Article

Not peer-reviewed version

Comparison of SARS-CoV-2 Delta Versus Omicron Variant and Its Impact on Immunocompromised Versus Immunocompetent Population

Sadia Z. Shah *, Parthkumar Satashia, Shahin Isha, Patrick Johnson, Katie Kunze, Abdul Moiz Khan *, Jorge Sinclair, Rose Mary Attieh, Anirban Bhattacharyya, Ricardo Diaz Millian, Michael Anthony Edwards, Rickey E. Carter, Leigh Speicher, Pablo Moreno Franco, Devang Sanghavi, Hani M. Wadei

Posted Date: 8 May 2026

doi: 10.20944/preprints202605.0560.v1

Keywords: COVID-19; immunocompromised; omicron; delta; solid organ transplant

 doi:10.20944/preprints202605.0560.v1

Article

Comparison of SARS-CoV-2 Delta Versus Omicron Variant and Its Impact on Immunocompromised Versus Immunocompetent Population

Sadia Z. Shah [1,*,†], Parthkumar Satashia [2,†], Shahin Isha [2], Patrick Johnson [3], Katie Kunze [4], Abdul Moiz Khan [1], Jorge Sinclair [2], Rose Mary Attieh [1], Anirban Bhattacharyya [2], Ricardo Diaz Millian [2], Michael Anthony Edwards [5], Rickey E. Carter [3], Leigh Spiecher [6], Pablo Moreno Franco [2], Devang Sanghavi [2,‡] and Hani M Wadei [1,‡]

[1] Department of Transplantation, Mayo Clinic, Jacksonville, Florida, USA
[2] Department of Critical Care Medicine, Mayo Clinic, Jacksonville, Florida
[3] Department of Quantitative Health Sciences, Mayo Clinic, Jacksonville, Florida
[4] Department of Quantitative Health Sciences, Mayo Clinic, Scottsdale, AZ
[5] Division of Advanced GI and Bariatric Surgery, Mayo Clinic, Jacksonville, FL
[6] Division of General Internal Medicine, Mayo Clinic, Jacksonville, Florida
* Correspondence: shah.sadia@mayo.edu
† Both authors have contributed equally as the first authors.
‡ Both authors contributed equally as the senior authors.

Abstract

The Omicron variant of SARS CoV-2 is associated with milder symptoms and lower hospitalization and mortality rates than Delta variants, although the impact of Omicron on immunocompromised patients, especially Solid Organ Transplant (SOT) recipients, is still unclear. This study compares the hospitalization rate and outcomes between immunocompromised, immunocompetent, and SOT patients during the Delta and Omicron periods. We included adult patients who tested positive for SARS-CoV-2 on PCR or nasopharyngeal antigen test between June 26, 2021 to September 8, 2022, at our institution. 12,401 COVID-19 patients were included, of which 11,055 were immunocompetent, and 1,346 were immunocompromised (375 SOT recipients). Throughout the Delta and Omicron outbreaks, immunocompromised patients exhibited higher comorbidities and 30-day hospitalizations, but rates of mechanical ventilation and ICU-level care were like immunocompetent patients. During the Omicron wave, immunocompromised patients had higher unadjusted relative risk estimates (RR=2.37, 95% CI 1.96-2.87, p<0.05) than Delta (RR=1.58, 95% CI 1.24-2.01, p<0.05) with higher adjusted relative risk for hospitalization in Omicron (RR=1.50, 95% CI 1.10-2.03, p=0.01). Analyses show increased hospitalization risk in immunocompromised during the Omicron wave compared to the Delta wave with no significant difference in hospitalization outcomes. The relative risk of hospitalization for SOT patients was higher in both waves.

Keywords: COVID-19; immunocompromised; omicron; delta; solid organ transplant

1. Introduction

Since the first reported case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan, China [1], the virus has continued to mutate and has given rise to multiple variants [2]. Of the variants reported by World Health Organization (WHO), the Alpha (B.1.1.7 and Q lineages), Beta (B.1.351 and descendent lineages), Delta (B.1.617.2 and AY lineages), and Omicron (B.1.1.529, BA.1, BA.1.1, BA.2, BA.3, BA.4 and BA.5 lineages) variants, thus far, are the most concerning, as they were responsible for major Coronavirus Disease 2019 (COVID-19) outbreaks worldwide [3]. In addition to their structural differences, these variants differ with regards to their virulence, infectivity, target

 doi:10.20944/preprints202605.0560.v1

population, and response to therapy [4]. Before the emergence of the Omicron variants, data suggested that the immunocompromised population faced an increased risk of developing severe COVID-19, requiring hospitalization, admission to the Intensive Care Unit (ICU), and mortality, especially in Solid Organ Transplant (SOT) recipients [5]. SOT recipients had a 15 times higher incidence of COVID-19 infection as compared to the general population [5]. Prior to vaccine availability, this was associated with at least a 10-fold higher mortality rate in SOT recipients (20%) compared to immunocompetent patients (0.8-2%) [5].

In late 2021, the SARS-COV-2 Delta variants were replaced by the Omicron variants. With more than 40 mutations in the spike protein gene [6,7], the Omicron variants proved to be more infectious to the general population, with less response to immunity conferred by neutralizing antibodies from previous infections or vaccinations [7]. Yet, the Omicron variants were associated with less severe symptoms, a shorter duration of illness, a lower hospitalization rate, and a lower mortality rate than the Delta variants [8,9]. However, limited information is available regarding the severity of the Omicron variant in immunocompromised patients and SOT recipients. In this retrospective cohort study, we sought to compare the hospitalization rate and duration, need and duration for ICU stay, and mortality in hospitalized immunocompromised as well as SOT patients in comparison to immunocompetent patients between Delta predominant and Omicron predominant eras.

2. Materials and Methods

2.1. Study Population

After obtaining approval from the Institutional Review Board, data was extracted from the Mayo Clinic electronic health record system. Inclusion criteria included adults 18 years of age or older with a positive polymerase chain reaction (PCR) or nasopharyngeal antigen test for the SARS-CoV-2 between June 26, 2021, and September 8, 2022, at Mayo Clinic Florida. Patients were excluded if their SARS-CoV-2 test was performed under contract through a third-party, had one or more Janssen vaccination against SARS-CoV-2 (removed due to limited sample size and difficulty standardizing data to multi-shot vaccination series), or if the solid organ transplant was performed after the COVID-19 infection (Figure 1).

The latency period between the Delta-predominant and Omicron-predominant waves of infection was defined as October 18, 2021, through December 17, 2021. Patients testing positive during this period were excluded to eliminate any ambiguity due to unavailability of genetic sequencing of variants. Eligible patients were identified as immunocompromised (as defined by CDC criteria [10], immunocompromised SOT recipients, and immunocompetent (if they lacked the above two criteria). Data related to patient demographics, comorbidities, vaccination status, COVID-19 Risk Score, admission status, type of solid organ transplant, length of hospital stay, requirement of ICU care, mechanical ventilation requirements, status of COVID-19 related medications (I.e., Molnupiravir, Nirmatrelvir/ritonavir, Remdesivir), COVID-19 convalescent plasma, monoclonal antibodies (Bebtelovimab, Casirivimab and Imdevimab, Sotrovimab), and Tixagevimab/cilgavimab, was collected through automatic electronic data pool from patients' medical records. Vaccination status was defined by the total number of COVID-19 vaccinations reported prior to infection.

2.2. Analysis

Patient demographics, comorbidities, and vaccination status, along with disease characteristics and treatment information, were analyzed using descriptive statistics. Comparisons of variables between immunocompromised and immunocompetent as well as sub-analysis between immunocompromised and immunocompromised secondary to being a SOT recipient, were explored using Pearson $\chi 2$ test. Unadjusted rates of 30-day hospital admission were calculated for each group overall, by wave, and by type of solid organ transplant. The unadjusted relative risk of admission for SOT patients by predominant-variant wave was also estimated.

 doi:10.20944/preprints202605.0560.v1

To estimate the relative risk for hospital admission in SOT recipients during various waves, we constructed an adjusted relative risk regression model for hospital admission using the interaction of SOT and predominant-variant wave. Additionally, we conducted a Cochran-Mantel-Haenszel analysis comparing immunocompromised and SOT recipients with subgroups defined by the predominant-variant wave. Finally, to examine the relationship between SOT and hospital admission, a random forest analysis was constructed in order to allow for the inclusion of a larger number of covariates and interactions between these covariates. Variables of interest included: type of SOT, age at positive SARS-CoV-2 test, gender, existing heart and lung conditions, calculated COVID-19 risk score [11], time from transplant to positive test, number of COVID-19 vaccinations, Tixagevimab/cilgavimab use, COVID-19 treatments (e.g., monoclonal antibody treatments, COVID-19 Convalescent Plasma, molnupiravir, nirmatrelvir/ritonavir, and remdesivir), and the predominant-variant wave.

To further explore the effects of different types of SOTs and time from transplant to COVID-19 diagnosis, we performed additional relative risk regression models within only the SOT subgroup. Outcomes for hospitalized patients were summarized. Lastly, we compared the marginal relative risk of admission between all immunocompromised patients and immunocompetent patients using the results from propensity score matching with subclassification methods. Patients were matched using age at positive SARS-CoV-2 test, gender, predominant-variant wave, and number of COVID-19 vaccinations. Analyses were conducted using R version 4.0.3. Reported p-values were two-tailed and not adjusted for multiple comparisons. All confidence intervals were calculated at the 95% confidence level. Unadjusted confidence intervals were calculated using binomial proportions.

3. Results

3.1. Patients

Out of the 12,401 patients who tested positive for COVID-19 during the study period, 11,055 were immunocompetent, and 1,346 were immunocompromised. Of the immunocompromised cohort, 375 patients were SOT recipients (heart, kidney, liver, lung, pancreas, or multi-organ) (Figure 1)

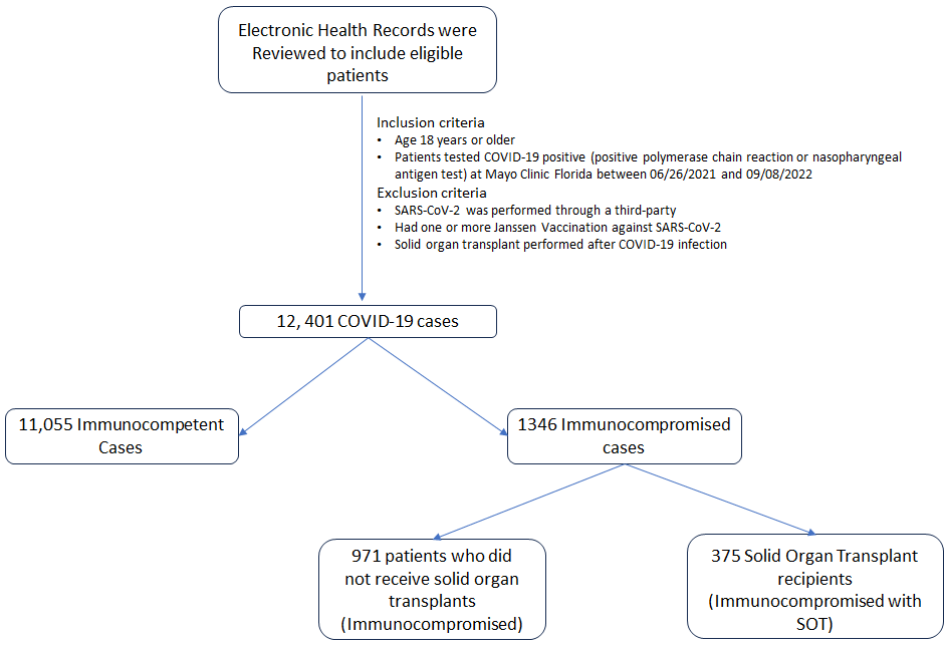

Figure 1. Study Flowchart describing inclusion and exclusion of patients.

 doi:10.20944/preprints202605.0560.v1

3.2. Thirty-Day Hospitalization Rate and Hospital Resource Utilization in Immunocompetent vs. Immunocompromised Patients

Table 1 summarizes the comparison of baseline demographics, comorbidities, monoclonal antibody use, and hospital resource utilization between all immunocompromised versus immunocompetent patients. Immunocompromised patients had more comorbidities, a higher COVID-19 risk score (2 or greater), higher rates of 30-day admission (13.8% vs. 7.1%, $p<0.05$), higher rates of monoclonal antibody infusions (19.6% vs. 7.0%, $p<0.05$), and higher rates of Tixagevimab/cilgavimab infusion (2.4% vs. 0%, $p<0.05$) when compared to immunocompetent patient. No statistically significant differences were observed for mechanical ventilation needs, length of hospital stay, and ICU level care between the two groups (Table 1).

Table 1. Cohort stratified by immunocompromised and immunocompetent for all PCR positive patients at Mayo Clinic Florida.

	Immunocompetent (N=11055)	**Immunocompromised (N=1346)**	**Total (N=12401)**	**P value**
Age at COVID-19 Test				**<0.001**
Median (Range)	52.0 (18.0, 102.3)	60.0 (18.7, 99.3)	53.1 (18.0, 102.3)	
Q1, Q3	36.8, 65.2	48.9, 70.4	37.9, 66.0	
Gender				0.49
N-Miss	2	0	2	
Female	6154 (55.7%)	736 (54.7%)	6890 (55.6%)	
Male	4899 (44.3%)	610 (45.3%)	5509 (44.4%)	
Solid Organ Transplant	0 (0.0%)	375 (27.9%)	375 (3.0%)	**<0.001**
SOT Type				
N-Miss	11055	971	12026	
Heart	0	58 (15.5%)	58 (15.5%)	
Kidney	0	137 (36.5%)	137 (36.5%)	
Liver	0	73 (19.5%)	73 (19.5%)	
Lung	0	63 (16.8%)	63 (16.8%)	
Multi-Organ Transplant	0	41 (10.9%)	41 (10.9%)	
Pancreas	0	3 (0.8%)	3 (0.8%)	
Time from SOT transplant to infection (years)				
Median (Range)	NA	3.9 (0.0, 35.0)	3.9 (0.0, 35.0)	
Q1, Q3	NA	1.5, 8.7	1.5, 8.7	
Chronic Kidney Disease Score	138 (1.2%)	161 (12.0%)	299 (2.4%)	**<0.001**
Diabetes	1170 (10.6%)	359 (26.7%)	1529 (12.3%)	**<0.001**
Congestive Heart Failure	475 (4.3%)	161 (12.0%)	636 (5.1%)	**<0.001**
Congenital Heart Disease	132 (1.2%)	16 (1.2%)	148 (1.2%)	0.99
Coronary Artery Disease	1174 (10.6%)	246 (18.3%)	1420 (11.5%)	**<0.001**
Hypertension	3610 (32.7%)	773 (57.4%)	4383 (35.3%)	**<0.001**
Chronic Respiratory Condition	1913 (17.3%)	451 (33.5%)	2364 (19.1%)	**<0.001**
COVID Risk Score				**<0.001**
0	2915 (26.4%)	0 (0.0%)	2915 (23.5%)	
1	3216 (29.1%)	148 (11.0%)	3364 (27.1%)	
2	1646 (14.9%)	232 (17.2%)	1878 (15.1%)	
3	1152 (10.4%)	219 (16.3%)	1371 (11.1%)	
4	849 (7.7%)	215 (16.0%)	1064 (8.6%)	
5	582 (5.3%)	196 (14.6%)	778 (6.3%)	
6	383 (3.5%)	140 (10.4%)	523 (4.2%)	
7	202 (1.8%)	102 (7.6%)	304 (2.5%)	

 doi:10.20944/preprints202605.0560.v1

8	74 (0.7%)	61 (4.5%)	135 (1.1%)	
9	32 (0.3%)	26 (1.9%)	58 (0.5%)	
10	4 (0.0%)	6 (0.4%)	10 (0.1%)	
11	0 (0.0%)	1 (0.1%)	1 (0.0%)	
Number of COVID-19 Vaccinations				**<0.001**
0	3192 (28.9%)	256 (19.0%)	3448 (27.8%)	
1	354 (3.2%)	37 (2.7%)	391 (3.2%)	
2	3822 (34.6%)	396 (29.4%)	4218 (34.0%)	
3+	3687 (33.4%)	657 (48.8%)	4344 (35.0%)	
Ethnicity				0.11
N-Miss	569	30	599	
Hispanic or Latino	824 (7.9%)	87 (6.6%)	911 (7.7%)	
Not Hispanic or Latino	9662 (92.1%)	1229 (93.4%)	10891 (92.3%)	
Race				**<0.001**
N-Miss	468	28	496	
American Indian/Alaskan Native	25 (0.2%)	5 (0.4%)	30 (0.3%)	
Asian	630 (6.0%)	42 (3.2%)	672 (5.6%)	
Black or African American	1043 (9.9%)	191 (14.5%)	1234 (10.4%)	
Native Hawaiian/Pacific Islander	31 (0.3%)	3 (0.2%)	34 (0.3%)	
White	8638 (81.6%)	1066 (80.9%)	9704 (81.5%)	
Other	220 (2.1%)	11 (0.8%)	231 (1.9%)	
Admission (30-day)	789 (7.1%)	186 (13.8%)	975 (7.9%)	**<0.001**
Monoclonal Antibody Infusion	769 (7.0%)	264 (19.6%)	1033 (8.3%)	**<0.001**
Monoclonal Antibody Infusion Type				**<0.001**
N-Miss	10286	1082	11368	
Bebtelovimab	281 (36.5%)	103 (39.0%)	384 (37.2%)	
Casirivimab and Imdevimab	423 (55.0%)	69 (26.1%)	492 (47.6%)	
Sotrovimab	65 (8.5%)	92 (34.8%)	157 (15.2%)	
Evusheld Infusion	0 (0.0%)	32 (2.4%)	32 (0.3%)	**<0.001**
Outpatient Molnupiravir	13 (0.1%)	5 (0.4%)	18 (0.1%)	**0.021**
Outpatient Paxlovid	400 (3.6%)	47 (3.5%)	447 (3.6%)	0.81
Remdesivir	2 (0.0%)	1 (0.1%)	3 (0.0%)	0.21
Ventilation				**0.019**
N-Miss	10266	1160	11426	
0	685 (86.8%)	173 (93.0%)	858 (88.0%)	
1	104 (13.2%)	13 (7.0%)	117 (12.0%)	
Mechanical Ventilation				0.090
N-Miss	10266	1160	11426	
0	738 (93.5%)	180 (96.8%)	918 (94.2%)	
1	51 (6.5%)	6 (3.2%)	57 (5.8%)	
Length of Stay (days)				0.62
Median (Range)	5.0 (1.0, 178.0)	5.0 (1.0, 46.0)	5.0 (1.0, 178.0)	
Q1, Q3	3.0, 8.0	3.8, 9.0	3.0, 8.0	
ICU Level of Care				0.22
N-Miss	10267	1161	11428	
0	695 (88.2%)	169 (91.4%)	864 (88.8%)	
1	93 (11.8%)	16 (8.6%)	109 1.2%)	

 doi:10.20944/preprints202605.0560.v1

As demonstrated in Supplemental Tables S1.1 and S1.2, during both waves, immunocompromised patients had higher rates of comorbidities, COVID-19 risk score, 30 days hospitalization rate (Delta predominant wave: 21.2% vs. 13.4% [p<0.001], Omicron predominant wave: 11.8% vs. 5.0% [p<0.001]), and monoclonal antibody infusion rate (Delta predominant wave: 20.2% vs. 13.7% [p=0.003], Omicron predominant wave 19.4% vs. 4.6% [p<0.001]). The rates of mechanical ventilation and the need for ICU level of care were comparable between the immunocompromised and immunocompetent patients. However, during the Omicron predominant wave, the median length of hospital stay was higher in immunocompromised patients [5 days, IQR: 3.2-8.0 vs. 4 days, IQR: 2.0-6.0 (p=0.029)] (Table S1.2).

Results of the marginal relative risk (RR) regression analysis of the propensity-matched cohort demonstrated that immunocompromised had a higher risk of hospitalization than immunocompetent patients (Marginal RR: 1.58 [1.24 – 2.01, p<0.05]). Results of the relative risk regression model showed that immunocompromised patients had a higher adjusted relative risk for hospitalization during the Omicron-predominant wave compared to the Delta-predominant wave (RR=1.50, 95% CI 1.10-2.03, p< 0.05) (Table 2).

Table 2. Adjusted Relative risk of hospitalization in Immunocompromised patients during Omicron wave.

Feature	Relative Risk	P-value
Immunocompromised	1.58 (1.24, 2.01)	<0.001
Omicron Wave	0.37 (0.32, 0.42)	<0.001
Immunocompromised*Omicron Wave	1.50 (1.10, 2.03)	0.010

3.3. Comparison of 30-Day Admission Rates After COVID-19 Diagnosis in Immunocompromised Patients During Delta Versus Omicron Waves

The crude 30-day admission rate in immunocompromised patients during the Omicron wave was much lower compared to the Delta wave (11.8% vs. 21.2%). However, the unadjusted relative risk point estimates for immunocompromised patients were higher during the Omicron wave (RR=2.37, 95% CI 1.96-2.87, p<0.05) than the Delta wave (RR=1.58, 95% CI 1.24-2.01, p<0.05). However, an overlapping confidence interval was observed (Figure 2).

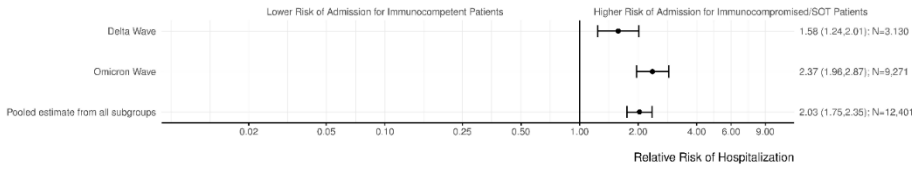

Figure 2. Unadjusted Relative Risk in Immunocompromised Patients during Delta and Omicron Wave.

3.4. Baseline Demographics and 30-Day Hospitalization Rate in SOT Recipients Versus Immunocompromised Without SOT

Solid Organ Transplant recipients had more comorbidities, a higher COVID-19 risk score (4 or greater), higher rates of 30-day admission (25.9% vs. 9.2%, p<0.001), higher rates of monoclonal antibody infusions (23.7% vs. 18.0%, p=0.018), and higher rates of Tixagevimab/cilgavimab infusion (4.5% vs. 1.5%, p=0.001) when compared to immunocompromised patients without SOT. No statistically significant differences were observed for COVID vaccination dosages, mechanical ventilation, length of hospital stay, and ICU level care between the two groups (Table 3).

 doi:10.20944/preprints202605.0560.v1

Table 3. Cohort stratified by SOT and Immunocompromised.

	Immunocompromised (N=971)	Immunocompromised SOT (N=375)	Total (N=1346)	P value
Age at COVID-19 Test				0.95
Median (Range)	59.8 (18.7, 99.3)	60.7 (21.5, 88.1)	60.0 (18.7, 99.3)	
Q1, Q3	48.6, 71.0	50.3, 69.1	48.9, 70.4	
Gender	409 (42.1%)	201 (53.6%)	610 (45.3%)	**<0.001**
SOT Type				
N-Miss	971	0	971	
Heart	0	58 (15.5%)	58 (15.5%)	
Kidney	0	137 (36.5%)	137 (36.5%)	
Liver	0	73 (19.5%)	73 (19.5%)	
Lung	0	63 (16.8%)	63 (16.8%)	
Multi-Organ Transplant	0	41 (10.9%)	41 (10.9%)	
Pancreas	0	3 (0.8%)	3 (0.8%)	
Time from SOT transplant to infection (years)				
Median (Range)	NA	3.9 (0.0, 35.0)	3.9 (0.0, 35.0)	
Q1, Q3	NA	1.5, 8.7	1.5, 8.7	
Chronic Kidney Disease Score	33 (3.4%)	128 (34.1%)	161 (12.0%)	**<0.001**
Diabetes	157 (16.2%)	202 (53.9%)	359 (26.7%)	**<0.001**
Congestive Heart Failure	70 (7.2%)	91 (24.3%)	161 (12.0%)	**<0.001**
Congenital Heart Disease	7 (0.7%)	9 (2.4%)	16 (1.2%)	**0.011**
Coronary Artery Disease	154 (15.9%)	92 (24.5%)	246 (18.3%)	**<0.001**
Hypertension	468 (48.2%)	305 (81.3%)	773 (57.4%)	**<0.001**
Chronic Respiratory Condition	288 (29.7%)	163 (43.5%)	451 (33.5%)	**<0.001**
COVID Risk Score				**<0.001**
1	146 (15.0%)	2 (0.5%)	148 (11.0%)	
2	214 (22.0%)	18 (4.8%)	232 (17.2%)	
3	171 (17.6%)	48 (12.8%)	219 (16.3%)	
4	137 (14.1%)	78 (20.8%)	215 (16.0%)	
5	113 (11.6%)	83 (22.1%)	196 (14.6%)	
6	82 (8.4%)	58 (15.5%)	140 (10.4%)	
7	63 (6.5%)	39 (10.4%)	102 (7.6%)	
8	29 (3.0%)	32 (8.5%)	61 (4.5%)	
9	13 (1.3%)	13 (3.5%)	26 (1.9%)	
10	2 (0.2%)	4 (1.1%)	6 (0.4%)	
11	1 (0.1%)	0 (0.0%)	1 (0.1%)	
Number of COVID-19 Vaccinations				0.64
0	192 (19.8%)	64 (17.1%)	256 (19.0%)	
1	26 (2.7%)	11 (2.9%)	37 (2.7%)	
2	279 (28.7%)	117 (31.2%)	396 (29.4%)	
3+	474 (48.8%)	183 (48.8%)	657 (48.8%)	
Ethnicity				0.55
N-Miss	27	3	30	
Hispanic or Latino	60 (6.4%)	27 (7.3%)	87 (6.6%)	
Not Hispanic or Latino	884 (93.6%)	345 (92.7%)	1229 (93.4%)	
Race				**<0.001**
N-Miss	27	1	28	
American Indian/Alaskan Native	4 (0.4%)	1 (0.3%)	5 (0.4%)	

 doi:10.20944/preprints202605.0560.v1

Asian	30 (3.2%)	12 (3.2%)	42 (3.2%)	
Black or African American	96 (10.2%)	95 (25.4%)	191 (14.5%)	
Native Hawaiian/Pacific Islander	2 (0.2%)	1 (0.3%)	3 (0.2%)	
White	804 (85.2%)	262 (70.1%)	1066 (80.9%)	
Other	8 (0.8%)	3 (0.8%)	11 (0.8%)	
Admission (30-day)	89 (9.2%)	97 (25.9%)	186 (13.8%)	**<0.001**
Monoclonal Antibody Infusion	175 (18.0%)	89 (23.7%)	264 (19.6%)	**0.018**
Monoclonal Antibody Infusion Type				**0.003**
N-Miss	796	286	1082	
Bebtelovimab	68 (38.9%)	35 (39.3%)	103 (39.0%)	
Casirivimab and Imdevimab	56 (32.0%)	13 (14.6%)	69 (26.1%)	
Sotrovimab	51 (29.1%)	41 (46.1%)	92 (34.8%)	
Evusheld Infusion	15 (1.5%)	17 (4.5%)	32 (2.4%)	**0.001**
Outpatient Molnupiravir	1 (0.1%)	4 (1.1%)	5 (0.4%)	**0.009**
Outpatient Paxlovid	44 (4.5%)	3 (0.8%)	47 (3.5%)	**<0.001**
Remdesivir	0 (0.0%)	1 (0.3%)	1 (0.1%)	0.11
Ventilation				0.11
N-Miss	882	278	1160	
0	80 (89.9%)	93 (95.9%)	173 (93.0%)	
1	9 (10.1%)	4 (4.1%)	13 (7.0%)	
Mechanical Ventilation				0.077
N-Miss	882	278	1160	
0	84 (94.4%)	96 (99.0%)	180 (96.8%)	
1	5 (5.6%)	1 (1.0%)	6 (3.2%)	
Length of Stay (days)				0.94
Median (Range)	5.0 (1.0, 46.0)	5.0 (1.0, 42.0)	5.0 (1.0, 46.0)	
Q1, Q3	3.5, 9.5	4.0, 9.0	3.8, 9.0	
ICU Level of Care				0.75
N-Miss	883	278	1161	
0	81 (92.0%)	88 (90.7%)	169 (91.4%)	
1	7 (8.0%)	9 (9.3%)	16 (8.6%)	

During both waves, 30-day admission rates after COVID-19 diagnosis (Delta predominant wave: 33.3% vs. 16.1% [p<0.001], Omicron predominant wave: 23.6% vs. 7.3% [p<0.001]) were higher in SOT patients. No differences were noted in vaccination status, mechanical ventilation, length of stay, and ICU level of care status between the two cohorts. While no difference was evident for monoclonal antibody infusion rates between SOT patients and immunocompromised groups during the Delta wave, monoclonal antibody infusion rate was higher during the Omicron wave in SOT patients (26.7% vs. 16.7%, p<0.001) (Tables S2.1 and S2.2).

3.5. Comparison of 30-Day Admission Rates After COVID-19 Diagnosis in SOT During Delta Versus Omicron Waves

The crude 30-day admission rate in SOT patients during the Omicron wave was much lower compared to the Delta wave (23.6% vs. 33.3%). On the other hand, the unadjusted relative risk point estimates showing risk of hospitalization for SOT patients, compared to non-SOT immunocompromised patients, were higher during the Omicron wave (RR=3.23, 95% CI 2.33-4.48, p<0.05) than the Delta wave (RR=2.07, 95% CI 1.35-3.19, p<0.05). However, the confidence interval was observed to be overlapping (Figure 3).

 doi:10.20944/preprints202605.0560.v1

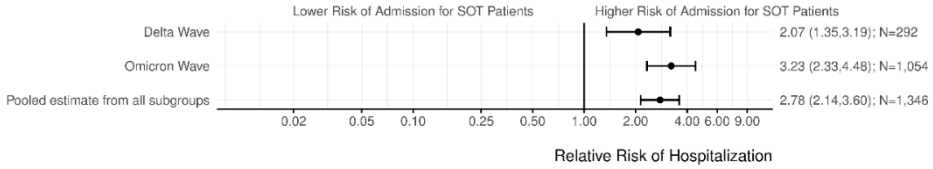

Figure 3. Unadjusted Relative Risk in SOT Patients during Delta and Omicron Wave.

A pooled estimate from all subgroups using the Cochran-Mantel-Haenszel technique showed an overall higher relative risk of admission in SOT patients compared to non-SOT immunocompromised patients [RR= 2.78 (95% CI: 2.14-3.60)]. Results of the relative risk regression model similarly showed an increased risk of admission for SOT patients, decreased risk during Omicron, and no significant interaction between SOT status and wave.

Based on the random forest model, the most important features (based on Gini-decrease) to predict 30-day admission were (1) age, (2) COVID risk score, (3) number of vaccinations, (4) chronic respiratory disease, (5) monoclonal antibody infusion, (6) wave, and (7) absence of a SOT transplant (Figure S1). The random forest also indicated there were no meaningful interactions between solid transplant type and time from transplant to positive test.

Of the 186 hospitalized immunocompromised and SOT patients, only five patients died in the hospital (four immunocompromised and one SOT). Three deaths occurred during the Delta-predominant wave and two during the Omicron-predominant wave. Our event rate was too small to estimate predictors of mortality.

3.6. Effect of Organ Transplant Type on 30-Day Admission Rate in the Delta Versus Omicron Waves

Most SOT recipients had received a kidney transplant (N=137), followed by liver (N=73), lung (N=63), and heart (N=58). The remaining 41 patients were classified as recipients of multi-organ transplants. Although lower risk of admission was observed during the Omicron-predominant wave, no significant difference in risk of 30-day admission was observed across different transplant types (Figure S2).

4. Discussion

Since the emergence of the COVID-19 pandemic in 2019, SARS-CoV-2 variants have continued to evolve which has affected the overall viral infectivity, virulence, and resistance to therapeutic interventions [3,4]. Efforts to combat the spread of SARS-CoV-2 have also evolved with the availability of vaccinations, prophylactic antibody infusions such as Tixagevimab/cilgavimab, and treatment regimens for treatment of both outpatient and hospitalized patients. The aim of our study was to compare the more virulent Delta variant to the highly infectious but less virulent Omicron variant and determine its effects on 30-day hospitalization and hospital resource utilization in the immunocompromised versus immunocompetent populations in a tertiary care center with a large population of SOT recipients and immunocompromised patients without SOT.

In our study, we found that the hospital admission rate for COVID-19 was higher in immunocompromised patients compared to their immunocompetent counterparts during both the Delta and Omicron waves (Tables S1.1 and S1.2). These results were consistent with several other studies, including COVID-NET (US COVID-19 Associated Hospitalization Surveillance Network), that identified immunosuppression as an independent risk factor for hospitalization following SARS-CoV-2 infection [12,13]. The novel finding of our current study is the result of the regression model that demonstrated 50% higher rate of hospitalization during the Omicron predominant wave than the Delta-predominated wave in the immunocompromised population (Table 2). The reasons for this higher hospitalization rate are unclear but can only be hypothesized. One possible explanation is the published higher mortality rates in immunocompromised patients with the Delta variant could have

 doi:10.20944/preprints202605.0560.v1

led to higher rates of precautionary admissions with the emergence of the Omicron wave. Another possible explanation is that with the less severe symptoms observed with the Omicron variant, especially in immunocompetent patients, more hospital beds became available for the more vulnerable immunocompromised patients. A third possibility is related to significant drug-drug interaction with oral Nirmatrelvir/ritonavir and calcineurin inhibitors which has limited this drug's utilization in the SOT and other immunocompromised patients taking calcineurin inhibitors. Irrespective of the explanation, our results indicated that many of these hospitalizations could have been avoided, especially given the rates of mechanical ventilation and ICU level of care were very low and were comparable between the immunocompromised and immunocompetent patients in both the Delta and Omicron waves.

Amidst a challenging need to confer an adequate immune response in the immunocompromised populations, Evusheld (a combination of two long-acting monoclonal antibodies - tixagevimab co-packaged with cilgavimab) received emergency use authorization by US Food and Drug Administration (FDA) on December 8, 2021 [14]. Post-hoc analysis of the ongoing PROVENT trial and a retrospective cohort study performed by Jurdi et al. showed an effective immune response as well as a low risk of adverse effects in the immunocompromised and SOT populations [15,16]. Since SOT recipients and immunocompromised patients without SOT have been receiving Tixagevimab/Cilgavimab, unlike immunocompetent patients, it is hard to determine the role of this drug in decline in post-hospitalization outcomes. Since FDA, on January 26, 2023, revised the EUA for Tixagevimab/Cilgavimab is currently not authorized to be used in USA [17]. This decision was made to limit its use to when the combined frequency of non-susceptible SARS-CoV-2 variants nationally is less than or equal to 90%.

A sub-analysis of our immunocompromised patients showed that patients who received SOT had a higher 30-day admission rate, but their post-hospitalization outcomes, such as mechanical ventilation, length of hospital stay, and need for ICU level of care did not vary significantly between the two groups (Table 3). These findings were consistent with past studies, which suggested there was no difference in COVID-19-associated outcomes in the SOT population compared to the general population [18–20] but were contrary to Robert et al. findings which demonstrated an increased rate of hospitalization, ICU requirement, mechanical ventilation, and mortality in their study [21]. In our study cohort, since we had very few mortalities within the SOT group (1 death during the Omicron wave) and non-SOT group (3 deaths during the Delta wave and 1 during the Omicron wave), it did not allow us to make a statistical comparison of mortality rates.

Given the mortality outcomes between SOT recipients and general population were comparable, despite a higher hospitalization rate in SOT population raises questions about the protective rather than deleterious effect of immunosuppression in this patient cohort. This perspective was brought forward by some of the studies that reported comparable mortality, outcomes, and a faster decline in the severity of COVID-19 in SOT patients compared to the general population [18,19]. This hypothesis has been explored pre-COVID while exploring the protective role of immunosuppressed status in septic patients. Cytokine storm in COVID-19 results from a hyper-inflammatory state [22–24]. Cell-mediated immune system dysfunction due to pre-existing immunosuppression can potentially attenuate the inflammation and disease severity in the SOT population and has been hypothesized as the potential reason for the differences in outcomes [25,26]. However, Maggiore et al. suggested that comparable in-hospital mortality percentages between SOT and the general population may not accurately reflect the true mortality in the SOT population being studied as an increased hospitalization rate may indicate elevated absolute mortality in the SOT population [26]. Furthermore, Heldman et al. also highlighted that majority of literature focuses on 28-day hospital mortality for COVID-19, but from their registry-based study, they were able to demonstrate that the delayed 29–90-day mortality amongst hospitalized SOT recipients with COVID-19 is 23%; in addition, to the initial 20% within 28-days [27].

Past research has shown a diminished immune response in the form of lower anti-spike antibodies and breakthrough infection following COVID-19 vaccination in the immunosuppressed

 doi:10.20944/preprints202605.0560.v1

SOT population [28–31]. However, the mortality and morbidity outcomes associated with vaccination status in the SOT population are yet to be fully explored. A large-scale registry database-based retrospective study done by Ravanan et al. and another registry-based study done by Aslam et al. suggested a decline in mortality rates associated with vaccination in the SOT population, although their studies did not control for confounders [32,33]. Hailey et al. performed a single-center propensity-matched analysis on kidney transplant recipients based on historical data and found a five-fold risk of mortality in the unvaccinated cohort, although their results did not reach statistical significance [34].

The varying trends with COVID-19-related outcomes in the SOT population over time have been reported by several studies, which also explored the possible factors behind such differences. An improvement in resource utilization, vaccination, and fluctuating virulence of the variants of concern has contributed to some improvements in mortality and morbidity metrics [35]. However, limited literature is available comparing Delta-wave versus Omicron wave in terms of outcome in the SOT population. In our cohort, outcomes in the SOT group and non-SOT group did not vary across Delta-wave and Omicron wave except that hospitalized SOT group had a significantly higher rate of mechanical ventilation during the Delta wave, which was not noted in Omicron wave as well as in the full cohort analysis. The risk of admission in the SOT group was higher across the Delta wave [OR: 2.07 (1.35, 3.19)], the Omicron wave [OR: 3.23 (2.33, 4.48)] as well as for the whole cohort [OR: 2.78 (2.14, 3.60)], thus pointing towards a sustained risk of hospitalization in SOT population despite the changing virulence in SARS-CoV-2.

Infection with the Omicron variant has been associated with diminished morbidity and mortality for the general population, most likely due to vaccination coverage, and altered pathogenicity of the variant [36–38]. This has led to a loosening of certain public health measures all over the world and a general change in the attitude toward the pandemic. The UNOS policy changes to adjust for COVID-19 associated burden on the transplant waiting list and caregivers that were introduced in response to earlier COVID waves are also lifted [39,40]. On the background of these measures, a sustained risk of COVID-19-associated mortality and morbidity outcomes irrespective of the waves, as seen in our study, raises the question of whether we need to take a closer look at the impact on this high-risk population. Moreover, the increased virus circulation in the general population due to the inherent capacity of the virus and the aforementioned changes in public health policy amplifies the risk to the SOT population.

In conclusion, our analysis shows the increased risk of hospitalization in immunocompromised patients during Omicron dominant wave with no major difference in hospitalization days, ICU days and mortality when compared to the Delta predominant wave. The SOT patients had higher risk of admission compared to non-SOT immunocompromised patients during Delta as well as Omicron wave although the risk of hospitalization did not statistically vary between the waves. Preventative strategies such as safe distancing, quarantining sick contacts, masking, booster dose vaccination, etc., should be followed aggressively considering the limited efficiency of Tixagevimab/cilgavimab, previously effective monoclonal antibodies and inability to utilize the current oral antiviral medications (molnupiravir, nirmatrelvir/ritonavir).

5. Conclusions

Our analyses show increased hospitalization risk in immunocompromised patients during the Omicron wave compared to the Delta wave with no significant difference in hospitalization outcomes. The relative risk of hospitalization for SOT patients was higher in both waves.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

Author Contributions Following are the author contributions for each author: Sadia Z. Shah: Conceptualization, methodology, investigation, resources, writing-original draft, writing- review and editing, supervision; **Parthkumar Satashia:** Conceptualization, methodology, investigation, writing-original draft,

 doi:10.20944/preprints202605.0560.v1

writing- review and editing; **Shahin Isha:** Conceptualization, methodology, writing-original draft, writing-review and editing; **Patrick Johnson:** Conceptualization, methodology, investigation, formal analysis, data curation, visualization, writing-original draft, writing- review and editing; **Katie Kunze:** Conceptualization, methodology, investigation, formal analysis, data curation, visualization, writing-original draft, writing- review and editing; **Abdul Moiz Khan**: Conceptualization, methodology, writing-original draft, writing- review and editing; **Jorge Sinclair**: investigation, writing-original draft, writing- review and editing; **Rose Mary Attieh**: investigation, writing-original draft, writing- review and editing **Anirban Bhattacharyya**: Conceptualization, investigation, writing-original draft, writing- review and editing; **Ricardo Diaz Millian**: Conceptualization, investigation, writing-original draft, writing- review and editing; **Michael Anthony Edwards:** Conceptualization, investigation, writing-original draft, writing- review and editing; **Rickey E. Carter:** Conceptualization, methodology, investigation, data curation, visualization, writing-original draft, writing-review and editing; **Leigh Spiecher**: Conceptualization, investigation, writing-original draft, writing- review and editing; **Pablo Moreno Franco**: Conceptualization, investigation, writing-original draft, writing- review and editing; **Devang Sanghavi**: Concetualization, investigation, resources, writing-original draft, writing- review and editing; **Hani M Wadei:** Conceptualization, investigation, resources, writing-original draft, writing- review and editing. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Mayo Clinic Florida. The requirement for a protocol code and approval date was not applicable for this study.

Informed Consent Statement: Patient consent was waived due to the retrospective nature of the study and the use of de-identified electronic health record data.

Data Availability Statement: Access to the data used in this research is available upon request to the corresponding authors. Patients' privacy concerns, HIPPA regulation, and institutional rules will be strictly considered while providing the data.

Acknowledgments: There are no acknowledgements to be added.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

COVID-19	Corona Virus Disease 2019.
FDA	Food and Drug Administration.
ICU	Intensive Care Unit.
PCR	Polymerase Chain Reaction.
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2.
SOT	Solid Organ Transplant.
WHO	World Health Organization.

References

1. Li Q, Guan X, Wu P, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *N Engl J Med*. 2020;382(13):1199-1207. https://doi.org/10.1056/NEJMoa2001316
2. CDC. Coronavirus Disease 2019 (COVID-19). Centers for Disease Control and Prevention. Published February 11, 2020. Accessed March 10, 2023. https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-classifications.html
3. Tracking SARS-CoV-2 variants. Accessed March 10, 2023. https://www.who.int/activities/tracking-SARS-CoV-2-variants
4. SeyedAlinaghi S, Mirzapour P, Dadras O, et al. Characterization of SARS-CoV-2 different variants and related morbidity and mortality: a systematic review. *Eur J Med Res*. 2021;26:51. https://doi.org/10.1186/s40001-021-00524-8

 doi:10.20944/preprints202605.0560.v1

5. Pereira MR, Mohan S, Cohen DJ, et al. COVID-19 in solid organ transplant recipients: Initial report from the US epicenter. *Am J Transplant*. 2020;20(7):1800-1808. https://doi.org/10.1111/ajt.15941
6. Wei C, Shan KJ, Wang W, Zhang S, Huan Q, Qian W. Evidence for a mouse origin of the SARS-CoV-2 Omicron variant. *J Genet Genomics*. 2021;48(12):1111-1121. https://doi.org/10.1016/j.jgg.2021.12.003
7. Chen J, Wang R, Gilby NB, Wei GW. Omicron (B.1.1.529): Infectivity, vaccine breakthrough, and antibody resistance. *ArXiv*. Published online December 1, 2021:arXiv:2112.01318v1.
8. Menni C, Valdes AM, Polidori L, et al. Symptom prevalence, duration, and risk of hospital admission in individuals infected with SARS-CoV-2 during periods of omicron and delta variant dominance: a prospective observational study from the ZOE COVID Study. *The Lancet*. 2022;399(10335):1618-1624. https://doi.org/10.1016/S0140-6736(22)00327-0
9. Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: a cohort study - ScienceDirect. Accessed March 10, 2023. https://www.sciencedirect.com/science/article/pii/S0140673622004627
10. CDC. COVID-19 and Your Health. Centers for Disease Control and Prevention. Published February 11, 2020. Accessed March 10, 2023. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-who-are-immunocompromised.html
11. Nyman MA, Jose T, Croghan IT, et al. Utilization of an Electronic Health Record Integrated Risk Score to Predict Hospitalization Among COVID-19 Patients. *J Prim Care Community Health*. 2022;13:21501319211069748. https://doi.org/10.1177/21501319211069748
12. Kim L, Garg S, O'Halloran A, et al. Risk Factors for Intensive Care Unit Admission and In-hospital Mortality Among Hospitalized Adults Identified through the US Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET). *Clin Infect Dis*. 2021;72(9):e206-e214. https://doi.org/10.1093/cid/ciaa1012
13. Li J, Huang DQ, Zou B, et al. Epidemiology of COVID-19: A systematic review and meta-analysis of clinical characteristics, risk factors, and outcomes. *J Med Virol*. 2021;93(3):1449-1458. https://doi.org/10.1002/jmv.26424
14. Commissioner O of the. Coronavirus (COVID-19) Update: FDA Authorizes New Long-Acting Monoclonal Antibodies for Pre-exposure Prevention of COVID-19 in Certain Individuals. FDA. Published December 8, 2021. Accessed March 10, 2023. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-new-long-acting-monoclonal-antibodies-pre-exposure
15. Al Jurdi A, Morena L, Cote M, Bethea E, Azzi J, Riella LV. Tixagevimab/cilgavimab pre-exposure prophylaxis is associated with lower breakthrough infection risk in vaccinated solid organ transplant recipients during the omicron wave. *Am J Transplant*. 2022;22(12):3130-3136. https://doi.org/10.1111/ajt.17128
16. Levin MJ, Ustianowski A, De Wit S, et al. Intramuscular AZD7442 (Tixagevimab–Cilgavimab) for Prevention of Covid-19. *N Engl J Med*. Published online April 20, 2022:NEJMoa2116620. https://doi.org/10.1056/NEJMoa2116620
17. Research C for DE and. FDA announces Evusheld is not currently authorized for emergency use in the U.S. *FDA*. Published online January 25, 2023. Accessed March 10, 2023. https://cacmap.fda.gov/drugs/drug-safety-and-availability/fda-announces-evusheld-not-currently-authorized-emergency-use-us
18. Rinaldi M, Bartoletti M, Bussini L, et al. COVID-19 in solid organ transplant recipients: No difference in survival compared to general population. *Transpl Infect Dis*. 2021;23(1):e13421. https://doi.org/10.1111/tid.13421
19. Avery RK, Chiang TPY, Marr KA, et al. Inpatient COVID-19 outcomes in solid organ transplant recipients compared to non-solid organ transplant patients: A retrospective cohort. *Am J Transplant*. 2021;21(7):2498-2508. https://doi.org/10.1111/ajt.16431
20. Chaudhry ZS, Williams JD, Vahia A, et al. Clinical characteristics and outcomes of COVID-19 in solid organ transplant recipients: A cohort study. *Am J Transplant*. 2020;20(11):3051-3060. https://doi.org/10.1111/ajt.16188

 doi:10.20944/preprints202605.0560.v1

21. Roberts MB, Izzy S, Tahir Z, Al Jarrah A, Fishman JA, El Khoury J. COVID-19 in solid organ transplant recipients: Dynamics of disease progression and inflammatory markers in ICU and non-ICU admitted patients. *Transpl Infect Dis*. 2020;22(5):e13407. https://doi.org/10.1111/tid.13407
22. Kalil AC, Florescu DF. Mortality in solid organ transplant recipients hospitalized for COVID-19. *Am J Transplant*. 2022;22(1):12-13. https://doi.org/10.1111/ajt.16885
23. Kalil AC, Syed A, Rupp ME, et al. Is bacteremic sepsis associated with higher mortality in transplant recipients than in nontransplant patients? A matched case-control propensity-adjusted study. *Clin Infect Dis*. 2015;60(2):216-222. https://doi.org/10.1093/cid/ciu789
24. Donnelly JP, Locke JE, MacLennan PA, et al. Inpatient Mortality Among Solid Organ Transplant Recipients Hospitalized for Sepsis and Severe Sepsis. *Clin Infect Dis*. 2016;63(2):186-194. https://doi.org/10.1093/cid/ciw295
25. Choi H, Shin EC. Hyper-inflammatory responses in COVID-19 and anti-inflammatory therapeutic approaches. *BMB Rep*. 2022;55(1):11-19. https://doi.org/10.5483/BMBRep.2022.55.1.152
26. Maggiore U, Riella LV, Azzi J, Cravedi P. Mortality in solid organ transplant recipients with COVID-19: More than meets the eye. *Am J Transplant*. 2022;22(5):1496-1497. https://doi.org/10.1111/ajt.16942
27. Heldman MR, Kates OS, Safa K, et al. Delayed mortality among solid organ transplant recipients hospitalized for COVID-19. *Clin Infect Dis*. Published online February 25, 2022:ciac159. https://doi.org/10.1093/cid/ciac159
28. Sanghavi DK, Bhakta S, Wadei HM, et al. Low antispike antibody levels correlate with poor outcomes in COVID-19 breakthrough hospitalizations. *J Intern Med*. 2022;292(1):127-135. https://doi.org/10.1111/joim.13471
29. Bosch W, Cowart JB, Bhakta S, et al. Coronavirus Disease 2019 Vaccine-Breakthrough Infections Requiring Hospitalization in Mayo Clinic Florida Through August 2021. *Clin Infect Dis*. 2022;75(1):e892-e894. https://doi.org/10.1093/cid/ciab932
30. Feikin DR, Higdon MM, Abu-Raddad LJ, et al. Duration of effectiveness of vaccines against SARS-CoV-2 infection and COVID-19 disease: results of a systematic review and meta-regression. *Lancet*. 2022;399(10328):924-944. https://doi.org/10.1016/S0140-6736(22)00152-0
31. Sanders JSF, Bemelman FJ, Messchendorp AL, et al. The RECOVAC Immune-response Study: The Immunogenicity, Tolerability, and Safety of COVID-19 Vaccination in Patients With Chronic Kidney Disease, on Dialysis, or Living With a Kidney Transplant. *Transplantation*. 2022;106(4):821-834. https://doi.org/10.1097/TP.0000000000003983
32. 32. Ravanan R, Mumford L, Ushiro-Lumb I, et al. Two Doses of SARS-CoV-2 Vaccines Reduce Risk of Death Due to COVID-19 in Solid Organ Transplant Recipients: Preliminary Outcomes From a UK Registry Linkage Analysis. *Transplantation*. 2021;105(11):e263-e264. https://doi.org/10.1097/TP.0000000000003908
33. 33. Aslam S, Adler E, Mekeel K, Little SJ. Clinical effectiveness of COVID-19 vaccination in solid organ transplant recipients. *Transpl Infect Dis*. 2021;23(5):e13705. https://doi.org/10.1111/tid.13705
34. Hardgrave H, Wells A, Nigh J, et al. COVID-19 Mortality in Vaccinated vs. Unvaccinated Liver & Kidney Transplant Recipients: A Single-Center United States Propensity Score Matching Study on Historical Data. *Vaccines (Basel)*. 2022;10(11):1921. https://doi.org/10.3390/vaccines10111921
35. Heldman MR, Kates OS, Safa K, et al. Changing trends in mortality among solid organ transplant recipients hospitalized for COVID-19 during the course of the pandemic. *Am J Transplant*. 2022;22(1):279-288. https://doi.org/10.1111/ajt.16840
36. Nyberg T, Ferguson NM, Nash SG, et al. Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: a cohort study. *Lancet*. 2022;399(10332):1303-1312. https://doi.org/10.1016/S0140-6736(22)00462-7
37. Keeton R, Tincho MB, Ngomti A, et al. T cell responses to SARS-CoV-2 spike cross-recognize Omicron. *Nature*. 2022;603(7901):488-492. https://doi.org/10.1038/s41586-022-04460-3
38. GeurtsvanKessel CH, Geers D, Schmitz KS, et al. Divergent SARS-CoV-2 Omicron-reactive T and B cell responses in COVID-19 vaccine recipients. *Sci Immunol*. 2022;7(69):eabo2202. https://doi.org/10.1126/sciimmunol.abo2202

 doi:10.20944/preprints202605.0560.v1

39. Reinstatement of Updates to Candidate Data During the COVID-19 Emergency - OPTN. Accessed March 10, 2023. https://optn.transplant.hrsa.gov/policies-bylaws/public-comment/reinstatement-of-updates-to-candidate-data-during-the-covid-19-emergency/
40. Covid-19 Emergency Policy Package.