitalization, critical COVID-19 illness (need for intensive care unit, invasive mechanical ventilation, or death), length of stay (LOS).
Results: A total of 773 (42%) vaccinated and 1073 (58%) unvaccinated patients with reinfection were included. Most patients (62.7%) were asymptomatic. Median time to reinfection was longer with hybrid immunity (391 [311–440] vs 294 [229–406] days, $p < 0.001$). Cases were less likely to be symptomatic (34.1% vs 39.6%, $p = 0.001$) or develop critical COVID-19 (2.3% vs 4.3%, $p = 0.023$). However, there was no significant difference in rates of COVID-19-related hospitalization (2.6% vs 3.8%, $p = 0.142$) or LOS (5 [2–9] vs 5 [3–10] days, $p = 0.446$). Boosted patients had longer time to reinfection (439 [IQR 372–467] vs 324 [IQR 256–414] days, $p < 0.001$) and were less likely to be symptomatic (26.8% vs 38%, $p = 0.002$) compared to unboosted patients. Rates of hospitalization, progression to critical illness and LOS were not significantly different between the two groups.
Conclusions: Natural and hybrid immunity provided protection against SARS-CoV-2 reinfection and hospitalization. However, hybrid immunity conferred stronger protection against symptomatic disease and progression to critical illness and was associated with longer time to reinfection. The stronger protection conferred by hybrid immunity against severe outcomes due to COVID-19 should be emphasized with the public to further the vaccination effort, especially in high-risk individuals.
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Introduction

As of January 15, 2023, SARS-CoV-2 has infected over 101 million people in the United States and 667 million worldwide, with more than 1.1 million and 6.7 million deaths since the beginning of the pandemic, respectively [23]. o Vaccines against COVID-19 have been shown to reduce the risk of SARS-CoV-2 infection and severe COVID-19, including severe illness, hospitalization and death, in randomized clinical trials and real-world observational studies [14,15,28,34]. All adults in the United States became eligible for COVID-19 vaccination on April 20, 2021; however, 81% of the United States population is fully vaccinated [10], with 662.3 million vaccine doses administered [23]. Worldwide, 13.2 billion vaccine doses have been administered [23].

Observational studies have also demonstrated that individuals who survive a previous SARS-CoV-2 infection generate a robust immune response and develop durable protective immunity against reinfection and hospitalization [1,24–26,31]. In a large cohort study, natural immunity provided robust protection against hospitalization, progression to critical illness and death, regardless of variant

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(Au-Raddad et al., 2021). Moreover, recent studies suggest natural immunity conferred a stronger protection than vaccine-induced immunity against the Delta and Omicron variants [18,26,3]. Data on effectiveness of prior infection and/or vaccines against reinfections with the Omicron variants are limited [3]. There is evidence that vaccination generates hybrid immunity or an enhanced immune response in individuals who recover from SARS-CoV-2 infection [16,19,3,5]. Nonetheless, it is recommended that these individuals complete the primary vaccine series and be "up to date" with their vaccines [11].

Reinfection with SARS-CoV-2 have been increasingly reported in individuals with natural and hybrid immunity; however, there is scarcity of studies comparing outcomes between natural immunity and hybrid immunity [26,3,31]. In this retrospective cohort study, we compared reinfection and outcomes, including symptom severity, need for hospitalization, progression to critical illness and length of stay (LOS) among individuals with natural immunity and hybrid immunity.

Methods

Study design and participants

This was a retrospective cohort study comparing SARS-CoV-2 reinfection among patients with hybrid immunity, including those who received boosters (cases) and natural immunity (controls) evaluated at Henry Ford Health, a comprehensive, integrated health care organization that includes 5 hospitals, 9 emergency departments and more than 200 ambulatory sites in metropolitan Detroit, Michigan, United States, from March 1, 2020 to February 28, 2022. Reinfection was defined as positive polymerase chain reaction test > 90 days after the initial laboratory-confirmed SARS-CoV-2 infection. The first SARS-CoV-2 test within this eligibility period was used.

Natural immunity was defined as documented previous infection in an unvaccinated individual. Hybrid immunity was defined as documented previous infection in a vaccinated individual.

Vaccination status (vaccine type and date of administration) was confirmed in the electronic medical records and state immunization registry. Full vaccination was defined as completion of two doses of mRNA-1273 (Moderna) or BNT162b2 (Pfizer–BioNTech), or one dose of JNJ78436735 (Janssen) ≥ 14 days before the reinfection date. Boosted individuals included those who received a third vaccine dose; for patients whose primary series was JNJ78436735, boosted patients included those who received a second JNJ78436735 or mRNA vaccine. Subjects were excluded if they were partially vaccinated (< 14 days since completing the primary series or not completing the series before the reinfection date).

This study was approved by the Henry Ford Health institutional review board (IRB #15157).

Data collection

A retrospective review of the electronic medical records was performed to obtain demographic, clinical and laboratory data. County of residence and zip codes were also collected, with income status determined based on zip code household income data per the most current 2020 census data, through a third-party site. Comorbidities associated with higher risk of developing severe outcomes of COVID-19 [12] were extracted using the International Classification of Diseases, 10th Revision, codes. Immunocompromised state was defined as presence of any of the following: immunosuppressive or immunomodulatory medication use, > 20 mg prednisone or equivalent per day for > 2 weeks, history of hematopoietic stem cell transplant or solid organ transplantation and receipt of immunosuppressive therapy, solid tumor or hematologic malignancies on active treatment, or advanced or untreated HIV.

The distribution of reinfections and hospitalization over the course of the pandemic and the reported activity of the SARS-CoV-2 in the United States was also assessed [30].

Outcomes

Outcomes included time to reinfection, symptom severity, COVID-19-related hospitalization, critical COVID-19 illness, and LOS. Critical COVID-19 was defined as need for intensive care unit (ICU), invasive mechanical ventilation (IMV), or death.

Time to reinfection was calculated using days from the second positive polymerase chain reaction to first positive polymerase chain reaction for cases and controls. For severity of symptoms, patients were grouped into asymptomatic and symptomatic infection.

COVID-19–related hospitalization was defined as hospitalization in a symptomatic individual with a positive SARS-CoV-2 assay. COVID-19–related mortality occurred in a person with a documented COVID-19 diagnosis who died as a result of or from complications of COVID-19 disease. LOS was calculated from index admission to discharge in days, alive or expired at time of discharge.

Statistical analysis

Descriptive statistics were performed to characterize each group in the case-control analysis. Groups were left unmatched in an attempt to fully describe each group. Frequency and count data were displayed for categorical variables, mean with standard deviation (SD) for normally distributed continuous variables, and median with interquartile range (IQR) for skewed continuous variables. The chi-square or Fisher's exact tests were applied for computation of categorical variables, and the t-test or Mann-Whitney U tests were used for continuous variables. The multivariable logistic regression analysis was performed to evaluate risk of developing critical COVID-19 disease, and the model included all risk factors identified as statistically significant with p values < 0.05 on univariate analysis. Odds ratios were reported with 95% confidence intervals (CI). A Kaplan-Meier analysis was used to compare time to reinfection with SARS-CoV-2 among cases and controls. Analyses were performed using SAS 9.4 (SAS Institute Inc, Cary, NC, USA).

Results

Patient characteristics

A total of 1846 patients with previous SARS-CoV-2 infection met eligibility criteria and were included in the final analysis, of which 773 (42%) were vaccinated and 1073 (58%) were unvaccinated prior to reinfection. Among the two cohorts included in the study, the median age was 41 years old (IQR 27–54), 1175 (63.7%) were female, and 1093 (59.2%) were white. Most patients (62.7%) were asymptomatic. Compared with controls, case patients were older (45 [IQR 31–56] vs 37 [IQR 24–52] years, $p < 0.001$) and were more likely to be female (67.1% vs 61.2%, $p = 0.011$) and white (61.1% vs 57.9%, $p < 0.047$). Patients with hybrid immunity had a higher number of comorbidities (1.99 [SD 2.09] vs 1.73 [SD 2.02], $p = 0.002$), with a higher proportion of obstructive sleep apnea (16.3% vs 11.7%), diabetes mellitus (22.2% vs 16.8%, $p = 0.004$), hypertension (40.3% vs 29.2%, $p < 0.001$), and immunocompromising conditions (26% vs 21%, $p < 0.001$), whereas controls were more likely to be smokers (11.2% vs 7.6%) or pregnant (9.2% vs 5.7, $p = 0.005$). Among case patients, the majority were vaccinated with BNT162b2 (69%), while 24% were vaccinated with mRNA1273, and 7.1% with JNJ78436735; of these patients, 15.9% were boosted prior to reinfection. Fifty-seven (3.1%) patients were of high-income status, 356 (19.3%) of middle-

Table 1
Baseline characteristics of patients with hybrid immunity (including booster) and natural immunity reinfected with SARS-CoV-2.

Variable		Total N = 1846	Hybrid Immunity n = 773	Natural Immunity n = 1073	p-value
Age – *years*	median (IQR)	41 (27–54)	45 (31–56)	37 (24–52)	**< 0.001**
Gender	n (%)				**0.011**
Female		1175 (63.7)	518 (67.1)	657 (61.2)	
Male		671 (36.3)	225 (32.9)	416 (38.8)	
Race	n (%)				**0.047**
White		1093 (59.2)	472 (61.1)	621 (57.9)	
Black		520 (28.2)	199 (25.8)	321 (29.9)	
Other		233 (12.6)	101 (13.1)	130 (12.1)	
BMI – *kg/m²*	median (IQR)	30 (24.9–35.9)	31.2 (25.7–35.9)	29.8 (24.3–35.9)	0.163
Number of comorbid conditions	mean (SD)	1.84 (2.05)	1.99 (2.09)	1.73 (2.02)	**0.002**
Smoker	n (%)	179 (9.7)	59 (7.6)	120 (11.2)	**0.011**
Alcohol use disorder	n (%)	181 (9.8)	85 (11.0)	96 (8.9)	0.144
Chronic kidney disease	n (%)	148 (8.0)	68 (8.8)	80 (7.5)	0.295
ESRD on hemodialysis	n (%)	24 (1.3	7 (0.9)	17 (1.6)	0.204
COPD	n (%)	105 (5.7)	46 (6.0)	59 (5.5)	0.679
Asthma	n (%)	371 (20.1)	152 (19.7)	219 (20.4)	0.693
Obstructive sleep apnea	n (%)	252 (13.7)	126 (16.3)	126 (11.7)	**0.005**
Diabetes mellitus	n (%)	351 (19.0)	171 (22.2)	180 (16.8)	**0.004**
Hypertension	n (%)	624 (33.8)	311 (40.3)	313 (29.2)	**< 0.001**
Coronary artery disease	n (%)	121 (6.6)	54 (7.0)	67 (6.2)	0.526
Heart failure	n (%)	75 (4.1)	32 (4.1)	43 (4.0)	0.887
Pregnancy	n (%)	143 (7.7)	44 (5.7)	99 (9.2)	**0.005**
Inflammatory bowel disease	n (%)	45 (2.4)	25 (3.2)	20 (1.9)	0.060
Immunocompromised	n (%)	423 (22.9)	201 (26.0)	222 (21.0)	**< 0.001**
HIV		4 (0.2)	1 (0.1)	3 (0.3)	0.494
Solid organ transplant		19 (1.0)	9 (1.2)	10 (0.9)	0.626
Prior BMT		2 (0.1)	1 (0.1)	1 (0.1)	0.816
Active cancer		173 (9.4)	86 (11.1)	87 (8.1)	**0.028**
Immunoglobulin deficiency		4 (0.2)	2 (0.3)	2 (0.2)	0.742
On systemic steroid therapy		246 (13.3)	113 (14.6)	133(12.4)	0.166
On active chemotherapy		48 (2.6)	18 (2.3)	30 (2.8)	0.534
On immunosuppression		32 (1.7)	17 (2.2)	15 (1.4)	0.193
Income status	n (%)				**0.042**
High		57 (3.1)	35 (4.5)	26 (2.4)	
Middle		356 (19.3)	154 (19.9)	224 (20.9)	
Low		1408 (76.3)	584 (75.5)	823 (76.7)	
Vaccine type received	n (%)				
BNT162b2			533 (69.0)		
mRNA1273			185 (24)		
JNJ78436735			55 (7.1)		
Booster prior to reinfection	n (%)		123 (15.9)		
BNT162b2			77 (62.6)		
mRNA1273			46 (37.4)		

BMI=body mass index; COPD=chronic obstructive pulmonary disease; ESRD=end stage renal disease; HIV=human immunodeficiency virus; BMT=bone marrow transplant; BNT162b2=Pfizer vaccine; mRNA1273 =Moderna vaccine; JNJ78436735 =Janssen vaccine
kg/m^2=kilogram per meter squared
Significant p-values are bolded

income status, and 1408 (76.3%) of low-income status. A higher proportion of case patients were of high-income status (4.5% vs 2.4%), and vaccination rate based on income status was statistically significant (p = 0.042). Table 1 summarizes baseline characteristics among cases and controls.

Most (78%) reinfections occurred during the period of reported Omicron activity. Fig. 1 demonstrates the distribution of reinfections and hospitalizations over the course of the pandemic.

Outcomes

The median time to reinfection was significantly longer in case patients compared to controls (391 [IQR 311–440] vs 294 [229–406] days, p < 0.001). Compared with JNJ78436735 (345 [IQR 283–411] days), the mRNA vaccines (BNT162b2 and mRNA1273) were associated with longer time to reinfection (401 [IQR 284–458] and 393 [IQR 278–428] days, respectively). Fig. 2 includes the Kaplan Meier analysis of time to reinfection among cases according to vaccine subtype and controls.

After reinfection, case patients were less likely to be symptomatic (34.1% vs 39.6%, p = 0.001). Although there was no significant difference in rates of COVID-19-related hospitalization (2.6% vs 3.8%, p = 0.142), case patients were less likely to develop critical COVID-19 (2.3% vs 4.3%, p = 0.023); COVID-19-related mortality was low in cases and controls (0.2% vs 0.5%, p = 0.478). Length of stay was similar between the two groups. Outcomes related to reinfection are summarized in Table 2.

Approximately 16% of case patients were boosted prior to reinfection, with the predominant subtype being BNT162b2 (62.6%). Boosted patients were older (51.5 [SD 14.7] vs 40.6 [SD 18.4] years, p < 0.001) and had a higher average BMI (32.5 [IQR 28.3–37.7] vs 29.9 [IQR 24.8–35.5] kg/m^2, p = 0.047). When the outcomes were analyzed according to booster status, boosted patients had longer time to reinfection (439 [IQR 372–467] vs 324 [IQR 256–414] days, p < 0.001) and were less likely to be symptomatic (26.8% vs 38%, p = 0.002) compared to unboosted patients. Rates of COVID-19-related hospitalization, progression to critical COVID-19 illness and length of stay were not significantly different between the two groups. Table 2 highlights the outcomes of patients based on booster status. When comparing boosted to vaccinated patients, there was no difference in outcomes (data not shown).

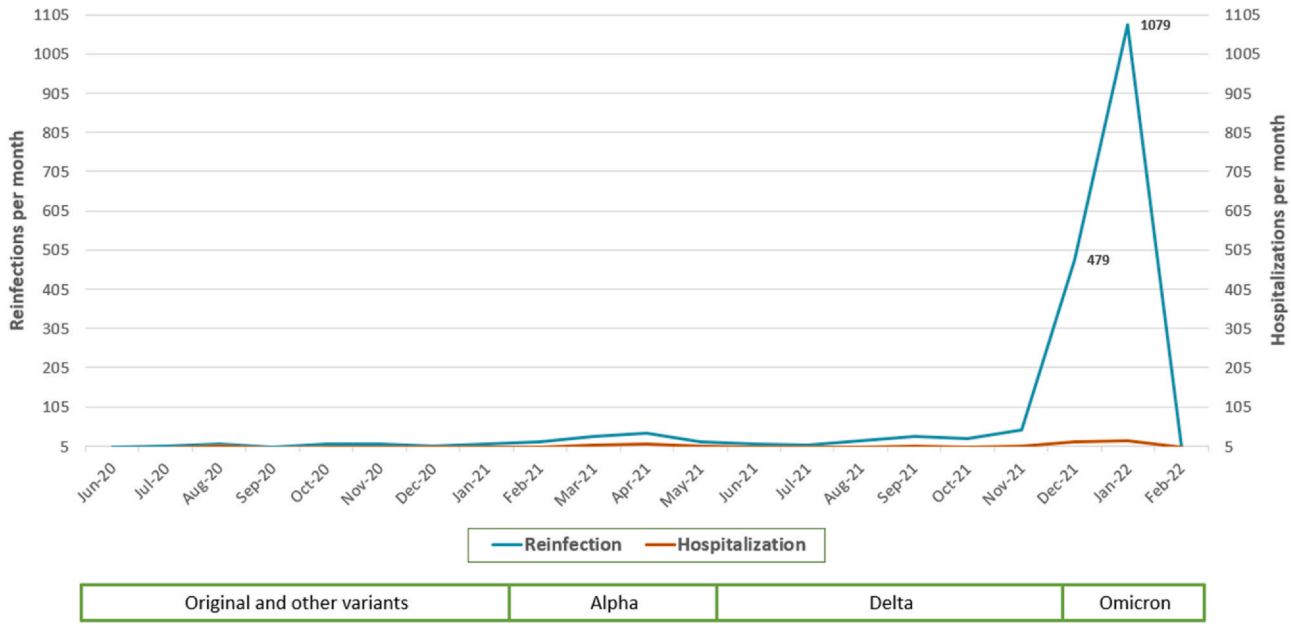

Fig. 1. Distribution of reinfections and hospitalizations over the course of the pandemic.

Age (OR 1.042, 95% CI 1.025–1.067, $p < 0.001$), diabetes mellitus (OR 2.320, 95% CI 1.245–4.119, $p = 0.006$, and immunocompromised state (OR 2.313, 95% CI 1.348–4.110, $p = 0.003$) were independently associated with higher odds and hybrid immunity (OR 0.348, 95% CI 0.187–0.662, $p = 0.001$) and female gender (OR 0.562, 95% CI 0.319–0.978, $p = 0.041$) with lower odds of critical COVID-19 progression. A booster prior to reinfection did not reduce the odds of developing critical COVID-19 (OR 0.737, 95% CI 0.188–2.590, $p = 0.675$). Table 3 includes the multivariate logistic regression analysis summarizing these results.

Discussion

This large study among patients who were reinfected with SARS-CoV-2 demonstrated that hybrid immunity was associated with lower odds of progression to critical illness, longer time to reinfection and attenuated symptom severity compared to natural immunity. However, COVID-19-related hospitalization and mortality were similar between the two groups.

Research shows that natural immunity and/or receipt of at least 1 dose of a COVID-19 vaccine among patients who had recovered from COVID-19 infection was associated with a significantly lower risk of recurrent infection before the widespread circulation of the SARS-CoV-2 Omicron variants [1,18,2,20–22,26,31,9]. Notably, our study includes the period during which Omicron was the predominant variant, and most of our reinfections occurred during this time. In a recently published study, Nordstrom et al. [31] demonstrated that natural immunity reduced risk of reinfection and COVID-19-related hospitalization, and this risk was further decreased by 1-dose and 2-dose hybrid immunity. Disease severity and mortality data were not provided. Prior to Delta, case and hospitalization rates were lowest among vaccinated individuals compared to patients with previous COVID-19 diagnosis [26,6,9]. However, when Delta became predominant, a large multi-state study demonstrated that previous infection substantially lowered the odds of reinfection and COVD-19-related hospitalization among both vaccinated and unvaccinated individuals [26]. Altarawneh et al. [3] evaluated the effects of natural and hybrid immunity against symptomatic Omicron infections. The effectiveness of hybrid immunity and natural immunity were similar. However, hybrid immunity with recent booster dose conferred stronger protection.

Similar to previous studies [2,21,26,31,33], reinfection was uncommon among our cohorts before 9 months. A large retrospective cohort study showed that immunity from natural infection lasted for at least 13 months [26]. Nordstrom et al. [31] demonstrated that natural immunity reduced risk of reinfection for up to 20 months. Prior to Omicron, hybrid immunity remained consistently higher than 90% in persons infected more than 18 months previously in one study [21] and provided greater protection than natural immunity alone for up to 9 months in another study [31]. With the emergence of the highly contagious Omicron variant, natural, vaccine-induced and hybrid immunity were diminished [13,3,4]. Recent findings

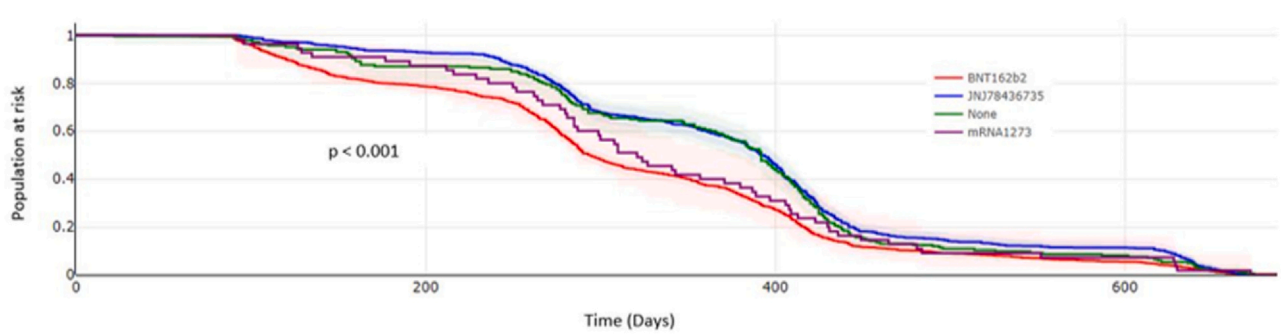

Fig. 2. Kaplan Meier analysis of time to reinfection with SARS-CoV-2 after vaccination (by sub-type) as compared to no prior vaccination.

Table 2
Outcomes of reinfection with SARS-CoV-2 among patients with natural and hybrid immunity (including booster) and patients who received booster.

Outcome		Total n = 1846	Natural Immunity n = 1073	Hybrid Immunity n = 773	p-value	No booster n = 1723	Booster n = 123	p-value
Time to re-infection – *days*	median (IQR)	351 (265–424)	294 (229–406)	391 (311–440)	**< 0.001**	324 (256–414)	439 (372–467)	**< 0.001**
BNT162b2				401 (284–458)				
mRNA1273				393 (278–428)				
JNJ78436735				345 (283–411)				
No vaccination								
Symptomatic*	n (%)	668 (37.3)	425 (39.6)	263 (34.1)	**0.001**	655 (38.0)	33 (26.8)	**0.002**
COVID-19-related hospitalization		87 (4.7)	58 (5.4)	29 (3.7)	0.098	84 (4.9)	3 (2.4)	0.218
Critical COVID-19 development	n (%)	64 (3.0)	46 (4.3)	18 (2.3)	**0.023**	61 (3.5)	3 (2.4)	0.519
Required intensive care		40 (2.2)	29 (2.7)	11 (1.4)	0.063	37 (2.1)	3 (2.4)	0.832
Required intubation		26 (1.4)	19 (1.8)	7 (0.9)	0.120	25 (1.5)	1 (0.8)	0.561
COVID-19-related mortality		7 (0.4)	5 (0.5)	2 (0.3)	0.475	7 (0.4)	0 (0)	0.478
Hospital length of stay – *days*	median (IQR)	5 (2–9)	5 (2–9)	5 (3–10)	0.446	5 (2–9)	11 (7–11)	0.605

Critical COVID-19 development: composite of ICU admission, mechanical ventilation, and death
Significant p-values are bolded
* Symptoms reported for 1526/1846 patients in the cohort; the remainder did not have symptoms reported or documented on SARS-CoV-2 testing

Table 3
Multivariable logistic regression analysis of Critical COVID-19 development in cohort (N = 1846).

Variable	Odds Ratio	95% CI	p-value
Age	1.042	1.025–1.067	**< 0.001**
Female sex	0.562	0.319–0.978	**0.041**
Black race	1.421	0.887–1.477	0.247
Tobacco use	1.377	0.634–4.037	0.509
Obstructive sleep apnea	0.842	0.469–1.734	0.628
Diabetes Mellitus	2.320	1.245–4.119	**0.006**
Hypertension	1.837	0.820–4.115	0.139
Pregnancy	1.710	0.432–6.772	0.445
Immunocompromised state	2.313	1.348–4.110	**0.003**
Symptoms	1.341	0.826–2.297	0.219
Hybrid immunity	0.348	0.187–0.662	**0.001**
Boosted prior to re-infection	0.737	0.188–2.590	0.675
Income status	0.918	0.543–1.551	0.750

Critical COVID-19 development: composite of ICU admission, mechanical ventilation, and death
Significant p-values are bolded

suggest mRNA vaccines have negligible protection against Omicron infection after 6 months [4,13], and protection in persons with hybrid immunity originated from the previous infection and not from vaccination [4]. In our report, hybrid immunity and a booster dose provided longer time to reinfection compared with natural immunity. However, the duration was shorter compared with previous studies published before the Omicron surge as mentioned above. In Michigan, the Omicron variant became dominant in late December, and our study period was through February 2022. Consequently, the time to reinfection may have been shorter in our study.

In contrast to breakthrough or postvaccine infections [24,25,35,38,39], reinfections are more commonly reported in younger persons [13,18,24,25,3,31,4]. In the present study, the patient population was also younger, with a median age of 41 years. Moreover, patients with hybrid immunity were older and more likely to have underlying comorbidities than those with natural immunity. However, the median number of comorbidities was lower in patients with reinfection compared with breakthrough infections or hospitalization [35,36]. Immunocompromised patients who are at higher risk for breakthrough infections and reinfection represented almost a quarter of our cohort and had higher odds of disease progression, findings that were similar to previous reports [17,29,35,36,39,7].

Compared to previous studies [24,25], less than half of our patients were symptomatic and likely represented exposed patients who were tested during the Omicron surge. In findings that were consistent with prior studies [3], natural and hybrid immunity were effective against COVID-19-related hospitalization, but hybrid immunity conferred stronger protection against symptomatic disease and progression to critical illness and was associated with longer time to reinfection. Booster vaccine may have contributed to the lower symptomatic disease and longer time to reinfection. ICU admission and need for IMV occurred in low numbers and were not adequately powered to detect any significant difference, but there was a trend toward vaccination and booster association with reduced ICU admission and need for IMV. Mortality rates were very low in both groups. Age and immunocompromised status, particularly among those with active malignancy, were risk factors for progression to critical illness. Older age, multiple comorbidities and immunocompromised state were risk factors for hospitalization and disease progression regardless of vaccination status [29,35–37,39,7]. Protection conferred by prior infection with or without vaccination, lower number of comorbidities and younger age may in part explain the similar hospitalization and low mortality rates.

Although symptomatic infection was lower and time to reinfection was longer in patients who were boosted, there was no significant difference in rate of hospitalization or progression to critical illness. These results should be interpreted with caution as the sample size of boosted patients was too small to detect any significant difference. However, these findings are supported by prior studies that showed 3 doses provided marginal benefit to individuals with natural immunity [24,25,27,8]. Boosters became available to select groups of individuals in September 2021 and widely in November 2021, less than 3 months prior to the Omicron surge, which may explain the higher effectiveness in this group. Significant waning of vaccine effectiveness of the third dose against the Omicron variant has been reported [3,32].

This study has a few limitations. It was a single system retrospective study. Most reinfections in our cohort were asymptomatic and occurred in December 2021 and January 2022 with a significant drop the following month (see Fig. 1). We are unable to explain the sudden drop in February, and we did not collect data for the subsequent months to evaluate the trend. However, we do not believe this was due to a delay in reporting since results were available within 24–48 h of sample collection. We stopped routine testing of fully vaccinated asymptomatic patients or those who had recovered from COVID-19 on admission or for procedures, and it is possible that there were additional asymptomatic reinfections that were not detected. Patients who are asymptomatic or mildly symptomatic may not seek testing and be underrepresented. Given the large sample size, we do not believe the results were significantly affected. Additionally, strain typing was not performed, and asymptomatic reinfections could have represented residual viral shedding from prior infection and contributed to the higher reinfection rate during this period. Although inpatient COVID-19 treatment was

standardized, we did not take into consideration the use and impact of outpatient treatment modalities, including monoclonal antibodies, Evusheld, and PAXLOVID, on outcomes.

Strengths of our study include the large sample size that include both symptomatic and asymptomatic individuals. We were able to characterize and compare reinfections among individuals with natural and hybrid immunity. Reinfections spanning the course of the pandemic were captured and included the Omicron period where most of the reinfections occurred.

Conclusion

Natural and hybrid immunity provided protection against SARS-CoV-2 reinfection and hospitalization with very low mortality rates. However, hybrid immunity conferred stronger protection against symptomatic disease and progression to critical illness and was associated with longer time to reinfection compared to natural immunity among patients with SARS-CoV-2 reinfection. Booster vaccination did not result in additional protection among previously infected people. Recovery from previous SARS-CoV-2 infection should be taken into consideration for purposes related to public health policies. Additionally, the stronger protection conferred by hybrid immunity against severe outcomes due to COVID-19 should be emphasized with the public to further the vaccination effort, especially in high-risk individuals such as older adults and immunocompromised individuals.

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CRediT authorship contributors statement

Geehan Suleyman conceived the study, conducted the background literature search and review, and designed the analysis plan with Raef Fadel, Indira Brar and George Alangaden. Data collection was performed by Geehan Suleyman, Raef Fadel, Kunj Patel,nAl Muthanna Shadid, Haim Bernardo Cotlear Stuart, Michael Kattula, Andrea Janis, Mohamed Maki, Shing Chao, and verified by Geehan Suleyman, Raef Fadel, and Indira Brar. Raef Fadel analyzed the data, and Geehan Suleyman and Raef Fadel designed the figures. All authors contributed to and reviewed the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Ethical approval

The study was approved by the Institutional Review Board of Henry Ford Health, Detroit, Michigan. Informed consent was waived given that the study exclusively used de-identified data.

Data Availability

De-identified participant data are available upon a reasonable request to Dr. Geehan Suleyman (gsuleym2 @hfhs.org).

Declaration of Competing Interest

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

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