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Disease Severity in COVID-19 Breakthrough Cases

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Disease Severity in COVID-19 Breakthrough Cases

Abstract

Background

Vaccine breakthrough is a phenomenon wherein vaccinated individuals become infected with disease despite adequate protection. During this study period, the Centers for Disease Control (CDC) reported 66.6% of US people have been fully vaccinated. Any measures to improve trust would increase vaccination rates. This study aims to understand vaccine breakthrough cases in COVID-19 by comparing their severity to unvaccinated cases. Our objective is to compare disease severity based on the worst initial vital signs (temperature, respiratory rate, oxygen saturation), length of stay (LOS), and age between vaccinated and unvaccinated COVID-19 cases.

Methods

We conducted a retrospective cohort study at Berkshire Medical Center between July 15, 2021, through October 31, 2021. IRB exemption was obtained. Patient records were reviewed for vaccination status, age, vital signs, and LOS. We used forward and backward logistic regressions to determine significant variables and odds ratios to quantify the association between them. We then computed two-sample t-tests to compare the variables between vaccinated and unvaccinated groups.

Results

There were 151 vaccinated and 141 unvaccinated COVID-19 cases. Using a forward logistic regression model, we found significant associations between vaccination status, age (p

Discussion

Our results suggest that vaccination may lead to milder disease even against virulent strains such as the Delta variant. These findings were similar to another study during the Alpha variant peak that demonstrated that vaccinated patients had less disease severity. Vaccination was associated with a 7.25% higher likelihood of being older, a 66.08% lower likelihood of having a higher temperature, and an 8.73% higher likelihood of having lower SpO2. There were significant differences in age and max Temp between vaccinated and unvaccinated groups indicating that vaccination may be associated with less disease severity even in an older population.

Keywords

COVID-19, vaccine breakthrough, delta variant, vaccine

Conflict of Interest Statement

Dan Thai and Nick Sarcia are 3rd-year medical students from the University of New England College of Osteopathic Medicine (UNECOM) who are on clinical rotation at Berkshire Medical Center in Pittsfield MA. Andrea Bodine is an American College of Obstetrics and Gynecology certified physician, Associate Clinical Professor at UNECOM, and research mentor. We do not have conflicts of interest or financial disclosures.

Cover Page Footnote

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ORIGINAL ARTICLE

Disease Severity in COVID-19 Breakthrough Cases☆

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Abstract

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Results: **There were 151 vaccinated and 141 unvaccinated COVID-19 cases. Using a forward logistic regression model, we found significant associations between vaccination status, age ($p < 0.005$), and max Temp ($p < 0.005$). Using a backward logistic regression model, we found significant associations between vaccination status, age ($p < 0.005$), max Temp ($p < 0.005$), and min SpO2 ($p < 0.031$). Odds ratios were 1.0725 (age), 0.6608 (max Temp), and 1.0873 (min SpO2). Two-sample t-tests showed significant differences in age and max Temp between vaccinated and unvaccinated groups while no significant differences were found in LOS, max RR, and min SpO2.**

Discussion: **Our results suggest that vaccination may lead to milder disease even against virulent strains such as the Delta variant. These findings were similar to another study during the Alpha variant peak that demonstrated that vaccinated patients had less disease severity. Vaccination was associated with a 7.25% higher likelihood of being older, a 66.08% lower likelihood of having a higher temperature, and an 8.73% higher likelihood of having lower SpO2. There were significant differences in age and max Temp between vaccinated and unvaccinated groups indicating that vaccination may be associated with less disease severity even in an older population.**

Keywords: COVID-19, Vaccine breakthrough, Delta variant, Vaccine

1. Introduction

COVID-19 vaccine breakthrough is a phenomenon wherein vaccinated individuals become infected with COVID-19. The Centers for Disease Control (CDC) assures us that this is to be expected as no vaccine has 100% effectiveness due to microbiologic mutations which have produced COVID-19 variants.[1] Furthermore, it is unclear whether vaccine breakthrough patients have better outcomes or are at risk of spreading COVID-19, leading to the propagation of misinformation regarding vaccine effectiveness. This contributes to overall reduced vaccination compliance in the public, and accordingly, the CDC reports that only 66.6% of the total population in the United States eligible for vaccination have been fully vaccinated during this study period.[2] Although many factors may have resulted in

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this suboptimal percentage, vaccine hesitancy due to lack of confidence in its efficacy is likely among the most modifiable factors. Any measures to improve vaccine compliance and trust would increase the likelihood that the remaining unvaccinated population would consider receiving a COVID-19 vaccine and future vaccination.

The risk of vaccine breakthrough remains a challenging obstacle to the resolution of the pandemic. Initially, it appeared that the percentage of breakthrough cases amongst the vaccinated was low, however, the body of research is still growing with each passing day.[2] In a study conducted in early 2021, vaccine breakthrough cases amongst healthcare workers were low (0.03%).[3] Although, there was conflicting information regarding the number of breakthrough cases and the disease severity.[3] Nissimov et al. compiled data from 152 breakthrough cases in multiple hospitals in Israel and found that 64% required hospitalization for severe symptoms and the mortality rate was 22% suggesting caution regarding vaccination as a panacea.[4] During the summer of 2021, breakthrough cases increased exponentially with the emergence of the Delta variant. A Houston study from September 2021 found the Delta variant had the highest rate of breakthrough cases compared to all other variants combined.[5] Additionally, in a review of breakthrough cases looking at the severity of symptoms, 46% were asymptomatic and only 26% had severe disease.[6] Although there were studies into symptomology and hospitalization rates, there are insufficient reviews on United States hospitals quantifying disease severity in vaccine breakthrough cases.

COVID-19 vaccine breakthrough cases present a challenge to the healthcare system as they create skepticism on vaccine effectiveness. This study aims to further the understanding of COVID-19 vaccine breakthrough cases by comparing their severity to unvaccinated COVID-19 cases. A large cohort study from China in 2020 classified COVID-19 based on severity of symptoms with mild to moderate disease representing mild symptoms up to mild pneumonia, severe disease representing symptoms such as dyspnea, hypoxia, or more than 50% lung involvement on imaging, and critical disease representing symptoms such as respiratory failure, shock, or multiorgan system dysfunction.[7] This is the standard utilized by the CDC along with laboratory tests such as lymphopenia, neutrophilia, elevated serum alanine aminotransferase and aspartate aminotransferase levels, elevated lactate dehydrogenase, high C-reactive protein, and high ferritin levels which are associated with greater illness severity.[8] However, these laboratory tests are not routinely done on outpatients and individuals with mild disease. We sought to find a less invasive and more readily accessible method to classify disease severity such as through early vital sign analysis.

Our primary objective was to compare disease severity based on the worst initial vital signs (temperature, respiratory rate, and oxygen saturation) between vaccinated and unvaccinated COVID-19 cases. Our secondary objective was to compare the length of stay (LOS) and age between vaccinated and unvaccinated COVID-19 positive patients. We hypothesized that COVID-19 vaccinated patients that test positive for COVID-19 would have less severe symptoms than unvaccinated patients. Secondarily, we hypothesized that COVID-19 vaccinated patients would have shorter LOS than unvaccinated patients and be older.

2. Methods

We conducted a retrospective cohort study at Berkshire Medical Center (BMC), Pittsfield MA with a designated study period between July 15, 2021, through October 31, 2021 (Fig. 1). IRB exemption was obtained. The goal of this study was to determine the disease severity and LOS between vaccinated and unvaccinated COVID-19 patients. The study population was identified using BMC Medical Records Department records for Emergency Department (ED) patients over 18 years old with International Classification of Disease-10 codes for COVID- 19 as a diagnosis.

Using the electronic medical record, patient records were reviewed for patients' ages to verify inclusion criteria. Inclusion criteria consisted of all records of patients who were greater than or equal to 18 years old with a COVID-19 diagnosis. Exclusion criteria consisted of records of patients who were under 18 years old, those without a vaccination status recorded in the medical record, and those missing vital signs data during their LOS. Duplicate visits for the same COVID-19 diagnosis were treated as a single visit. The worst vital signs and longest LOS over the course of all duplicate visits were recorded. Vaccination status was designated as vaccinated with a history of at least 1 COVID-19 vaccine administration found in either the immunization records or if the COVID-19 ED triage screening recorded “vaccinated”. Vaccination status was designated as unvaccinated if the COVID-19 ED triage screening recorded “not vaccinated".

Diagnosis of COVID-19 utilized a rapid antigen test or nucleic acid amplification test.

The vital signs reviewed in each patient record were highest temperature (max Temp) in

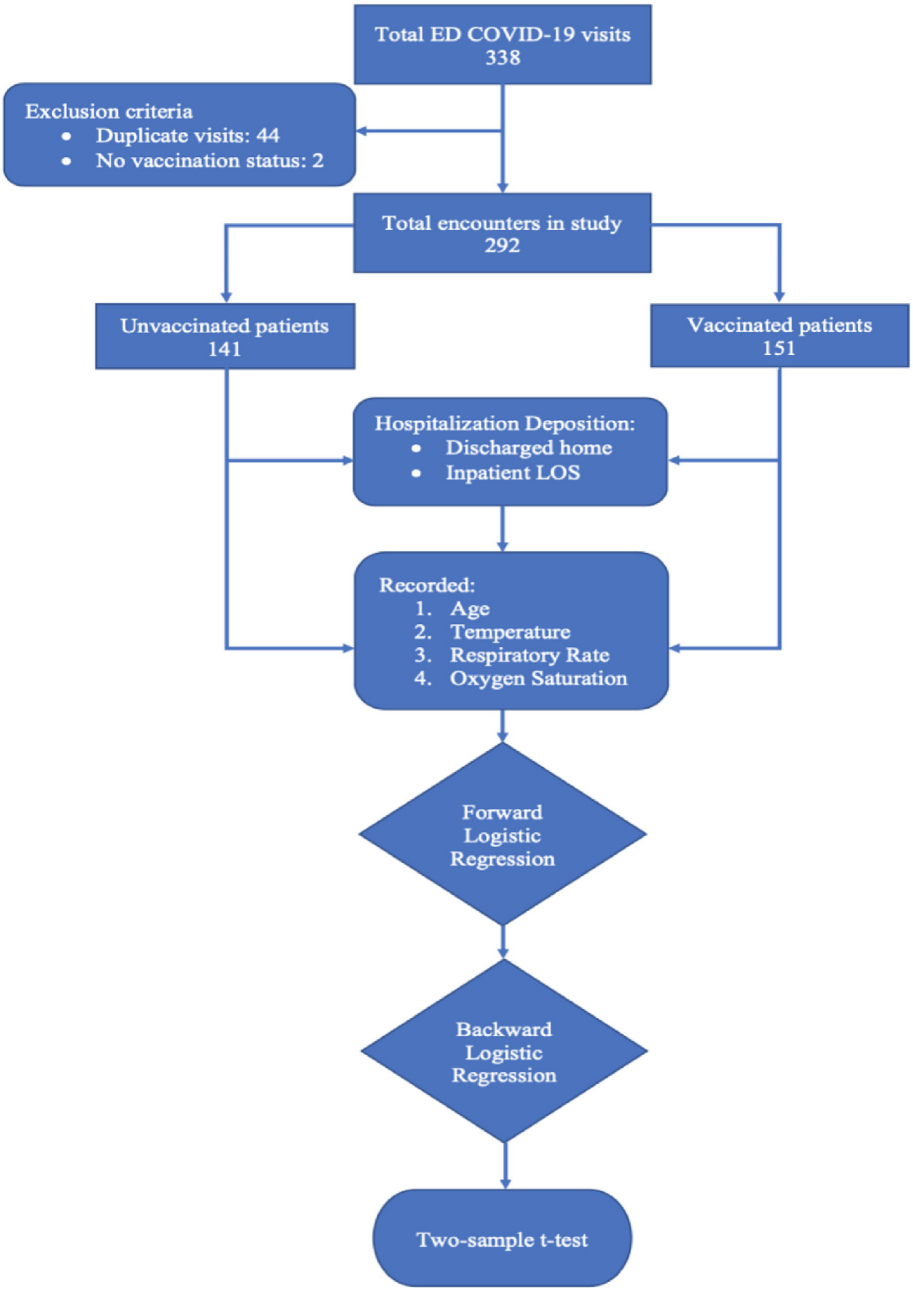

Fig. 1. Study design flowchart.

Fahrenheit (F), highest respiratory rate (max RR) in breaths per minute, and lowest oxygen saturation (min SpO2) in percentage. The worst vital sign for each category during the entire duration of the ED visit was recorded. ED disposition, hospital LOS in days, and age were independently recorded. Same-day discharge from the ED was recorded as a value of zero LOS.

COVID-19 vaccinated and unvaccinated patients that tested positive for COVID-19 were compared to determine disease severity. A forward logistic regression model which sequentially adds variables to maximize their significance was computed utilizing the following variables (LOS, age, max Temp, max RR, min SpO2) to determine if the variables were significantly associated with vaccination status. A backward logistic regression model which sequentially removes variables to maximize their significance was computed utilizing the same variables to determine which ones remained significant after the removal of the remaining variables. Odds ratios (OR) and two-sample t-tests were then

computed on the variables deemed significant by the backward logistic regression model to determine strength of association and disease severity.

3. Results

During the 3.5-month study period from July 15th, 2021 through October 31st, 2021, 338 COVID-19 encounters were recorded at the BMC ED. 44 duplicate visits where patients came multiple times for the same COVID-19 diagnosis were removed leaving 294 cases. There were two cases without vaccination statuses recorded that were excluded resulting in 292 encounters. There were two cases missing temperature as a vital sign which were excluded for temperature analyses leaving 290 encounters when evaluating temperature. A total of 292 encounters were used for all other analyses. The number of vaccinated cases was 151, and the number of unvaccinated cases was 141.

LOS ranged from 0 to 40 days cumulatively (vaccinated and unvaccinated), from 0 to 21 days (vaccinated), and from 0 to 40 days (unvaccinated). Age ranged from 18 to 99 years old cumulatively (vaccinated and unvaccinated), from 20 to 99 years (vaccinated), and from 18 to 97 (unvaccinated). Max Temp ranged from 96.0 to 103.4F cumulatively (vaccinated and unvaccinated), from 96.0 to 103.4F (vaccinated), and from 96.5 to 103.3F (unvaccinated). Max RR ranged from 12 to 48 breaths/minute cumulatively (vaccinated and unvaccinated), from 15 to 48 breaths/min (vaccinated), and from 12 to 48 breaths/min (unvaccinated). Min SpO2 ranged from 70% to 100% cumulatively (vaccinated and unvaccinated), from 70 to 100% (vaccinated), and from 73 to 100% (unvaccinated) (Table 1).

Forward logistic regression model with the following variables (LOS, age, max Temp, max RR, min SpO2) yielded statistically significant associations between vaccination status, age ($p < 0.005$), and max Temp ($p < 0.005$). The overall worst predictor of vaccination status was max RR ($p < 0.797$). Backward logistic regression model with the same variables and an alpha threshold of 0.1 yielded statistically significant associations between vaccination status, age ($p < 0.005$), max Temp ($p < 0.005$), and min SpO2 ($p < 0.031$). The OR for age was 1.0725 (95% CI 1.0534, 1.0920); for max Temp was 0.6608 (95% CI 0.5277, 0.8275); and for min SpO2 was 1.0873 (95% CI 1.0065, 1.1746).

Table 1. Patient cumulative descriptive statistics.

Variable	Mean (M)	SE	SD	Min	Max
LOS (days)	2.213	±0.295	5.051	0.000	40.00
Age (years)	54.22	±1.200	20.53	18.00	99.00
Max Temp (F)	99.16	±0.0814	1.391	95.80	103.4
Max RR (breaths/min)	20.58	±0.290	4.973	12.00	48.00
Min SpO2 (%)	94.28	±0.347	5.951	70.00	100.0

Two-sample t-tests were conducted to explore the differences between LOS, age, max Temp, max RR, and min SpO2 in vaccinated and unvaccinated individuals. An alpha value of 0.05 was utilized. Statistically significant differences were evident between the ages of the vaccinated group ($M = 63.7$, $SD = 19.1$) and the unvaccinated group ($M = 44.0$, $SD = 16.5$); $t(288) = -9.48$, $p = 0.005$. Significant differences were also found in the max Temp of the vaccinated group ($M = 98.88$, $SD = 1.27$) and the unvaccinated group ($M = 99.47$, $SD = 1.47$); $t(273) = 3.66$, $p = 0.005$. These results suggest that the vaccinated individuals tended to be older and had lower temperatures than unvaccinated individuals. No differences were seen in the LOS when comparing the vaccinated group ($M = 1.98$, $SD = 3.47$) and the unvaccinated group ($M = 2.49$, $SD = 6.35$); $t(211) = 0.85$, $p = 0.399$. No significant differences were observed in the max RR between the vaccinated group ($M = 20.68$, $SD = 4.80$) and the unvaccinated group ($M = 20.48$, $SD = 5.20$); $t(283) = -0.34$, $p = 0.734$. No differences were detected in the min SpO2 between the vaccinated group ($M = 94.38$, $SD = 3.71$) and the unvaccinated group ($M = 94.69$, $SD = 4.19$); $t(279) = 0.67$, $p = 0.504$. These findings indicate that vaccination was not associated with a shorter length of stay, lower respiratory rate, or higher SpO2 (Table 2).

4. Discussion

In this retrospective cohort study, we found that COVID-19 vaccination status was associated with the variables of age, temperature, and SpO2. Vaccination was associated with a 7.25% higher likelihood of being older (OR 1.0725, 95% CI 1.0534, 1.0920), a 66.08% lower likelihood of having an increase in temperature (OR 0.6608 95% CI 0.5277, 0.8275), and an 8.73% higher likelihood of having a lower SpO2 (OR 1.0873, 95% CI 1.0065, 1.1746). Through two-sample t-tests comparisons of vaccinated and unvaccinated individuals, we found significant differences in age (−19.72 years, 95% CI -23.83, −15.64, $p < 0.005$) and max Temp (0.591 degrees F, 95% CI 0.273, 0.909, $p < 0.005$) and no significant differences in LOS (0.513 days, 95% CI -0.683, 1.709, $p < 0.399$), max RR (−0.200 breaths/min, 95% CI -1.354, 0.955, $p < 0.734$), min SpO2 (0.310%, 95% CI -0.603, 1.224, $p < 0.504$).

We were able to satisfy our hypothesis that being vaccinated was associated with increasing age and

Table 2. Patient vaccinated and unvaccinated descriptive statistics.

Variable	Vaccinated n = 151		Unvaccinated n = 141		t-test	P
	M	SD	M	SD		
LOS (days)	1.98	3.47	2.49	6.35	0.85	0.399
Age (years)	63.7	19.1	44.0	16.5	−9.48	0.005
Max Temp (F)	98.88	1.27	99.47	1.47	3.66	0.005
Max RR (breaths/min)	20.68	4.80	20.48	5.20	−0.34	0.734
Min SpO2 (%)	94.38	3.71	94.69	4.19	0.67	0.504

lower temperature. These results indicate that vaccination may be associated with less disease severity as indicated by lower temperature even in an older population. However, we were unable to support our hypothesis that being vaccinated was associated with a shorter length of hospital stay, lower RR, and higher SpO2. Although there was a significant difference in temperature between both groups, the averages of both groups remained in the normal range for temperature and did not exceed 100.4 degrees F. The vaccinated group (n = 25) had a lower number of individuals with a temperature over 100.4 degrees F than the unvaccinated group (n = 32).

During the study period, the most dominant COVID-19 variant in the United States was the Delta variant (B.1.617.2), which had higher virulence and infectivity even in fully vaccinated individuals.[9] These results, which highlight data during the peak of the Delta variant's lifecycle, show that vaccination was associated with a milder form of the disease. However, both groups had a similar LOS suggesting the variant's morbidity was unaffected by vaccination. RR and SpO2 were also similar among groups suggesting that these variables may not be useful in characterizing disease severity, supporting the CDC's caution against pulse oximetry in disease severity characterization with darker skinned populations.[8] Nevertheless, these findings were supported by a study conducted at the Yale New Haven Health System that demonstrated that fully vaccinated patients had less disease severity during the peak of the Alpha variant (B.1.1.7).[6,9] Although vaccines are generally associated with less disease severity, research during the peak of the Delta variant showed decreased vaccine efficacy and higher vaccine breakthrough due to immune evasion mechanisms when compared to the Alpha variant.[10]

5. Limitations and future directions

Limitations of this study include the parameters we chose to represent disease severity. For example, a possible explanation for no observed significant differences in respiratory rate and SpO2 in vaccinated and unvaccinated groups may be due to changes in these vital signs being observed later in the disease course. Other comorbid conditions may have also confounded the vital signs and LOS in such a way that cannot be isolated without more restrictive study exclusions such as limiting subjects to healthy individuals or stratifying groups by certain preexisting disease groups such as chronic obstructive pulmonary disease, asthma, and congestive heart failure. Since the vital sign value used was the worst presenting sign during the ED stay and not followed for admitted patients, recording the worst vital signs throughout the entire hospital stay may capture a more representative picture of the disease severity. Although there was a significant difference in temperature between groups, this could be explained by the differences in age rather than vaccination as the logistic regression does not prove a causal relationship between vaccination and age or temperature. The ED COVID-19 vaccination screening did not differentiate between fully vaccinated and single dose vaccination which may have skewed the findings as partially vaccinated individuals may have not mounted an appropriate response to a breakthrough infection resulting in no significant differences in min SpO2 and Max RR.

This study benefited from the amount and variety of variables selected. The statistical analysis methods chosen such as logistic regression permitted the evaluation of many variables at the same time and helped explain the interaction between multiple variables. Of the cohort groups, both vaccinated (n = 151) and unvaccinated patients (n = 141) were similar in size, and the study period coincided with the onset, peak, and decline of the Delta variant. This provides a unique perspective on vaccine efficacy during a highly virulent strain.

Future studies that record radiographic image findings or pulmonary spirometry findings could better assess the disease severity. Classification of the variant strain of COVID-19 could also determine

whether the data was capturing the efficacy of vaccination against a particular virus subtype in vivo. A larger study with age matched individuals could better determine whether vaccination had a causal effect on lowering temperature in breakthrough cases.

6. Conclusion

In conclusion, we found that during the study period of July 15th, 2021 through October 31st, 2021, COVID-19 vaccination was associated with less disease severity as shown by lower temperature and older age in COVID-19 breakthrough cases when compared to unvaccinated individuals. Hospital length of stay, respiratory rate, and SpO2 did not differ significantly between vaccinated and unvaccinated groups. Vaccination was associated with a 7.25% higher likelihood of being older, a 66.08% less likelihood of having an increase in temperature, and an 8.73% higher likelihood of having a lower SpO2 while evaluating odds ratios in isolation.

Conflict of interest

Dan Thai and Nick Sarcia are 3rd-year medical students from the University of New England College of Osteopathic Medicine (UNECOM) who are on clinical rotation at Berkshire Medical Center in Pittsfield MA. Andrea Bodine is an American College of Obstetrics and Gynecology certified physician, Associate Clinical Professor at UNECOM, and research mentor. We do not have conflicts of interest or financial disclosures.

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