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Risk Factors Associated With Hospitalization and Death in COVID-19 Breakthrough Infections

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Background. Characterizations of coronavirus disease 2019 (COVID-19) vaccine breakthrough infections are limited. We aim to characterize breakthrough infections and identify risk factors associated with outcomes.

Methods. This was a retrospective case series of consecutive fully vaccinated patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in a multicenter academic center in Southeast Michigan, between December 30, 2020, and September 15, 2021.

Results. A total of 982 patients were identified; the mean age was 57.9 years, 565 (59%) were female, 774 (79%) were White, and 255 (26%) were health care workers (HCWs). The median number of comorbidities was 2; 225 (23%) were immunocompromised. BNT162b2 was administered to 737 (75%) individuals. The mean time to SARS-CoV-2 detection was 135 days. The majority were asymptomatic or exhibited mild to moderate disease, 154 (16%) required hospitalization, 127 (13%) had severe–critical illness, and 19 (2%) died. Age (odds ratio [OR], 1.14; 95% CI, 1.04–1.07; $P < .001$), cardiovascular disease (OR, 3.02; 95% CI, 1.55–5.89; $P = .001$), and immunocompromised status (OR, 2.57; 95% CI, 1.70–3.90; $P < .001$) were independent risk factors for hospitalization. Additionally, age (OR, 1.06; 95% CI, 1.02–1.11; $P = .006$) was significantly associated with mortality. HCWs (OR, 0.15; 95% CI, 0.05–0.50; $P = .002$) were less likely to be hospitalized, and prior receipt of BNT162b2 was associated with lower odds of hospitalization (OR, 0.436; 95% CI, 0.303–0.626; $P < .001$) and/or death (OR, 0.360; 95% CI, 0.145–0.898; $P = .029$).

Conclusions. COVID-19 vaccines remain effective at attenuating disease severity. However, patients with breakthrough infections necessitating hospitalization may benefit from early treatment modalities and COVID-19-mitigating strategies, especially in areas with substantial or high transmission rates.

Keywords. breakthrough infections; COVID-19; hospitalizations; outcomes.

Vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is highly effective at preventing disease progression and mortality and is the leading strategy to change the trajectory of the coronavirus 2019 (COVID-19) pandemic worldwide. Randomized clinical trials have demonstrated high vaccine efficacies (>94%) for the mRNA-based vaccines against COVID-19 [1, 2]. Several other studies have redemonstrated their high effectiveness among various patient populations against severe disease, hospitalization, and death in real-world data [3–8]. Early surveillance data from a nationwide mass vaccination campaign in Israel suggested that 2 doses of BNT162b2 were effective against overall infection, severe disease, hospitalization, and death [3]. More recently, a large multistate analysis of >63 000 medical visits showed that COVID-19 vaccines remained effective against COVID-19-related hospitalizations and ambulatory visits [6].

However, COVID-19 mRNA vaccine effectiveness (VE) in preventing laboratory-confirmed COVID-19 has declined due to waning immunity and/or variant immune evasion, especially during the Omicron-predominant period [9]. During a 6-month follow-up of the BNT162b2 mRNA COVID-19 Vaccine clinical trial, VE gradually declined; VE was 96.2% (95% CI, 93.3%–98.1%) ≥7 days and 83.7% (95% CI, 74.7%–89.9%) 4 months after the second dose [10]. Moreover, lower VE in preventing COVID-19-related hospitalization has been observed among older adults and high-risk groups [4, 11]. Despite the emergence of breakthrough infections, the cumulative COVID-19-associated hospitalization rate remained 12 times higher in unvaccinated persons compared with vaccinated individuals. Moreover, an unvaccinated individual has significantly greater risk of testing positive for SARS-CoV-2 and dying from

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COVID-19 [12]. As of December 2021, the Centers for Disease Control and Prevention (CDC) has reported rates as high as 130 per 100 000 COVID-19 breakthrough infections among fully vaccinated persons, with low hospitalization and mortality rates [12]. Studies characterizing breakthrough infections among the general patient population across all age groups and outcomes with respect to hospitalization, intensive care unit (ICU) admission, need for invasive mechanical ventilation (IMV), and mortality are limited. Previous studies in unvaccinated and vaccinated individuals have shown that age and multiple comorbid conditions are associated with disease progression and adverse outcomes [7, 11, 13]. Further studies are needed to identify specific characteristics associated with disease progression in breakthrough infections and determine which individuals may benefit from additional vaccine doses and therapeutic modalities and mitigating COVID-19 strategies. Therefore, we aimed to describe SARS-CoV-2 breakthrough infections, risk factors associated with disease progression, and outcomes among our patient population.

METHODS

Study Design and Participants

This was a case series of consecutive patients, including health care workers (HCWs) diagnosed with COVID-19 vaccine breakthrough or postvaccine infections in the Henry Ford Health System (HFHS), a comprehensive, integrated health care organization that includes 5 hospitals and 9 emergency departments (EDs) in Southeast Michigan, from December 30, 2020 (2 weeks after the introduction of a COVID-19 vaccine) to September 15, 2021.

In our health system, HCWs exhibiting symptoms and/or signs consistent with COVID-19 infection and exposed asymptomatic HCWs were referred to employee health for SARS-CoV-2 testing; however, routine asymptomatic testing was not performed.

A vaccine breakthrough infection was defined as detection of SARS-CoV-2 ≥14 days after receipt of 2 doses of mRNA-1273 (Moderna) or BNT162b2 (Pfizer-BioNTech) or 1 dose of JNJ78436735 (Janssen), confirmed by state immunization registry. Patients with positive polymerase chain reaction (PCR) for SARS-CoV-2 in a respiratory specimen were included. The first SARS-CoV-2 test within this eligibility period was used. Partially vaccinated participants (<14 days since completing the primary series or not completing the series before the specimen collection date) were excluded.

Covariates of Interest

We performed a retrospective review of electronic health records (EHRs) using Epic to obtain data on a standardized data collection form. Demographic data, chronic comorbid conditions, prior COVID-19 infection, SARS-CoV-2 test results, severity of illness, vaccine type and date, prior COVID-19 history, receipt of monoclonal antibody (MAB), hospital admission status, and clinical outcomes were evaluated. Viral load as expressed by the PCR cycle threshold (Ct) was obtained from the microbiology laboratory when available.

Race/ethnicity data were collected in EHRs by self-report using standard classification. Based on the most recent recorded body mass index (BMI), obesity was defined as a BMI ≥30 kg/m^2, and morbid obesity as a BMI ≥40 [14]. Comorbidities associated with higher risk of developing severe outcomes of COVID-19 [15] were extracted using International Classification of Diseases (ICD), 10th revision, codes. Vaccination status, including specific vaccine type and vaccination dates, was extracted and verified in state immunization registry. Possible reinfection was defined as an infection in a person with a specimen collected ≥90 days after a positive SARS-CoV-2 diagnostic test, based on current CDC guidelines. Severity of illness was determined using established guidelines [16], and patients were grouped into the following categories: asymptomatic infection, mild or moderate illness, severe illness, critical illness. Days from the second dose of mRNA vaccine or first dose of Janssen to positive PCR were calculated.

Immunocompromised state was defined as presence of any of the following: immunosuppressive or immunomodulatory medication use, chronic steroid use, history of bone marrow transplant (BMT) or solid organ transplantation (SOT) and receipt of immunosuppressive therapy, solid tumor or hematologic malignancies on active treatment, advanced or untreated HIV. Length of stay (LOS) was calculated from index admission to discharge in days, alive or expired at time of discharge. Cardiovascular disease was defined as presence or history of cardiomyopathy, coronary artery disease (CAD), or congestive heart failure (CHF). Substance use disorder was defined as use of cocaine, heroin, marijuana, alcohol use >3 drinks per day or moderate–severe alcohol dependence. Missing data for substance abuse and alcohol use were excluded from final analysis.

Outcomes

The primary outcomes included COVID-19-associated hospitalization and mortality. COVID-19-related hospitalization was defined as hospitalization in a symptomatic person within 30 days of a SARS-CoV-2-positive specimen collection. 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. Secondary outcomes were ICU admission, need for IMV, 30-day readmission, and LOS.

Statistical Analysis

We used descriptive statistics to characterize the patient cohort. We display frequency and count data for categorical variables and mean (SD) or median (interquartile range [IQR]) for continuous variables. Median (IQR) was favored for non–normally

distributed data. For comparisons between patients based on admission or mortality status, we performed univariate analysis with the chi-square test or Fisher exact test where applicable for categorical variables and *t* test or Mann-Whitney *U* test for continuous variables. Analysis of variance (ANOVA) was performed for evaluation of vaccine type and days to diagnosis of COVID-19 breakthrough infection, with Kaplan-Meier analysis used to analyze the time to diagnosis per vaccine type. We performed multivariable logistic regression to model the relationship between COVID-19-related hospitalization and the following covariates based on statistical significance as determined by univariate analysis: sex, age, HCW status, smoking history, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM), CHF, CAD, hypertension (HTN), vaccine type, and immunocompromised state. The testing level for all analyses was .05. We performed analyses using SAS 9.4 (SAS Institute Inc, Cary, NC, USA).

Patient Consent

The study was approved by the Institutional Review Board of HFHS, Detroit, Michigan. Informed consent was waived given that the study exclusively used deidentified data.

RESULTS

Between December 30, 2020, and September 15, 2021, there were 982 breakthrough infections among ~350 000 vaccinated individuals identified in our health care system. Almost two-thirds of infections occurred in August and the first half of September 2021 (Supplementary Figure 1). Most patients were White and male, with a mean age (SD) of 57.9 (18) years. The median (interquartile range [IQR]) number of comorbidities was 2 (0–4). There were 225 (23%) immunocompromised patients and 255 (26%) HCWs in this cohort. The majority had mild or moderate symptoms; 171 (17.4%) were asymptomatic, and 127 (12%) had severe or critical illness. Of the total patients included in the study, 737 (75%) were administered BNT162b2, 185 (19%) mRNA1273, and 57 (6%) JNJ78436735. Table 1 summarizes the baseline characteristics and outcomes of the entire cohort.

The mean time from final vaccine dose to SARS-CoV-2 detection (SD) was 135 (61) days among the entire cohort, with no significant difference between hospitalized and nonhospitalized patients. Patients vaccinated with BNT162b2 exhibited the most days free from COVID-19 breakthrough infection (138 ± 62 days) as compared with both mRNA1273 (131 ± 49 days) and JNJ78436735 (99 ± 47 days) vaccination ($P < .001$). Figure 1 demonstrates the KM curve for time to breakthrough infection with SARS-CoV-2 from complete vaccination.

Of the 154 (15.7%) COVID-19-related hospitalizations, 127 (83%) had severe or critical COVID-19. Hospitalized patients were significantly older and male and had a higher prevalence of smoking history and a higher median number (IQR) of comorbidities (4 [2–6] vs 1 [0–3]; $P < .001$). Seventy-two (32%) of the immunocompromised patients were hospitalized for COVID-19, as compared with 82 (10.8%) immunocompetent patients. Among hospitalized patients, 18 (12%) received JNJ78436735, 43 (28%) received mRNA1273, and 93 (60%) received BNT162b2 vaccines ($P < .001$). Hospitalized patients exhibited lower PCR Ct as compared with nonhospitalized patients (21 ± 5 vs 28 ± 10 cycles; $P = .003$). Similarly, symptoms also correlated with Ct values, with symptomatic patients exhibiting lower Ct values (21.8 ± 6.5 cycles) as compared with asymptomatic patients (34.2 ± 8.7 cycles; $P < .001$). Table 1 highlights the univariate analysis for hospitalization for COVID-19. Supplementary Figure 2 demonstrates the mean Ct values for SARS-CoV-2 PCR identification among patients in the cohort.

Of those hospitalized, 30 (19%) required ICU admission and 19 (12%) IMV. The mean LOS was 6.7 (6.3) days, with no significant difference in patients alive or dead at the time of discharge. Nineteen (12%) patients died due to COVID-19 while hospitalized and within 30 days of diagnosis. Of those who were discharged, 11 (7%) were readmitted within 30 days for COVID-19. Table 1 further highlights these findings.

Patients who expired from COVID-19 infection were older in age (76.1 ± 11.1 vs 57.6 ± 18.2 years; $P < .001$), with a higher prevalence of chronic kidney disease ($P = .039$), COPD ($P = .003$), and cardiovascular disease ($P = .002$). Time to breakthrough infection after vaccination was also longer in patients who died (155 ± 30 vs 135 ± 61 days; $P = .011$). Table 2 highlights the univariate analysis of mortality among this cohort.

On multivariate analysis for COVID-19-related hospitalization, older age (odds ratio; OR], 1.14; 95% CI, 1.04–1.07; $P < .001$), immunocompromised status (OR, 2.57; 95% CI, 1.70–3.90; $P < .001$), and cardiovascular disease (OR, 3.02; 95% CI, 1.55–5.89; $P = .001$) were associated with need for hospitalization. HCWs (OR, 0.15; 95% CI, 0.05–0.50; $P = .002$) were less likely to be hospitalized. Furthermore, prior receipt of JNJ78436735 (OR, 2.68; 95% CI, 1.49–4.82; $P < .001$) or mRNA1273 (OR, 1.82; 95% CI, 1.23–2.71; $P < .001$) was significantly associated with need for hospitalization compared with receipt of BNT162b2 (OR, 0.436; 95% CI, 0.303–0.626; $P < .001$). These findings are highlighted in Table 3.

On multivariate analysis of COVID-19-related mortality, age (OR, 1.06; 95% CI, 1.02–1.11; $P = .006$) alone was associated with increased mortality. Prior receipt of BNT162b2 vaccination was significantly associated with decreased mortality (OR, 0.360; 95% CI, 0.145–0.898; $P = .029$). Table 4 demonstrates these findings.

DISCUSSION

We describe 982 fully vaccinated individuals with vaccine breakthrough COVID-19 infections in our health system over a

Table 1. Baseline Characteristics and Outcomes of all Patients With COVID-19 Breakthrough Infection, Including Univariate Analysis of COVID-19-Related Hospitalization

Baseline Characteristics		Total Patients	Not Hospitalized for COVID-19[a]	Hospitalized for COVID-19	*P* Value
		N = 982	n = 828	n = 154	
Vaccine type	No. (%)				**<.001**
JNJ78436735		57 (6)	39 (5)	18 (12)	
mRNA1273		185 (19)	145 (18)	43 (28)	
BNT162b2		737 (75)	644 (78)	93 (60)	
Age	Mean ± SD	57.9 ± 18	55.2 ± 17.7	72.6 ± 13.8	**<.001**
Male sex	No. (%)	417 (43)	339 (41)	78 (51)	**.025**
Race/ethnicity	No. (%)				.728
White		774 (79)	655 (79)	119 (77)	
Black		107 (11)	86 (10)	21 (14)	
Latino		21 (2)	18 (2)	3 (2)	
Other		80 (8)	69 (8)	11 (7)	
Health care worker	No. (%)	255 (26.0)	252 (30)	3 (2)	**<.001**
No. of total comorbidities	Median [IQR]	2 [0–4]	1 [0–3]	4 [2–6]	**<.001**
Body mass index	No. (%)				.634
30–39 kg/m^2		261 (26.6)	215 (33)	46 (30)	
≥40 kg/m^2		76 (7.7)	59 (9)	17 (11)	
Smoking history	No. (%)	383 (39.0)	306 (37)	77 (50)	**.002**
Substance abuse	No. (%)	63 (6.4)	54 (7)	9 (6)	.859
Chronic kidney disease	No. (%)	69 (7.0)	42 (5)	27 (18)	**<.001**
ESRD	No. (%)	12 (1.2)	5 (1)	7 (5)	**<.001**
COPD	No. (%)	112 (11.4)	75 (9)	37 (24)	**<.001**
Asthma	No. (%)	126 (12.8)	113 (14)	13 (8)	.088
Pulmonary hypertension	No. (%)	8 (0.8)	8 (1)	0 (0)	.619
Interstitial lung disease	No. (%)	2 (0.2)	2 (0)	0 (0)	1.00
Obstructive sleep apnea	No. (%)	123 (12.5)	100 (12)	23 (15)	.353
Diabetes mellitus	No. (%)	207 (21.1)	151 (18)	56 (36)	**<.001**
Cardiovascular disease	No. (%)	142 (15)	90 (11)	56 (36)	**<.001**
Hypertension	No. (%)	444 (45.2)	338 (41)	106 (69)	**<.001**
Cirrhosis	No. (%)	16 (1.6)	11 (1)	5 (3)	.091
Inflammatory bowel disease	No. (%)	24 (2.4)	13 (2)	11 (7)	.112
Rheumatoid arthritis	No. (%)	10 (1.0)	6 (1)	4 (3)	.057
Systemic lupus	No. (%)	11 (1.1)	7 (1)	4 (3)	.078
Sarcoidosis	No. (%)	5 (0.5)	3 (0)	2 (1)	.177
Immunocompromised	No. (%)	225 (22.9)	153 (18)	72 (47)	**<.001**
Solid organ transplant	No. (%)	33 (3.4)	11 (1)	11 (7)	**<.001**
Bone marrow transplant	No. (%)	0 (0)	0 (0)	0 (0)	1.00
Active hematologic malignancy	No. (%)	23 (2.3)	11 (1)	12 (8)	**<.001**
HIV	No. (%)	2 (0.2)	2 (0)	0 (0)	1.000
Systemic steroid use	No. (%)	131 (13.3)	85 (10)	46 (30)	**<.001**
On active chemotherapy	No. (%)	63 (6.4)	40 (5)	23 (15)	**<.001**
On immunosuppression	No. (%)	69 (7.0)	41 (5)	28 (18)	**<.001**
Time to breakthrough infection, d[b]	Mean ± SD	135 ± 61	-	-	**<.001**
JNJ78436735		99 ± 47	-	-	
mRNA1273		131 ± 49	-	-	
BNT162b2		138 ± 62	-	-	
SARS-CoV-2 PCR Ct[c]	Mean ± SD	28 ± 10	28 ± 10	21 ± 5	**.003**
Prior COVID infection	No. (%)	29 (3.0)	27 (3)	2 (1)	.296
Possible reinfection[d]	No. (%)	26 (2.6)	24 (2.7)	2 (1)	
Received monoclonal antibody	No. (%)	115 (11.7)	104 (13)	11 (7)	.056
Symptom severity	No. (%)				**<.001**
Asymptomatic		171 (17.4)	170 (20)	1 (1)	
Mild or moderate		684 (69.7)	658 (80)	26 (17)	
Severe		89 (9.1)	0 (0)	89 (58)	
Critical		38 (3.9)	0 (0)	38 (25)	

Table 1. Continued

Baseline Characteristics		Total Patients	Not Hospitalized for COVID-19[a]	Hospitalized for COVID-19	*P* Value
Outcomes					
ICU admission	No. (%)		-	30 (20)	
Mechanical ventilation	No. (%)		-	19 (12)	
COVID-19-related death	No. (%)		-	19 (12)	
Hospital LOS, d	Mean ± SD		-	6.71 ± 6.34	
30-d readmission	No. (%)		-	11 (7)	

Mean is presented with standard deviation; median is presented with interquartile range. Significant *P* values are bolded.

Abbreviations: ANOVA, analysis of variance; BNT162b2, Pfizer vaccine; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; Ct, cycle threshold; ESRD, end-stage renal disease; ICU, intensive care unit; IQR, interquartile range; JNJ78436735, Janssen vaccine; LOS, length of stay; mRNA1273, Moderna vaccine; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Includes 73 patients admitted for non-COVID-19-related causes and 755 patients who were not admitted at all.

[b]Analyzed with ANOVA of mean time to diagnosis according to vaccination type.

[c]CT values available for 77 patients in total (60 patients not admitted for COVID-19 and 17 patients admitted for COVID-19).

[d]Six patients were symptomatic, with 4 having mild symptoms; Ct values for asymptomatic patients who were tested on admission or before a procedure were >30.

9-month period. Most breakthrough infections occurred during the Delta surge. The majority of patients were asymptomatic or had mild to moderate disease, 13% had severe or critical illness, 16% required hospitalization, and 2% died.

In a multistate analysis of 1 228 664 individuals who completed primary vaccination series through October 2021, 2246 (0.18%) acquired COVID-19 infection; among these patients, 327 (14.6%) were hospitalized, 189 (8.4%) had severe COVID-19 outcomes (acute respiratory failure, need for noninvasive ventilation, admission to an ICU, or death), and 36 (1.6%) died [17]. Although the proportion of hospitalized patients in our cohort was similar, it is unknown what proportion of patients had COVID-19-related vs incidental COVID-19 hospitalizations in this study. However, the proportion of patients with severe COVID-19 outcomes in our cohort was higher.

The dramatic change in the number of breakthrough infections since July 2021 in our study is likely multifactorial and may be due to the emergence of the more contagious Delta variant and waning vaccine immunity over time, as previously reported [10, 11, 18–22]; the Delta variant became the dominant strain in Michigan, accounting for 99% of all viral samples sequenced since the last week in July 2021. In addition, lifting of the mask mandate and restrictions on July 1, 2021, in Michigan may also have resulted in greater community exposure risk. As of July 7, we stopped testing fully vaccinated asymptomatic patients or those who had recovered from COVID on admission or for procedures. It is possible that there were additional asymptomatic breakthrough infections that were not detected.

Risk factors for disease progression and hospitalization in our study are similar to those previously reported for unvaccinated and vaccinated individuals [7, 13, 15, 17, 18, 23–31]. Our hospitalized patients were also older and had a higher prevalence of preexisting conditions. A third of our immunocompromised patients were hospitalized. In the multivariate analysis, older age, cardiovascular disease including CHF, and immunocompromised status were associated with increased odds of hospitalization. Older age is a well-established risk factor for infection and disease progression and has been associated with breakthrough hospitalization [7, 13, 17, 18, 23–31].

Certain comorbidities, including CHF, CKD, DM, and malignancy, are also associated with higher risk of developing

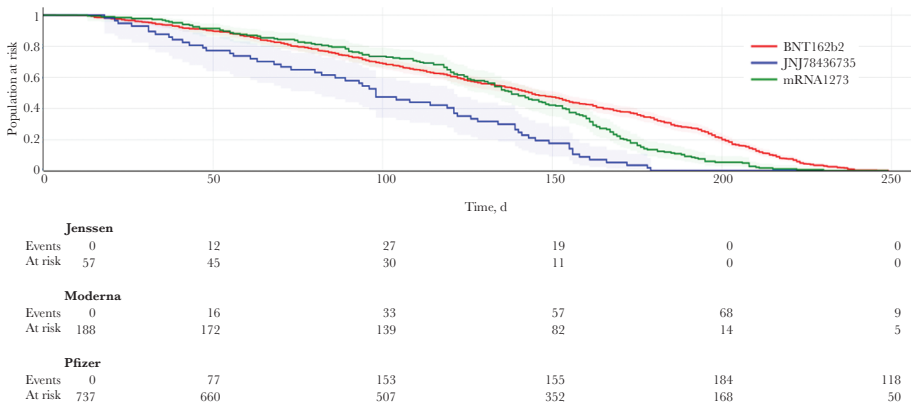

Figure 1. Days to breakthrough coronavirus disease 2019 infection according to vaccine type.

Table 2. Univariate Analysis of Mortality in Patients With COVID-19 Breakthrough Infection

Variable		Alive	Died From COVID-19[a]	*P*
		n = 951	n = 19	
Age, y	Mean ± SD	57.6 ± 18.2	76.1 ± 11.1	**<.001**
Male sex	No. (%)	409 (42)	8 (42)	.974
Health care worker	No. (%)	254 (26)	1 (5)	**.035**
Body mass index	No. (%)			.365
30–39 kg/m^2		254 (32)	7 (37)	
≥40 kg/m^2		72 (9)	4 (21)	
Smoking history		372 (39)	11 (58)	.100
Chronic kidney disease	No. (%)	65 (7)	4 (21)	**.039**
COPD	No. (%)	105 (11)	7 (37)	**.003**
Cardiovascular disease	No. (%)	132 (14)	10 (53)	**.002**
Immunocompromised		218 (23)	7 (37)	.167
Solid organ transplant		31 (3)	2 (11)	.131
Hematologic malignancy	No. (%)	21 (2)	2 (11)	.070
Vaccine type	No. (%)			.059
JNJ78436735		55 (6)	2 (11)	
mRNA1273		181 (19)	7 (37)	
BNT162b2		727 (75)	10 (53)	
Time to diagnosis, d	Mean ± SD	135 ± 61	155 ± 30	**.011**

Mean is presented with standard deviation. Significant *P* values are bolded.

Abbreviations: BNT162b2, Pfizer vaccine; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; ICU, intensive care unit; JNJ78436735, Janssen vaccine; LOS, length of stay; mRNA1273, Moderna vaccine.

[a]Twelve patients were excluded due to death from non-COVID-19-related events.

severe COVID-19 [13, 17, 18, 23–29]. In a report published during the early stages of the pandemic, the mean (SD) number of comorbidities of hospitalized patients was 3.2 (1.8) compared with 1.9 (1.7) in patients who were not hospitalized (difference, 1.3; 95% CI, 0.96–1.72; $P < .001$) [13]. In a case series of 54 hospitalized patients with breakthrough infections, 14 (26%) had severe or critical illness, with a median age (IQR) of 80.5 (76.5–85.0) years, and multiple comorbidities, including cardiovascular disease and lung disease [27]. In another observational case series, 10 Veterans Affairs hospitalized patients with breakthrough infection were >70 years of age with multiple comorbidities, including CHF, COPD, DM, and HTN [18].

Table 4. Multivariate Analysis of COVID-19 Mortality in Patients With COVID-19 Breakthrough Infection

Covariate	OR	95% CI	*P*
Male sex	0.720	0.250–2.13	.558
Age	1.06	1.02–1.11	**.006**
Health care worker	1.03	0.100–10.5	.979
Smoking history	1.07	0.360–3.20	.907
Chronic kidney disease	1.21	0.310–4.76	.787
COPD	1.73	0.550–5.42	.347
Diabetes mellitus	0.870	0.270–2.82	.812
Cardiovascular disease	2.83	0.730–11.0	.131
Hypertension	0.640	0.200–2.10	.463
Immunocompromised	0.870	0.300–2.52	.793
Vaccine type			
JNJ78436735	1.21	0.190–7.83	.843
mRNA1273	0.970	0.310–3.06	.955
BNT162b2	0.360	0.145–0.898	**.029**

Significant *P* values are bolded. Number of observations in the original data set = 982. Number of observations used = 970; 12 patients excluded due to death from non-COVID-19-related events.

Abbreviations: BNT162b2, Pfizer vaccine; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; JNJ78436735, Janssen vaccine; mRNA1273, Moderna vaccine; OR, odds ratio.

Tenforde et al. reported that 20 of 45 patients with vaccine-breakthrough COVID hospitalizations were immunocompromised, and VE was lower in this group (62.9%; 95% CI, 20.8%–82.6%) compared with those without immunosuppression (91.3%; 95% CI, 85.6%–94.8%) [26]. In a recently published multistate analysis of >89 000 hospitalized patients, the VE of the mRNA vaccines against COVID-19-associated hospitalization was 77% (95% CI, 74%–80%) in immunocompromised adults compared with 90% (95% CI, 89%–91%) in immunocompetent adults, irrespective of age. Moreover, VE varied across this patient population and ranged from 59% in SOT or BMT patients to 81% in patients with a rheumatologic or inflammatory disorder [32]. This was further supported by another study that demonstrated that the association between mRNA vaccination and reduced risk of COVID-19 hospitalization was notably weaker in the immunocompromised patient population [7].

Comparative data on secondary outcomes (LOS, ICU-level care, need for IMV, readmission) and mortality in hospitalized patients with breakthrough infections are limited [6, 7, 17, 25–27, 33]. Our findings support the observations of earlier studies of ICU-level care [6, 7]. In a large multistate study involving adults ≥50 years of age, 2470 of 15 581 or 16%

Table 3. Multivariate Analysis of COVID-19 Hospitalization in Patients With COVID-19 Breakthrough Infection

Covariate	OR	95% CI	*P*
Male sex	1.14	0.76–1.70	.539
Age	1.06	1.04–1.07	**<.001**
Health care worker	0.15	0.05–0.50	**.002**
Smoking history	0.92	0.60–1.40	.685
Chronic kidney disease	1.19	0.64–2.19	.583
COPD	1.05	0.63–1.77	.848
Diabetes mellitus	1.37	0.87–2.15	.171
Cardiovascular disease	3.02	1.55–5.89	**.001**
Hypertension	0.86	0.54–1.37	.521
Immunocompromised	2.57	1.70–3.90	**<.001**
Vaccine type			
JNJ78436735	2.68	1.49–4.82	**<.001**
mRNA1273	1.82	1.23–2.71	**.003**
BNT162b2	0.436	0.303–0.626	**<.001**

Odds ratio is presented with 95% CI. Significant *P* values are bolded. Number of observations in the original data set = 982. Number of observations used = 982.

Abbreviations: BNT162b2, Pfizer vaccine; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; JNJ78436735, Janssen vaccine; mRNA1273, Moderna vaccine; OR, odds ratio.

of patients with breakthrough infections required ICU-level care [6].

The overall mortality among those with breakthrough infections was low [17]. However, mortality was 12% among our hospitalized patients and 15% among those with severe or critical COVID-19. This is in contrast to a recent study where the need for IMV was 7.7% and mortality 6.3% among 142 hospitalized patients [7]. Our patients who expired from COVID-19 had a mean age >75 years and had higher prevalence of underlying comorbidities, in addition to longer time from final vaccine dose to SARS-CoV-2 detection. In the multivariable analysis, age was the only risk factor associated with mortality. This may be attributed to lower immune response to vaccines and waning immunity.

In our study, prior receipt of BNT162b2 vaccine was associated with significantly lower odds of breakthrough hospitalization compared with receipt of JNJ78436735 or mRNA1273 vaccine and mortality, independent of age, HCW status, and other variables. Interestingly, this contrasts with previous studies that reported higher VE in mRNA1273 [5, 7, 17, 20]. Thirty percent of our cohort were HCWs with a mean age of 45 years, which may have affected the results; however, our overall study population contained a diverse group of patients. HFHS expanded the BNT162b2 vaccine to elderly and immunocompromised patients after prioritizing our HCWs early on. These groups are known to have a less robust response to vaccines with possible waning immunity overtime and are at higher risk for severe COVID-19 [19].

To conclude, the odds of COVID-19-related hospitalization after breakthrough infection increased in older adults, patients who were immunocompromised, or patients with multiple comorbidities and decreased in HCWs and those who received BNT162b2. Despite vaccination, older age remained a significant risk factor for mortality. Thus, patients who are older, have underlying comorbidities, or are immunocompromised may benefit from early treatment modalities and COVID-19-mitigating strategies, especially in areas with substantial or high transmission rates.

Limitations

The findings in this report are subject to several limitations. It was a retrospective study conducted at a single large health system in Southeast Michigan; however, a diverse patient population was included in the study. It is possible that not all breakthrough infections were captured in our health system, including those who had at-home or MinuteClinic testing, which might introduce selection bias. This was less of a concern since Epic was integrated with other health care systems that utilized EHRs. Moreover, patients who are asymptomatic or mildly symptomatic may not seek testing and be underrepresented. We did not measure immunity or report VE in our cohort due to multiple prior studies having assessed this. We did not compare risk factors and outcomes in hospitalized patients (alive vs dead) due to the small sample size. In addition, the primary goal of this investigation was to characterize and describe demographics and outcomes of breakthrough infections, so no control group was used. This limits the conclusions that can be made regarding vaccine efficacy in breakthrough infections as compared with unvaccinated controls.

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