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Low antispike antibody levels correlate with poor outcomes in COVID-19 breakthrough hospitalizations

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Abstract. Sanghavi DK, Bhakta S, Wadei HM, Bosch W, Cowart JB, Carter RE, et al. Low antispike antibody levels correlate with poor outcomes in COVID-19 breakthrough hospitalizations. *J Intern Med.* 2022;**292**:127–135.

Background. While COVID-19 immunization programs attempted to reach targeted rates, cases rose significantly since the emergence of the delta variant. This retrospective cohort study describes the correlation between antispike antibodies and outcomes of hospitalized, breakthrough cases during the delta variant surge.

Methods. All patients with positive SARS-CoV-2 polymerase chain reaction hospitalized at Mayo Clinic Florida from 19 June 2021 to 11 November 2021 were considered for analysis. Cases were analyzed by vaccination status. Breakthrough cases were then analyzed by low and high antibody titers against SARS-CoV-2 spike protein, with a cut-off value of ≥132 U/ml. Outcomes included hospital length of stay (LOS), need for intensive care unit (ICU), mechanical ventilation, and mortality. We used 1:1 nearest neighbor propensity score matching without replacement to assess for confounders.

Results. Among 627 hospitalized patients with COVID-19, vaccine breakthrough cases were older with more comorbidities compared to unvaccinated. After propensity score matching, the unvaccinated patients had higher mortality (27 [28.4%] vs. 12 [12.6%], $p = 0.002$) and LOS (7 [1.0–57.0] vs. 5 [1.0–31.0] days, $p = 0.011$). In breakthrough cases, low-titer patients were more likely to be solid organ transplant recipients (16 [34.0%] vs. 9 [12.3%], $p = 0.006$), with higher need for ICU care (24 [51.1%] vs. 22 [11.0%], $p = 0.034$), longer hospital LOS (median 6 vs. 5 days, $p = 0.013$), and higher mortality (10 [21.3%] vs. 5 [6.8%], $p = 0.025$) than high-titer patients.

Conclusions. Hospitalized breakthrough cases were more likely to have underlying risk factors than unvaccinated patients. Low-spike antibody titers may serve as an indicator for poor prognosis in breakthrough cases admitted to the hospital.

Keywords: antispike antibodies, COVID-19, delta, SARS-CoV-2, vaccine breakthrough

Introduction

Current COVID-19 vaccines promote immunity by stimulating the production of antispike antibodies against SARS-CoV-2 [1, 2]. *In vitro* neutralizing antispike antibodies appear to correlate with immune protection from the virus [3]. In recent months, when the delta variant dominated, more "breakthrough" infections of COVID-19 after vaccination were reported. Although most breakthroughs are associated with milder symptoms, thousands have required hospitalization [4]. Understanding what drives breakthrough cases, particularly severe breakthrough cases, is urgent. Proposed mechanisms include impaired immune

response to vaccination, waning protective immunity over time, or immune evasion by viral variants of concern.

Variants of concern—namely B.1.1.7 (alpha), B.1.3.51 (beta), P.1 (gamma), and B.1.617.2 (delta)—include mutations of the spike protein and may reduce the effectiveness of available vaccines [5]. By the last week of June 2021, the delta variant became the dominant variant in southeastern USA [6]. Some studies have reported decreased vaccine effectiveness against symptomatic disease associated with the delta variant [7, 8]. Our study's aim is to describe the clinical characteristics of COVID-19 vaccine breakthrough cases that were hospitalized at our institution and analyze the correlation between antibody titers and clinical outcomes.

Materials and methods

Study setting and population

The Mayo Clinic Institutional Review Board determined the current study to be exempt from review (IRB 21-002944). We extracted electronic data from the Mayo Clinic electronic health records on patients admitted with COVID-19 at Mayo Clinic's campus, a tertiary destination medical center, in Jacksonville, Florida, between 19 June 2021 and 11 November 2021. This was a period when the delta variant (B.1.617.2 and AY lineages) was predominant in our southeastern region of the USA, based on the US Department of Health & Human Services (HHS) reports [6, 9]. Additionally, we updated our immunization data based on the state immunization databases for all hospitalized patients in this study. The state immunization data, known as Florida Shots, is queried every 2 weeks to update our electronic health records. The data is available for all patients of 5 years of age or older in the state of Florida.

We included any patient admitted during the study period with a positive nasopharyngeal polymerase chain reaction test for SARS-CoV-2 with semiquantitative antispike antibody titer assay obtained on admission. Vaccination status was assessed at the time of admission and specimen collection. We considered patients as fully vaccinated (>14 days after the second dose [mRNA-1273, BNT162b2 vaccine, or ChAdOx1] or after single dose [Ad26.CoV2.S vaccine]) or unvaccinated. We excluded patients who (a) had monoclonal antibody infusion therapy received before admission to avoid interference with the antispike antibody assay, (b) had a declination to participate in research on file, or (c) did not have adequate follow-up time (known discharge date, date of death, or hospital length of stay [LOS] less than 30 days).

Antispike antibody titers

According to hospital protocols in hospitalized patients with COVID-19, we used Elecsys® Anti-SARS-CoV-2 S (Roche Diagnostics GmbH, Mannheim, Germany) as the immunoassay for semiquantitative determination of antibodies against SARS-CoV-2 spike protein. The measuring interval ranges from 0.40 to 250 U/mL (up to 2500 U/mL with 1:10 dilution), and a concentration of ≥0.80 U/ml is considered a positive assay [10]. For this study, values <0.40 U/mL and >2500 U/mL were recorded as 0.40 U/mL and 2500 U/mL, respectively.

The Food and Drug Administration (FDA) approved the use of this assay to qualify the manufacture of high-titer COVID-19 convalescent plasma (cut-off value of ≥132 U/mL for Elecsys® Anti-SARS-CoV-2 S) [11]. Therefore, we classified patients into two cohorts based on being in the low-titer or high-titer group using this cut-off value.

If desired, the World Health Organization International Standard for anti-SARS-CoV-2 immunoglobulin can be calculated by using the following conversion factors, as recommended by the manufacturers: BAU/mL = (U/mL) × 1 or BAU/mL = (U/mL) × 1.0288 [12, 13].

Primary and secondary outcomes

The primary outcome was to identify clinical characteristics for breakthrough cases compared to unvaccinated patients. Secondary outcomes included hospital LOS, need for intensive care unit (ICU; captured as Current Procedural Terminology codes of 99291 and 99292 billed at any time during hospital stay), need for mechanical ventilation, and mortality in breakthrough cases concerning antispike antibody titers.

Statistical analysis

The primary focus of the analyses was on the breakthrough infections that lead to hospital admission. To test for differences in breakthrough infections between antispike antibody levels (high vs. low as described above), the Fisher's exact test was used to compare categorical variables. In con-

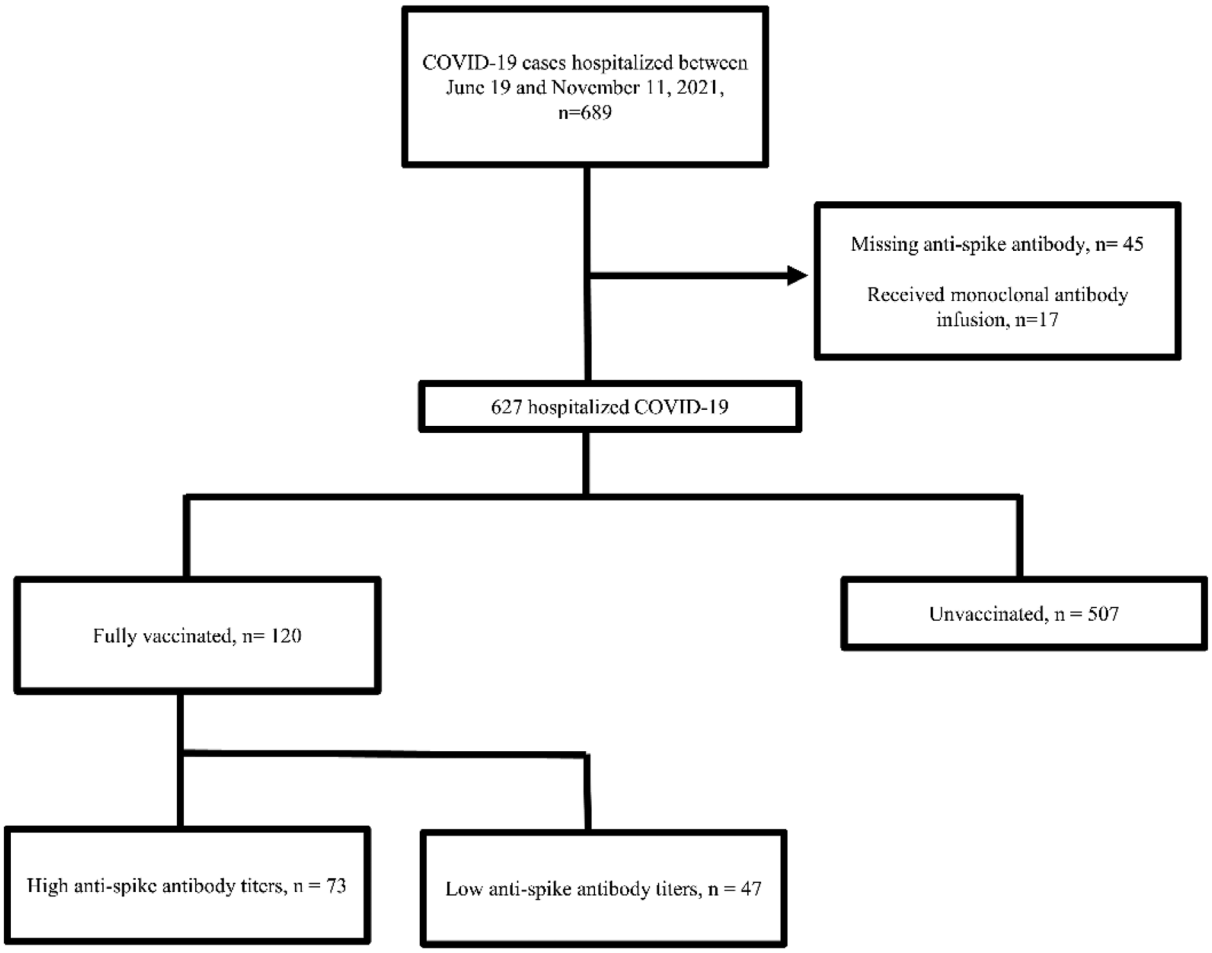

Fig. 1 *Consort diagram showing patient population selection.*

trast, the Mann–Whitney nonparametric test was used to compare continuous variables. All events were censored at the time of hospital discharge, death, or 30 days from admission. Hospital readmissions were not considered and were omitted when calculating patient follow-up time. All analysis was completed using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

We used propensity score matching to assess outcomes in breakthrough versus unvaccinated cases when accounting for confounding by covariates. We used 1:1 nearest neighbor propensity score matching without replacement based on patient age, race, sex, presence of chronic kidney disease, and overall COVID Complications Risk Score. All patients with solid organ transplants (SOTs) were removed prior to matching.

Results

A total of 689 cases of COVID-19 required hospitalization at Mayo Clinic, Florida, between 19 June 2021 and 5 November 2021, and were considered for analysis. On admission, semiquantitative antispike antibody levels were obtained in 644 cases. Of these, 17 patients had received monoclonal antibodies prior to admission and were excluded. Figure 1 presents the consort diagram for the study population selection. Hospital protocols guided inpatient management of all patients.

Comparison between breakthrough and unvaccinated hospitalized cases

Unvaccinated cases represented 80.1% (n = 507) of total hospitalizations due to COVID-19, whilst breakthrough infections were 19.1% (n = 120).

Breakthrough patients were older (72.5 [36.0–99.0] vs. 57.0 [21.0–98.0], $p < 0.001$) and were more likely to have a history of chronic kidney disease (21 [17.5%] vs. 17 [3.4%], $p < 0.001$), congestive heart failure (20 [16.7%] vs. 44 [8.7%], $p = 0.018$), coronary artery disease (33 [27.5%] vs. 73 [14.4%], $p = 0.001$), diabetes (44 [36.7%] vs. 112 [22.1%], $p = 0.001$), hypertension (80 [66.7%] vs. 237 [46.7%], $p < 0.001$), and SOT (25 [20.8%] vs. 19 [3.7%], $p < 0.001$). Overall COVID-19 Risk of Complications Score [14] (median [range]) was higher in the breakthrough cases (5 [1–9] vs. 3 [0–9], $p < 0.001$). Hospital LOS (median [range]) was numerically lower in the breakthrough cases, but this did not reach statistical significance (5 [1–41] days in breakthrough vs. 6 [1–81] days in unvaccinated patients, $p = 0.081$). A higher number of unvaccinated patients (n = 3) remained hospitalized at time of date extraction compared to no breakthrough cases. Once admitted, both breakthrough and unvaccinated cases had comparable need for ICU (46 [38.3%] vs. 203 [40.0%], $p = 0.76$), need for mechanical ventilation (10 [8.3%] vs. 52 [10.3%], $p = 0.61$), and mortality (15 [12.5%] vs. 58 [11.4%], $p = 0.75$) (Table 1). However, propensity score matching revealed higher mortality (27 [28.4%] vs. 12 [12.6%], $p = 0.002$) and LOS (7 [1.0–57.0] vs. 5 [1.0–31.0] days, $p = 0.011$) in the unvaccinated cohort (Table S2).

Antispike antibody was positive (≥0.8 U/ml) in 98 (81.7%) breakthrough cases and 250 (49.3%) unvaccinated cases, $p < 0.001$. The median (range) of antispike antibody titer was higher in breakthrough (450 [0.4–2500]) U/ml than unvaccinated patients (0.6 [0.4–2500]) U/ml, $p < 0.001$ (Fig. 2). Due to a small number of patients with prior COVID-19 infection (n = 2, unvaccinated; n = 13, breakthrough cases), we did not consider further analysis for this subgroup. Also, none of the breakthrough patients received a booster dose prior to admission.

Relationship between antispike antibody titer and outcomes in breakthrough cases

Most patients with vaccine breakthrough infections had high antispike antibody titers (n = 73, 60.1%). Table 2 summarizes baseline clinical characteristics and outcomes of the 120 breakthrough cases by antispike antibody titers. There was no difference in age, sex, race, and comorbidities between the low and high antibody titer patients (cut-off value of ≥132 U/mL). The median duration from vaccination to hospitalization was lower in the low-titer group (136 [15–244] vs. 162 [37–256]). In the low-titer antibody cohort, patients were more likely to be a SOT recipient (16 [34%] vs. 9 [12.3%], $p = 0.006$), require ICU (24 [51.1%] vs. 22 [30.1%], $p = 0.034$), have longer hospital LOS (median [range] 6 [2–41] vs. 5 [1–31] days, $p = 0.013$), and have higher mortality (10 [21.3%] vs. 5 [6.8%], $p < 0.025$) than their high-titer counterparts.

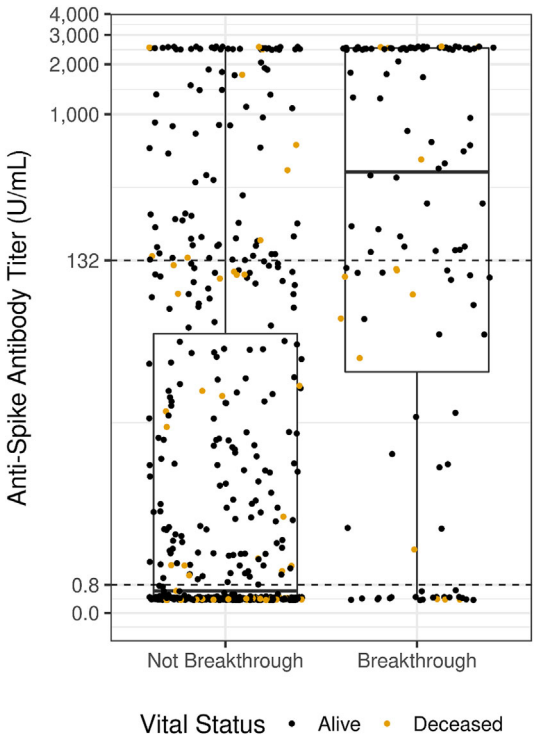

Fig. 2 *Box plot presentation for antispike antibody titers (U/ml) by vaccination status. Boxes and horizontal bars denote interquartile range (IQR) and median of antispike antibody titer, respectively. The cut-off value for a positive Elecsys ® Anti-SARS-CoV-2 S assay is ≥0.80 U/ml, and in our study, the value ≥132 U/ml defined the high-titer group. Whisker endpoints are equal to the maximum and minimum values below or above the median +/− 1.5 × IQR. The individual points are the observed titer levels by case after "jittering" to avoid overlapping points on the figure. The black points are the patients who did not expire whereas the gold points are those who died.*

Figure 3 summarizes patient outcomes in the breakthrough and unvaccinated cohorts based on antispike antibody titers.

Table 1. *Clinical characteristics of hospitalized COVID-19 patients according to breakthrough infection status*

	Not breakthrough (N = 507)	Breakthrough (N = 120)	Total (N = 627)	*P*-value
Age (years)	57.0 (21.0, 98.0)	72.5 (36.0, 99.0)	60.0 (21.0, 99.0)	**<0.001**
Sex (male)	303 (59.8%)	73 (60.8%)	376 (60.0%)	0.92
Race				0.15
American Indian/Alaskan Native	2 (0.4%)	0 (0.0%)	2 (0.3%)	
Asian	24 (4.7%)	2 (1.7%)	26 (4.1%)	
Black or African American	60 (11.8%)	16 (13.3%)	76 (12.1%)	
White	391 (77.1%)	100 (83.3%)	491 (78.3%)	
Other/Unknown	30 (5.9%)	2 (1.7%)	32 (5.1%)	
Diabetes mellitus	112 (22.1%)	44 (36.7%)	156 (24.9%)	**0.001**
Hypertension	237 (46.7%)	80 (66.7%)	317 (50.6%)	**<0.001**
Chronic lung disease	400 (78.9%)	94 (78.3%)	494 (78.8%)	0.90
Chronic kidney disease	17 (3.4%)	21 (17.5%)	38 (6.1%)	**<0.001**
End-stage renal disease on dialysis	507 (100.0%)	120 (100.0%)	627 (100.0%)	
Chronic kidney disease (no dialysis)	9 (1.8%)	20 (16.7%)	29 (4.6%)	**<0.001**
Congestive heart failure	44 (8.7%)	20 (16.7%)	64 (10.2%)	**0.018**
Coronary artery disease	73 (14.4%)	33 (27.5%)	106 (16.9%)	**0.001**
Solid organ transplant recipient	19 (3.7%)	25 (20.8%)	44 (7.0%)	<0.001
Overall COVID-19 Risk of Complications Score	3.0 (0.0, 9.0)	5.0 (1.0, 9.0)	3.0 (0.0, 9.0)	<0.001
Vaccine type at first immunization				0.15
Astrazeneca	1 (2.0%)	0 (0.0%)	1 (0.6%)	
Johnson & Johnson	1 (2.0%)	10 (8.3%)	11 (6.5%)	
Moderna	14 (28.0%)	40 (33.3%)	54 (31.8%)	
Pfizer	34 (68.0%)	70 (58.3%)	104 (61.2%)	
High antispike antibody levels (≥132 U/ml)	92 (18.1%)	73 (60.8%)	165 (26.3%)	**<0.001**
Positive antispike antibody levels (≥0.8 U/ml)	250 (49.3%)	98 (81.7%)	348 (55.5%)	**<0.001**
Antispike antibody level (U/ml)	0.6 (0.4, 2500.0)	450.0 (0.4, 2500.0)	2.0 (0.4, 2500.0)	**<0.001**
Need for intensive care unit care	203 (40.0%)	46 (38.3%)	249 (39.7%)	0.76
Need for mechanical ventilation	52 (10.3%)	10 (8.3%)	62 (9.9%)	0.61
Length of hospital stay (days)				0.081
N-Miss	3	0	3	
Median (range)	6.0 (1.0, 81.0)	5.0 (1.0, 41.0)	5.0 (1.0, 81.0)	
Mortality	58 (11.4%)	15 (12.5%)	73 (11.6%)	0.75

Note: Categorical variables represented as count (percent), numeric as median (range). *P*-values come from the Fisher's exact test or Mann–Whitney nonparametric test.

Discussion

During the delta variant surge, COVID-19 breakthrough infections that required hospitalization had favorable outcomes compared to unvaccinated individuals. In the low-antispike antibody titer group, longer length of hospitalization, a higher mortality rate, and greater utilization of ICU were identified.

In our analysis, breakthrough infections represented 120 (19.1%), and 507 (81%) were unvaccinated. Our percentage of hospitalized cases that qualified as breakthrough infections was significantly higher than earlier reports through July 2021 from Kaiser Family Foundation, which ranged from 0.1% in the state of New Jersey to 5% in the state of Alaska [15]. Also, emerging data in healthcare workers in California noted a

Table 2. *Clinical characteristics of hospitalized breakthrough infections based on antispike antibody levels*

	Antispike <132 (N = 47)	Antispike ≥132 (N = 73)	Total (N = 120)	*P*-value
Age (years)	72.0 (38.0, 96.0)	73.0 (36.0, 99.0)	72.5 (36.0, 99.0)	0.20
Sex (Male)	29 (61.7%)	44 (60.3%)	73 (60.8%)	1.00
Race				0.39
Asian	1 (2.1%)	1 (1.4%)	2 (1.7%)	
Black or African American	9 (19.1%)	7 (9.6%)	16 (13.3%)	
White	36 (76.6%)	64 (87.7%)	100 (83.3%)	
Other/Unknown	1 (2.1%)	1 (1.4%)	2 (1.7%)	
Admitted for COVID-19	40 (85.1%)	60 (82.2%)	100 (83.3%)	0.80
Diabetes mellitus	20 (42.6%)	24 (32.9%)	44 (36.7%)	0.33
Hypertension	31 (66.0%)	49 (67.1%)	80 (66.7%)	1.00
Chronic lung disease	36 (76.6%)	58 (79.5%)	94 (78.3%)	0.82
Chronic kidney disease (no dialysis)	9 (19.1%)	11 (15.1%)	20 (16.7%)	0.62
Solid organ transplant recipient	16 (34.0%)	9 (12.3%)	25 (20.8%)	**0.006**
Overall COVID-19 Risk of Complications Score	5.0 (2.0, 9.0)	5.0 (1.0, 9.0)	5.0 (1.0, 9.0)	0.78
Vaccine type at first immunization				**0.025**
Johnson & Johnson	7 (14.9%)	3 (4.1%)	10 (8.3%)	
Moderna	19 (40.4%)	21 (28.8%)	40 (33.3%)	
Pfizer	21 (44.7%)	49 (67.1%)	70 (58.3%)	
Days from last vaccine dose to admission	136.0 (15.0, 244.0)	162.0 (37.0, 256.0)	149.0 (15.0, 256.0)	**0.011**
Antispike antibody level (U/ml)	2.9 (0.4, 121.0)	2500.0 (149.0, 2500.0)	450.0 (0.4, 2500.0)	**<0.001**
Need for intensive care unit care	24 (51.1%)	22 (30.1%)	46 (38.3%)	**0.034**
Need for mechanical ventilation	6 (12.8%)	4 (5.5%)	10 (8.3%)	0.19
Length of hospital stay (days)	6.0 (2.0, 41.0)	5.0 (1.0, 31.0)	5.0 (1.0, 41.0)	**0.013**
Mortality	10 (21.3%)	5 (6.8%)	15 (12.5%)	**0.025**

Note: Categorical variables represented as count (percent), numeric as median (range). *P*-values come from the Fisher's exact test or Mann–Whitney nonparametric test.

dramatic increase of vaccine breakthrough infections from June 2021 to July 2021 [7]. Our higher percentage of hospitalizations occurring from breakthrough infections likely is explained by the greater transmissibility of the delta variant compared to the alpha variant, virulence factors of the delta variant increasing its infectivity, and possibly less prevention measures such as masking, quarantining, and social distancing occurring in this state. Also, a greater proportion of the population was unvaccinated, thus at risk of infection in times of high community spread.

In our study, hospitalized vaccine breakthrough patients were older, had a higher COVID-19 Risk of Complications Score, and had SOT prior to COVID-19 infection compared to unvaccinated cases. These results are consistent with studies published prior to the circulation of the delta variant, with immunocompromised patients making up a high proportion (≥40%) of patients hospitalized for vaccine breakthrough infections [16–18].

Previous studies have shown mixed results in vaccine breakthrough clinical outcomes, with Butt et al. [19] describing a threefold higher risk of severe disease or death in unvaccinated hospitalized patients, and Brosh-Nissimov et al. [16] finding no difference in clinical outcomes between hospitalized breakthrough and unvaccinated cases. Our study reported similar clinical outcomes between these groups before matching. However, we emphasize that numerically the patient population was represented mostly by unvaccinated individuals rather than vaccinated individuals, and the baseline characteristics were different. Therefore,

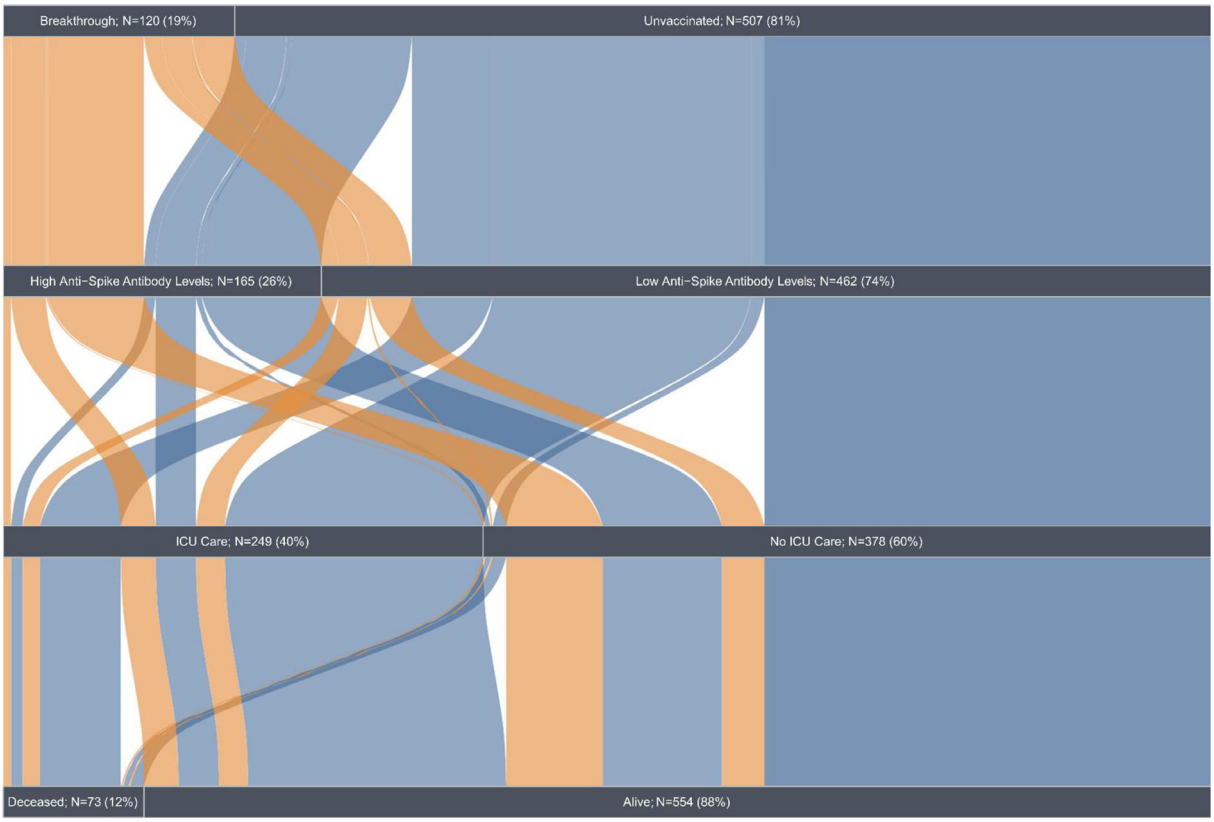

Fig. 3 *Sankey diagram of patient outcomes with high and low antispike antibody titers in the breakthrough and unvaccinated cohorts.*

propensity score matching revealed that unvaccinated patients had a longer hospital LOS and twofold higher mortality than the breakthrough patients. This trend emphasizes the protective nature of vaccination against SARS-CoV-2 amidst the delta variant surge.

Further analysis of the vaccine breakthrough cases revealed that high antispike antibody levels correlated with favorable clinical outcomes, including shorter hospital stay, less need for critical care services, and lower in-hospital mortality. In previous studies, increasing levels of antispike antibodies in vaccinated individuals were associated with decreased risk of symptomatic COVID-19 in the outpatient setting [20, 21]. Our study focuses on hospitalized breakthrough patients and highlights that higher antispike antibodies correlate with better outcomes.

The high proportion of organ transplant recipients in the low-titer group is explained by the effect of immunosuppression, leading to low antibody levels following vaccination. Boyarsky et al. [22, 23] published their data on antispike antibody production post one and two doses of mRNA COVID vaccine among SOT. They found that 46% of SOTs in their cohort did not develop antibody response despite two doses of mRNA vaccine for COVID-19. In previous studies, these high-risk patients had poor seroconversion after being fully vaccinated compared to immunocompetent patients and had an in-hospital mortality rate of 34% [24–26].

In our study, most fully immunized, breakthrough hospitalized cases had high antispike antibody titers on admission. Few unvaccinated patients also had detectable antispike antibody with high titers. This was likely a reaction to their current COVID-19 infection, as only two of these patients had confirmed prior infection.

There are limitations to this study. The Mayo Clinic in Florida is a tertiary destination medical

center for cancer and SOT, with a higher rate of immunocompromised patients compared to other centers. Thus, this retrospective study may have limited generalizability. After excluding transplant patients in the propensity score matching, the results can be more generalizable. In addition, we did not analyze differences in clinical treatments between the two groups. All patients at the Mayo Clinic in Florida were treated according to institutional treatment review panel guidelines, which account for individual patient risk factors, including immunosuppression and comorbidities. No significant treatment algorithm changes occurred during the study period, and it is unlikely this impacted our findings. An additional limitation is that this study was not designed to test differences in admission rates between unvaccinated and vaccinated patients. Similarly, the design did not allow for an estimated vaccination efficacy. Lastly, the reporting of days from onset of symptoms was not reliable to correlate with antibody titers on admission, which is a major limitation. As a patient-reported and physician-documented variable, we did not validate the data due to high heterogeneity and missing values. The symptoms onset data could shed more light on antibody titers on hospital admission, highlighting the need to report them consistently for future studies.

Conclusion

In summary, the experience of our site during the delta variant surge has shown that while most patients admitted with COVID-19 infection were unvaccinated, a rising number of patients with vaccine breakthrough infection required hospitalization. Some of these breakthrough cases suffered severe morbidity and even mortality, despite complete vaccination. Breakthrough hospitalized cases in vaccinated patients with low antibody titers, many of whom were immunocompromised, were associated with worse clinical outcomes than vaccinated patients with high antibody titers. This difference in antibody titer on admission may allow for prognostication in hospitalized COVID-19 patients and lead to different in-patient management strategies for high-risk, low-titer patients.

Acknowledgment

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Data availability statement

All requests for raw and analyzed data and related materials, excluding programming code, will be reviewed by the Mayo Clinic legal department and Mayo Clinic Ventures to verify whether the request is subject to any intellectual property or confidentiality obligations. Requests for patient-related data not included in the paper will not be considered. Any data and materials that can be shared will be released via a Material Transfer Agreement.

Conflict of interests

R. E. C. serves as an advisory board member for Anumana, Inc. All other authors declare no competing interests.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Box plot presentation for anti-spike antibody titers (U/ml) by vaccination status.

Table S1. Clinical characteristics of hospitalized COVID-19 patients based on vaccination status.

Table S2. Clinical characteristics of hospitalized COVID-19 patients according to breakthrough status in a matched cohort. ■

