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Geehan Suleyman

Raef Fadel

Ayman Alsaadi

Luis Ng Sueng

Ali H. Ghandour

See next page for additional authors

Authors

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MAJOR ARTICLE

Progression to Critical Illness and Death in Patients With Breakthrough Hospitalizations

Geehan Suleyman,[1,2,*] Raef Fadel,[3,*] Ayman Alsaadi,[3] Luis Ng Sueng,[3] Ali Ghandour,[3] Ahmad Alkhatib,[3] Tarandeep Singh,[3] Austin Parsons,[3] Joseph Miller,[2,4] Mayur Ramesh,[1] Indira Brar,[1,2] and George Alangaden[1,2]

[1]Division of Infectious Disease, Henry Ford Hospital, Detroit, Michigan, USA, [2]Wayne State University School of Medicine, Detroit, Michigan, USA, [3]Department of Internal Medicine, Henry Ford Hospital, Detroit, Michigan, USA, and [4]Department of Emergency Medicine, Henry Ford Hospital, Detroit, Michigan, USA

Background. Characterization of disease progression and outcomes after coronavirus disease 2019 (COVID-19)–related hospitalization in vaccinated compared with unvaccinated individuals is limited.

Methods. This was a retrospective case–control study of symptomatic vaccinated (cases) and unvaccinated (controls) participants hospitalized for COVID-19 between December 30, 2020, and September 30, 2021, in Southeast Michigan. Hospitalized adult patients with lab-confirmed COVID-19 were identified through daily census report. Breakthrough infection was defined as detection of severe acute respiratory syndrome coronavirus 2 ≥14 days after completion of the primary vaccination series. The association between prior vaccination and critical COVID-19 illness (composite of intensive care unit [ICU] admission, invasive mechanical ventilation [IMV], 28-day mortality) was examined.

Results. Two hundred ten (39%) fully vaccinated and 325 (61%) unvaccinated patients were evaluated. Compared with controls, cases were older, had more comorbidities (4 [3–7] vs 2 [1–4]; $P < .001$), and were more likely to be immunocompromised. Cases had less severe symptoms compared with controls (2 [1–2] vs 2 [2–3]; $P < .001$) and were less likely to progress to critical COVID-19 illness (33.3% vs 45.5%; $P < .001$); 28-day mortality was significantly lower in cases (11.0% vs 24.9%; $P < .001$). Symptom severity (odds ratio [OR], 2.59; 95% CI, 1.61–4.16; $P < .001$) and modified Sequential Organ Failure Assessment score on presentation (OR, 1.74; 95% CI, 1.48–2.06; $P < .001$) were independently associated with development of critical COVID-19 illness. Prior vaccination (OR, 0.528; 95% CI, 0.307–0.910; $P = .020$) was protective.

Conclusions. COVID-19-vaccinated patients were less likely to develop critical COVID-19 illness and more likely to survive. Disease severity at presentation was a predictor of adverse outcomes regardless of vaccination status.

Keywords. breakthrough hospitalizations; COVID-19; critical illness; mortality; risk factors.

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in >289 million cases and 5.4 million deaths globally as of January 2, 2022 [1]. COVID-19 vaccines are the leading strategy to change the course of the ongoing global pandemic. Randomized clinical trials have demonstrated COVID-19 vaccines to be highly effective in preventing symptomatic infections [2, 3], and observational studies have shown that COVID-19 vaccines are highly effective at preventing severe symptomatic disease, hospitalization, and death [4–7]. Early in the course of the pandemic, vaccine

effectiveness against COVID-19-related hospitalization was found to be 97% in a national registry in Israel [8]. Vaccine effectiveness for the prevention of hospitalization due to COVID-19 was >85% in several postmarketing studies [4, 9].

Despite high vaccine efficacy, vaccine breakthrough infections are now commonly reported. As vaccines are not 100% effective, the number of breakthrough infections and hospitalizations is expected to increase when community spread is high, particularly with emergence of new COVID-19 variants. Lower vaccine effectiveness in preventing COVID-19-related hospitalization has been observed among older and immunocompromised patients in previous studies [4, 7, 10–12]. In a large multistate analysis, the vaccine effectiveness of the mRNA vaccines against COVID-19-associated hospitalization was 77% in the immunocompromised adults compared with 90% in the immunocompetent adults [12].

A recent study showed that vaccinated individuals with breakthrough infections had a lower risk of disease progression [7]. However, this study was limited by the small number of hospitalized patients. The objective of our study was to assess the impact of prior vaccination on disease progression and outcomes among hospitalized patients with COVID-19.

METHODS

Study Design and Participants

This was a case–control study of consecutive adult patients hospitalized with COVID-19 vaccine breakthrough 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 the first COVID-19 vaccine), to September 30, 2021. All clinical outcomes were monitored for 28 days.

Hospitalized adult patients with positive SARS-CoV-2 diagnostic assays were identified through the daily census report. Cases included fully vaccinated patients hospitalized for symptomatic lab-confirmed COVID-19 from December 30, 2020, to September 30, 2021. Full vaccination was defined as completion of 2 doses of mRNA-1273 (Moderna) or BNT162b2 (Pfizer-BioNTech) or 1 dose of JNJ78436735 (Janssen) ≥14 days before the testing date. Similarly, control patients were defined as consecutive unvaccinated adults hospitalized for symptomatic lab-confirmed COVID-19 within 2 weeks of hospitalization of identified cases. The first SARS-CoV-2 test within this eligibility period was used. Subjects were excluded if they were partially vaccinated (<14 days since completing the primary series or not completing the series before the specimen collection date), were not hospitalized for COVID-19 infection, had incomplete data, expired in the ED, or were asymptomatic with positive repeat polymerase chain reaction tests within 90 days of a previous SARS-CoV-2 infection.

Definitions

Vaccine breakthrough infection was defined as detection of SARS-CoV-2 ≥14 days after receipt of the primary COVID-19 vaccine series. Possible reinfection was defined as an infection in a person with a specimen collected ≥90 days after a positive SARS-CoV-2 diagnostic test. 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.

Data Collection

A retrospective review of electronic medical records (EMRs) was performed to obtain demographic, clinical, and laboratory data. Race/ethnicity data were collected in the EMR by self-report using standard classification. Comorbidities associated with higher risk of developing severe outcomes of COVID-19 [13] were extracted using International Classification of Diseases (ICD), 10th revision, codes. Based on the most recent recorded body mass index (BMI), obesity was defined as a BMI ≥ 30 kg/m^2, and morbid obesity as BMI ≥40 (CDC obesity) [14]. Immunocompromised state was defined as presence of any of the following: immunosuppressive or immunomodulatory medication use, >20 mg of prednisone or equivalent per day for >2 weeks, history of hematopoietic stem cell transplant (HCT) or solid organ transplantation (SOT) and receipt of immunosuppressive therapy, solid tumor or hematologic malignancy on active treatment, and advanced or untreated HIV [15]. Cardiovascular disease was defined as presence or history of cardiomyopathy, coronary artery disease (CAD), or congestive heart failure (CHF). Chronic kidney disease (CKD) was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria (KDIGO 2012) [16].

Vaccination status, including specific vaccine type and vaccination dates, was verified in the EMR and state immunization registry. Receipt of monoclonal antibodies (MABs) was recorded.

Severity of illness was determined using established guidelines [17], and patients were grouped into the following categories: 0 for asymptomatic infection, 1 for mild or moderate illness, 2 for severe illness, 3 for critical illness. Modified Sequential Organ Failure Assessment (mSOFA) scores were calculated and used as a well-validated predictor of mortality [18]. Oxygen saturation (SpO2) to fraction of inspired oxygen (FiO2) ratio was used as part of the mSOFA score to calculate patient hypoxia on admission.

Complications included acute kidney injury (AKI), need for renal replacement therapy (RRT), venous thromboembolism (VTE), secondary bacterial infections or candidemia, acute respiratory distress syndrome (ARDS), and shock requiring vasopressors. ARDS was defined in accordance with the Berlin Definition [19]. Acute kidney injury was identified according to the Kidney Disease: Improving Global Outcomes definition [16]. Receipt of COVID-19 treatment (corticosteroids, remdesivir, tocilizumab, or baricitinib) and antibiotics was evaluated. Primary outcomes included critical COVID-19 illness (ICU admission, invasive mechanical ventilation [IMV], 28-day mortality), and secondary outcomes included extubated alive, ventilator-free days, length of stay (LOS), and 28-day readmission. Ventilator-free days were calculated as: 28 days minus the number of days on mechanical ventilation. LOS was calculated from index admission to discharge in days, either alive or expired at the time of discharge.

Laboratory Studies

Methods for laboratory confirmation of SARS-CoV-2 infection have been previously described [20]. Creatinine, total bilirubin, absolute lymphocyte count, C-reactive protein (CRP), troponin, creatine phosphokinase (CPK), ferritin, D-dimer, and interleukin 6 were collected when available on admission.

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 SD for normally distributed continuous variables, and median with interquartile range (IQR) for skewed continuous variables. The chi-square or Fisher exact test was applied for computation of categorical variables, and the t test or Mann-Whitney U test was used for continuous variables. Kaplan-Meier analysis was used to evaluate 28-day mortality in both vaccinated and unvaccinated populations. Multivariable logistic regression was performed to model the relationship between COVID-19-related death and the following covariates: age, race, immunocompromised state, vaccination status, symptom severity, mSOFA, and intubation. Additionally, a second multivariable logistic regression was performed to model the relationship between critical COVID-19 development and the following covariates: age, immunocompromised state, vaccination status, symptom severity, mSOFA, and SpO2/FiO2 on admission. A third multivariable logistic regression was performed with fully vaccinated patients, modeling the following covariates: age, immunocompromised state, symptom severity, mSOFA score on presentation, and SpO2/FiO2 on admission. Such covariates were selected based on statistical significance in univariate analysis ($P < .05$). SpO2/FiO2 was used in the model for critical COVID-19 development given its utility in determining hypoxia and guiding medical decision-making in the mSOFA score. The testing level for all analyses was .05 for statistical significance. Analyses were performed 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

A total of 535 patients, consisting of 210 (39%) vaccinated or case patients and 325 (61%) unvaccinated patients or controls, were included in the case–control analysis. Eighty-five vaccinated patients were hospitalized for alternative diagnoses, had incomplete data, or died in the ED and were excluded.

Compared with unvaccinated patients, vaccine breakthrough cases were older (72.7 ± 13.4 vs 57.2 ± 17.3 years; $P < .001$), less likely to be Black (13.3% vs 32.6%; $P < .001$), and had a higher number of comorbidities (4 [3–7] vs 2 [1–4]; $P < .001$). Case patients had a lower average BMI (31.5 ± 7.8 vs 33.4 ± 9.3; $P = .013$), with no significant difference in sex. Comorbidities, including tobacco use history (52.9% vs 33.5%; $P < .001$), CKD (42.4% vs 18.5%; $P < .001$), COPD (25.7% vs 14.5%; $P = .001$), OSA (14.8% vs 8.3%; $P = .019$), diabetes mellitus (38.6% vs 27.4%; $P = .007$), cardiovascular disease (32.4% vs 12.6%; $P < .001$), and hypertension (71.4% vs 36.2%; $P < .001$), were more prevalent in the vaccinated group. Vaccinated patients were also more likely to be

immunocompromised ($P = .002$). The majority of vaccinated patients received the BNT162b2 vaccine.

On presentation to the hospital, vaccinated patients were less symptomatic (96.7% vs 100%; $P = .013$) and had less severe symptoms on presentation (2 [1–2] vs 2 [2–3]; $P < .001$). There was no statistical difference in mSOFA score between the 2 groups, and there was no difference in rate of admission to the general practice unit (GPU) or ICU. Additionally, there was no significant difference in SpO2/FiO2 on admission. Vaccinated patients were less likely to require corticosteroids (82.9% vs 92.3%; $P = .011$) or tocilizumab (8.1% vs 17.5%; $P = .002$) during their index hospitalization. Table 1 demonstrates the results of the baseline characteristics of included patients.

During hospitalization, vaccinated patients were less likely to progress to critical COVID-19 illness ($P < .001$), including lower rates of admission to the ICU (32.4% vs 42.8%; $P = .016$), mechanical ventilation (13.3% vs 21.8%; $P = .013$), and 28-day mortality (11.0% vs 24.9%; $P < .001$). Additionally, vaccinated patients had more ventilator-free days (27 ± 4.2 vs 28.0 ± 2.6 days; $P = .041$) and lower rates of ARDS (10% vs 19.7%; $P = .003$) and venous thromboembolism development (3.3% vs 8.6%; $P = .016$). Otherwise, there was no significant difference in rates of being extubated alive (32% vs 10%; $P = .158$) or complications, including secondary bacterial or fungal infection, acute kidney injury requiring RRT, shock, hospital LOS, or readmission within 28 days for COVID-19. Table 2 highlights the complications and primary and secondary outcomes.

On multivariable logistic regression, symptom severity (OR, 2.59; 95% CI, 1.61–4.16; $P < .001$) and mSOFA score on presentation (OR, 1.74; 95% CI, 1.48–2.06; $P < .001$) were independently associated with development of critical COVID-19 illness in both groups. Additionally, age (OR, 1.05; 95% CI, 1.02–1.08; $P < .001$), symptom severity (OR, 17.4; 95% CI, 5.58–54.1; $P < .001$), mSOFA score on presentation (OR, 1.24; 95% CI, 1.04–1.47; $P = .012$), and IMV (OR, 4.66; 95% CI, 1.54–14.1; $P = .006$) were found to be independently associated with COVID-19-related death. Prior vaccination was protective against disease progression (OR, 0.528; 95% CI, 0.307–0.910; $P = .020$) and mortality (OR, 0.184; 95% CI, 0.080–0.440; $P < .001$). In the vaccinated cohort, only mSOFA score on admission (OR, 1.64; 95% CI, 1.31–2.05; $P < .001$) was significantly associated with development of critical COVID-19 illness. Figure 1 and Supplementary Tables 1–3 demonstrate the 3 multivariable logistic regression analyses with associated odds ratios. Vaccination status was significantly associated with a lower 28-day mortality on Kaplan-Meier analysis ($P < .001$), as demonstrated in Figure 2.

DISCUSSION

In this large case–control study, hospitalized patients with prior COVID-19 vaccination were less likely to experience severe

Table 1. Baseline Characteristics of Vaccinated (n = 210) vs Unvaccinated (n = 325) Patients Hospitalized for COVID-19

		Total	Vaccinated	Unvaccinated	P Value*
Baseline characteristics		n = 535	n = 210	n = 325	
Age, y	Mean (SD)	63 (18)	73 (13)	57 (17)	**<.001**
Male sex	No. (%)	262 (49.0)	106 (50.5)	156 (48.0)	.577
Black race	No. (%)	134 (25.0)	28 (13.3)	106 (32.6)	**<.001**
Health care worker	No. (%)	7 (1.3)	6 (2.9)	1 (0.3)	.126
BMI, kg/m²	Mean (SD)	32.6 (8.8)	31.5 (7.8)	33.4 (9.3)	**.013**
Comorbid conditions	Median (IQR)	3 (2–5)	4 (3–7)	2 (1–4)	**<.001**
Obesity	No. (%)	296 (55.3)	107 (51.0)	189 (58.2)	.102
Tobacco smoking history	No. (%)	220 (41.1)	111 (52.9)	109 (33.5)	**<.001**
Chronic kidney disease	No. (%)	149 (27.9)	89 (42.4)	60 (18.5)	**<.001**
End-stage renal disease	No. (%)	7 (1.3)	6 (2.9)	1 (0.3)	**.011**
COPD	No. (%)	101 (18.9)	54 (25.7)	47 (14.5)	**.001**
Asthma	No. (%)	67 (12.5)	20 (9.5)	47 (14.5)	.092
Obstructive sleep apnea	No. (%)	58 (10.8)	31 (14.8)	27 (8.3)	**.019**
Diabetes mellitus	No. (%)	170 (31.8)	81 (38.6)	89 (27.4)	**.007**
Cardiovascular disease	No. (%)	109 (20.4)	68 (32.4)	41 (12.6)	**<.001**
Hypertension	No. (%)	300 (56.1)	150 (71.4)	150 (46.2)	**<.001**
Inflammatory bowel disease	No. (%)	12 (2.2)	6 (2.9)	6 (1.8)	.442
Rheumatoid arthritis	No. (%)	7 (1.3)	5 (2.4)	2 (0.6)	.080
Sarcoidosis	No. (%)	77 (14.4)	74 (35.2)	3 (0.9)	**<.001**
Immunocompromised state	No. (%)	224 (41.9)	105 (50.0)	119 (36.6)	**.002**
HIV		6 (1.1)	4 (1.9)	2 (0.6)	.167
Solid organ transplant		26 (4.9)	17 (8.1)	9 (2.8)	**.005**
Solid tumor		26 (4.9)	18 (8.6)	8 (2.5)	**.001**
Hematologic Malignancy		14 (2.6)	13 (6.2)	1 (0.3)	**<.001**
Systemic steroid use		171 (32.0)	72 (34.3)	99 (30.5)	.355
On active chemotherapy		30 (5.6)	25 (11.9)	5 (1.5)	**<.001**
Immunosuppressant use		38 (7.1)	31 (14.8)	7 (2.2)	**<.001**
Vaccine type	No. (%)				
JNJ78436735			25 (11.9)		
mRNA1273			62 (29.5)		
BNT162b2			123 (58.6)		
Prior COVID-19	No. (%)	5 (0.9)	4 (1.9)	1 (0.3)	.061
Symptoms on admission	No. (%)	532 (99.4)	203 (96.7)	325 (100.0)	**.013**
Symptom severity	Median (IQR)	2 (2–3)	2 (1–2)	2 (2–3)	**<.001**
MAB treatment	No. (%)	40 (7.5)	20 (9.5)	20 (6.2)	.148
Admit floor	No. (%)				.119
GPU		377 (70.5)	156 (74.0)	221 (68.0)	
ICU		158 (29.5)	54 (26.0)	104 (32.0)	
mSOFA on presentation	Median (IQR)	2 (1–4)	3 (1–4)	2 (1–5)	.168
Required O2 on admission	No. (%)	384 (71.8)	147 (70.0)	237 (72.9)	.464
SpO2/FiO2 on admission	Mean (SD)	285.3 (130.6)	293.5 (129.6)	279.9 (130.9)	.239
Treatments received	No. (%)				
Remdesivir		340 (63.6)	133 (63.3)	207 (63.7)	.933
Systemic corticosteroids		474 (88.6)	174 (82.9)	300 (92.3)	**.011**
Tocilizumab		74 (13.8)	17 (8.1)	57 (17.5)	**.002**
Baricitanib		20 (3.7)	9 (4.3)	11 (3.4)	.592
Antibiotics		135 (25.2)	58 (27.6)	77 (23.7)	.308

Mean is presented with SD; median is presented with interquartile range.

Abbreviations: BMI, body mass index; BMT, bone marrow transplant; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; FiO2, fraction of inspired oxygen; GPU, general practice unit; ICU, intensive care unit; IQR, interquartile range; MAB, monoclonal antibody; mSOFA, modified sequential organ failure assessment; O2, oxygen; SLE, systemic lupus erythematosus; Spo2, oxygen saturation.

*Significant P values are bolded.

illness and to progress to ICU-level care, IMV, or death as compared with unvaccinated controls. Additionally, vaccination status was the strongest independent predictor of survival of COVID-19 disease. Administration of corticosteroids or tocilizumab and complications such as VTE and ARDS also occurred less commonly among the vaccinated cohort. These

Table 2. Complications and Outcomes of Vaccinated (n = 210) vs Unvaccinated (n = 325) Patients Hospitalized for COVID-19

		Total n = 535	Vaccinated n = 210	Unvaccinated n = 325	P Value*
Primary outcomes					
Critical COVID-19	No. (%)	218 (41.0)	70 (33.3)	148 (45.5)	<.001
ICU admission		207 (38.7)	68 (32.4)	139 (42.8)	.016
Mechanical ventilation		99 (18.5)	28 (13.3)	71 (21.8)	.013
28-d mortality		104 (19.4)	23 (11.0)	81 (24.9)	<.001
Secondary outcomes					
Extubated alive[a]	No. (%)	16 (16)	9 (32)	7 (10.0)	.158
Ventilator-free d	Mean (SD)	27.4 (3.2)	27.0 (4.2)	28.0 (2.6)	.041
Hospital LOS, d	Median (IQR)	5 (3–10)	6 (3–10)	5.5 (4–10)	.093
30-d readmission for COVID-19	No. (%)	37 (6.9)	14 (6.7)	23 (7.1)	.855
Complications					
Acute kidney injury	No. (%)	184 (34.4)	73 (34.8)	111 (34.2)	.885
Required renal replacement therapy	No. (%)	28 (5.2)	10 (4.8)	18 (5.5)	.621
Acute respiratory distress syndrome	No. (%)	85 (15.9)	21 (10.0)	64 (19.7)	.003
Venous thromboembolism	No. (%)	35 (6.5)	7 (3.3)	28 (8.6)	.016
Ventilator-associated pneumonia	No. (%)	43 (8.0)	12 (5.7)	31 (9.5)	.113
Bacteremia	No. (%)	23 (4.3)	11 (5.2)	12 (3.7)	.390
Candidemia	No. (%)	2 (0.4)	0 (0.0)	2 (0.6)	.256
Required vasopressor support	No. (%)	30 (5.8)	11 (5.2)	19 (5.8)	.781

Mean is presented with SD; median is presented with interquartile range.

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay.

*Significant P values are bolded.

[a]Analyzed based on the number of patients requiring mechanical ventilation (n = 99) and not the entire population.

findings are consistent with prior studies that suggest that SARS-CoV-2 vaccination attenuates disease severity and critical COVID-19 development among vaccine breakthrough infections [7].

Among our cohort, Blacks were less likely to be vaccinated. As of December 20, 2021, only 36.5% of Blacks were fully vaccinated, compared with 50.4% of Whites and 52.3% of American Indians/Alaska Natives in Michigan [21]. In Metropolitan Detroit, 57.9% of the population was fully vaccinated [21]; however, in the City of Detroit, where 77% of the population is Black [22], only 41.6% of residents were fully vaccinated [21]. Studies suggest that Blacks are less likely to be vaccinated against COVID-19 compared with Whites or other racial and ethnic minority groups due to multiple challenges, including but not limited to distrust of the health care system, lack of access to a personal vehicle or reliable transportation, and lack of access to quality health care [23].

Risk factors for hospitalization and disease progression among vaccine breakthrough infections in our study are similar to those previously reported. Our vaccinated cohort was older and had a higher number of comorbidities compared with the unvaccinated group. Older age and underlying medical conditions are risk factors for disease progression, including death, in both vaccinated and unvaccinated patients [7, 8, 10, 11, 14, 24–28]. A higher proportion of older adults have been fully vaccinated compared with younger ones, and older adults may be more likely to be represented in breakthrough cases [27].

Nevertheless, a disproportionately large share of breakthrough COVID-19 hospitalizations occurs in those who are 65 years and older [27]. Similar to previous studies, the vaccinated cohort was more likely to have diabetes, hypertension, CAD, and CKD [26]. Older adults are more likely to be affected by underlying comorbidities, which predisposes them to greater risk for severe disease, regardless of vaccination status. They also have a less robust immune response than younger individuals, with waning immunity over time. An analysis demonstrated that more than two-thirds of breakthrough COVID-19 hospitalizations occurred among people ≥65 years of age who had certain chronic conditions, including hypertension, diabetes, and cardiovascular disease, compared with unvaccinated hospitalized younger patients [29].

Half of breakthrough hospitalizations occurred in immunocompromised patients, particularly among those who received systemic steroids, immunosuppressive agents, or chemotherapy. Multiple studies have demonstrated lower antibody response and vaccine effectiveness against vaccine breakthrough infection and hospitalization in the immunocompromised patient population, which predispose them to higher risk for worse outcomes [7, 12]. The risk varies by type, severity, and activity of the underlying condition, immunosuppressive treatment regimen, age, and comorbidities, among others. Boyarsky and colleagues evaluated more than 400 SOT recipients who received an mRNA COVID-19 vaccine and found that only 17% had detectable antibodies after 1 dose [30]. In a subsequent study of >650 transplant recipients, almost half had no detectable
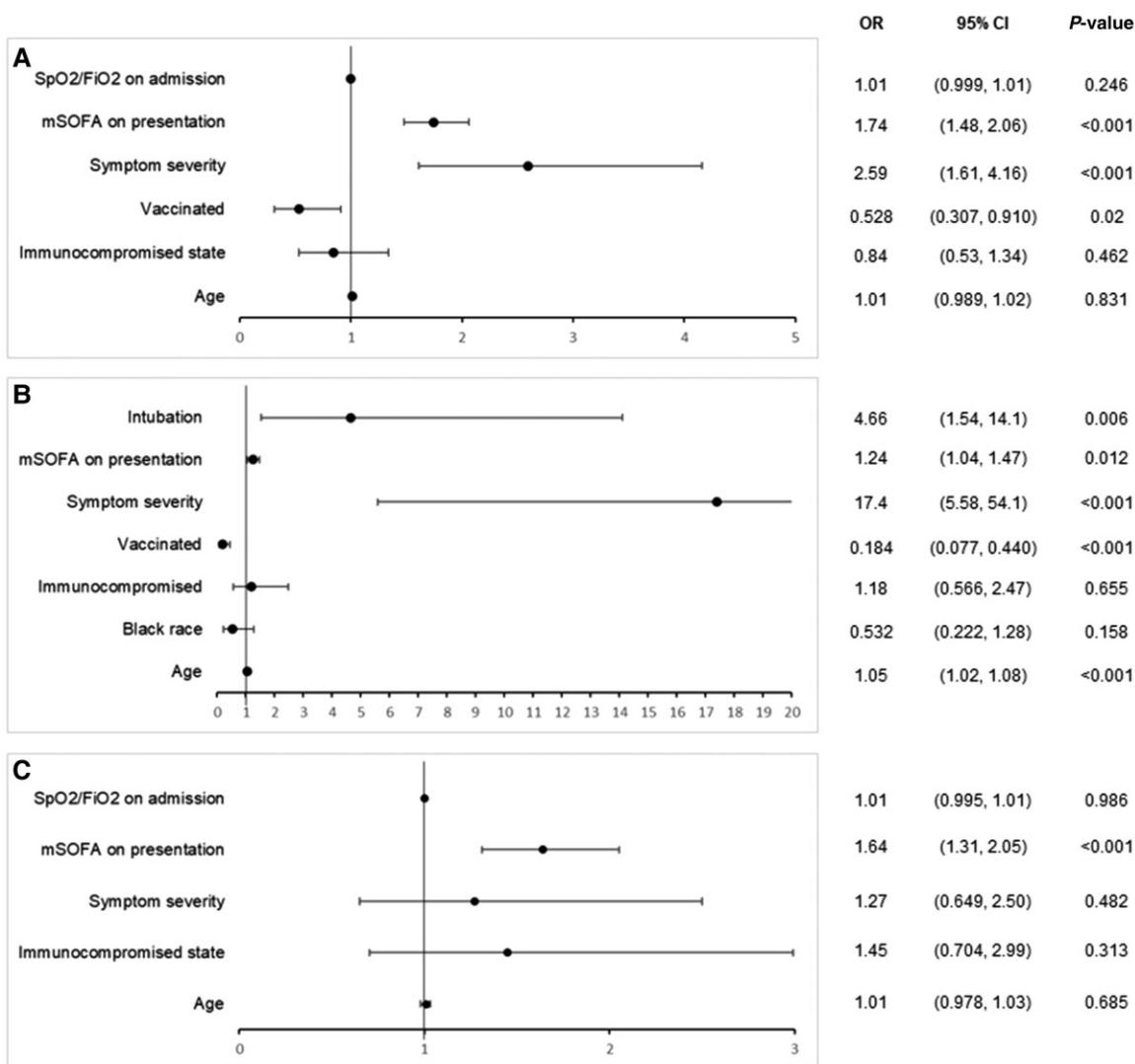
Figure 1. Three-panel scatter plot demonstrating multivariable logistic regression of (A) critical COVID-19 development in vaccinated and unvaccinated cohorts, (B) COVID-19-related 28-day mortality in vaccinated and unvaccinated cohorts, and (C) critical COVID-19 development in the vaccinated cohort. Dependent variable for (A) = composite of admission to ICU, need for mechanical ventilation, development of ARDS, and/or COVID-19-related death. Dependent variable for (B) = COVID-19-related death. Dependent variable for (C) = composite of admission to ICU, need for mechanical ventilation, development of ARDS, and/or COVID-19-related death. Abbreviations: ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; FiO2, fraction of inspired oxygen; ICU, intensive care unit; mSOFA, modified Sequential Organ Failure Assessment; Spo2, oxygen saturation.

response after 1 or 2 doses of the mRNA vaccines; 39% did not respond to the first dose but did to the second dose [31]. A recent report found that mRNA vaccine effectiveness ranged widely among immunocompromised subgroups and was lowest in SOT or HCT recipients and highest in patients with rheumatologic or inflammatory disorders [12]. In a systematic review of cancer, HCT, and SOT patients with COVID-19 infection, adult cancer and SOT patients had more comorbidities, greater need for intensive care support, and higher rates of hospital mortality than the general population [32].

Emerging data suggest that vaccination is not only associated with reduced risk of symptomatic infection but also severe COVID-19 illness [7]. Upon presentation, unvaccinated patients had more severe symptoms, which was a strong predictor of disease progression and death. For the vaccinated patients, a higher mSOFA score on presentation, which is a marker of disease severity and a prognostic indicator, was the only independent risk factor associated with critical illness progression. During the hospitalization, vaccinated patients were less likely to progress to critical COVID-19 illness compared with controls even though the mSOFA score was similar between the groups. Our findings support the observations of a recently published study, which demonstrated that hospitalized breakthrough cases were less likely to receive ICU-level care and IMV and less likely to progress to death [7].
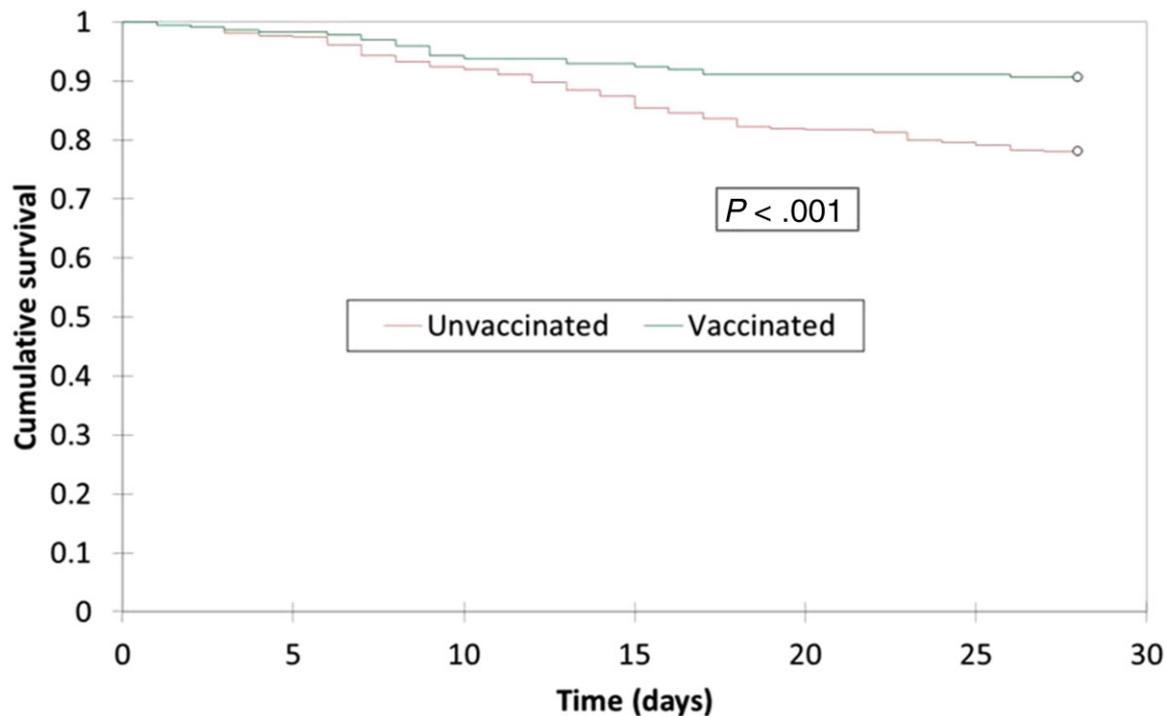
Figure 2. Kaplan-Meier analysis of 28-day mortality in vaccinated (n = 210) vs unvaccinated (n = 325) patients hospitalized for COVID-19. Abbreviation: COVID-19, coronavirus disease 2019.

Although mortality was lower after vaccination than in unvaccinated patients, it remained high in our hospitalized individuals: Overall mortality was 11%. This was higher than the 6.3% that was recently reported among 142 hospitalized patients [7]. Our breakthrough cases were older, with a mean age of 73, and had a higher prevalence of underlying comorbidities compared with previous reports [7, 25]. Additionally, half were immunocompromised. Age (OR, 1.05; 95% CI, 1.02–1.08; $P < .001$) was independently associated with COVID-19-related death in our cohort, which may be attributed to lower immune response to vaccines and waning immunity. Although prior vaccination was protective against disease progression and death, higher mSOFA score, which correlated with severe COVID-19, was independently associated with COVID-19-related death.

The association of disease severity at presentation with progression to critical COVID-19 and death in vaccinated patients highlights the role of early testing to detect breakthrough infections. Early diagnosis could lead to prompt treatment with novel therapies, including MABs and antiviral agents, in patients at high risk for severe outcomes.

Limitations

This study has a few 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. We did not measure immunity or report vaccine effectiveness in our cohort due to multiple prior studies having assessed this. It is possible that vaccination status was not captured for individuals who received their vaccines out of state, and these patients could have been inadvertently excluded or placed in the control group. Although there is concern for selection bias, controls who met inclusion criteria were randomly selected.

CONCLUSIONS

Our findings suggest that SARS-CoV-2 vaccination attenuates disease severity and critical COVID-19 development among vaccine breakthrough infections. Disease severity at presentation was a predictor of adverse outcomes in both vaccinated and unvaccinated patients. In addition to the vaccines, early testing of symptomatic individuals and prompt administration of effective therapy such as MABs and/or oral antivirals should be the next priority to prevent disease progression and reduce mortality in high-risk patients regardless of vaccination status.

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