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Clinical Features and Outcomes of Hospitalized Adult Patients With Breakthrough COVID-19 Infections: A Propensity-Score–Matched Observational Study

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In this study, we aimed to evaluate the impact of vaccination on intensive care unit (ICU) admission and in-hospital mortality among breakthrough coronavirus disease 2019 (COVID-19) infections. A total of 3,351 adult patients hospitalized with COVID-19 in the Memorial Healthcare System (Hollywood, Florida) between June 1 and September 20, 2021, were included; 284 (8.5%) were fully vaccinated. A propensity-score–matched analysis was conducted to compare fully vaccinated patients with unvaccinated controls. Propensity scores were calculated on the basis of variables associated with vaccination status. A 1:1 matching ratio was applied using logistic regression models, ensuring balanced characteristics between the two groups. The matched samples were then subjected to multivariate analysis. Among breakthrough infections, vaccinated patients demonstrated lower incidences of ICU admission (10.3% vs. 16.4%; $P = 0.042$) and death (12.2% vs. 18.7%; $P = 0.041$) than the matched controls. Risk-adjusted multivariate analysis demonstrated a significant inverse association between vaccination and ICU admission (odds ratio = 0.52, 95% confidence interval: 0.31, 0.89; $P = 0.019$) as well as in-hospital mortality (odds ratio = 0.57, 95% confidence interval: 0.34, 0.94; $P = 0.027$). Vaccinated individuals experiencing breakthrough infections had significantly lower risks of ICU admission and in-hospital mortality. These findings highlight the benefits of COVID-19 vaccines in reducing severe outcomes among patients with breakthrough infections.

breakthrough infection; coronavirus disease 2019; COVID-19; in-hospital mortality; intensive care; SARS-CoV-2; SARS-CoV-2 Delta variant

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; COVID-19, coronavirus disease 2019; HIV, human immunodeficiency virus; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; MHS, Memorial Healthcare System; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Coronavirus disease 2019 (COVID-19) vaccines have drastically changed the course of the COVID-19 pandemic worldwide. Many studies have shown that the BNT162b2 (Pfizer-BioNTech; Pfizer, Inc. (New York, New York) and BioNTech SE (Mainz, Germany)) and mRNA-1273 (Moderna; Moderna, Inc., Cambridge, Massachusetts) vaccines, the predominant mRNA vaccines that require 2 doses to complete COVID-19 vaccination, can effectively prevent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, hospitalization, and death among vaccinated individuals (1–3). However, as COVID-19 variants have emerged, breakthrough COVID-19 infections among fully vaccinated individuals have been increasingly reported, particularly in those with advanced age and underlying comorbid conditions (4, 5). Newer SARS-CoV-2 variants, including the Delta (B.1.617.2) and Omicron (B.1.1.529) variants, have shown increased rates of transmission and breakthrough infection in comparison with older variants (6, 7). Studies have suggested that decreased neutralization of the variants by the vaccinee's serum is one possible explanation for increased numbers of breakthrough cases caused by SARS-CoV-2 variants in vaccinated individuals (8–10). Waning of immunity may also cause loss of the vaccine's effectiveness over time, leading to increased breakthrough cases of SARS-CoV-2 variants (10–12). There is also increasing evidence of breakthrough-infection–related

hospitalizations and deaths among vaccine recipients, especially in high-risk populations, such as older people (2, 13–15).

As of September 2021, Florida remained burdened by COVID-19 cases, with more than 17% of residents testing positive for COVID-19 (16). Memorial Healthcare System (MHS), located in Hollywood, Florida, serves a diverse community with the greatest proportion of an older population in the United States (17). This older age group is considered to be a population with a higher risk of breakthrough infections due to impaired vaccine response and associated risk factors, such as age-related immunosenescence and comorbidity (5, 18). To understand better how immune responses triggered by vaccination protect against the SARS-CoV-2 variants in these unique populations, we conducted a cohort study in patients aged ≥18 years who were hospitalized between June 1 and September 20, 2021, during which the Delta variant was the predominant SARS CoV-2 variant in the United States. We employed a propensity-score–matched approach in which we matched each vaccinated patient with a similar patient who was not vaccinated. Our objective was to evaluate the impact of vaccination on intensive care unit (ICU) admission and in-hospital mortality among breakthrough COVID-19 infections, while controlling for differences in baseline characteristics between the two groups of patients.

METHODS

Study design and population

This was a retrospective chart review of patients aged ≥18 years who were consecutively hospitalized at MHS between June 1 and September 20, 2021, with a diagnosis of COVID-19 confirmed by polymerase chain reaction testing of a nasopharyngeal swab. Patients with a primary diagnosis of COVID-19 without a positive SARS-CoV-2 test were excluded. This study was approved by MHS's Institutional Review Board with a waiver of informed consent.

Data collection and definitions

Data were extracted from the MHS electronic medical records. We collected information on patients' demographic characteristics (age, sex, race/ethnicity), body mass index (BMI; weight (kg)/height $(m)^2$), smoking history (current or former smoker), comorbid conditions (diabetes mellitus, hypertension, heart disease, lung disease, solid-organ or hematopoietic stem-cell transplant, human immunodeficiency virus (HIV) infection, and cancer), laboratory data (white blood cell count, lymphocyte count, hemoglobin level, platelet count, and levels of creatinine, aspartate transaminase, alanine transaminase, lactate dehydrogenase, ferritin, D-dimer, C-reactive protein, and procalcitonin), oxygen requirements, mechanical ventilation, admission to the ICU, hospital length of stay (LOS), ICU LOS, and in-hospital death. LOS is defined as the time between admission and discharge, measured in days. In cases of hospital readmissions during the study period, only the first hospital admission was considered. For patients who were vaccinated, data on vaccine type, date of vaccination, and number of doses were collected based on electronic health records linking to credible vaccination registries.

Patients were stratified by vaccination status as either unvaccinated or fully vaccinated. Individuals who had no record of vaccination against COVID-19 or were vaccinated with a single-dose vaccine or fewer than 14 days after receipt of the second dose before illness onset were defined as unvaccinated patients (19). Individuals who received 2 doses of vaccine per the vaccination protocol with ≥14 days after receipt of the second dose before illness onset were defined as fully vaccinated patients (19). Vaccine breakthrough infection was defined as having a positive SARS-CoV-2 test in a respiratory specimen collected from a fully vaccinated individual (19).

Propensity score matching to construct a control cohort for breakthrough infection

The propensity-score–matched analysis was performed to minimize any potential bias from baseline covariates between the two groups (20). The propensity scores were computed with a multivariable logistic regression model, based on key variables associated with vaccination status. Both age and BMI were used as continuous variables, and sex, race/ethnicity, smoking, diabetes, hypertension, chronic lung disease, chronic kidney disease, coronary heart disease, liver disease, cerebrovascular disease, cancer, and HIV infection were used as categorical variables to calculate the propensity scores. We matched vaccinated cases with unvaccinated cases who had similar propensity scores using 1:1 nearest-neighbor matching without replacement and a caliper width of 0.02. The balance of baseline characteristics between the two cohorts was evaluated using the absolute standardized mean differences. A standardized mean difference less than 10% indicates a covariate that is well-balanced between the two cohorts (21).

Outcome measures

The primary outcomes of the study were rates of ICU admission and in-hospital death among the vaccinated patients and propensity-matched unvaccinated patients. The other outcome examined was LOS in the ICU or in the hospital. The risks of ICU admission and in-hospital death according to age (<65 years or ≥65 years), sex (male or female), and BMI (<30 or ≥30) were also examined. Differences in ICU admission or in-hospital mortality by vaccine type (BNT162b2 vs. mRNA-1273) among vaccinated patients were also assessed.

Statistical analysis

Data for categorical variables are presented as numbers and percentages. Data for continuous variables are presented as mean values and standard deviations or median values and interquartile ranges (IQRs). Differences in baseline characteristics between groups were determined by the Mann-Whitney *U* test or Student's *t* test for continuous variables and by Pearson's χ^2 test or Fisher's exact test for categorical variables. Logistic regression analyses were conducted to examine the risk of ICU admission or in-hospital death

according to vaccination status in the entire cohort. Results are expressed as odds ratios (ORs) with 95% confidence interval (CIs).

To explore whether the difference in baseline characteristics between these two cohorts might influence the outcomes, we computed the ORs again while adjusting for potentially confounding factors, including age, sex, race/ethnicity, BMI, smoking, diabetes, hypertension, chronic lung disease, chronic kidney disease, coronary heart disease, liver disease, cerebrovascular disease, cancer, and HIV infection. The magnitude of bias for each variable was defined as the percent difference between the crude and adjusted ORs, calculated as (crude OR – adjusted OR)/adjusted OR × 100%. If the percent difference between the two measurements was 10% or greater, we concluded that there was confounding bias.

To account for potential confounding, we performed a sensitivity analysis using a matched propensity score analysis. Logistic regression models, adjusting for the same variables as those used to generate the propensity score, were fitted to derive risk-adjusted ORs for ICU admission or in-hospital death. Univariate and multivariate logistic regression models were applied to determine variables that were independently associated with ICU admission or in-hospital death. Variables with a P value less than 0.2 in the univariate logistic regression analysis and other variables of known clinical importance were included in multivariate analysis. Differences in ICU admission or in-hospital death by vaccine type (BNT162b2 vs. mRNA-1273) among vaccinated patients were also assessed with multivariate analysis. All statistical tests were 2-tailed, and results were considered significant at $P < 0.05$. Statistical analyses were performed using SPSS, version 28 (IBM SPSS Inc., Armonk, New York) and GraphPad Prism, version 7.0 (GraphPad Software Inc., San Diego, California).

Sensitivity analysis

An additional matched data set with sensitivity analyses was used to further examine the reliability of the findings. Each patient in the breakthrough group was matched to 3 patients in the unvaccinated group (1:3 matching). The outcomes of interest were analyzed using the same methodology as that employed for the main analysis. When the standardized mean difference between the baseline characteristics of the vaccinated and unvaccinated groups exceeded 10%, the covariates were included in the multivariable regression models.

RESULTS

A total of 3,810 adult COVID-19 patients were admitted to the MHS between June 1 and September 20, 2021. After exclusion of 3 patients who died during the first 24 hours of hospitalization, 212 patients with missing data for key covariates, and 244 patients with duplicate records, the study included 3,351 patients, with 284 (8.5%) fully vaccinated ("breakthrough infections") and 3,067 (91.5%) unvaccinated ("nonbreakthrough infections"). Among the 284 vaccinated patients, 22 (7.7%) patients who were not well matched with unvaccinated controls according to propensity scores were omitted from all analyses. The final analysis of outcome measures included 262 vaccinated patients and 262 matched controls. Of the 262 fully vaccinated patients, 225 (86%) patients received the BNT162b2 vaccine (Pfizer-BioNTech) and 37 (14%) patients received the mRNA-1273 vaccine (Moderna) (Figure 1).

Clinical features of patients with breakthrough COVID-19 infections

Table 1 summarizes the patients' clinical characteristics. Breakthrough infections were associated with a higher median age, a higher proportion of White individuals, and a significantly greater burden of comorbidity compared with nonbreakthrough infections. A significantly higher prevalence of age ≥65 years was observed in breakthrough infections compared with nonbreakthrough infections (67% vs. 29%; $P < 0.001$) (see Web Figure 1A, available at https://doi.org/10.1093/aje/kwad199). Obesity (BMI ≥30) was less common in persons with breakthrough infections than in those without breakthrough infections (42% vs. 51%; $P = 0.004$) (Web Figure 1B). Chronic liver disease and HIV infection were more common among persons with breakthrough infections than among unvaccinated patients, although the differences were not statistically significant (Table 1).

After propensity score matching, visual inspection of mirrored histograms showed an adequate propensity score overlapping in the two cohorts (Web Figures 2A and 2B). The observed covariate imbalances between the two cohorts were alleviated, as evidenced by the Love plot showing absolute standardized mean differences of less than 10% (Table 1; Web Figure 2C), indicating that the baseline characteristics between the two groups were well balanced.

Patient outcomes in the entire cohort and propensity-score–matched cohorts

On univariable analysis in the entire cohort, breakthrough COVID-19 cases had comparable rates of ICU admission (9.8% vs. 12.6%) and in-hospitality mortality (11.6% vs. 11.9%) as the unvaccinated patients, with unadjusted ORs of 0.76 (95% CI: 0.51, 1.14; $P = 0.178$) and 0.97 (95% CI: 0.61, 1.43; $P = 0.889$), respectively (Figures 2A and 2B). Analysis of potential baseline confounding factors that might influence the outcomes of interest revealed that age, smoking, diabetes, hypertension, chronic lung disease, chronic kidney disease, coronary heart disease, and cancer had a greater impact on the risk of ICU admission or in-hospital mortality than the null (Web Table 1). After adjustment for these confounding factors using multivariable regression models, lower rates of ICU admission (adjusted OR (aOR) = 0.47 (95% CI: 0.29, 0.76); $P = 0.002$) and in-hospital mortality (aOR = 0.40 (95% CI: 0.26, 0.62); $P < 0.001$) were observed in the breakthrough cases versus the unvaccinated patients (Figures 2A and 2B).

After confounding bias between the two cohorts had been accounted for in the propensity-score–matched model, the breakthrough cases had significantly lower rates of ICU

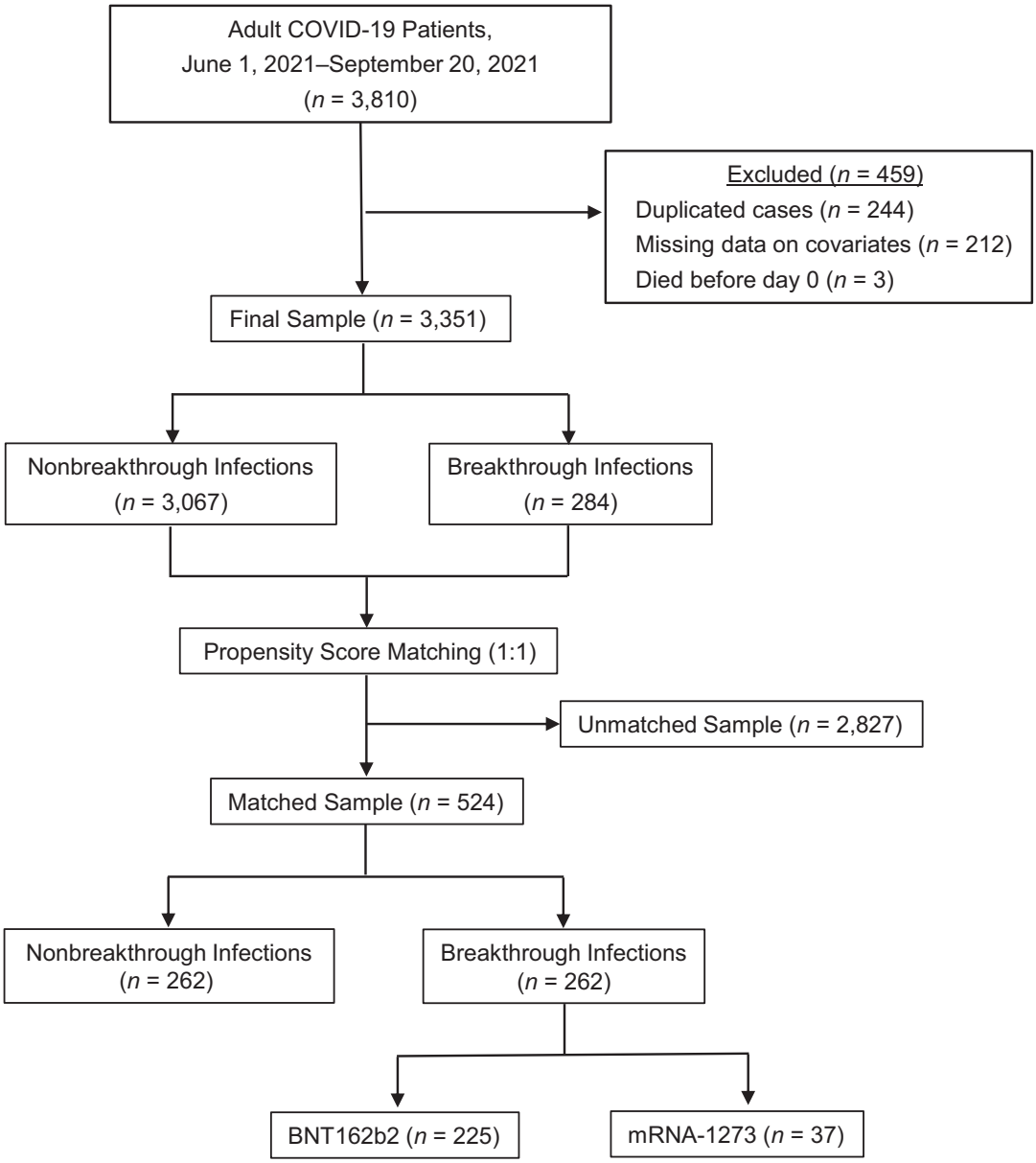

Figure 1. Participant selection in a study of the impact of coronavirus disease 2019 (COVID-19) vaccination on intensive care unit admission and in-hospital mortality among breakthrough COVID-19 infections, Memorial Healthcare System, Hollywood, Florida, June 1–September 20, 2021. In the propensity-score–matched population, subjects in the COVID-19 breakthrough group and their corresponding matches were selected using propensity score matching without replacement (ratio 1:1, caliper = 0.02) based on patient age, sex, race/ethnicity, body mass index (weight (kg)/height $(m)^2$), smoking status, and comorbid conditions (chronic obstructive pulmonary disease, chronic kidney disease, coronary heart disease, cerebrovascular disease, hypertension, diabetes, chronic liver disease, cancer, and human immunodeficiency virus infection).

admission (10.3% vs. 16.4%) and in-hospital mortality (12.2% vs. 18.7%) than the matched controls, with unadjusted ORs of 0.58 (95% CI: 0.35, 0.98; $P = 0.042$) and 0.61 (95% CI: 0.37, 0.98; $P = 0.041$), respectively (Figures 2C and 2D). After adjustment for demographic characteristics and comorbid conditions, the breakthrough cases persistently had better outcomes, with multivariable-adjusted ORs of 0.52 (95% CI: 0.31, 0.89; $P = 0.019$) for ICU admission and 0.57 (95% CI: 0.34, 0.94; $P = 0.027$) for in-hospital mortality, respectively (Figures 2C and 2D).

Subgroup analyses

Figure 3 shows the outcomes for breakthrough infections as compared with matched controls across all of the examined subgroups. The benefit of vaccination compared with that of nonvaccination was consistent across almost all subgroups examined. Older adult patients (age ≥65 years) with breakthrough infections showed better outcomes for ICU admission (Figure 3A) and in-hospital mortality (Figure 3B), with multivariable-adjusted ORs of 0.34 (95%

Table 1. Baseline Characteristics of Hospitalized Persons With Breakthrough and Nonbreakthrough COVID-19 Infections in an Original Unmatched Sample and a Propensity-Score–Matched Sample, Memorial Healthcare System, Hollywood, Florida, June 1–September 20, 2021

Variable	Sample and Breakthrough COVID-19 Infection Status											
	Entire Cohort (*n* = 3,351)						Propensity-Score–Matched Cohort (*n* = 524)					
	Nonbreakthrough Group (*n* = 3,067)		Breakthrough Group (*n* = 284)		SMD	*P* Value	Nonbreakthrough Group (*n* = 262)		Breakthrough Group (*n* = 262)		SMD	*P* Value
	No.	%	No.	%			No.	%	No.	%		
Age, years[a]	54 (40–67)		72 (61–82)		−0.903	<0.001	71 (59.8–80)		71.5 (61–81)		−0.065	0.485
Sex						0.349						0.793
Male	1,520	49.6	149	52.5	−0.064		136	51.9	133	50.8	0.025	
Female	1,547	50.4	135	47.5	0.007		126	48.1	129	49.2	−0.003	
Race/ethnicity						<0.001						0.996
White	558	18.2	125	44.0	−0.661		77	29.4	77	29.4	0.000	
Black	1,171	32.5	68	23.9	0.372		75	28.6	71	27.1	0.042	
Hispanic or Latino	1,199	39.1	82	28.9	0.253		108	41.2	112	42.7	−0.035	
Asian	27	0.9	4	1.4	−0.262		1	0.4	1	0.4	0.000	
Other	112	3.7	5	1.8	0.413		1	0.4	1	0.4	0.000	
Body mass index[a,b]	30.1 (26.3–35.1)		28.3 (24.4–33.9)		0.236	<0.001	29.4 (25.4–34.3)		28.8 (24.5–34.5)		0.069	0.490
Smoking	648	21.1	127	44.7	−0.3631	<0.001	126	48.1	118	45	0.067	0.484
Comorbidity												
Hypertension	1,592	51.9	243	85.6	−0.939	<0.001	227	86.6	227	86.6	0.000	>0.999
Diabetes	976	31.8	130	45.8	−0.327	<0.001	115	42.8	122	43.4	0.026	0.791
Chronic lung disease	176	5.7	63	22.2	−0.851	<0.001	54	20.6	55	20.9	−0.013	0.914
Chronic kidney disease	379	12.4	87	30.6	−0.629	<0.001	85	32.4	79	30.2	−0.058	0.572
Coronary heart disease	347	11.3	104	36.6	−0.832	<0.001	88	33.6	93	35.5	−0.046	0.646
Cerebrovascular disease	147	4.8	50	17.6	−0.851	<0.001	48	18.3	44	16.8	0.058	0.646
Liver disease	43	1.4	8	2.8	−0.393	0.062	9	3.4	8	3.1	0.067	0.805
Cancer	136	4.4	49	17.1	−0.828	<0.001	45	17.2	43	16.4	0.030	0.815
HIV infection	29	0.9	6	2.1	−0.449	0.064	5	1.9	5	1.9	0.000	>0.999

Abbreviations: HIV, human immunodeficiency virus; SMD, standardized mean difference.

[a] Values are expressed as median (interquartile range).

[b] Body mass index was calculated as weight (kg)/height $(m)^2$.

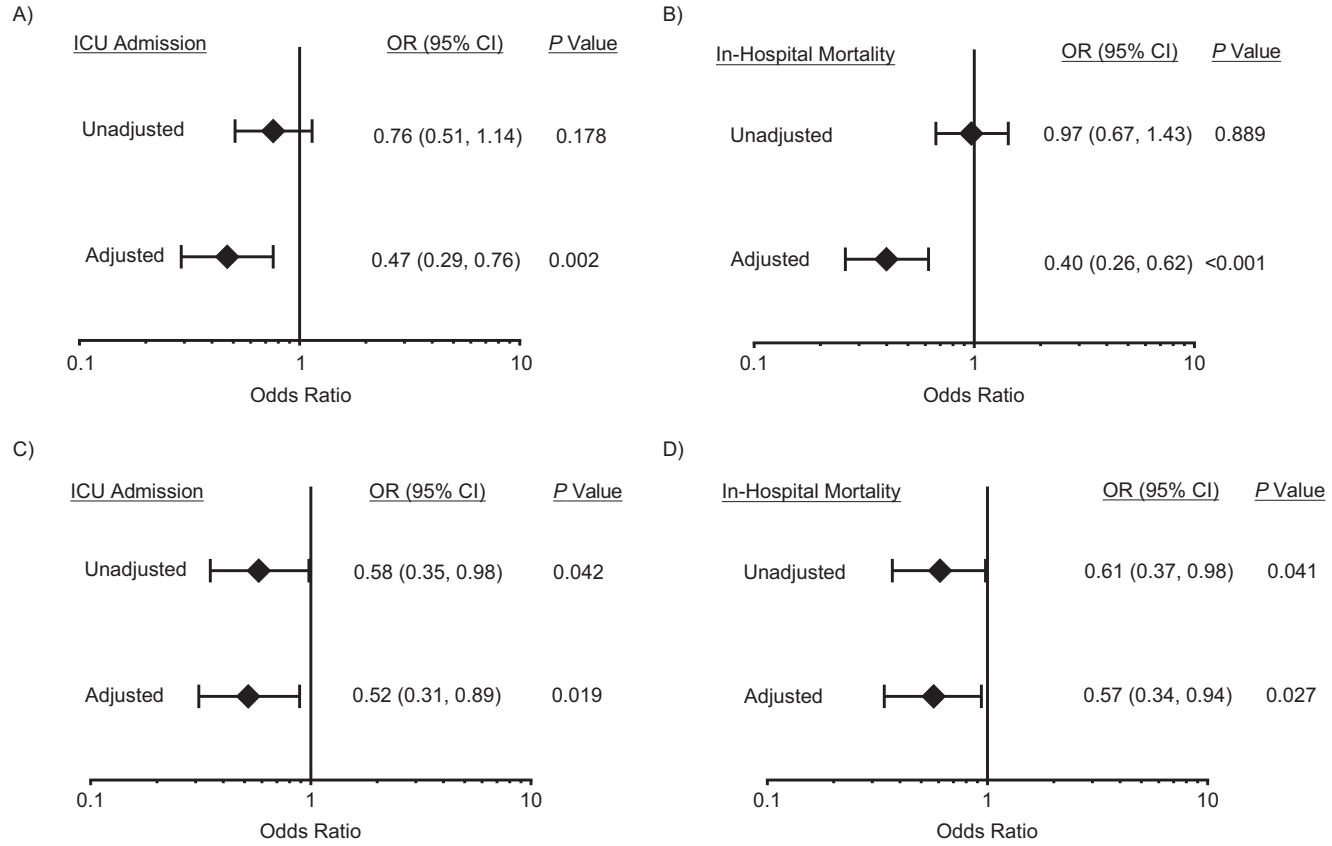

Figure 2. Effects of vaccination on severe coronavirus disease 2019 (COVID-19) outcomes in an original unmatched cohort and a propensity-score–matched cohort, Memorial Healthcare System, Hollywood, Florida, June 1–September 20, 2021. Forest plots on the log scale show unadjusted and multivariable-adjusted odds ratios (ORs; indicated by diamonds) and 95% confidence intervals (CIs; indicated by the horizontal bars) for breakthrough versus nonbreakthrough COVID-19 infection for intensive care unit (ICU) admission (left) and in-hospital mortality (right), respectively, in the original unmatched cohort (panels A and B) and the propensity-score–matched cohort (panels C and D). The variables included in the multivariable regression models were age, sex, race/ethnicity, body mass index (weight (kg)/height (m)^2), smoking, diabetes, hypertension, chronic lung disease, chronic kidney disease, coronary heart disease, liver disease, cerebrovascular disease, cancer, and human immunodeficiency virus infection.

CI: 0.16, 0.71; $P = 0.004$) and 0.55 (95% CI: 0.32, 0.98; $P = 0.041$), respectively. The benefit of vaccination as compared with nonvaccination showed significant interaction between patients aged ≥65 years (aOR = 0.34, 95% CI: 0.16, 0.71) and patients aged <65 years (aOR = 0.98, 95% CI: 0.41, 2.35) (P for interaction = 0.025) with regard to ICU admission (Figure 3A), suggesting that the COVID-19 vaccine was more effective in preventing severe illness among older individuals (age ≥65 years) than among younger individuals. There were no significant interactions between sex and the benefit of vaccination with respect to ICU admission (P for interaction = 0.399; Figure 3A) and in-hospital mortality (P for interaction = 0.645; Figure 3B), although a lower risk of ICU admission was noted in women with breakthrough infections versus the matched controls (aOR = 0.40, 95% CI: 0.17, 0.94). When patients were stratified by BMI, there were no significant interactions in the adjusted risk of ICU admission (P for interaction = 0.961; Figure 3A) or in-hospital death (P for interaction = 0.994; Figure 3B) between breakthrough infections and the matched controls.

ICU stays (ICU LOS) among patients with breakthrough COVID-19 infections were slightly shorter, but this did not reach statistical significance in comparison with unvaccinated patients (median, 5 (IQR, 1–13) days vs. 7 (IQR, 1–12) days; $P = 0.926$) (Figure 4A). The lengths of hospital stays (hospital LOS) were comparable between the breakthrough cases and unvaccinated patients (median, 7 (IQR, 4–12) days vs. 7 (IQR, 4–13) days; $P = 0.678$) (Figure 4B).

Risk factors associated with ICU admission or death in the study population

Factors associated with the risk of ICU admission or death in multivariate analysis are presented in Web Table 2. In addition to vaccination being independently associated with lower odds of ICU admission and in-hospital death, age ≥65 years was independently associated with increased

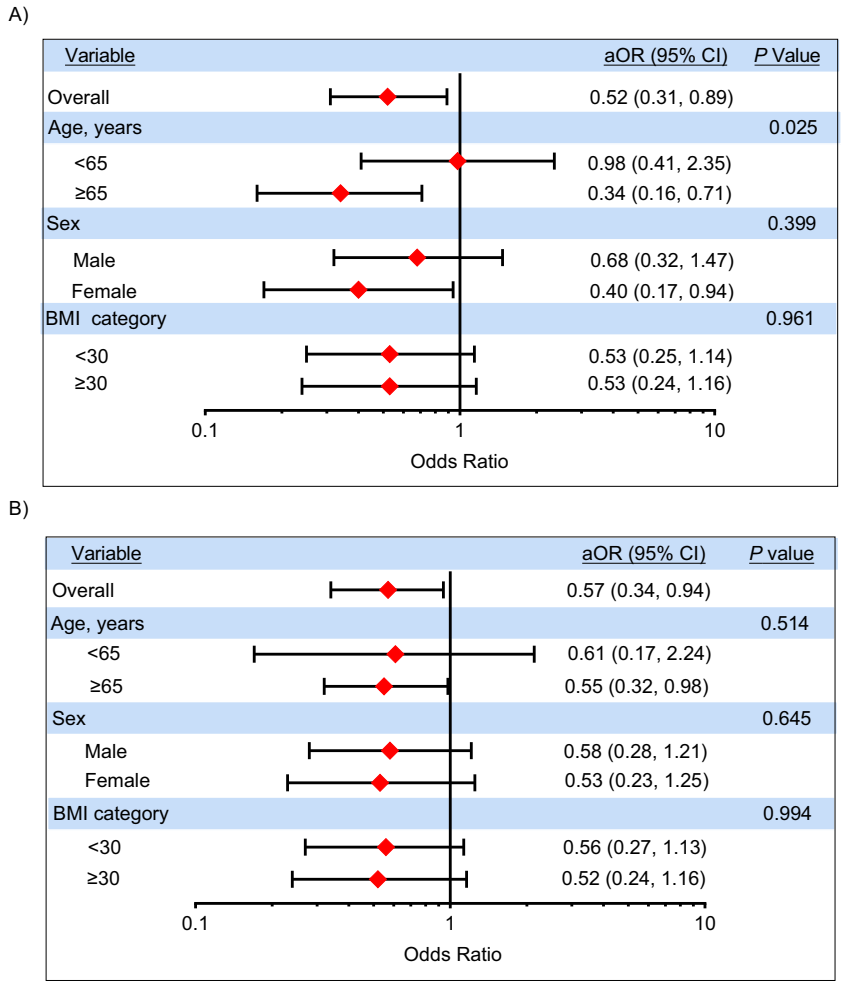

Figure 3. Risk of severe coronavirus disease 2019 (COVID-19) outcomes among vaccinated individuals with breakthrough COVID-19 infections and persons with nonbreakthrough infections in a propensity-score–matched cohort, by age, sex, and body mass index (BMI; weight (kg)/height $(m)^2$) group, Memorial Healthcare System, Hollywood, Florida, June 1–September 20, 2021. Forest plots on the log scale show age-, sex-, and BMI-specific risks of intensive care unit (ICU) admission (A) and in-hospital mortality (B) among subjects with breakthrough infection versus nonbreakthrough cases. The adjusted odds ratios (aORs; red diamonds) comparing the breakthrough group with the nonbreakthrough group were obtained from multivariable logistic regression models. The models adjusted for age, sex, race/ethnicity, BMI, smoking, diabetes, hypertension, chronic lung disease, chronic kidney disease, coronary heart disease, liver disease, cerebrovascular disease, cancer, and human immunodeficiency virus infection. We conducted a test for interaction, using multivariable models, to search for statistically significant subgroup differences; *P* values for interaction are shown. The effect of vaccination on the risk of ICU admission differed by age group (<65 years vs. ≥65 years). Horizontal bars show 95% confidence intervals (CIs).

odds of both ICU admission (aOR = 1.92, 95% CI: 1.11, 3.45; $P = 0.020$) and in-hospital death (aOR = 2.42, 95% CI: 1.26, 4.62; $P = 0.008$). Additional variables that were independently associated with mortality included chronic kidney disease (aOR = 1.78, 95% CI: 1.07, 2.94; $P = 0.027$) and malignancy (aOR = 2.38, 95% CI: 1.36, 4.16; $P = 0.002$).

Comparison of BNT162b2 and mRNA-1273 vaccines with regard to risk of ICU admission or death in COVID-19 breakthrough cases

There were no differences between patients who received BNT162b2 vaccine and those who received mRNA-1273 vaccine in terms of age, sex, race/ethnicity, BMI, or preexisting medical conditions (Web Table 3). Patients who received BNT162b2 vaccine had outcomes comparable to those of patients who received mRNA-1273 vaccine in terms of the incidences of ICU admission (10.2% vs. 10.8%; $P = 0.913$) and in-hospital death (13.3% vs. 5.4%; $P = 0.276$), with multivariable-adjusted ORs of 0.80 (95% CI: 0.23, 2.79; $P = 0.731$) and 2.99 (95% CI: 0.59, 15.23; $P = 0.187$), respectively (Web Figure 3). In addition, no difference in hospital LOS (median, 8 (IQR, 4–14) days vs. 10 (IQR, 5–16) days; $P = 0.363$) or ICU LOS (median, 6 (IQR, 1–12) days vs. 12 (IQR, 4–36) days; $P = 0.240$) was observed between patients who received

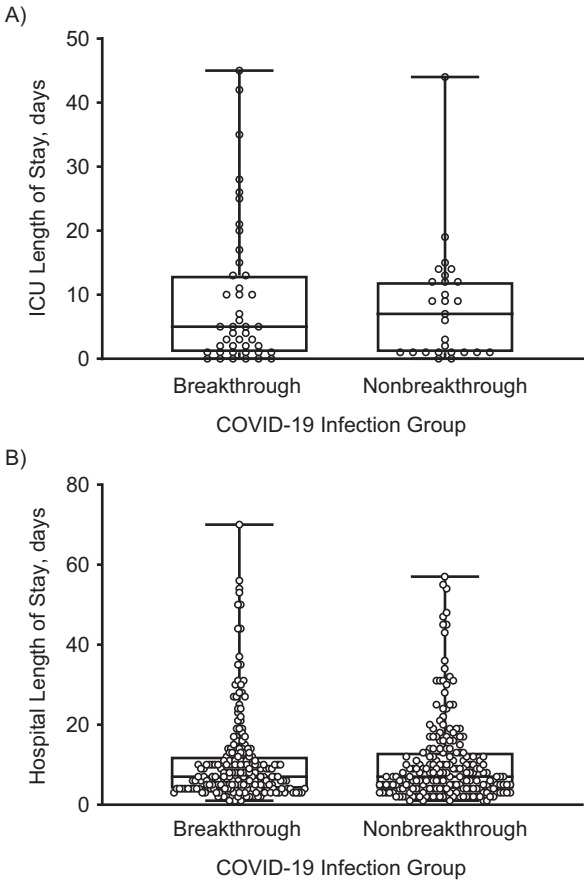

Figure 4. Lengths of intensive care unit (ICU) stay (A) and hospital stay (B) according to coronavirus disease 2019 (COVID-19) infection status in a propensity-score–matched cohort, Memorial Healthcare System, Hollywood, Florida, June 1–September 20, 2021. Box-and-whisker plots show median values (center lines), 25th and 75th percentiles (lower and upper box limits), and whiskers (T-shaped bars) of the data range in the COVID-19 vaccine breakthrough infection group and the nonbreakthrough group. Dots display the distributions of the sample data. No differences in length of ICU stay or length of hospital stay were observed between the breakthrough group and the nonbreakthrough group.

BNT162b2 and those who received mRNA-1273 (Web Table 3).

Results derived from the additional matched (1:3 matching) subjects

By expanding the matching ratio to 1:3, we aimed to further strengthen the validity of the above findings. The results for the 1:3 matching data set with sensitivity analyses are shown in Web Tables 4 and 5. The data set included 202 breakthrough infections and 606 matched controls. The median age of the matched cohort was 65 (IQR, 56–75) years, and 51% were male (Web Table 4). Estimates from sensitivity analyses adjusting for the covariates (age, sex, race/ethnicity, BMI, smoking, and prior health status) showed that patients who experienced breakthrough infections had significantly lower risks of both ICU admission and death from COVID-19 than the matched controls, with adjusted ORs of 0.45 (95% CI: 0.24, 0.82; $P = 0.009$) and 0.44 (95% CI: 0.24, 0.79; $P = 0.006$), respectively (Web Table 5).

The outcomes of breakthrough infections as compared with the matched controls showed consistency across all of the examined subgroups (Web Table 5). There were no significant interactions with respect to ICU admission and in-hospital mortality between breakthrough infections and the matched controls across all subgroups, except for ICU admission in the subgroup stratified by age. Older patients aged ≥65 years who were vaccinated had a lower risk of ICU admission than the matched controls (P for interaction = 0.004). In general, these results derived from the 1:3-matched samples are consistent with those from the main analysis (1:1 matching) presented in Figures 2 and 3, suggesting a beneficial role of COVID-19 vaccines in reducing adverse outcomes in the context of breakthrough infections.

DISCUSSION

Despite aggressive vaccination efforts, Florida remained burdened by COVID-19 cases during our study period, highlighting the need to quantify the benefit of these efforts. This study demonstrated that 91.5% of the hospitalized adults with COVID-19 were unvaccinated and that 8.5% of hospitalizations occurred among breakthrough cases. Breakthrough COVID-19 infections were much more common in older patients (age ≥65 years), and patients with breakthrough infections had a higher prevalence of underlying risk factors than unvaccinated patients. In propensity-score–matched analysis, the breakthrough cases had a lower risk of ICU admission and in-hospital death compared with the matched controls, which supports the effectiveness of vaccination in preventing adverse outcomes associated with COVID-19, even in the context of breakthrough infections. Our results also highlight that advanced age (≥65 years), chronic kidney disease, and malignancy are factors that influence outcomes in breakthrough infections, as other investigators have reported (22–24).

COVID-19 breakthrough infections have been increasingly reported, with incidences ranging from 0.4% to 9.5% depending on the vaccine type, time elapsed after vaccination, percentage of vaccinated people, and viral variants (4, 25). In our study, breakthrough infections accounted for 8.5% of adult patients hospitalized with COVID-19. The observed differences in clinical characteristics are consistent with previously published reports showing higher rates of breakthrough infection among persons with advanced age and underlying comorbidity (4, 15). They may also reflect differences in vaccination priorities, as people aged 65 years or older and those with high-risk underlying conditions were priority targets for COVID-19 vaccination prior to June 2021. Florida ranks among the top states with the highest prevalence of older residents (17), which may also explain the higher prevalence of older patients and comorbid conditions observed among the breakthrough infections in our study. We also observed that patients with breakthrough

infections had a lower BMI than unvaccinated patients, which could be due to the higher prevalence of older patients, in whom there is a lower prevalence of obesity (26).

COVID-19 vaccines have been shown to be effective in reducing severe illness and death from COVID-19 (1–3). In a comparison analysis of 142 vaccinated cases with 1,055 unvaccinated adult patients hospitalized with COVID-19 between March 11, 2021, and July 14, 2021, the vaccinated cases less commonly received ICU care and had a lower risk of death than the unvaccinated patients (2). In a cohort of 716 hospitalized patients with COVID-19, the frequency of ICU admission was significantly lower in the vaccinated group than in the unvaccinated group (27). In our analysis of the propensity-score–matched cohorts, the breakthrough cases had a lower risk of both ICU admission and in-hospital mortality than the matched controls, supporting the beneficial role of COVID-19 vaccines in reducing the risk of severe illness and the need for ICU care, even in the context of breakthrough infections.

Both aging and obesity are characterized by reduced innate and adaptive immune responses (28) and have been found to increase the risk of severe COVID-19 illness and death (22, 23). While COVID-19 vaccines are highly effective in preventing COVID-19–associated adverse outcomes in older adults (age ≥65 years), the results may not translate to younger age groups as younger age groups may have different responses to the vaccine than older adults (5, 29). In our subgroup analyses, patients aged 65 years or more who were vaccinated had a lower risk of both ICU admission and in-hospital death than persons who were unvaccinated. This observation agrees with the available data that COVID-19 vaccines are highly effective in preventing COVID-19–associated adverse outcomes in older adults (27, 30–32). In our analysis, the small number of vaccinated patients aged <65 years may have affected the results of the study. The breakthrough infections appeared to have a trend towards larger relative reductions in the risks of ICU admission and in-hospital death, regardless of whether or not patients were obese, but the results did not reach statistical significance in comparison with the unvaccinated patients. The small sample size might have reduced the ability to detect differences between these subgroups, which should be considered when interpreting the results. The numbers of vaccinated patients, when subdivided into subgroups and propensity-matched, might not have been sufficient to make definite conclusions for each subgroup; however, the trends for each subgroup were consistent with the overall vaccination results, and the *P* values for interaction were nonsignificant, except for ICU admission in the subgroup stratified by age.

Investigators have reported effectiveness differences between the mRNA-1273 and BNT162b2 vaccines in inpatient and outpatient settings (33). Breakthrough COVID-19 hospitalization appeared to be more common with the BNT162b2 vaccine than with the mRNA-1273 vaccine; this has been suggested to be associated with greater antibody responses triggered by the mRNA-1273 vaccine, which has a higher antigen content than the BNT162b2 vaccine (34, 35). In our study, most of our patients had received the BNT162b2 vaccine, while small numbers of patients had received the mRNA-1273 vaccine. The two vaccines showed similar efficacy in reducing the risk of ICU admission or death, which is in line with the previous studies showing no significant difference regarding the incidence of ICU admission or death between immunization with mRNA-1273 and immunization with BNT162b2 (12, 36).

Some limitations of this study should be mentioned. This was a single-center observational study conducted in South Florida, and the study population was elder, with a higher burden of chronic diseases; therefore, the results can only be extrapolated to similar populations. Patients in the two groups were not randomized to vaccine administration, so differences in baseline clinical characteristics may have influenced our results. Although propensity score matching was used to control for these biases, the severity of chronic conditions within each category and unmeasured confounding variables may still have been present. Nevertheless, data on certain characteristics, such as variation in treatment of patients, time elapsed between vaccination and hospitalization, etc., were not collected, which may have had an impact on patient clinical courses and outcomes. Most of our patients had received the BNT162b2 vaccine; hence, a comparison between characteristics, clinical profiles, and outcomes of COVID-19 infection among different vaccines was not possible due to the smaller number of patients who received the mRNA-1273 vaccine. Our results should also be interpreted with caution, since our analysis did not exclude patients who might have been hospitalized for an unrelated reason and diagnosed incidentally with COVID-19, which may have affected patient clinical courses and outcomes.

In conclusion, breakthrough COVID-19 infections requiring hospitalization were rare events in our hospital in South Florida. These infections were most prevalent in older individuals with preexisting medical conditions. The efficacy of the vaccine was demonstrated in terms of reduced risk of ICU admission or in-hospital mortality among breakthrough COVID-19 infections. Recently, studies have shown that vaccine effectiveness against symptomatic disease caused by the Omicron variant is substantially lower than with the Delta variant (37, 38). Several additional vaccines have been developed in response to mutations of the virus, with some studies showing good efficacy in preventing severe outcomes of COVID-19. Examples of these vaccines include the Pfizer-BioNTech and Moderna mRNA adapted vaccines, which have been developed to target specific mutations of the virus and have shown to be effective in providing protection against the mutated strains (39–41). Continuous research is needed to ensure the effectiveness of existing COVID-19 vaccine strategies.

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