12-2022

The Risk Factors of Long COVID in the Acute COVID and Solid Organ Transplant Retrospective Cohorts

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December 6, 2022

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Abstract

Background: Coronavirus disease 2019 (COVID-19) in solid organ transplant (SOT) patients is associated with more severe outcomes than non-immunosuppressed hosts. The risk factors for developing the long COVID in acute COVID remain unknown, and the survival outcomes of long COVID in SOT patients remain understudied.

Methods: We developed several retrospective cohorts. This project included all patients identified with acute COVID in the National COVID Collaborative Cohort Registry from July 1, 2020, to June 30, 2022.

Patients with long COVID were compared to those without long COVID in the acute COVID cohorts. Similarly, we compared the patient demographic with long COVID vs. those without long-term COVID in the SOT cohort. Univariable and multivariable logistics regression was used to determine the factors related to the probability of the long COVID in the acute COVID and SOT cohorts. To investigate the patient survival of long COVID in SOT cohort, Multi-variables Cox regression was used to determine the time-to-event outcome of patient survival (death) after adjusting for another demographic. **Results:** This study included 6,416,500 acute COVID patients. 31,744 patients were with long COVID, and 6,384,756 patients were with acute COVID without long-COVID. The mean (q1, q3) age was 39 [22, 57] years; 55% of patients were female. In the SOT recipient cohort, 511 patients were identified with long-COVID from ICD diagnosis and 37,771 patients with acute COVID (mean age 56 [40, 66] years; 41% of patients are female). In the long COVID SOT, age was most likely between 50-60 years and white non-Hispanic. Most SOT were kidney transplanted recipients. The Cox regression analysis revealed many significant factors related to patient survival (death), especially older SOT patients with a much higher hazard ratio. **Conclusion:** This study has identified the risk factors

for developing long COVID more likely in both acute COVID and SOT cohorts. For the SOT cohort, we also investigated hazard ratios of patient survival based on multivariable Cox models. We find that older patients in SOT were much more likely to die when long COVID.

Chapter 1 Introduction

The coronavirus disease 19 (COVID-19) pandemic's impact on solid organ transplantation recipients has been reflective, from patients with acute Covid, long Covid, acute Covid without long-term Covid. Since the very first year of the emergence of the novel coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), in 2019, several critical questions about COVID-19 in transplantation have surfaced. Long Covid is a novel syndrome that is broadly defined by the persistence of physical and/or psychological and cognitive symptoms following a probable or confirmed SARS-CoV-2 infection, usually 3 months from acute infection and lasting longer than 2 months, with no probable alternative diagnosis.

While it is evident that people with certain underlying risk factors including high blood pressure, smoking, diabetes, obesity, and other conditions (Garg et al., 2020) are more likely to have severe outcomes associated with acute COVID-19. There is no distinct link between these underlying risk factors and long-term problems in those surviving acute COVID-19. But it is notable that long-COVID-19 syndrome is not just affecting people who were very ill with the coronavirus. Some patients who were never severely ill with COVID-19 are experiencing long-term symptoms.

Available evidence suggests that Long COVID is a substantial public health problem with severe consequences for affected individuals and society at large. Patients commonly report being emotionally affected by health problems related to Long COVID. In the United States, patients have reported mild to severe financial impacts related to acute COVID-19 (Chopra et al.,2020; Arab-Zozani et al.,2020). This concern is underlined by reports that Long COVID patients experience increased disability related to breathlessness and decreased quality of life (Tabacof et al., 2020). Understanding the needs of these patients will allow for the development of healthcare,

rehabilitation, and other resources needed to support their recovery (Menges et al.,2021; Sheehy et al.,2020). Some data on long COVID-19 outcomes in the population of solid organ transplant (SOT) patients are available; however, it is undecided if these patients fare better or worse compared with acute COVID patients.

This data further summarizes immunocompromised patients, such as SOT patients, with a reported concern for worse outcomes and high mortality (Pereira et al., 2020). In contrast, patients who undergo transplants with a considerable comorbidity burden of dementia, asthma, hypertension, heart disease, and diabetes mellitus, among others, have previously been shown to pose a risk of worse outcomes (Guan et al., 2020). Erstwhile studies on COVID-19 in SOT patients are limited by sample size and focus on hospitalized patients (Pereira et al., 2020). Therefore, this study wants to investigate the likelihood of long COVID patients in Acute COVID patients and SOT and patient survival in SOT cohorts with long COVID.

Chapter 2 Research question and Data resource

Literature reviews: Long Covid-19 is the common term used to describe signs and symptoms that last for longer than four weeks after getting COVID-19. It is also referred to as Post Covid-19 condition. The World Health Organization (WHO) in 2021 defines Long Covid as follows: "Post Covid-19 condition occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually three months from the onset of Covid-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis." The SOT patients with COVID-19 appear to be at higher risk of severe outcomes based on their chronically immunosuppressed state and underlying medical comorbidities (Elias et al., 2020; Pereira et al., 2020; Kates et al., 2020).

Despite the relatively early recognition of this condition, an ICD-10-CM code (U09.9, "Post COVID-19 condition, unspecified") was not made available for use in the clinical setting until October 2021. Moreover, this single code may prove insufficient. Considering the phenotypic and severity variation seen in Long COVID patients, it is likely that subtypes of Long COVID exist, and such subtypes may correlate with specific underlying mechanisms that different interventions should target.

Regardless, the fact remains that there is more naming to be done and a particular need to define and refine computable phenotypes for Long COVID and its subtypes. As can be seen, by the widely differing estimates of long COVID prevalence across many studies, a lack of definitional consistency is affecting the accuracy and reproducibility of otherwise robust research (Ledford, 2022). Among other advantages, refined definitions will enable us to appropriately define cohorts for clinical studies, provide more precise treatment and clinical decision support, and accurately estimate long COVID incidence and prevalence. This is a crucial priority for the

parent program for this work, the NIH Researching COVID to Enhance Recovery (RECOVER) Initiative (RECOVER, 2022), which seeks to understand, treat, and prevent PASC through a wide variety of research modalities, including electronic health record (EHR) and real-world data.

Despite widespread concern about the potential for high prevalence and severity of COVID-19 among transplant recipients, data on this population is lacking aside from a few single patient case reports (Michaels et al., 2020; Guillen et al., 2020; Zhu et al., 2020). SOT patients with long COVID-19 are particularly unknown due to high prevalence of underlying chronic kidney disease, diabetes mellitus, hypertension, and calcineurin inhibitor (CNI) use. In a multicenter study of 482 SOTR with COVID-19, 44% of hospitalized patients developed AKI and 15% required renal replacement therapy (Kates et al., 2020). SOT patients with COVID-19 appear to be at an even higher risk than the general population based on their exposure to chronic maintenance immunosuppression and underlying comorbidities (Elias et al., 2020; Pereira et al., 2020; Kates et al., 2020). In this population, older individuals with COVID-19 have a 28-day case fatality rate of ~20% (Kates et al., 2020; Hilbrands et al., 2020) compared to a 0.8%–2% risk in the general population (Pastor-Barriuso et al., 2020). Likewise, the risk of AKI in SOT patients with COVID-19 is increased at ~50% (Cravedi et al., 2020), with one study demonstrating a need for renal replacement therapy in 23% and graft loss in 6.3% of kidney transplant recipients (Azzi et al., 2020).

Most SOT patients have one or several associated risk factors for severe or death COVID-19, such as hypertension, cardiovascular disease, and chronic kidney disease (Burra et al., 2020). Hence, some studies reported that SOT patients had a higher COVID-19-related mortality rate than non-transplant patients (Caillard et al., 2020; Hadi et al., 2021; Miarons et al., 2021; Rinaldi et al., 2021; Vinson et al., 2021). Due to the novelty of SARS-CoV-2, there is a paucity of data regarding

many aspects, including its natural course within immunocompromised hosts, the utility of current treatment regimens employed in non-transplant individuals for SOT patients, the effect of immunosuppression on the course of the disease, and much more (Cao, 2020; Guillen et al., 2020). Even though comorbidities, such as obesity, have been reported as risk factors for severe disease (Singh, 2020), an immunocompromised state has not yet been proven to have a worse clinical outcome than SARS-CoV-2 infection. Also, as Vishnevetsky correctly points out, viruses that belong to the same coronavirus family, such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome Coronavirus 1 (SARS), have not shown an increased risk of infection or worse outcome in immunocompromised patients (Chan et al., 2003; Parks et al., 2018; Vishnevetsky & Levy, 2020).

Specific Aims

The overall goal of this project is to synthesize existing evidence on the prevalence as well as demographics and comorbidities aspects of Long COVID-19 in SOT**.** Information from this study could also be used to impact transplant patients with long Covid and acute Covid by identifying gaps in demographics and clinical characteristics within the study period. Therefore, the researchers are proposing the following specific aims to be addressed in this project.

Aim 1: This study aimed to describe the frequency of long COVID-19 in acute COVID and SOT recipients.

Hypothesis: The study hypothesizes that there are risk factors related to the probability of long COVID in acute COVID and SOT.

Approach: We defined the cohorts presented by assigned groups from the ICD 9/10 diagnosis code for long COVID during the duration of follow-up for 90 days. The detail statistical methods will be specified in Chapter 3 methods.

Aim 2: This study aimed to identify the impact and potential risk factors for the long COVID event in acute COVID and SOT cohorts.

Furthermore, we want to investigate patient survival for SOT patients when have a long COVID.

Hypothesis: The study hypothesizes that immunosuppressive therapy (IST) already results in long Covid like symptoms masking potential long Covid among SOT recipients.

Approach: The study compares the health outcome of SOT patients with long COVID and acute COVID, long COVID with acute COVID without long COVID as well as long term COVID patients with SOT and acute COVID cohorts. The proposed research is innovative as it is one of the few studies on COVID-19 in the SOT population in the US. The detail statistical methods will be presented in Chapter 3 methods.

Significance: Through this research, we are able to further compare the health outcome of long COVID with acute COVID without long COVID patients in the retrospective acute COVID and SOT patients' cohorts and determine the risk factors to developing long COVID to identify potential interventions. Furthermore, we are able to delineate if early anti-viral therapy lessens long COVID severity in solid organ transplant patients (Kumar et al., 2018). The study further evaluates whether or not long COVID affects risk factors for the time-to-event outcome of patient survival (mortality) among SOT patients while taking into consideration underlying medical conditions such as obesity, chronic lung disease, congestive heart failure (Kates et al., 2020; Webb et al., 2020). This will help to identify the frequency of patients who may have recovered from long COVID and acute COVID after a solid organ transplant, as well as patients who had experienced long COVID and acute COVID without long COVID. Furthermore, this study considers SOT patients facing infection, morbidity and mortality from long and acute COVID.

This study then determines if SOT patients with long COVID and acute COVID will be presented more often with diabetes, asthma, dementia, malignant cancer, congestive heart failure, hypertension, peripheral vascular disease, and coronary artery disease.

Data resource: The National COVID Cohort Collaborative (N3C) cohort has provided impactful insights into COVID-19. The N3C Data Enclave is a secure platform through which the clinical data provided by contributing members is stored in a harmonized format. The data itself can only be accessed through a secure cloud portal hosted by NCATS and cannot be downloaded or removed. The N3C is a health record repository containing the largest, most representative U.S. cohort of COVID-19 cases and controls to date.

Vinson et al. (2021) compared with COVID− patients, COVID+ SOT recipients were younger, less likely to be White race, and more likely to have had a kidney transplant than another organ. The sex-based protection from adverse events for acute COVID-19 were mitigated among transplant recipients, meaning females with SOT have less relative protection compared with the non-ISC population (Vinson et al., 2021). They also had greater levels of comorbidity, with a higher prevalence of hypertension, diabetes, CAD, peripheral vascular disease, and CKD. Despite the increased risk associated with male sex in the general population, (Pereira et al.,2020; Márquez et al.,2020) male SOT recipients were not more likely to test positive for COVID-19. Likewise, in the general population, older age is a risk for SARS-CoV-2 infection (Davis et al.,2020).

However, in the study population, (Vinson et al., 2020) saw the opposite in that SOT COVID+ recipients were significantly younger than those testing negative. Whether the association between male sex and older age with COVID-19 diagnosis in the general population relates to a biologic vulnerability to viral infection or to differences in behaviors and lifestyles

(potentially more travel and contact patterns in males or older individuals leading to more virus exposure) that might put these patients at increased risk of acquiring COVID-19 remains to be seen.

In the 90-d following COVID-19 diagnosis, (Vinson et al., 2020) identify that 42.9% of SOT recipients required hospitalization, compared with the hospitalization rate for COVID-19 in the general public which has been shown to be 14% to 46% (Kalyanaraman et al.,2020; Reese et al.,2021). While systematic review and meta-analysis have yielded sizable COVID+ SOT study populations, (Kremer et al. 2021) the largest COVID+ SOT cohort study to date includes just over 1000 transplant recipients and focuses on outcomes in SOT recipients with COVID-19, rather than predictors of testing positive for COVID-19 (Jager et al.,2020). The study conducted by (Vinson et al.,2021) is the largest to date to explore patient characteristics associated with a diagnosis of COVID-19 in a national cohort of SOT. This information is valuable in that it may help identify patients who require a lower threshold for COVID-19 screening and had >10k SOT recipients and the 2022 had >4k SOT recipients who were vaccinated.

In summary, using the N3C in a cohort of SOT patients diagnosed with long COVID, our main aim is to compare the health outcome of long COVID with acute COVID without long COVID as well SOT cohort by long COVID and acute COVID in the study population.

Chapter 3 Methods

Study design: A retrospective cohort study was conducted using data from the N3C platform. The N3C platform is a multicenter federated research network in the United States that provides real-time access to de-identified healthcare record data of 16 million patients from the participating healthcare organizations (Haendel et al., 2020). In the real-time search, the data was collected as part of routine healthcare and is historical in nature. The data was extracted on June 30, 2022, from which N3C release, and was analyzed on the platform using (e.g., using Python, SQL, and R in the platform). The study evaluated pre-existing medical conditions and the research included all patients with long COVID and acute COVID in SOT, long COVID and acute COVID without long COVID, acute COVID cohort, long COVID patients, and SOT patients on the N3C platform. Patients included in this study were diagnosed with long Covid, acute COVID, and SOT patients between July 1, 2020, and June 30, 2022.

Every patient who had long COVID and acute COVID in transplant, including those with acute Covid without long COVID, were incorporated in the N3C data enclave platform before June 30, 2022, a cohort extraction date. As a result of the comparison, data released into the N3C data enclave after June 30, 2022, are difficult to use for studies requiring a true control arm; after this date, it was not possible to compare age, gender or race, or differences between long COVID and acute COVID in transplant, long COVID with acute COVID without long COVID. Because of this, the research limit to data collected as of June 30, which represents 16 million total patients.

Data elements and measurements

The long COVID and acute COVID patients with transplants, long COVID and acute COVID without long COVID, acute COVID cohort in long-term COVID patients, and SOT cohort in long-term COVID patients were determined a priori and included patient demographics, such

as age, race, sex, type of organ transplant (multiple transplantations, kidney transplantation, liver transplantation, heart transplantation, lung transplantation, and other/unknown transplantations), and comorbidities (hypertension, diabetes, asthma, malignant cancer, coronary artery disease [CAD], congestive heart failure [CHF], peripheral vascular disease (PVD), and obesity [i.e. body mass index (BMI) > 30 kg/m^2]). Given large amounts of missingness for BMI (>40%), an indicator was created for missing BMI and included as an adjustment variable in multivariate analyses.

Statistical Analyses

We used descriptive statistics including mean (SD) and median (q1 and q3) as appropriate to report baseline (demographic and clinical) characteristics for all different subgroups, where all patients were stratified by whether they had long-COVID into each group. Counts and percentages for demographic and clinical characteristics were used in the study population to describe categorical variables. The study considered a statistical significance of P value <0.05 when compared the demographic between different groups. In the analysis, among those tested in the acute COVID and SOT cohorts, the odds ratio of whether receiving a long COVID event were determined using univariable and multivariable logistic regressions. Any patient factors are significantly associated with a long COVID event if their P value of < 0.05. The proportion of patients experiencing an outcome was determined in the 90 d after being tested for long COVID-19 (among Acute COVID and SOT cohorts). Finally, the following co-variables including age (i.e., < 19, 19–34, 35–49, 50–64, and 65+ years), BMI (i.e., <18.5, 18.5 – 24.5, 25.0 – 29.9, 30+), sex subgroups (i.e., female and male sex) and transplant type (multiple, kidney, heart, lung, liver) were in Cox regression models for patient survival outcome in SOT cohort. The results of the Cox

regression analyses were displayed using hazard ratios (HRs) and 95% confidence intervals (CIs). P-values lower than 0.05 were considered statistically significant in the statistical models.

National Institute of Health's N3C Data Utilization Request Approval committee approved the data utilization request of this project. This retrospective cohort study received Institutional Review Board (IRB) approval from the University of Nebraska Medical Center (0853-21-EP) and Johns Hopkins University (IRB00309495). The N3C Data Access Committee approved this study, which operates under the authority of the National Institutes of Health IRB, with Johns Hopkins University School of Medicine serving as the central IRB. No informed consent was obtained because the study used a limited data set. This study followed the Enhancing the Quality and Transparency of Health Research (EQUATOR) reporting guidelines: Reporting of Studies Conducted Using Observational Routinely Collected Health Data (RECORD). All statistical analyses were performed using SQL and R.

Chapter 4 Model results

Study Population Summary

At the time of long-COVID analysis between July 1, 2020, to June 30, 2022, through the N3C data enclave platform, millions of long COVID patients were identified. Of the 6,416,500 patients who were identified to have long COVID-19 by the ICD 9/10 diagnosis criteria, 6,384,756 patients were acute COVID without long COVID, and the remaining 31,744 patients were long COVID patients.

Patient Demographic

The mean age (q1, q3) was 39 (22, 57) years, while 45% of patients were men and 55% of patients were women for the acute-COVID without long COVID, whereas the mean age was 52(39, 64) years, while 36% were men and 64% were women for long COVID, as shown in Figure 1. This was statistically significant with a p-value <0.001, as in Table 1. The overall comparison study results of acute COVID without long-COVID and long COVID in the Acute COVID cohort were shown in Table 1, where we have identified race and ethnicity, transplant type, and comorbidity to be statistically significant with p-value <0.001. The most common findings on the overall race and ethnicity, as indicated in Table 1, were 60% White non-Hispanic followed by 13% Black-African American non-Hispanic, 12% Hispanic or Latino any Race, 2.1% Asian non-Hispanic, 0.3% Other non-Hispanic, and 12% unknown were all statistically significant. The most common transplant type was kidney, followed by liver, heart, and lung were also statistically significant. The distribution of the percentage of transplant type was also statistically significant. Similarly, comorbidity in dementia, diabetes, asthma, malignant cancer, coronary artery disease, peripheral vascular disease, congestive heart failure, and hypertension showed statistically significant with a p-value <0.001.

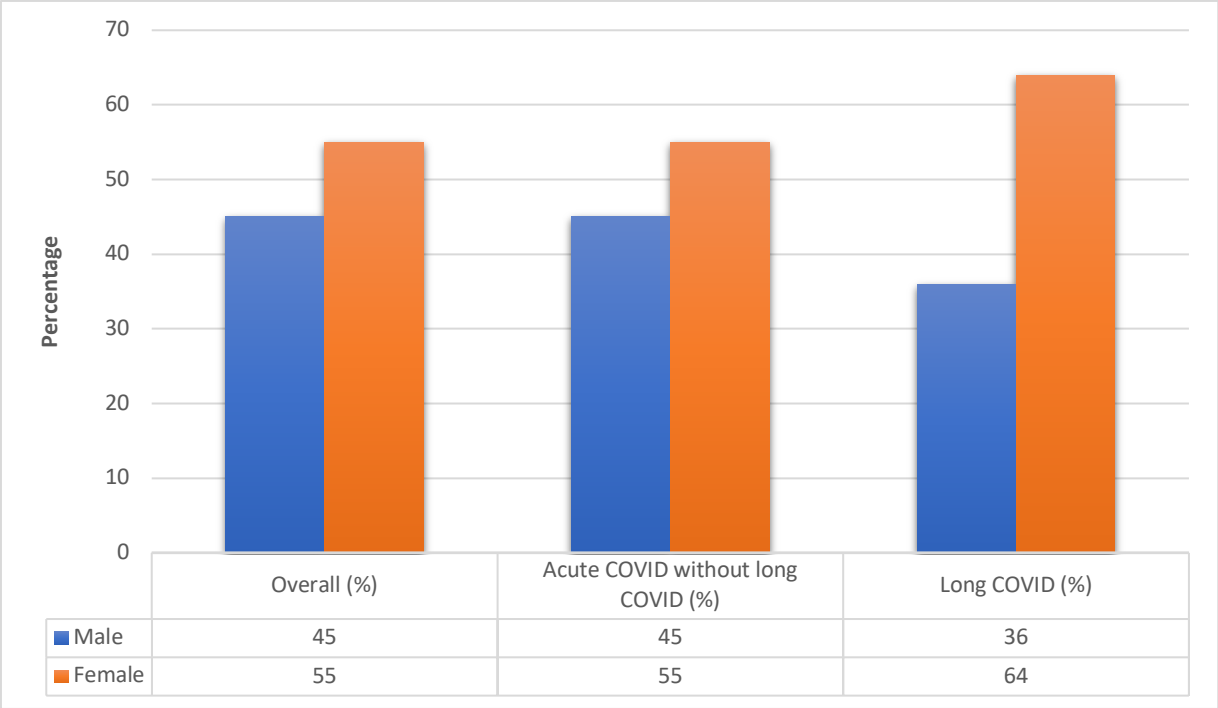
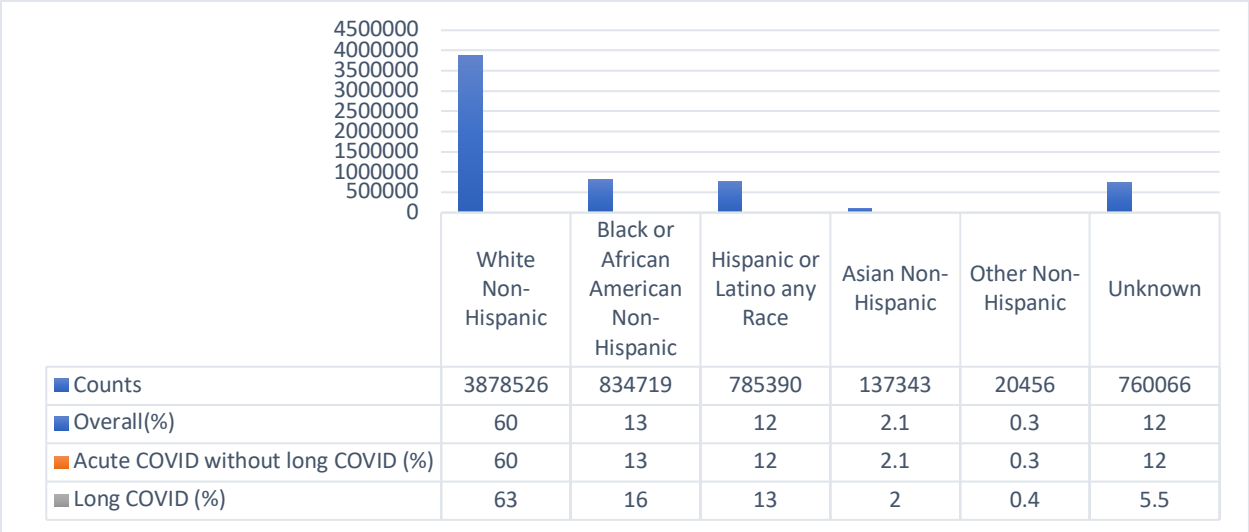


Figure 1. Distribution of sex in Acute COVID and long COVID. Percentage of sex is significantly difference in Acute COVID and long COVID. There are about 10% more female patients in long COVID

The White non-Hispanic race was the most common, comprising 60%, followed by Black or African American non-Hispanic (13%), Hispanic or Latino any Race (12%), Asian non-Hispanic (2.1%), Other non-Hispanic (0.3) and unknown (12%) for acute COVID without long COVID. For the long COVID, The White non-Hispanic race was the most common, comprising 63%, followed by Black or African American non-Hispanic (16%), Hispanic or Latino any Race (13%), Asian non-Hispanic (2.0%), Other non-Hispanic (0.4%) and unknown (5.5%) in Figure 2.



	White Non-Hispanic	Black or African American Non-Hispanic	Hispanic or Latino any Race	Asian Non-Hispanic	Other Non-Hispanic	Unknown
Counts	3878526	834719	785390	137343	20456	760066
Overall(%)	60	13	12	2.1	0.3	12
Acute COVID without long COVID (%)	60	13	12	2.1	0.3	12
Long COVID (%)	63	16	13	2	0.4	5.5

Figure 2. Demographic and clinical characteristics of race and ethnicity. Black or African American non-Hispanic are more likely to have long COVID.

Transplanted organs for acute COVID without long COVID and long COVID included kidneys in 24,129 (55%) patients, liver in 6,998 (16%) patients, heart transplant in 4,587 (11%) patients, and lung transplant in 3,068 (7.0%) patients. Among these patients, 6,372,935 had solitary SOT, while 4,783 patients had multiple transplanted organs.

Comparison of acute COVID without long COVID and long COVID patients showed several differences (Table 1.). At comorbidities, significant difference between acute COVID without long COVID and long COVID patients was found for dementia before covid indicator lower (1.5% vs 2.1%, P value < 0.001) than dementia post covid indicator (0.9% vs 1.8%, P value < 0.001), malignant cancer before covid indicator was higher (5.0% vs 9.9%, P value < 0.001) than malignant cancer post covid indicator (3.4% vs 7.8%, P value < 0.001), diabetes before covid indicator was higher (4.9% vs 12.0%, P value < 0.001) than diabetes post covid indicator (3.5% vs 12.0%, P value <0.001), congestive heart failure before covid indicator was higher (4.1% vs 10%, P value < 0.001) than congestive heart failure post covid indicator (3.0% vs 12.0%, P < value

0.001), coronary artery disease before covid indicator was higher (5.0% vs 10.0%, P value < 0.001) than coronary artery disease post covid indicator (3.3% vs 11.0%, P value< 0.001), hypertension before covid indicator was higher (22% vs 44%, P value< 0.001) than hypertension post covid indicator (15% vs 43%, P value < 0.001), peripheral vascular disease before covid indicator was higher (2.2% vs 5.1%, P value < 0.001) than peripheral vascular disease post covid indicator (1.4% vs 4.4%, P value < 0.001). As for asthma before covid indicator, acute COVID without long COVID patients received less frequently than long COVID patients (6.9% vs. 17.0%, P value < 0.001). All comorbidities, including before and post covid indicators, are statistically significant with a P value < 0.001.

Table 1: Patient demographics and clinical characteristics among long COVID and acute COVID Without long COVID

Characteristic variables	Overall	Acute COVID without long COVID	Long COVID	P value
Gender				<0.001
Male	2872550 (45%)	2861210 (45%)	11340 (36%)	
Female	3543950 (55%)	3523546 (55%)	20404 (64%)	
Mean (Q_1, Q_3) of age	39 (22, 57)	39 (22, 57)	52 (39, 64)	<0.001
<19	1269106 (20%)	1267444 (20%)	1662 (5.2%)	
19-34	1503840 (23%)	1499755 (23%)	4085 (13%)	
35-49	1334706 (21%)	1326222 (21%)	8484 (27%)	
50-64	1279002 (20%)	1268832 (20%)	10170 (32%)	
≥ 65	1029846 (16%)	1022503 (16%)	7343 (23%)	
BMI Category				
<18.5	214595 (3.8%)	214258 (3.8%)	337 (1.3%)	
18.5-24.9	541029 (9.5%)	538123 (9.5%)	2906 (11%)	
25-29.9	<20	<20	<20	
≥ 30	1374865 (24%)	1360018 (24%)	14847 (57%)	
Missing/Unknown	3560962 (63%)	3552824 (63%)	8138 (31%)	
Unknown	725049	719533	5516	
Race Ethnicity				<0.001
White Non-Hispanic	3878526 (60%)	3858476 (60%)	20050 (63%)	
Black or African American Non-Hispanic	834719 (13%)	829734 (13%)	4985 (16%)	
Hispanic or Latino any Race	785390 (12%)	781181 (12%)	4209 (13%)	
Asian Non-Hispanic	137343 (2.1%)	136718 (2.1%)	625 (2.0%)	
Other Non-Hispanic	20456 (0.3%)	20339 (0.3%)	117 (0.4%)	
Unknown	760066 (12%)	758308 (12%)	1758 (5.5%)	

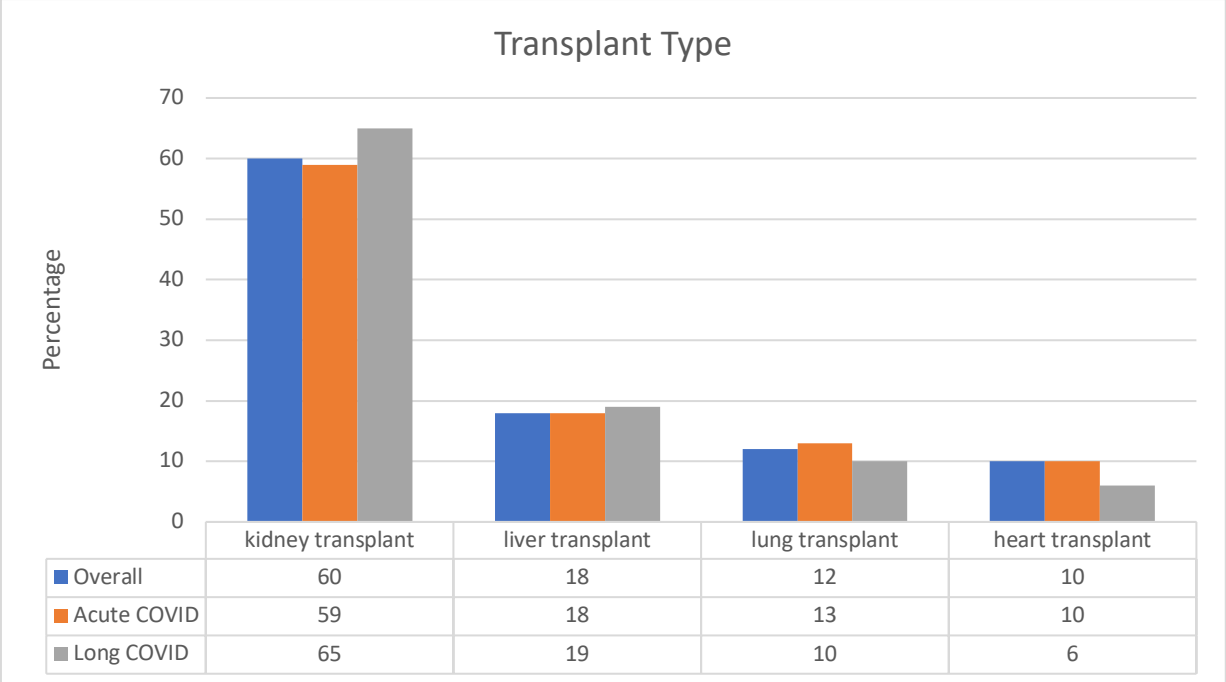
Transplant Type				<0.001
Multiple	4783 (11%)	4671 (11%)	112 (16%)	
Kidney	24129 (55%)	23813 (56%)	316 (45%)	
Liver	6998 (16%)	6933 (16%)	65 (9.3%)	
Lung	3068 (7.0%)	2946 (6.9%)	122 (17%)	
Heart	4587 (11%)	4504 (11%)	83 (12%)	
Unknown	6372935	6341889	31046	
Dementia before covid indicator	93516 (1.5%)	92852 (1.5%)	664 (2.1%)	<0.001
Dementia post covid indicator	59318 (0.9%)	58744 (0.9%)	574 (1.8%)	<0.001
Asthma before covid indicator	445268 (6.9%)	439770 (6.9%)	5498 (17%)	<0.001
Malignant cancer before covid indicator	322293 (5.0%)	319164 (5.0%)	3129 (9.9%)	<0.001
Malignant cancer post covid indicator	220637 (3.4%)	218161 (3.4%)	2476 (7.8%)	<0.001
Diabetes complicated before covid indicator	315855 (4.9%)	312144 (4.9%)	3711 (12%)	<0.001
Diabetes complicated post covid indicator	230135 (3.6%)	226388 (3.5%)	3747 (12%)	<0.001
Congestive heart failure before covid indicator	264487 (4.1%)	261211 (4.1%)	3276 (10%)	<0.001
Congestive heart failure post covid indicator	197006 (3.1%)	193116 (3.0%)	3890 (12%)	<0.001
Coronary artery disease before covid indicator	321043 (5.0%)	317735 (5.0%)	3308 (10%)	<0.001
Coronary artery disease post covid indicator	211673 (3.3%)	208276 (3.3%)	3397 (11%)	<0.001
Hypertension before covid indicator	1388522 (22%)	1374529 (22%)	13993 (44%)	<0.001
Hypertension post covid indicator	959356 (15%)	945853 (15%)	13503 (43%)	<0.001
Peripheral vascular disease before covid indicator	143177 (2.2%)	141552 (2.2%)	1625 (5.1%)	<0.001
Peripheral vascular disease post covid indicator	91267 (1.4%)	89884 (1.4%)	1383 (4.4%)	<0.001

BMI, body mass index; COVID-19, coronavirus disease 2019; Statistically significant at a $P < 0.05$; data are percentages unless otherwise specified.

Comparison of Acute COVID and Long COVID in the SOT cohort

We identified 38,282 SOT patients, with 37,771 patients with acute COVID and 511 having long COVID. The demographic comparison of these groups is shown in Table 2. Acute COVID patients showed lower median age (56 vs. 60 years, P value< 0.001), but the same BMI max observed or calculated before covid (31 vs. 31, P value= 0.13), lower BMI max observed or calculated post covid (29 vs. 30, P value = 0.009) than long COVID patients and less likely to be a White non-Hispanic race (53% of acute COVID SOT were White versus 57% of long COVID SOT, P value <0.001). Those who were acute COVID were significantly more likely to be

kidney transplanted recipients than other organ transplant types (58 % of acute COVID versus 51% of long COVID SOT had a kidney transplant, P value < 0.001) because most patients in SOT are kidney transplanted recipients. Interestingly, liver transplant recipients had 15% of acute COVID versus 9.8% of long COVID (P value < 0.001). Conversely, lung (7.0% vs. 13.0%, P value< 0.001) and heart (10% vs. 13.0%) transplant recipients made up a smaller proportion of those patients testing for acute COVID than those testing long COVID. Hypertension before and post covid indicators, diabetes before and post covid indicators, congestive heart failure before and post covid indicators, CAD before and post COVID indicators, and peripheral vascular disease before and post covid indicators and were common comorbidities in all SOT but significantly more common in those who were long COVID. The categorical transplant variables include kidney transplant (61%), the highest of the transplants, followed by liver transplant (19%), lung transplant (18%), and heart transplant (16%), as in figure 3.



	kidney transplant	liver transplant	lung transplant	heart transplant
Overall	60	18	12	10
Acute COVID	59	18	13	10
Long COVID	65	19	10	6

Figure 3. Outcome of the acute COVID-19 and long COVID by the Transplant types. It is interesting to find that lung transplanted recipients are statistically significantly double to have long COVID.

All patients for comorbidities reported whether there was a statistical difference based on P-values. Hypertension, diabetes, coronary artery disease, peripheral vascular disease, and congestive heart failure were common comorbidities in the SOT cohort but significantly more common in those who had long COVID and acute COVID. Further analysis in more recent cohorts can be done through some sensitivity analysis by the inclusion of acute COVID without long COVID individuals matched by age, sex, and race.

Table 2: Patient Demographic Comparison of long COVID and Acute COVID patients in SOT cohort.

Characteristic Variables	Overall	Acute COVID	Long COVID	P value
Gender				0.7
Male	22422 (59%)	22127 (59%)	295 (58%)	
Female	15860 (41%)	15644 (41%)	216 (42%)	
Mean (Q1, Q3) of age	56 (40, 66)	56 (40, 65)	60 (48, 68)	<0.001
<19	3858 (10%)	3849 (10%)	<20	
19-34	3331 (8.7%)	3308 (8.8%)	23 (4.5%)	
35-49	7297 (19%)	7190 (19%)	107 (21%)	
50-64	13171 (34%)	12989 (34%)	182 (36%)	
≥ 65	10625 (28%)	10435 (28%)	190 (37%)	
Race Ethnicity				
White Non-Hispanic	20484 (54%)	20192 (53%)	292 (57%)	
Black or African American Non-Hispanic	8097 (21%)	7969 (21%)	128 (25%)	
Hispanic or Latino any Race	5606 (15%)	5548 (15%)	58 (11%)	
Asian Non-Hispanic	1283 (3.4%)	1274 (3.4%)	<20	
Other Non-Hispanic	95 (0.2%)	95 (0.3%)	<20	
Unknown	2717 (7.1%)	2693 (7.1%)	24 (4.7%)	
Transplant Type				<0.001
Multiple	3538 (9.2%)	3474 (9.2%)	64 (13%)	
Kidney	22191 (58%)	21928 (58%)	263 (51%)	
Liver	5847 (15%)	5797 (15%)	50 (9.8%)	
Lung	2718 (7.1%)	2651 (7.0%)	67 (13%)	
Heart	3988 (10%)	3921 (10%)	67 (13%)	
kidney transplant	25233 (66%)	24922 (66%)	311 (61%)	0.017
liver transplant	8277 (22%)	8180 (22%)	97 (19%)	0.2
lung transplant	3594 (9.4%)	3502 (9.3%)	92 (18%)	<0.001
heart transplant	4971 (13%)	4889 (13%)	82 (16%)	0.045
Dementia before covid indicator	655 (1.7%)	647 (1.7%)	<20	>0.9
Dementia post covid indicator	409 (1.1%)	400 (1.1%)	<20	0.2
BMI max observed or calculated before covid	31 (27, 36)	31 (27, 36)	31 (27, 36)	0.13

Unknown	10895	10763	132	
BMI max observed or calculated post covid	29 (25, 34)	29 (25, 34)	30 (26, 35)	0.009
Unknown	16163	16014	149	
BMI Category				0.2
<18.5	399(1.0%)	397(1.1%)	2(0.4%)	
18.5-24.9	3635(9.5%)	3594(9.5%)	41(8.0%)	
25.0-29.9	7633(20%)	7525(20%)	108(21%)	
≥ 30	15750(41%)	15492(41%)	228(45%)	
Missing/Unknown	10895(28%)	10763(28%)	132(26%)	
Asthma before covid indicator	3859 (10%)	3799 (10%)	60 (12%)	0.2
Malignant cancer before covid indicator	7578 (20%)	7448 (20%)	130 (25%)	0.002
Malignant cancer post covid indicator	4264 (11%)	4181 (11%)	83 (16%)	<0.001
Diabetes complicated before covid indicator	14958 (39%)	14698 (39%)	260 (51%)	<0.001
Diabetes complicated post covid indicator	9427 (25%)	9209 (24%)	218 (43%)	<0.001
Congestive heart failure before covid indicator	11222 (29%)	11026 (29%)	196 (38%)	<0.001
Congestive heart failure post covid indicator	6634 (17%)	6454 (17%)	180 (35%)	<0.001
Coronary artery disease before covid indicator	10593 (28%)	10399 (28%)	194 (38%)	<0.001
Coronary artery disease post covid indicator	5589 (15%)	5427 (14%)	162 (32%)	<0.001
Hypertension before covid indicator	31513 (82%)	31044 (82%)	469 (92%)	<0.001
Hypertension post covid indicator	21632 (57%)	21211 (56%)	421 (82%)	<0.001
Peripheral vascular disease before covid indicator	5856 (15%)	5740 (15%)	116 (23%)	<0.001
Peripheral vascular disease post covid indicator	2826 (7.4%)	2749 (7.3%)	77 (15%)	<0.001

Note: age at COVID; BMI body mass index; Statistically significant at a $P < 0.05$; COVID coronavirus disease

In the acute COVID cohort, results of the logistics regression analysis of long-term COVID in Table 3 with higher odds of mortality were present amongst patients older than 65 years (odds ratio (OR):1.73, 95% CI: 1.66–1.81), with a BMI of 30+ (OR: 1.24, 95% CI: 1.19–1.29), hypertension (OR: 1.36, 95% CI: 1.32–1.40), diabetes (OR: 1.09, 95% CI: 1.05–1.14), asthma (OR:1.85, 95% CI: 1.79–1.91), malignant cancer (OR: 1.12, 95% CI: 1.07–1.16), congestive heart failure (OR: 1.27, 95% CI: 1.22–1.32), peripheral vascular disease (OR: 1.02, 95% CI: 0.96–1.07), and dementia (OR: 1.18, 95% CI: 1.08–1.29).

Results from Statistical Models

Table 3: Odd Ratio (95% CI) of the long COVID outcome from multivariable logistical regression in the acute COVID cohort.

Variables	Odd Ratio (95% CI)	P value
Gender		
Male	Ref.	
Female	1.35 (1.32, 1.38)	<0.001
Age Group		
19-34	Ref.	
<19	0.55 (0.52, 0.58)	<0.001
35-49	2.05 (1.97, 2.13)	<0.001
50-64	2.24(2.16, 2.33)	<0.001
≥ 65	1.73(1.66, 1.81)	<0.001
BMI Category		
18.5-24.9	Ref.	
<18.5	0.57(0.51, 0.64)	<0.001
25.0-29.9	1.07(1.02, 1.12)	0.005
≥ 30	1.24(1.19, 1.29)	<0.001
Missing/Unknown	0.40(0.38, 0.42)	<0.001
Race Ethnicity		
White Non-Hispanic	Ref.	
Black or African American Non-Hispanic	1.02(0.99, 1.05)	0.3
Hispanic or Latino any Race	1.18(1.14, 1.22)	<0.001
Asian Non-Hispanic	0.98(0.90, 1.06)	0.6
Other Non-Hispanic	1.42(1.17, 1.69)	<0.001
Unknown	0.59(0.56, 0.62)	<0.001
Hypertension before covid indicator	1.36(1.32, 1.40)	<0.001
Diabetes complicated before covid indicator	1.09(1.05, 1.14)	<0.001
Asthma before covid indicator	1.85(1.79, 1.91)	<0.001
Malignant cancer before covid indicator	1.12(1.07, 1.16)	<0.001
Congestive heart failure before covid indicator	1.27(1.22, 1.32)	<0.001
Peripheral vascular disease before covid indicator	1.02(0.96, 1.07)	0.6
Dementia post covid indicator	1.18(1.08, 1.29)	<0.001
Transplant Type		
Non-Transplant	Ref.	
Multiple	2.29(1.88, 2.75)	<0.001
Kidney	1.33(1.19, 1.49)	<0.001
Liver	1.04(0.81, 1.32)	0.7
Lung	4.06(3.36, 4.85)	<0.001
Heart	1.72(1.37, 2.13)	<0.001

Abbreviations: CI confidence interval; BMI body mass index; Statistically significant at a $P < 0.05$

Results of univariable analysis in the SOT cohort examining predictors of testing long-term COVID are shown in Table 4. Among those tested, older age was associated with testing (odds ratio [OR] 2.08; 95% CI, 1.36 -3.34 for that > 65 y of age versus those aged 19–34 y) followed by BMI of 30+ (OR: 1.03, 95% CI: 0.74–1.47), hypertension (OR: 1.44, 95% CI: 1.03–2.06), diabetes (OR: 1.22, 95% CI: 1.01–1.48), asthma (OR:1.06, 95% CI: 0.80–1.39), malignant cancer (OR: 1.18, 95% CI: 0.95–1.45), congestive heart failure (OR: 1.09, 95% CI: 0.88 –1.33), peripheral vascular disease (OR: 1.24, 95% CI: 0.99–1.54), and dementia (OR: 1.30, 95% CI: 0.61–2.40). Male gender was more common in the SOT cohort (P value <0.001), and transplant recipient long-term COVID patients had a higher mean age (P value <0.001) for 19-34 years, and the White non-Hispanic race was more common in the long-term COVID at baseline (P value <0.001). Normal weight, hypertension, diabetes, and congestive heart failure were more common in transplant recipients (all P < 0.001). When tested, those of non-White Hispanic ethnicity and recipients of kidney versus other organ transplants were more likely to have a greater test result than patients with any comorbidity other than liver disease. Among those with the SOT cohort, hypertension, asthma, and congestive heart failure were each associated with increased odds of testing for long-term COVID-19. In analysis, age over 65, and liver or lung transplant, were independently associated with a lower likelihood of testing for long-term COVID-19. In contrast, the test result was more common in the non-White Hispanic race, those with hypertension, diabetes, peripheral vascular disease, and congestive heart failure immunosuppressive therapy.

Table 4: Odds Ratio (95% CI) of the long COVID outcome from multivariable logistical regression in the SOT cohort

Variables	Odd Ratio (95% CI)	P value
Gender		
Male	Ref.	
Female	1.11 (0.93, 1.33)	0.200

Age Group		
19-34	Ref.	
<19	0.42 (0.18, 0.88)	0.029
35-49	2.06(1.33, 3.33)	0.002
50-64	1.75(1.15, 2.80)	0.013
≥ 65	2.08(1.36, 3.34)	0.001
BMI Category		
18.5-24.9	Ref.	
<18.5	0.71(0.12, 2.35)	0.6
25.0-29.9	1.10(0.77, 1.60)	0.6
≥ 30	1.03(0.74, 1.47)	0.8
Missing/Unknown	0.88(0.62, 1.27)	0.5
Race Ethnicity		
White Non-Hispanic	Ref.	
Black or African American Non-Hispanic	1.15(0.92, 1.43)	0.2
Hispanic or Latino any Race	0.96(0.71, 1.27)	0.8
Asian Non-Hispanic	0.64(0.30, 1.18)	0.2
Other Non-Hispanic	0.00(0.00, 0.02)	>0.9
Unknown	0.70(0.45, 1.04)	0.093
Hypertension before covid indicator	1.44(1.03, 2.06)	0.038
Diabetes complicated before covid indicator	1.22(1.01, 1.48)	0.039
Asthma before covid indicator	1.06(0.80, 1.39)	0.7
Malignant cancer before covid indicator	1.18(0.80, 1.39)	0.12
Congestive heart failure before covid indicator	1.09(0.88, 1.33)	0.4
Peripheral vascular disease before covid indicator	1.24(0.99, 1.54)	0.062
Dementia post covid indicator	1.30(0.61, 2.40)	0.4
Transplant Type		
Kidney	Ref.	
Multiple	1.48(1.11, 1.94)	0.007
Liver	0.83(0.60, 1.12)	0.2
Lung	2.24(1.68, 2.96)	<0.001
Heart	1.43(1.06, 1.90)	0.018

Abbreviations: CI confidence interval.; BMI body mass index; Statistically significant at a P value < 0.05

The results of patient survival from the Cox regression models were shown in Table 5. Female were likely to have a death with Hazard Ratio (HR) = 0.69, (95% CI: 0.68–0.70) while adjusting for Male patients. HR of age categories were ranged from 2.74 (95% CI: 2.57–2.92) in patients with aged < 19 years to 27.8 (95% CI: 26.3–29.4) in those elder patients with aged more than 65

years old. It is very dangerous for elder patients to have a long COVID in SOT because hazard ratio was so high with 27.8 (26.3, 29.4). It is very interesting to find that overweight and obesity is beneficial for patient survival in BMI categories.

Table 5: Hazard Ratio of the time-to-event outcome of patient survival from multivariable Cox models in the SOT cohort with long COVID.

Variables	Hazard Ratio (95% CI)	P value
Gender		
Male	Ref.	
Female	0.69(0.68, 0.70)	<0.001
Age Group		
19-34	Ref.	
<19	2.74(2.57, 2.92)	<0.001
35-49	3.16(2.97, 3.36)	<0.001
50-64	9.19(8.69, 9.72)	<0.001
≥ 65	27.8(26.3, 29.4)	<0.001
BMI Category		
18.5-24.9	Ref.	
<18.5	0.94(0.88, 1.00)	0.037
25.0-29.9	0.80(0.78, 0.83)	<0.001
≥ 30	0.81(0.79, 0.83)	<0.001
Missing/Unknown	0.61(0.59, 0.63)	<0.001
Race Ethnicity		
White Non-Hispanic	Ref.	
Black or African American Non-Hispanic	1.13(1.11, 1.16)	<0.001
Hispanic or Latino any Race	1.11(1.08, 1.15)	<0.001
Asian Non-Hispanic	1.28(1.21, 1.35)	<0.001
Other Non-Hispanic	0.44(0.33, 0.57)	<0.001
Unknown	1.03(1.01, 1.06)	0.019
Hypertension covid indicator	1.57(1.54, 1.60)	<0.001
Diabetes complicated covid indicator	1.34(1.31, 1.37)	<0.001
Asthma covid indicator	0.71(0.69, 0.73)	<0.001
Malignant cancer covid indicator	1.51(1.48, 1.54)	<0.001
Congestive heart failure covid indicator	2.69(2.64, 2.74)	<0.001
Peripheral vascular disease covid indicator	1.16(1.13, 1.18)	<0.001
Dementia covid indicator	1.15(1.11, 1.19)	<0.001
Transplant Type		
Non-Transplant	Ref.	
Multiple	1.19(1.05, 1.35)	0.006
Kidney	1.87(1.78, 1.97)	<0.001

Liver	1.63(1.47, 1.81)	<0.001
Lung	2.05(1.80, 2.32)	<0.001
Heart	0.91(0.80, 1.03)	0.14
Long covid flag	0.47(0.42, 0.52)	<0.001

Abbreviations: HR hazard ratio; BMI body mass index; Statistically significant at a P-Value < 0.05

Chapter 5 Discussion and conclusion

This study is one of the first comprehensive analyses of long COVID in patients enrolled in the N3C data enclave platform in those with acute COVID and the SOT transplant groups. We have identified a SOT cohort of 31,744 with either acute COVID or long COVID. The comorbidity levels are greater in elderly adults and over, with a higher prevalence of hypertension, diabetes, coronary artery disease, malignant cancer, congestive heart failure, peripheral vascular disease, asthma, and dementia. We found that long COVID increased patient survival risk with male than female male SOT patients, although it was not likely to have COVID (Vinson et al., 2020). The association between males and older age with long COVID diagnosis in the overall population relates to a biological vulnerability to viral infection or to differences in behaviors and lifestyles that might put these male and older patients at increased risk of acquiring COVID-19 remains to be seen (Vinson et al., 2020). Hence, there may be speculation that older male SOT patients are not at increased risk for acquiring long COVID-19 because of better adherence to physical distancing and using personal protective equipment (like N-95 mask, hand sanitizer, Etc.), thereby mitigating any behavioral differences observed in the overall population.

The present study adds to this literature by showing that long-term COVID is positively and significantly associated with transplants even after adjusting for potential confounding factors. Interestingly, this association was further found to be significant in all age and sex subgroups and BMI categories. Moreover, HRs increased with increasing age, suggesting that the deleterious effects of this long-term COVID on comorbidities may be stronger in older adults than in their younger counterparts. The limitations of our study include its retrospective design and the biases inherent to studies conducted on the N3C data enclave platform. We were able to

analyze a large sample and control for possible confounders that should strengthen the validity of our findings. As our data are derived primarily from large academic centers in the United States, generalizability to other specific populations may be limited. Furthermore, patients with an asymptomatic course of infection for a long COVID diagnosis based on past covid and a series of symptoms remain uncaptured in our study. Thus, it can be inferred that our analysis includes a relatively more "severe" part of the disease spectrum.

In conclusion, we have identified the risk factors to be more likely to develop long COVID in both acute COVID and SOT cohorts. Importantly, we have investigated hazard ratios of patient survival based on multivariable Cox models. We find that elderly patients in SOT were much more likely to die when long COVID. The study underlines patient survival in managing SOT patients with long COVID. Careful assessment seems important for recognizing patients at risk of a complicated course. Finally, future research should investigate the potential mediating factors involved in the relationship between long COVID and transplant centers, such as cluster statistical models.

Ethical considerations

The only ethical issues that were required to be addressed were managed through the IRB application for the long COVID transplantation program. The IRB provides oversight, including ethical oversight, for all research involving humans or human biological material (HBM) at UNMC. Hence, the study protocol was approved by the UNMC Institutional Review Board followed by the N3C Data Access and Ethics Committee before analysis. National Institute of Health's N3C Data Utilization Request Approval committee approved the data utilization request of this project. NCATS reviewed all data elements before extraction.

Application of Public Health Competencies

The above project has uncovered me to a vast majority of public health competencies. The main foundational competency that this project focuses on is MPHF3: Analyze quantitative and qualitative data using biostatistics, informatics, computer-based programming and software, as appropriate. The thorough use of computer programming and biostatistics is at the fore front of this capstone project. Compilation of data as well as analyzing descriptive statistics are the basics of this project. All of these were conducted using computer programming software like SQL and R in the N3C data enclave platform.

The two concentration competencies that are more representative of this project include BIOSMPH2 and BIOSMPH4. BIOSMPH2 is the application of appropriate statistical methods for estimation and inference using a software package for data management, statistical analyses, and data presentation. Hence, the capstone project satisfies this competency through the application of appropriate statistical methods using SQL and R coding language software. BIOSMPH4 is the development of written and oral presentations based on the statistical findings for both public health professionals and lay audiences. The entire information for this project is obtained from the N3C data enclave platform through the National Institute of Health. Hence, it helps put presentation slides together that explain the capstone topic of the risk factors of long COVID in the acute COVID and solid organ transplant retrospective cohorts, emphasizing the specifics, including tables to professionals and lay audiences.

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