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Effects of COVID-19 on Ventilator Associated Events (VAEs) Due to Multi-Drug Resistant Organisms (MDROs)

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EFFECTS OF COVID-19 ON VENTILATOR ASSOCIATED EVENTS (VAEs) DUE TO MULTI-DRUG RESISTANT ORGANISMS (MDROs)

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ABSTRACT

The aim of this study was to assess the association between the coronavirus disease (COVID-19) and the odds of ventilator associated events (VAEs). Retrospective analysis on prospectively collected data from 11,307 patients admitted to the intensive care unit (ICU) at the University of Alabama at Birmingham hospital between January 2018 and June 2022 was used. Outcomes considered were Any VAE, IVAC/PVAP, PVAP and MDRO PVAP.

Crude and adjusted logistic regression models were used to evaluate the association between COVID-19 and the outcome variables. When a patient has Prior COVID-19, the odds of getting any VAE during the delta period is 1.59 times higher compared to the alpha period (OR=1.587; 95% CI=1.167-2.158; P=0.003). The study also found that, The odds of getting an IVAC/PVAP during the delta period is 1.90 times higher compared to Pre-COVID (OR=1.898; 95% CI=1.457-2.474; P <.00001). COVID-19 was associated with an increase in patients getting VAEs in hospitalized settings.

Keywords: COVID-19, ventilator associated events, infection related ventilator associated complication, multidrug resistant organisms.

DEDICATION

To my son, Eliel Jesse (E.J) Asiedu-Asubonteng, whom we had during this thesis writing period and who was a source of motivation for me throughout this period. I love and appreciate you!

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CHAPTER 1

INTRODUCTION

Mechanical ventilation is a life-sustaining intervention especially for patients with acute respiratory failure but being on a ventilator also increases the risk of an array of infections that can prolong dependence on a ventilator and sometimes increase the risk of death [21]. The daily cost of mechanical ventilation for ICU patients is estimated to be between $600 and $1500 per day [6]. In 2013, the Centers for Disease Control and Prevention (CDC) developed ventilator-associated event (VAE) surveillance to provide a more objective and broader measure of the potential complications of mechanical ventilation [13, 16]. VAEs are defined by ≥ 2 days of sustained increases in ventilator settings (rise in positive end-expiratory pressure (PEEP) of ≥ 3 cmH_2O and/or rise in the absolute fraction of inspired oxygen (FiO_2) of $\geq 20\%$) after ≥ 2 days of stable or decreasing ventilator settings [8].

The rates of ventilator-associated events which can be subdivided into ventilator associated condition (VAC), infection-related ventilator associated complication (IVAC) and possible ventilator associated pneumonia (PVAP) ranges from 5 to 10% prior to the coronavirus disease (COVID-19) pandemic although some studies have documented rates of more than 20% [10]. Incidence rates reported to the CDC for the first full year of VAE surveillance in 2014 changed from 2.59 to 11.79 per 1000 ventilator-days, with higher rates found in larger teaching hospitals [14]. The rates of possible pneumonia, based on older versions of the PVAP surveillance definition, also changed by ICU type ranging from 1.7 to 4.5 events per 1000 ventilator days. Likewise, the fraction of VACs that qualify as IVACs changed by ICU type and

varied from about one-third to one-half, with higher fractions in trauma, burn, and surgical ICUs compared with medical ICUs

An increasing number of studies are being published around the world describing VAE epidemiology. A study of more than 6000 ventilated patients in 5 ICUs across medical and surgical specialties at an academic medical center in China, for example, reported VAC, IVAC, and PVAP rates of 13.7, 6.3, and 2.2 per 1000 ventilator days, respectively [23]. However, lower rates were reported in a study of 7 urban hospitals in Japan (6.4 VAEs per 1000 ventilator days) and higher rates within a multinational cohort in Europe (40.8 VAEs per 1000 ventilator days) [17, 18]. Interestingly, the European cohort reported that 96% of VAEs qualified as IVACs or PVAPs (vs one-third to one-half in most US studies), a finding that may represent differences in patient populations and/or local practices in antimicrobial prescriptions.

Multidrug resistant organisms (MDROs) put intubated patients at higher risk of these respiratory tract infections as bacteria can colonize around the cuff of the tube, leading to infections and ventilator associated events (VAE) [12]. MDROs are microorganisms, predominantly bacteria, resistant to one or more classes of antimicrobial agents, killing 23,000 people and infecting another two million each year in the United States [7]. These organisms include methicillin-resistant *staphylococcus aureus* (MRSA), carbapenemase-producing *Enterobacterales*, and Gram-negative bacteria that produce extended spectrum beta-lactamases (ESBLs). The acquisition of an MDRO infection can limit treatment options for patients, making infection prevention critical to preventing further harm. The growing presence of resistant microbes is of particular concern for vulnerable patients, such as those who have received organ transplantation, those with cancer, preterm infants, and immune-suppressed and other medically vulnerable individuals [4].

The coronavirus disease has increased the burden of patients who need mechanical ventilation. Between 5 to 20% of patients hospitalized with COVID-19 require some type of ICU care, and many of these patients require mechanical ventilation [22]. The management of patients hospitalized with severe COVID-19 has changed over the period of the pandemic [21]. Many institutions have evolved to favor intubation-sparing modalities, reserving intubation for patients with more severe disease. Simultaneously, the use of medications associated with better outcomes, including dexamethasone, and remdesivir, has increased. Little is known, however, about the impact of these changes on the incidence of ventilator associated events (VAEs) in patients with COVID-19 [21]. Recent studies have showed that the ventilator-associated events (VAEs) rates per 100 episodes of mechanical ventilation and per 1,000 ventilator days were higher among COVID-19 positive versus negative patients, but most of these VAEs were due to progressive acute respiratory distress syndrome (ARDS), while the rate of infection-related ventilator-associated complications was similar between both groups [22].

Further, while investigators have documented the impact of COVID-19 on hospital-acquired infections with MDRO, no study has examined this impact on VAE during major waves of the COVID-19 pandemic (alpha, delta, and omicron). In this study, we investigated the association between COVID-19 and the odds of ventilator associated events in the largest academic hospital in Alabama.

CHAPTER 2

METHODS

2.1 Study Design and Setting

A retrospective study design was conducted to evaluate the association between COVID-19 and the odds of ventilator associated events (VAEs) among Intensive Care Unit (ICU) patients at the University of Alabama at Birmingham (UAB) hospital. The UAB hospital is a 1,157-bed tertiary hospital and an academic health science center located in Birmingham, Alabama. The study population consisted of patients admitted between January 2018 and June 2022. Patients of all age groups with at least three ventilator days were included in the study. This study was approved by the Institutional Review Board of the UAB.

2.2 Definitions

The COVID-19 disease was determined by either positive polymerase chain reaction or antigen without prior positive test in the past 90 days. This was defined based on three thresholds for the purposes of analyses. The first was that COVID-19 was defined as a time category using the patient's admission date to the hospital. This reflects the Pre-COVID period and the different variant periods during the pandemic. These variants were specified based on their prevalent times during the pandemic. Pre-COVID was the period between January 1, 2018 to January 1, 2020. The alpha variant was the period between March 1, 2020 to July 1,

2021. The delta variant was the period between July 1, 2021 to December 1, 2021. The omicron variant was the period between December 1, 2021 to June 1, 2022. The second threshold was whether a patient had COVID-19 prior to the development of a VAE. This was determined based on whether a patient had COVID-19 on admission to the hospital. A third threshold that was a combination of the first two was eventually adopted to effectively stratify the results by whether the patient had COVID-19 prior to the VAE and assess effect modification by COVID status.

2.3 Variables Analyzed

Patient data was derived from the hospital's electronic medical record system. For each patient, demographic data and infectious complications observed during hospitalizations including Multi-drug Resistant (MDR) infections were recorded. Variables analyzed included age group, gender, race, admission source and admission type. Three outcomes were evaluated in the study. The first outcome was if there was any VAE in any of the patients. The second outcome was if there was any infection-related ventilator-associated complication or possible ventilator-associated pneumonia (IVAC/PVAP). These two were combined because most of the infection related ventilator-associated complications are caused by pneumonia [11] and so it was important to understand the difference in effects between this combination and a stand alone PVAP outcome. The last outcome was only ventilator associated pneumonia (PVAP).

2.4 Statistical Analysis

A chi-square test was performed to assess the association between demographic variables and VAE status. Numerical variables were expressed as means and standard deviations whereas categorical variables as numbers and percentages. Crude, and adjusted logistic regression models were used to evaluate the association between COVID-19 and the odds of ventilator associated events. Logistic regression was used to calculate the odds ratios (ORs) and 95% confidence intervals for the association between the outcome variables (Any VAE, IVAC/PVAP, PVAP) and COVID adjusting for age group, gender, race, admission source and admission type.

A secondary analysis was performed to evaluate the association between an MDRO caused PVAP and the odds of ventilator associated events. Statistical analysis was conducted using the Statistical Analysis System (SAS) version 9.4, with α set to 0.05.

CHAPTER 3

RESULTS

The study was made up of 11,307 patients whose clinical characteristics by VAE status are presented in Table 3.1. A total of 9 participants were excluded due to missing and inapplicable data, resulting in a final analytic sample of 11298 patients to evaluate the association between COVID-19 and the odds of ventilator associated events (VAEs). The average age of the patients was 54 years old (54.99±18.85) with a range from 0 to 144 years. The larger overall sample was predominantly White (55.42%), male (57.58%) who are adults (25-64, 58.55%) and admitted through emergency (65.70%) Table 3.1.

The characteristics of the patients by VAE status are presented as follows; 62.4% of males were considered to have had a VAE. The percentage decreased in females with 37.6% who had a VAE. 71.6% of the patients admitted through emergency had a VAE whiles 14.5% of those admitted through the trauma center had a VAE. The emergency admission type was the highest when compared to the other admission types for both patients who had or never had a VAE. 61.4% of non-transfer patients never had a VAE compared to 38.5% transfer patients that had a VAE. For those that never had a VAE, 56.6% non-transfer patients and 43.3% were transfer patients.

When comparing race by VAE status, Whites had the highest percentage of those that had a VAE compared to the other races. 56.1% of whites followed by 35.3% of Blacks or African Americans. 55.4% of Whites never had a VAE and 37.9% of blacks also never had a VAE (Table 3.1). 58.2% of patients within the age

group 25-64 never had a VAE followed by patients who are 65+ (34.9%). For those that had a VAE, patients in the 25-64 group was the highest followed by 65+ patients (63.8% vs 29.8%). Patients with commercial insurance had the highest number of VAEs followed by Medicaid and Medicare patients (48.8% vs 21.3% vs 19.7% respectively) as shown in Table 3.1.

Table 3.1: Clinical Characteristics of Patients by VAE Status

Variables	VAE Status*			
	Never (N=10503)	Ever (N=795)	P-Value	Total (N=11298)
Admission Type			.0020	
Elective	764 (7.3%)	52 (6.5%)		816 (7.2%)
Emergency	6,853 (65.3%)	569 (71.6%)		7,422 (65.7%)
Trauma Center	2,055 (19.6%)	115 (14.5%)		2,170 (19.2%)
Urgent	829 (7.9%)	59 (7.4%)		888 (7.9%)
Admission Source			.0270	
Transfer	4,048 (38.5%)	344 (43.3%)		4,392 (38.9%)
Non-transfer	6,445 (61.4%)	450 (56.6%)		6,895 (61.0%)
Info Not Avail	8 (0.1%)	1 (0.1%)		9 (0.1%)
Race			.0020	
White	5,815 (55.4%)	446 (56.1%)		6,261 (55.4%)
Black or African American	3,979 (37.9%)	281 (35.3%)		4,260 (37.7%)
Asian	106 (1.0%)	10 (1.3%)		116 (1.0%)
Hispanic/Latino	171 (1.6%)	26 (3.3%)		197 (1.7%)
American Indian/Alaska Native	9 (0.1%)	3 (0.4%)		12 (0.1%)
Other/Unknown	423 (4.0%)	29 (3.6%)		452 (4.0%)
Gender			.0040	
Female	4,489 (42.8%)	299 (37.6%)		4,788 (42.4%)
Male	6,004 (57.2%)	496 (62.4%)		6,500 (57.6%)
Age Group			.0160	
0-14	210 (2.0%)	17 (2.1%)		227 (2.0%)
15-24	523 (5.0%)	34 (4.3%)		557 (4.9%)
25-64	6,108 (58.2%)	507 (63.8%)		6,615 (58.6%)
65+	3,662 (34.9%)	237 (29.8%)		3,899 (34.5%)
Insurance			.0007	
Commerical	4,705 (44.8%)	388 (48.8%)		5,093 (45.1%)
Medicaid	1,872 (17.8%)	169 (21.3%)		2,041 (18.1%)
Medicare	2,579 (24.6%)	157 (19.7%)		2,736 (24.2%)
Self pay	850 (8.1%)	47 (5.9%)		897 (7.9%)
Other	497 (4.7%)	34 (4.3%)		531 (4.7%)
MDRO PVAP			.0000001	
No	10,503 (100.0%)	754 (94.8%)		11,257 (99.6%)
Yes	0 (0.0%)	41 (5.2%)		41 (0.4%)

* Column percentages were used

VAE counts were compared throughout the various COVID-19 time periods and presented in Table 3.2. Before COVID-19, only 7% of the patients had any VAE. The number was highest during the delta period of COVID-19 (14.4%), followed by Omicron (11.1%). IVAC/PVAP was only 3.8% before COVID-19 but this increased to 6.9% during the delta period and was 5.4% during the alpha period. 1.7% of the patients had PVAP before COVID-19 but this increased to 2.9% and then to 3.7% during the alpha and delta periods respectively. When PVAPs that were caused by MDROs was examined the numbers were very low. 0.3% of the patients had MDRO PVAP before COVID-19 whiles 0.5% and 0.4% had it during the alpha and delta periods.

Table 3.2: Ventilator Associated Events (VAEs) by COVID-19 Time Periods

Variables	Pre-COVID (N=4665)	Alpha (N=3700)	Delta (N=1256)	Omicron (N=1283)	P-Value	Total (N=11298)
ANY VAE					.000001	
No	4,337 (93.0%)	3,319 (89.7%)	1,075 (85.6%)	1,141 (88.9%)		10,232 (90.6%)
Yes	328 (7.0%)	381 (10.3%)	181 (14.4%)	142 (11.1%)		1,066 (9.4%)
IVAC/PVAP					.00002	
No	4,489 (96.2%)	3,500 (94.6%)	1,169 (93.1%)	1,221 (95.2%)		10,757 (95.2%)
Yes	176 (3.8%)	200 (5.4%)	87 (6.9%)	62 (4.8%)		541 (4.8%)
PVAP					.00004	
No	4,586 (98.3%)	3,592 (97.1%)	1,209 (96.3%)	1,253 (97.7%)		11,028 (97.6%)
Yes	79 (1.7%)	108 (2.9%)	47 (3.7%)	30 (2.3%)		270 (2.4%)
MDRO PVAP					.5025	
No	4,652 (99.7%)	3,682 (99.5%)	1,251 (99.6%)	1,280 (99.8%)		11,257 (99.6%)
Yes	13 (0.3%)	18 (0.5%)	5 (0.4%)	3 (0.2%)		41 (0.4%)

3.1 Model 1: Association Between COVID-19 and the Odds of Any VAE

Crude and adjusted logistic regression models were used to evaluate the association between COVID-19 and the odds of Any VAE presented in Table 3.3. In the crude model, the odds of getting any VAE during the alpha period is 1.52 times higher compared to the Pre-COVID period (OR=1.518; 95% CI=1.301-1.771; P-value <.0001). The delta period had the highest association compared to the other COVID-19 time periods. The odds of getting any VAE during the delta period is 2.23 times higher compared to Pre-COVID (OR=2.226; 95% CI = 1.835-2.701; P-value <.0001). This association also decreased after adjusting for age group, race, gender, admission type and admission source (OR=1.568; 95% CI = 1.273-1.932; P-value <.0001). During the omicron period, the odds of getting any VAE is 1.65 times higher compared to Pre-COVID (OR=1.646; 95% CI = 1.337-2.025; P-value <.0001). There was a decrease in the association when adjusted for age group, race, gender, admission type and admission source (OR=1.255; 95% CI = 1.011-1.558; P-value=0.0394).

Table 3.3: The Association between COVID-19 and the Odds of Any VAE

Variables	Any VAE			
	Crude OR (95%CI)	P-Value	Adjusted OR (95%CI)	P-Value
Time Category				
Pre-COVID	Referent		Referent	
Alpha	1.518 (1.301-1.771)	<.0001	1.128 (0.954-1.333)	0.159
Delta	2.226 (1.835-2.701)	<.0001	1.568 (1.273-1.932)	<.0001
Omicron	1.646 (1.337-2.025)	<.0001	1.255 (1.011-1.558)	0.039

The association between COVID-19 and the odds of Any VAE was also

examined based on whether a patient had COVID-19 prior to admission at the hospital. A Prior COVID analysis could only be made during the COVID-19 period and will not cover the Pre-COVID period. This association is represented in Table 3.4 and Table A.1. If a patient had Prior COVID, the odds of getting Any VAE during the delta period is 1.59 times higher compared to the alpha period. There was no significant association when a patient did not have Prior COVID.

Table 3.4: The Association between COVID-19 and the Odds of Any VAE

Variables	Any VAE (Prior COVID)			
	Crude OR (95%CI)	P-Value	Adjusted OR (95%CI)	P-Value
Time Category				
Alpha	Referent		Referent	
Delta	1.587 (1.167-2.158)	0.003	1.540 (1.126-2.107)	0.007
Omicron	1.034 (0.710-1.505)	0.862	1.026 (0.701-1.500)	0.897

3.2 Model 2: Association Between COVID-19 and the Odds of IVAC/PVAP

Research suggests that most IVACs are due to pneumonia [11] and so it is important to examine the association between COVID-19 and the odds of IVAC/PVAP to understand the difference in effects between this combination and a stand alone PVAP outcome. The results of this association are shown in Table 3.5

Table 3.5: The Association between COVID-19 and the Odds of IVAC/PVAP

Variables	IVAC/PVAP			
	Crude OR (95%CI)	P-Value	Adjusted OR (95%CI)	P-Value
Time Category				
Pre-COVID	Referent		Referent	
Alpha	1.457 (1.185-1.793)	0.0004	1.092 (0.872-1.368)	0.444
Delta	1.898 (1.457-2.474)	<.0001	1.337 (1.005-1.780)	0.046
Omicron	1.295 (0.963-1.742)	0.087	0.982 (0.721-1.335)	0.906

The odds of getting an IVAC/PVAP during the alpha period is 1.46 times higher compared to the Pre-COVID period (OR=1.457; 95% CI=1.185-1.793; P-value=0.0004). During the delta period, the odds of getting an IVAC/PVAP is 1.90 times higher compared to Pre-COVID (OR=1.898; 95% CI=1.457-2.474; P-value<.0001). The association decreased after adjusting for age group, race, gender, admission type and admission source (OR=1.337; 95% CI=1.005-1.780; P-value=0.046). The delta period had the highest association compared to the other COVID-19 periods (Table 3.5). The odds of getting an IVAC/PVAP when a patient had Prior COVID-19 or no Prior COVID-19 at the time of admission was not significant for both groups and this result is shown in Table A.2 and Table A.3

3.3 Model 3: Association Between COVID-19 and the Odds of PVAP

An analysis of the association between COVID-19 and PVAP is presented in Table 3.6. The odds of getting a PVAP during the alpha period is 1.75 times higher compared to Pre-COVID (OR=1.745; 95% CI=1.302-2.341; P-value=0.0002). During the delta period, the odds of getting a PVAP is 2.26 times higher compared to Pre-COVID (OR=2.257; 95% CI=1.564-3.256; P-value<.0001). The association decreased after adjusting for age group, race, gender, admission type and admission source (OR=1.683; 95% CI=1.137-2.491; P-value=0.009) Table 3.6. There was no significant association between COVID-19 and the odds of PVAP when a patient had prior COVID or not (Table A.4) and (Table A.5).

Table 3.6: The Association between COVID-19 and the Odds of PVAP

Variables	PVAP			
	Crude OR (95%CI)	P-Value	Adjusted OR (95%CI)	P-Value
Time Category				
Pre-COVID	Referent		Referent	
Alpha	1.745 (1.302-2.341)	0.0002	1.363 (0.995-1.868)	0.054
Delta	2.257 (1.564-3.256)	<.0001	1.683 (1.137-2.491)	0.009
Omicron	1.390 (0.909-2.126)	0.129	1.097 (0.707-1.701)	0.679

3.4 Secondary Analysis of the Association Between COVID-19 and the Odds of MDRO PVAP

The incidence of PVAP due to MDR organisms has increased significantly in the last decade [9]. The association between COVID-19 and MDRO PVAP was also

assessed and presented in table Table 3.7 below. There was no significant association between COVID-19 and the odds of MDRO PVAP. We believe that the association the sample size of patients with MDRO PVAP was not large enough to detect any significant associations.

Table 3.7: The Association between COVID-19 and the Odds of MDRO PVAP

Variables	MDRO PVAP			
	Crude OR (95%CI)	P-Value	Adjusted OR (95%CI)	P-Value
Time Category				
Pre-COVID	Referent		Referent	
Alpha	1.749 (0.856-3.575)	0.125	1.308 (0.597-2.869)	0.502
Delta	1.430 (0.509-4.019)	0.497	0.967 (0.318-2.940)	0.952
Omicron	0.839 (0.239-2.948)	0.784	0.630 (0.173-2.298)	0.485

CHAPTER 4

DISCUSSION AND CONCLUSION

This study examined how COVID-19 is associated with different ventilator associated events in an inpatient setting. In terms of getting any VAE, the delta period had the highest association in patients getting any VAE, followed by the omicron period (OR=2.23 vs 1.65). When a patient has Prior COVID, the odds of getting any VAE during the delta period is 1.59 times higher compared to the alpha period (OR=1.587; 95% CI=1.167-2.158; P=0.003). The odds of getting an IVAC/PVAP during the delta period is 1.90 times higher compared to Pre-COVID (OR=1.898; 95% CI=1.457-2.474; P <.00001). Also, the odds of getting a PVAP during the delta period is 2.26 times higher compared to Pre-COVID (OR=2.257; 95% CI=1.564-3.256; P <.00001).

Weinberger et al found that VAEs were more frequent in COVID-19 positive patients, and the rate of VAEs per 100 episodes of mechanical ventilation was higher in 2020 (during COVID-19) than in prior years [22]. Also, Blonz et al showed that there was an unusually high incidence of VAP in patients admitted to the ICU for severe COVID-19 [2]. Conversely, Rhee et al [19] found that VAE rates per episode decreased, rates per ventilator day were stable, and most cases were caused by acute respiratory distress syndrome (ARDS). According to the CDC, the delta variant is more than twice as infectious as the original virus. Its high infectiousness could be due to its ability to replicate rapidly in the body. A study from China reported that people infected with the delta variant can carry 1,000 times the viral load as those infected with the original virus [1]. Because of the different structure of the spike

protein, the delta variant infects lung cells more easily, making it the most contagious version of the coronavirus in the world, and leading to more people becoming sicker [1].

The overall findings illustrate that COVID-19 is associated with an increase in patients getting VAEs in hospitalized settings, based on the fact that the delta variant had an increased association with IVAC/PVAP and PVAP. Research is needed to explore the relationship between antimicrobial prescription and the effects of COVID-19 vaccinations on patients with ventilator associated events.

CHAPTER 5

STRENGTHS AND LIMITATIONS

The strengths of this study include the use of VAE criteria as an objective and consistent means of measuring complication in patients. Data from electronic medical record used and collected prospectively by Physicians and Care Providers at the UAB hospital. The UAB hospital is the largest hospital in the State of Alabama and was consistently associated with high numbers of COVID-19 patients.

Limitations include the use of a single center data source and the center's focus on COVID-19 care during the pandemic period, which may have introduced a selection bias that limits generalizability. The study did not also consider ventilator days, which may lead to underestimation of the odds ratios leading to bias.

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APPENDIX A

RESULTS FROM PRIMARY ANALYSIS

A.1 Results from Primary Analysis

Table A.1: The Association between COVID-19 and the Odds of Any VAE

Variables	Any VAE (No Prior COVID)			
	Crude OR (95%CI)	P-Value	Adjusted OR (95%CI)	P-Value
Time Category				
Alpha	Referent		Referent	
Delta	1.260 (0.977-1.626)	0.075	1.253 (0.970-1.619)	0.084
Omicron	1.646 (0.903-1.489)	0.247	1.138 (0.885-1.464)	0.315

Table A.2: The Association between COVID-19 and the Odds of IVAC/PVAP

Variables	IVAC/PVAP (Prior COVID)			
	Crude OR (95%CI)	P-Value	Adjusted OR (95%CI)	P-Value
Time Category				
Alpha	Referent		Referent	
Delta	1.330 (0.900-1.968)	0.153	1.243 (0.835-1.852)	0.285
Omicron	0.617 (0.353-1.079)	0.090	0.581 (0.330-1.022)	0.059

Table A.3: The Association between COVID-19 and the Odds of IVAC/PVAP

Variables	IVAC/PVAP (No Prior COVID)			
	Crude OR (95%CI)	P-Value	Adjusted OR (95%CI)	P-Value
Time Category				
Alpha	Referent		Referent	
Delta	1.090 (0.759-1.565)	0.643	1.100 (0.765-1.581)	0.609
Omicron	1.060 (0.746-1.504)	0.746	1.036 (0.728-1.473)	0.845

Table A.4: The Association between COVID-19 and the Odds of PVAP

Variables	PVAP (Prior COVID)			
	Crude OR (95%CI)	P-Value	Adjusted OR (95%CI)	P-Value
Time Category				
Alpha	Referent		Referent	
Delta	1.460 (0.860-2.466)	0.162	1.415 (0.828-2.421)	0.205
Omicron	0.657 (0.302-1.428)	0.289	0.616 (0.282-1.346)	0.224

Table A.5: The Association between COVID-19 and the Odds of PVAP

Variables	PVAP (No Prior COVID)			
	Crude OR (95%CI)	P-Value	Adjusted OR (95%CI)	P-Value
Time Category				
Alpha	Referent		Referent	
Delta	1.003 (0.621-1.620)	0.991	1.012 (0.626-1.637)	0.961
Omicron	0.849 (0.522-1.382)	0.511	0.848 (0.517-1.376)	0.496