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The effect of SARS-COV-2 variant on non-respiratory features and mortality among vaccinated and non-fully vaccinated patients

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Abstract

Objective: To determine the effect of SARS-CoV-2 variants on non-respiratory features of COVID-19 in vaccinated and not fully vaccinated patients using a University of California database.

Methods: A longitudinal retrospective review of medical records (n = 63,454) from 1/1/2020–4/26/2022 using the UCCORDS database was performed to compare non-respiratory features, vaccination status, and mortality between variants. Chi-square tests were used to study the relationship between categorical variables using a contingency matrix.

Results: Fever was the most common feature across all variants. Fever was significantly higher in not fully vaccinated during the Delta and Omicron waves (p = 0.001; p = 0.001). Cardiac

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

features were statistically higher in not fully vaccinated during Omicron; tachycardia was only a feature of not fully vaccinated during Delta and Omicron; diabetes and GI reflux were features of all variants regardless of vaccine status. Odds of death were significantly increased among those not fully vaccinated in the Delta and Omicron variants (Delta OR: 1.64, $p = 0.052$; Omicron OR: 1.96, $p < 0.01$). Vaccination was associated with a decrease in the frequency of non-respiratory features.

Conclusions: Risk of non-respiratory features of COVID-19 is statistically higher in those not fully vaccinated across all variants. Risk of death and correlation with vaccination status varied.

Keywords

COVID-19; Vaccination; Organ dysfunction; Symptoms; COVID-19 mortality; Non-respiratory

1. Introduction

The novel SARS-CoV-2, colloquially known simply as COVID-19, has caused substantial mortality and morbidity worldwide, with multiple waves of infection and ongoing viral mutation. According to the Centers for Disease Control (CDC), over there have been over 667 million cases of SARS-CoV-2 resulting in 6.7 million deaths [1]. The initial virus, frequently termed the Founder or Wildtype variant, has mutated multiple times into other variants namely Alpha, Delta, and Omicron. With each wave of infection, differences in hospitalization rates and different signs and symptoms have been observed [2]. In the early days of the pandemic, SARS-CoV-2 was thought to be isolated predominantly to the respiratory system, however, because multiple tissues in the body have ACE receptors, the SARS-CoV-2 virus entered cells through nearly all organ systems and a diverse range of symptoms manifested with each wave [3].

Although the benefits of the vaccine may seem self-evident, the efficacy of the vaccine has still been questioned. Some have argued that vaccinated individuals may be systematically different from non-vaccinated individuals with regards to education, socioeconomic status, health literacy, and willingness to follow guidelines, for example masking, social distancing, etc. Thus, participation and selection bias may complicate interpretation of published literature, emphasizing the need for further research in this area (see Fig. 1).

Despite virus mutation, vaccination remains the best protection against hospitalization, death, and may lessen the risk for long-COVID [4]. As of January 2023, 80.9 % of the US population > 5 years old has received one vaccine dose, and 69.1 % are fully vaccinated. Additionally, of those that are fully vaccinated, new data show that 15.1 % or about 49.6 million people in the US over the age of five have received the bivalent booster [1].

Recent retrospective studies have also shown that co-infections during an acute Covid-19 infection may be present in up to 10 % of patients [5]. Because of risks of coinfections, including both bacterial and fungal organisms, the risk of mortality from Covid-19 may increase significantly and thus vaccination is of utmost importance, especially in patients with existing high-risk features. Both bacterial and fungal infections in patients with pre-

existing cardiovascular disease, diabetes, and obesity have a statistically significant higher risk of death when also infected with Covid-19 [6].

Using the UCCORDS dataset, we have shown the benefits of being fully vaccinated in reducing respiratory features of Covid-19 [16].[1] In our prior work, we identified key respiratory features associated with SARS-CoV-2 variants and the impact of vaccination status on morbidity and mortality. Data from numerous studies converge to illustrate that many body systems are affected when infected with the SARS-CoV-2 virus, resulting in a wide array of symptoms. This focus of the current study s was to identify and compare the non-respiratory features of COVID-19 by variant and evaluate the effect of vaccination status on non-respiratory features through a retrospective review of the University of California Health Covid Research Data set (UC CORDS).

2. Methods

2.1. University of California Health COvid Research Data Set (UC CORDS)

A longitudinal retrospective review of 63,454 medical records from patients with polymerase chain reaction (PCR) confirmed SARS-CoV-2 infection within the University of California Health Covid Research Data set (UC CORDS) was performed. The UC CORDS comprises de-identified health data across all facilities in the University of California (UC) Health system, encompassing 19 health professional schools, five academic medical centers, and 12 hospitals (University of California, USA). It contains the records of more than 700,000 patients with de-identified information to enable safe and secure clinical research. This dataset contains data from both hospitalized patients and outpatients. This study was determined to be IRB exempt by human research protections program at the University of California Irvine.

2.2. Variant categorization

The UC CORDS data set does not report variant type; therefore, variants were identified based upon dates when each variant was dominant as reported by the CDC data tracker [1]. Accordingly, the date ranges extended from 01/01/2020 to 06/30/2020 for the Founder variant, 06/30/2020 to 05/31/2021 for the Alpha variant, 06/01/2021 to 11/30/2021 for the Delta variant, and beginning 12/01/2021 to 4/26/22 (when our data was collected) for the Omicron variant. Although a few cases may be categorized incorrectly based on timeline, the size of our database and strength of our findings should offset this small number of incorrectly categorized variant cases. However, it should be noted that some cases may be miscategorized based on overlapping dates of variants in California.

2.3. Inclusion/Exclusion Criteria and Sample

The study involved review of electronic health record (EHR) data in the UC CORDS data set. Inclusion criteria for this study included all patients, regardless of age, who had a positive test anywhere in the hospital setting (i.e., emergency department, intensive care unit, or any other hospital unit). For any given positive test, non-respiratory features reported in the 5 days preceding the positive test result and up to 30 days after a positive RT-PCR test for SARS-CoV-2 were included. Exclusion criteria for the study included those whose

data was obtained from non-hospital (i.e., clinic-based) outpatient settings and those who had a positive RT-PCR SARS-CoV-2 test outside of the predetermined window. Vaccination status was also recorded. Patients who received at least two doses of the vaccine before their positive test result were considered fully vaccinated. Patients who did not receive at least two doses of the vaccine before their positive test result were considered not fully vaccinated (i.e., those who were only partially vaccinated (one dose) or did not receive any vaccinations).

2.4. Feature Identification and Extraction

The 40 most reported features across various body systems including respiratory features for each variant cohort were first extracted using ICD-10 code documentation. The ICD-10 codes for COVID-19 diagnosis were removed due to redundancy. The final set of features used in this analysis were common to three or more variants.

This resulted in 13 features from a total of six systems, which are as follows: cardiovascular, endocrine + metabolic, gastrointestinal, immunological, respiratory, and neurological. The focus of this study is on non-respiratory features. The reported frequency of each feature was then normalized per 100 cases.

2.5. Outcome measures

The primary outcome was frequency of non-respiratory features among the four variants and effect of vaccination status on the frequency of features within each variant cohort. Risk of death for each variant while accounting for vaccination status was examined as a secondary outcome.

Odds ratios were calculated to determine the risk of death for each variant while accounting for vaccination status. Chi-square test to study the effect of non-respiratory symptoms of COVID-19 on vaccination status across variants. Chi-square tests were used to study the relationship between categorical variables using a contingency matrix. The tests compared the relationship between the frequency of patients who did and did not report a particular symptom. The contingency matrices were created for each variant separately and compared the frequency of a particular symptom between fully and not fully vaccinated patients. A p-value of < 0.05 was considered statistically significant. Analyses were conducted using Python (version 3.6) and the SciPy package (version 1.8.0).

3. Results

A total of 65,158 patients were included in the study (Table 1). Of the 65,158 patients included, 3,465 were identified as Wildtype variant, 26,274 as Alpha variant, 7,786 as Delta variant, and 27, 633 as Omicron. The average age for the Omicron variant in our dataset was the youngest for both fully and not fully vaccinated. Of the total population 8,041 (12.3 %) were fully vaccinated while 57,117 (87.6 %) were not fully vaccinated. Of note vaccines were not available until the emergence of the Alpha variant. Vaccination rates have increased and as a result the ratio between vaccinated and not fully vaccinated individuals is higher for the Delta and Omicron variants. Feature aggregates were normalized across body systems and Chi square tests run to determine significance (Table 2) and the normalized cases of

specific features from each of these body systems were extracted and categorized (Figure 3). All the features were grouped by variant and vaccination status from the extracted patient records (see Table 3).

4. Non-respiratory features

4.1. Cardiovascular

Cardiovascular system signs or symptoms were common non-respiratory feature of COVID-19 overall. The most frequent cardiac features were anemia, chest pain, hypertension, and hyperlipidemia (Fig. 2). Hypertension was the most frequently reported feature regardless of vaccination status or variant. Tachycardia was not a feature identified in the Founder variant, and the only fully vaccinated individuals with tachycardia as a feature were those infected with the Alpha variant. For the Founder (n = 3465), hypertension occurred in 15.4 % of the patients. For the Alpha variant (n = 26274), except for anemia, which was only seen in non-vaccinated individuals (4.2 %), cardiac features were more prevalent for those vaccinated when compared to not fully vaccinated, however, the differences are not statistically significant: tachycardia 6 % vs 2.9 % ($p = 0.264$), chest pain 4.4 % vs 4.3 % ($p = 0.812$), hypertension 17.9 %% vs 14.6 % ($p = 0.559$), and hyperlipidemia 9 % vs 9.6 % ($p = 0.966$). When comparing vaccinated to not fully vaccinated for the Delta variant (n = 7786), anemia 2.67 % vs 3 % ($p = 0.529$), chest pain 3.75 % vs 3.28 % ($p = 0.456$), hypertension 7.5 % vs 10 % ($p =0.008$), and hyperlipidemia was equivalent at 6.3 % ($p = 0.982$). Tachycardia was only a feature of non-vaccinated appearing in 2.8 % of the sample. When comparing vaccinated to not fully vaccinated for the Omicron variant (n = 27633), anemia 1.7 % vs 2.6 % ($p < 0.001$), chest pain 2 % vs 2.67 % ($p = 0.006$), hypertension 6.6 % vs 8.9 % ($p < 0.001$), and hyperlipidemia 3.9 % vs 5.7 % ($p < 0.001$). Again, in the Omicron variant, tachycardia was only present in non-vaccinated people, affecting only 1.9 % of the sample.

4.2. Endocrine

Endocrine and metabolic features of COVID-19 were most frequent overall during the Alpha variant. Obesity was not a feature of vaccinated patients except during the Delta (2.3 %) and Omicron (1.56 %) variant. In contrast, diabetes was seen in all variants regardless of vaccine status.

4.3. Gastrointestinal

Gastrointestinal reflux was a feature of all variants regardless of vaccination status. In the Wildtype variant, reflux affected 5.14 % of patients. When comparing vaccinated to not fully vaccinated, Alpha was 10.4 % vs 4.7 % ($p = 0.052$), Delta was 3.5 % for both ($p = 0.953$), and Omicron was 2.5 % vs. 2.97 % ($p = 0.034$).

4.4. Immunological

Fever was one of the most common features across all variants. During the Wildtype COVID-19, 17.1 % of patients had fever. Although vaccination was available during the Alpha variant, only not fully vaccinated patients reported fever (9.6 %). When comparing fever in vaccinated to not fully vaccinated, Delta was 4.2 % vs 10.6 % ($p < 0.001$) and

Omicron was 2.7 % vs 7.5 % ($p < 0.001$). During Wildtype, sepsis was a feature of 10.9 % of our sample. Sepsis was only seen in non-vaccinated people with Omicron (2.4 %). When comparing vaccinated and not fully vaccinated sepsis features, for Alpha 6 % vs 6.6 % ($p = 0.981$) and Delta 2.9 % vs 5.6 % ($p < 0.001$).

4.5. Neurological

Two neurological features of COVID-19 were identified in the dataset: fatigue and headache. Fatigue was not reported in the Wildtype variant. Fatigue was a feature of the Alpha variant, affecting only those not fully vaccinated in 3.33 % of our sample. Fatigue affected those who were infected with the Delta variant, fully vaccinated 2.92 % and not vaccinated 2.9 % ($p = 0.95$). During the Omicron variant, fatigue was reported in 1.55 % of vaccinated and 1.86 % of not vaccinated ($p = 0.104$). Headache was a feature of the Wildtype variant, affecting 4.27 % of the sample. Headache only affected non vaccinated people with Alpha in 4.19 % of our sample. During the Delta wave, headache affected nearly the same amount of our sample for fully vaccinated and not fully vaccinated at 3.58 % and 3.83 % ($p = 0.747$). Finally, during the Omicron variant, headache affected 1.98 % of fully vaccinated people and 2.41 % on not fully vaccinated people ($p = 0.046$).

4.6. Mortality

Patients who were not fully vaccinated had a significantly higher likelihood of mortality during the Delta and Omicron periods compared with those who were fully vaccinated (Delta OR: 1.64, $p = 0.052$; Omicron OR: 1.96, $p < 0.01$) (Figure 4). There was no significant difference in likelihood of mortality during the Alpha wave based on vaccination status.

5. Discussion

Although COVID-19 infection is primarily a respiratory disease, it is necessary to investigate its impacts across other organ systems as new variants have emerged. We have previously reported on the respiratory features associated with SARS-CoV-2 infection by variant and the effect of vaccination status on morbidity and mortality [16]. The predilection for COVID-19 in causing respiratory impairment focused diagnosis and treatment in the early phases of the pandemic on those symptoms, namely, shortness of breath and respiratory failure [7,8]. However, subsequent Wildtype surges highlighted to clinicians the virus invades other organ systems causing symptoms such as diarrhea, hypertension, and cardiac arrhythmias. In this study we identified and compared the non-respiratory features of COVID-19 by variant as well as evaluated the effect of vaccination status on non-respiratory features. Our findings reveal distinct features of each wave and a significant association of most features with vaccination status. Interestingly, tachycardia and fatigue were not seen in our sample of people infected with the Wildtype variant. Our dataset shows the Alpha variant had the highest percentage of both hypertension (31 %) and diabetes mellitus (19 %) across both the fully and not fully vaccinated groups. Additionally, vaccinated Alpha patients in our sample never developed fever, however, fever was the most common feature of the Wildtype variant. However, it is important to note that the Alpha variant group contains n = 67 of fully vaccinated individuals. This is because during the Alpha variant, the

vaccine was only available to a select group of people, namely, healthcare workers and those in the most high-risk category as defined by the CDC. Finally, the fully vaccinated sample never reported obesity, except in the Delta variant. It is possible that correlating specific features by variant can help predict and determine treatment paths for those suffering long-term effects from an acute COVID-19 infection [9]. A few observations warrant additional discussion.

Interestingly, obesity was not a feature of the Omicron variant for vaccinated individuals, but diabetes was a feature affecting over 8 % of all cases. For diabetes, it is well known that people with metabolic disorders and increased age have an upregulation of angiotensin and a down regulation of ACE-2 and that this cascade leads to inflammatory and fibrotic states in multiple organ systems including in the lung and heart tissue [10]. One review of retrospective studies showed that poorly controlled hyperglycemia no matter the cause showed an increase in severity and mortality of Covid-19 [7].

Both hypertension and diabetes are classified as cardiovascular disease (CVD) risk factors. One *meta*-analysis found that although younger people have less prevalence of CVD risk factors, the relative risk of death from COVID-19 was higher than in elderly people with the same CVD risk factors [11]. The UCCORDS dataset shows that fully vaccinated people with CVD risk factors, namely hypertension and diabetes, have less risk of acquiring COVID-19 when compared to those that are not fully vaccinated. An international, observational study found cardiovascular factors (namely, coronary artery disease, heart failure, and arrythmias) were independently associated with a higher risk of in-hospital death when diagnosed with COVID-19 [12]. Finally, an observational study of 150 Spanish centers included over 12,000 patients concluded that hypertension had an “independent prognostic value for all-cause mortality in patients with COVID-19 who required hospitalization” [13]. Additionally, these comorbidities complicated by an acute COVID-19 infection could have disastrous effects, thus, full vaccination is recommended.

Among all non-respiratory features of all variants of COVID-19, the overall most common was fever, which was reported in 17 % of all people infected with the Wildtype variant. Our results corroborate findings from a recent *meta*-analysis confirming that fever overall is the most common feature of all variants of COVID-19 [14]. Of note, fever was significantly reduced as a feature of COVID-19 for fully vaccinated individuals, which may be relevant as fever is often used as a screening tool for potential infection but may not be present in vaccinated individuals.

Gastrointestinal features were present among all variants regardless of vaccine status. The common GI feature was reflux or gastrointestinal reflux disease (GERD), which has multiple causes and is often self-reported by the patient. Obesity is a risk factor for GI reflux [15]. We found the percent of non-vaccinated individuals with obesity is nearly equivalent to those non-vaccinated individuals with GERD, regardless of variant. Thus, obesity may play more of a role than COVID or vaccination status in the prevalence of GERD in this population. Additionally, recent studies suggest that inflammation affecting the vagus nerve in Covid-19 may lead to dysautonomia [17].[2] The impact of vagal nerve inflammation may

underpin some of the symptoms reported here such as GERD, as well as cardiovascular and other system features of Covid-19.

While mortality was high during the Wildtype variant, there was no vaccine available to determine the difference in risk of death. Additionally, during the Alpha variant, the risk of death was not statistically significant when comparing fully vaccinated and unvaccinated. However, our data show that the risk of death for unvaccinated individuals during the Delta variant was 1.64x higher ($p = 0.052$) and during the Omicron variant was 1.959x higher ($p=<0.01$) compared to the vaccinated group. Although Omicron was shown to affect mostly younger people, the risk of death was still higher in the unvaccinated population and thus the vaccine provided some protection from COVID-19 even among younger individuals.

6. Limitations

This study is not without limitations. First, the nature of the retrospective design is biased towards those who either sought care or required hospitalization for COVID-19; thus, these data will not include information regarding patients who did not seek care. Second, this study did not account for the timing of when patients received vaccination and when they became ill with COVID-19. The possibility remains that patients may have received the full doses of the vaccine, but perhaps developed COVID-19 prior to the time required by their body to develop sufficient antibodies. Third, this study did not account for demographic factors of the included patients; it is well-known that those who are older and have pre-existing conditions are more likely to develop worse outcomes than those who are generally younger and healthier. Fourth, although the UC CORDS dataset contains the records of over 2,500 patients infected with the Wildtype variant, at this stage of the pandemic, the virus was still a novel phenomenon and the UC CORDS database had not yet been fully set up; therefore, the records of some of the patients infected with the Wildtype variant may be lacking or missing. In addition, sample size varied between variants which likely affected associations between variants and non-respiratory features wherein non-respiratory features reported among variants with smaller sample sizes may neglect to fully identify variant-specific features. Fifth, symptom selection was determined through expert identification of symptoms and corresponding ICD-10 code obtained from the electronic health record, so there may be diagnoses which existed but were not captured in the UC CORDS database. Moreover, the database does not code for level of care which limited our ability to accurately evaluate variant features based on COVID-19 disease severity. Additionally, the time intervals for the variants were estimated based on CDC reporter so cannot be 100 % certain that every infection reported in the time frame was attributed to that specific variant, however based on CDC reporter trends in variant prevalence we believe that most of the cases did reflect the assigned variant. Despite these limitations, this study advances the science because of the large number of records reviewed and the ability to correlate the features of infection to a specific variant.

7. Conclusions and Public Health Implications

Overall, non-respiratory features of COVID-19 affect less of the fully vaccinated than non-vaccinated population in our dataset. Being fully vaccinated decreases the chances of having

features of COVID-19 severe enough to seek professional medical care. Fully vaccinated individuals have less risk of non-respiratory features of COVID-19 and thus should strongly consider full vaccination against the disease.

As ongoing research demonstrates the significant long-term effects of COVID-19 infection on developing post-acute sequelae of SARS-CoV-2 (PASC), it is imperative to assess how acute COVID-19 infection manifests for patients in the long term. Of particular concern is of how the different variants may be associated with the development of PASC symptoms. Although we don't know the extended consequences of an acute COVID-19 infection, documentation of features by variant is necessary in future investigations where the long-term effects and timing of infection are considered. Recent findings show that inflammation caused by COVID-19 can last for long periods of time despite negative antigen testing. Finally, as the COVID-19 pandemic continues to cause immense problems for patients and the healthcare system alike, it is essential to examine historical data to help inform present and future decision-making.

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Data availability

The data that has been used is confidential.

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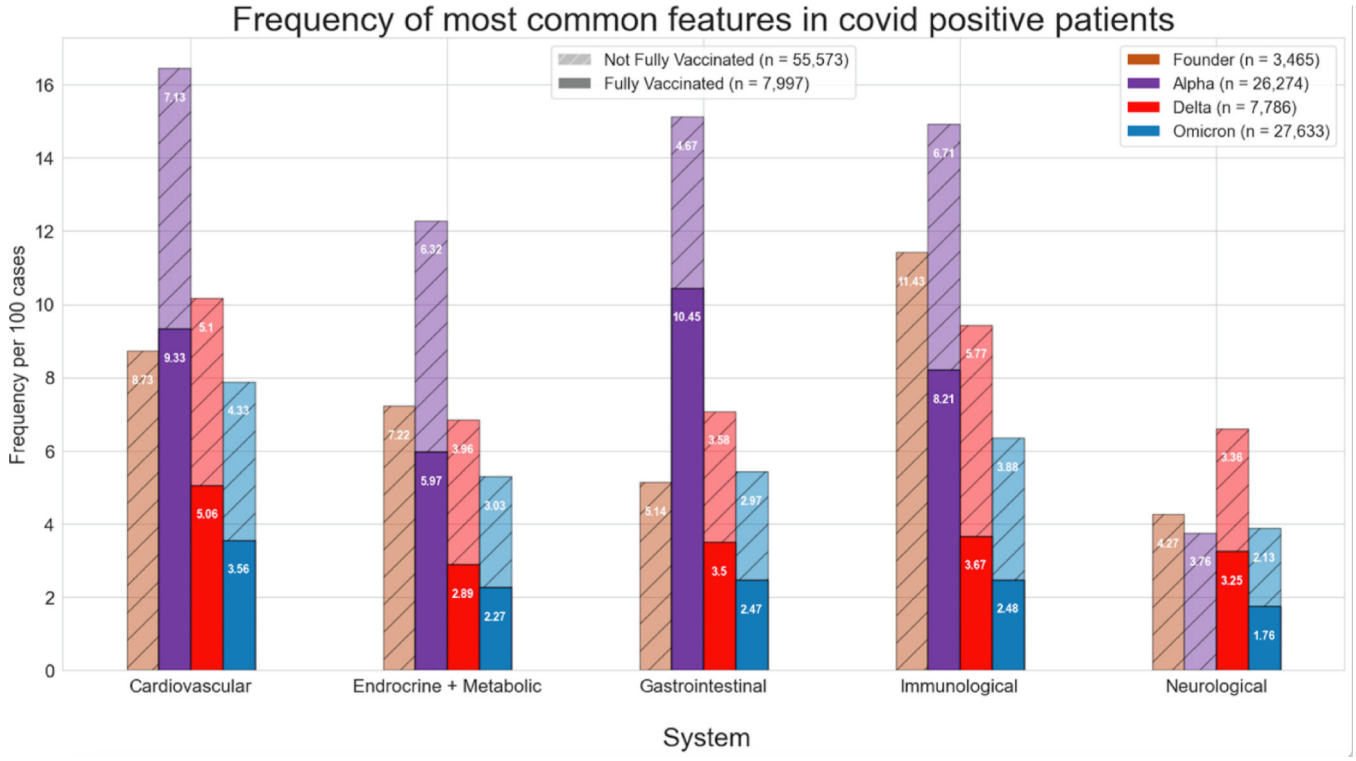

Fig. 1.
Frequency of Most Common Non-Respiratory Features of COVID-19.

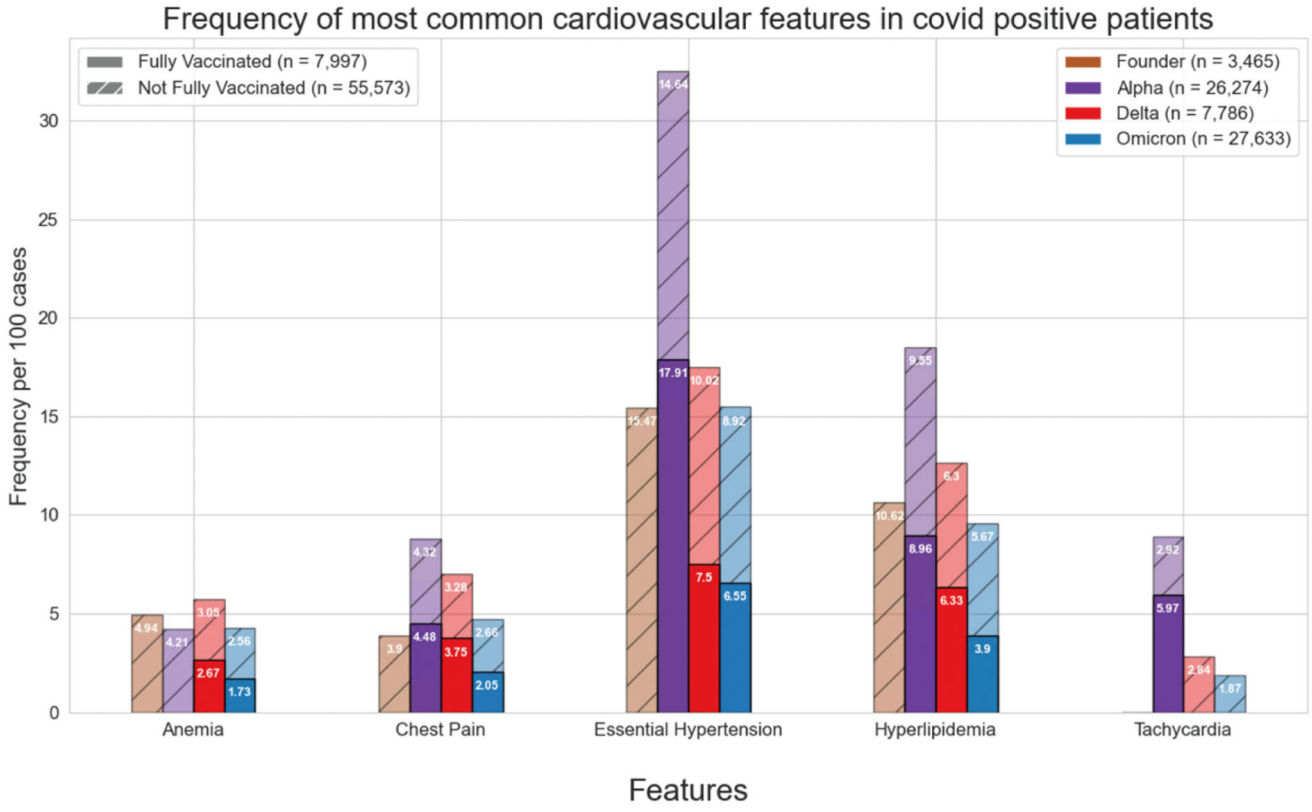

Fig. 2.
Frequency of most common cardiovascular features in COVID + patients.

Table 1

Demographic Information (n = 65,158 SARS-CoV-2 infections).

		Fully Vaccinated				Not Fully Vaccinated			
		Founder (n = 0)	**Alpha (n = 67)**	**Delta (n = 1200)**	**Omicron (n = 6774)**	**Founder (n = 3465)**	**Alpha (n = 26207)**	**Delta (n = 6586)**	**Omicron (n = 20859)**
Age, in years (mean)		N/A	61.25 ± 15.8	51.17 ± 18.4	45.27 ± 18.5	48.65 ± 19.9	46.72 ± 20.8	39.62 ± 21.6	38.54 ± 23.4
Gender (n, %)	Female	N/A	38 (56.72)	650 (54.17)	3911 (57.74)	1696 (48.95)	13,553 (51.72)	3378 (51.29)	11,340 (54.37)
	Male	N/A	29 (43.28)	547 (45.58)	2834 (41.84)	1769 (51.05)	12,647 (48.26)	3205 (48.66)	9496 (45.52)
	Unknown or Other	N/A	0	3 (0.25)	29 (0.43)	0	7 (0.02)	3 (0.05)	23 (0.11)
Race (n, %)	White	N/A	31 (48.44)	659 (58.16)	2986 (46.69)	958 (29.3)	8201 (33.47)	2548 (41.87)	7102 (37.43)
	Hispanic or Latino	N/A	15 (23.44)	205 (18.09)	1366 (21.36)	1585 (48.47)	10,184 (41.57)	1770 (29.08)	5797 (30.55)
	Asian	N/A	9 (14.06)	118 (10.41)	939 (14.68)	247 (7.55)	2090 (8.53)	418 (6.87)	2168 (11.43)
	African-American	N/A	2 (3.12)	47 (4.15)	411 (6.43)	175 (5.35)	1576 (6.43)	616 (10.12)	1589 (8.38)
	Native Hawaiian or Pacific Islander	N/A	2 (3.12)	10 (0.88)	81 (1.27)	20 (0.61)	177 (0.72)	39 (0.64)	126 (0.66)
	American Indian or Alaska Native	N/A	0	1 (0.09)	15 (0.23)	8 (0.24)	59 (0.24)	23 (0.38)	51 (0.27)
	Unknown or Other	N/A	8 (11.94)	160 (13.33)	976 (14.41)	472 (13.62)	3920 (14.96)	1172 (17.8)	4026 (19.3)

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Table 2

Chi-square Tests comparing feature significance in vaccinated versus unvaccinated patients.

Body System	Variant	Feature	Fully Vaccinated (n)	Not Fully Vaccinated (n)	Chi-square *p*-value
Cardiovascular	Delta	Essential Hypertension	90	660	< 0.01
		Tachycardia	18	187	0.010
	Omicron	Essential Hypertension	444	1860	< 0.01
		Tachycardia	44	390	< 0.01
		Hyperlipidemia	264	1182	< 0.01
		Chest Pain	139	555	< 0.01
		Anemia	117	533	< 0.01
Endocrine + Metabolic	Delta	Obesity	28	254	0.012
	Omicron	Type 2 Diabetes	162	738	< 0.01
Gastrointestinal	Omicron	Gastrointestinal Reflux without Esophagitis	167	619	0.034
Immunological	Alpha	Fever	1	2505	0.042
		Immunodeficiency Disorder	7	554	< 0.01
	Delta	Fever	51	696	< 0.01
		Sepsis	35	372	< 0.01
	Omicron	Fever	181	1573	< 0.01
		Sepsis	81	502	< 0.01
Neurological	Omicron	Headache	134	502	0.046

Table 3

Mortality Rate and Odds Ratio across variants.

Variant	Fully Vaccinated (n, %)	Not Fully Vaccinated (n, %)	Odds Ratio	*p*-value
Founder	N/A	89 (2.57)	N/A	N/A
Alpha	3 (4.48)	997 (3.80)	0.844	0.742
Delta	17 (1.42)	152 (2.31)	1.643	0.052
Omicron	35 (0.52)	210 (1.01)	1.958	< 0.01