The Dissertation Committee for Khamron Micheals certifies that this is the approved version of the following dissertation:

RESPIRATORY PARAMETERS, PULMONARY REHABILITATION and SURVIVAL in COVID-19 PATIENTS

Committee:

José D. Rojas, PhD, RRT, FAARC
Chairperson and Mentor

Soham Al Snih, MD, PhD.

Brian K. Walsh, PhD, RRT, FAARC

George Golovko, PhD

Carole A. Tucker, PhD, PT

Douglas S. Gardenhire, EdD, RRT, FAARC

RESPIRATORY PARAMETERS, PULMONARY REHABILITATION AND SURVIVAL IN COVID-19 PATIENTS

by

Khamron Micheals, MHA, RRT

Dissertation

Presented to the Faculty of the School of Public and Population Health

The University of Texas Medical Branch

in Partial Fulfillment

of the Requirements

for the Degree of

Doctor of Philosophy

The University of Texas Medical Branch

April 2024

DEDICATION

This dissertation is dedicated to my late Godfather and Uncle James Beard, my late cousin Dena François and the many individuals who lost their lives or loved ones due to the COVID-19 pandemic.

ACKNOWLEDGEMENTS

There are a plethora of individuals who have supported me on this journey, and they deserve a huge amount of kudos. First, I would like to thank my dissertation committee members, Drs. José D. Rojas, Soham Al Snih, Brian Walsh, George Golovko, Carole A. Tucker, and Douglas S. Gardenhire.

I want to thank the School of Public and Population Health's Ph.D. Program for providing me with a valuable opportunity and a high-quality educational program that will equip me with many advantageous tools for years to come. I extend deep gratitude to Dr. Al Snih for her patience and expertise, which have allowed me to become a more proficient writer, creative thinker, independent researcher, and upstanding individual overall.

A special thanks goes out to my non-traditional mentors and advisors, who encouraged my personal development and helped me understand my value as a person and researcher. Drs. Daniel Jupiter, Motamedi Massoud, and Lanette D. Harris from the Innovation and Entrepreneurship Studio and Drs. Diane M. Collins, Mi Jung Lee, Amber Armstead from the Post-Acute Sequelae of COVID-19 (PASC) research group. In addition, I would like to acknowledge my former professor, Dr. Melanie Lawson from Texas Southern University, for enlightening me to pursue my doctoral degree. I would also like to give a special acknowledgement to the National Board of Respiratory Care and the American College of Respiratory Therapy Education for providing me with their generous funding support on multiple occasions.

Through this rigorous process, I want to acknowledge my wife for being a cornerstone in my life. For her emotional support, supporting my ideas of taking a financial step back to pursue more education, listening to complex scientific theories, and caring for me during my mental trials of being a doctoral student. Of course, I thank my immediate family for always believing in me and supporting me while I pursue my education. Lastly, I must thank my neighborhood, extended family, and close friends for being my accountability partners and constantly motivating, encouraging, and inspiring me to live up to my highest potential.

RESPIRATORY PARAMETERS, PULMONARY REHABILITATION and SURVIVAL in COVID-19 PATIENTS

Publication No._____________

Khamron Micheals, PhD

The University of Texas Medical Branch, 2024

Supervisor: José D. Rojas, PhD, RRT, RPFT, FAARC

Background: Coronavirus disease 2019 (COVID-19) is a highly infectious viral illness, which targets patient's respiratory system. **Objectives:** To (1) determine whether respiratory mechanics, oxygenation impairment, sociodemographics, and multimorbidity of mechanically ventilated COVID-19 subjects are associated with survival; (2) determine the factors associated with physical function status after completing six weeks of pulmonary rehabilitation (PR) of COVID-19 subjects with persisting pulmonary symptoms; and (3) investigate the impact of socioeconomic (SES) disparities on participation in PR and morbidity of Long COVID patients. **Design:** Retrospective analysis using the electronic health records. **Participants:** Adults $\geq$ 18 years, with positive COVID-19 diagnosis that were mechanically ventilated (n = 415). Adults with positive COVID-19 diagnosis with persisting dyspnea that completed PR (n = 68). Adults with ICD-10 diagnosis for Long COVID within the TriNetX database (n = 67,019). **Measures:** Sociodemographics, comorbid conditions, respiratory mechanics, University of California – San Diego Shortness of Breath Questionnaire score, 6-minute walking distance, anxiety, depression, post-traumatic stress disorder, survival and morbidity. **Analysis:** Descriptive statistics were performed to assess the sample characteristics. Generalized estimating equation models was used to assess survival. Multivariate regression was used to assess improvement in physical function. Kaplan curve analysis was performed to assess participation of PR and morbidity. **Results:** Being younger, female, and Non-Hispanic White were associated with survival of mechanically ventilated COVID-19 patients. Most Long COVID patients had improved physical function following PR. **Conclusions:** Sociodemographic factors were significantly associated with survival. As pulmonary dynamic compliance increased, survival increased in mechanically ventilated COVID-19 subjects. Non-Hispanic Blacks had lower odds of physical function improvement after completing PR than Non-Hispanic Whites. Long COVID patients with SES disparities were more likely to have lasting morbidity issues.

Table of Contents

List of Tables

LIST OF FIGURES

List of Abbreviations

6MWD	6-Minute Walking Distance
6-MWT	6-Minute Walking Test
ADL	Activities of Daily Living
ARDS	Acute Respiratory Distress Syndrome
ATS	American Thoracic Society
AUC	Area Under Curve
BMI	Body Mass Index
BS	Bachelor of Science
CAD	Coronary Artery Disease
CDC	Centers for Disease Control and Prevention
CHF	Chronic Heart Failure
cmH2O	Centimeters of Water
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus 2019
C_{DYN}	Dynamic Compliance
CKD	Chronic Kidney Disease
C_{RS}	Respiratory System Compliance
C_{STAT}	Static Compliance
DLCO	Diffusion Capacity of the lung for Carbon Monoxide
DM	Diabetes Mellitus
DV	Dependent Variable

ED	Emergency Department
EHR	Electronic Health Record
EPIC	Epic Systems Corporation
GAD-7	General Anxiety Disorder - 7
GEE	Generalized Estimating Equation
GSBS	Graduate School of Biomedical Sciences
ESRD	End-Stage Renal Disease
FEV_1/FVC	Forced Expiratory Volume in 1 second/Forced Vital Capacity
FVC	Forced Vital Capacity
HCPCS	Healthcare Common Procedure Coding System
HR	Hazard Ratio
HRS	Health and Retirement Study
ICU	Intensive Care Unit
IES-6	Impact of Event Scale - 6
IOM	Institute of Medicine
IPF	Idiopathic Pulmonary Fibrosis
IV	Independent Variable
Kg	Kilograms
LLN	Lower Limit of Normal
LOS	Length of Stay
m	Meters
mL	Milliliters
MCID	Minimal Clinically Important Difference

NIH	National Institutes of Health
PASC	Post-Acute Sequelae of COVID-19
PEEP	Positive end-expiratory Pressure
PF ratio	PaO2/FiO2
P_{PLAT}	Plateau Pressure
PR	Pulmonary Rehabilitation
PTSD	Post-Traumatic Stress Disorder
R_{AW}	Airway Resistance
ROC	Receiver Operating Characteristic Curve
SOB	Shortness of Breath
SPPH	School of Public and Population Health
UCSD	The University of California – San Diego Shortness of Breath Questionnaire
UK	United Kingdom
US	United States of America
UTMB	University of Texas Medical Branch
V_T	Tidal Volume
WHO	World Health Organization

CHAPTER 1

Background/Introduction

Coronavirus disease 2019 (COVID-19) is a contagious viral disease that predominantly affects the respiratory system. (Cascella, 2023; Salzberger, 2021) COVID-19 was declared a global pandemic on March 11, 2020 (Cucinotta, 2020) and has since caused many hospitalizations and significant mortality worldwide. (Nasiri, 2020) As of February 2024, more 750 million people have been diagnosed with COVID-19 and COVID-19 has contributed to more than 7 million deaths worldwide. (WHO, 2023)

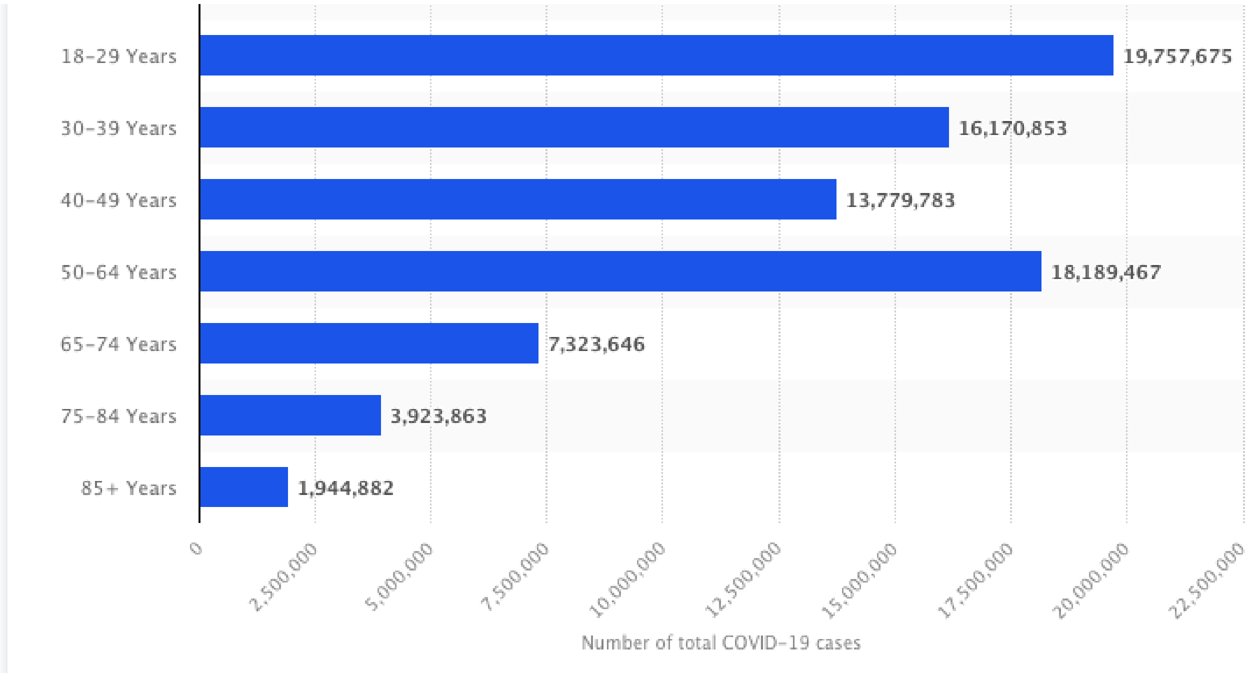
COVID-19 affects subjects of all ages, sexes, races, ethnicities and health statuses. (Baradaran, 2020) The risk of COVID-19 severity varies by age, sex, and presence of comorbid conditions, (Bergman, 2021; Liu, 2021) such as hypertension, diabetes mellitus, chronic heart failure and pulmonary disease. (Salzberger, 2021) Healthy subjects also struggle with morbidity and mortality issues related to COVID-19 infection. (Ronderos Botero, 2020)

Meta-analyses suggest that older age and comorbid conditions are associated with the severity and prognosis of COVID-19, while male sex is associated with a higher prevalence and disease severity than females. (Fang, 2020; Galbadage, 2020) Lack of understanding of COVID-19 epidemiology and clinical course hinder effective clinical practice and public health decision-making. (Kolifarhood, 2020)

SOCIODEMOGRAPHIC FACTORS ASSOCIATED WITH COVID-19

Older adults and minority groups are more susceptible to contracting COVID-19. (Khanijahani, 2021; Magesh, 2021) The clinical severity of the disease varies by race/ethnicity and comorbidities. (Pennington, 2021) Figure 1.1 shows data provided by the Centers for Disease Control and Prevention (CDC) on prevalence rates for COVID-19 by age group, in the United States of America (US) from the March 11, 2020 until April 26, 2023.

FIGURE 1.1 PREVALENCE RATES FOR COVID-19 BY AGE GROUP IN THE UNITED STATES



Source: **CDC, 2023**

Dai et al. concluded that the impact of COVID-19 varied by race and ethnicity, with a higher burden of underrepresented populations. (Dai, 2021) Non-Hispanic Blacks, specifically, are more vulnerable to COVID-19 than other ethnic groups. (Abedi, 2021)

SOCIOECONOMIC FACTORS ASSOCIATED WITH COVID-19

A retrospective study of primarily Hispanic/Latino subjects in Los Angeles County found that Hispanic/Latino subjects had socioeconomic and clinical characteristics that disproportionally affected their COVID-19 outcomes. (Casillas, 2021) Neighborhood socioeconomic status is a significant risk factor for COVID-19 incidence. (Zhang, 2021) In the US, financial burdens, lack of insurance coverage, and supply chain shortages have led subjects living in rural areas to have an increased risk of hospitalization and death from COVID-19. (Kaufman, 2020) Race/ethnicity and socioeconomic deprivation are associated with a greater likelihood of COVID-19 incidence and hospitalization. (Upshaw, 2021)

In the United States of America (US), county-level sociodemographic risk factors have also been associated with increased COVID-19 incidence and mortality rates. (Karmakar, 2021) Social determinants of health, including socioeconomic status, neighborhood environment, housing conditions, environmental exposures, and access to healthcare, have been demonstrated to impact various pulmonary disease populations across certain racial/ethnic groups. (Grant, 2022) A systematic review highlights that the COVID-19 pandemic has underscored the urgent need to address health disparities and social determinants of health, particularly impacting vulnerable populations with higher rates of hospitalizations and mortality. (Green, 2021) There has shown to be a significant impact of adverse social determinants of health on COVID-19 mortality rates of Black Americans. (Dalsania, 2022) Stanojevic et al. report that socioeconomic disadvantage is associated with poor lung health and causing a need for the need for targeted policies and interventions to improve lung health. (Stanojevic, 2021)

CLINICAL FACTORS – COMPLIANCE, RESISTANCE, AND OXYGENATION IMPAIRMENT

A compromised respiratory status upon admission exacerbates the outcomes of COVID-19 subjects. (Guan, 2020) Studies show that respiratory system compliance (C_{RS}) is compromised within COVID-19 subjects who develop acute respiratory distress syndrome

(ARDS), (Marini, 2020) and reported to be associated with mortality in critically ill COVID-19 subjects. (Ferreira, 2021) Gattinoni et al. described possible different clinical phenotypes of compliance changes within COVID-19 infection. Type L is characterized by high pulmonary compliance with low ventilation-to-perfusion ratio, lung weight, and recruitability; Type H is characterized by low pulmonary compliance with high right-to-left shunt, lung weight, and recruitability. (Gattinoni, 2020) Koppurapu et al. described a clinical presentation of airflow obstruction and increased resistance in mechanically ventilated subjects suffering from COVID-19. (Koppurapu, 2021) A Chinese study revealed that airway resistance (R_{AW}) was increased for subjects who died from COVID-19 and was decreased for subjects who survived within the critically ill COVID-19 population. (Pan, 2021)

PaO2/FiO2 (PF ratio) is widely used measurement for impaired oxygenation (Gilissen, 2022) and effectively predict severe respiratory failure in COVID-19 patients. (Sinatti, 2021) Pan et al. showed that lower C_{RS} and lower PF ratio affected mortality in a small observational study. (Pan, 2020) Longino et al. reported that PF ratios in COVID-19 subjects receiving mechanical ventilation were significantly lower in those who died versus those who survived. (Longino, 2021) However, in a more extensive cohort study of subjects with acute ARDS receiving mechanical ventilation and prone positioning, Tisminetzky et al. report that PF ratios were not associated with ICU mortality. (Tisminetzky, 2022) Li Bassi et al. report that mechanically ventilated COVID-19 patients have heterogenous C_{RS}, with females having lower values than males. (Li Bassi, 2021)

There are conflicting results within the literature regarding ARDS and COVID-19. Some research shows moderate to severe COVID-19 infection affects the respiratory system and increases the possibility of pneumonitis and ARDS. (George, 2020; Wu, 2020) The development of ARDS in COVID-19 subjects is negatively associated with a patient's likelihood of survival. (de Terwangne, 2021) There are reports that COVID-19 ARDS patients have similar C_{RS} as traditional ARDS patients. (Mart, 2020; Pearce, 2021) Whereas other research states that COVID-19 ARDS subjects demonstrate different respiratory mechanics than traditional ARDS subjects, (Cereda, 2020; Chiumello, 2020) specifically worse static compliance (C_{STAT}). (Jagan, 2023) However, studies show that this does not necessarily imply worse ICU outcomes nor an increased risk of mortality rates of COVID-19 subjects compared to traditional ARDS subjects. (Dmytriw, 2021; Jagan, 2023)

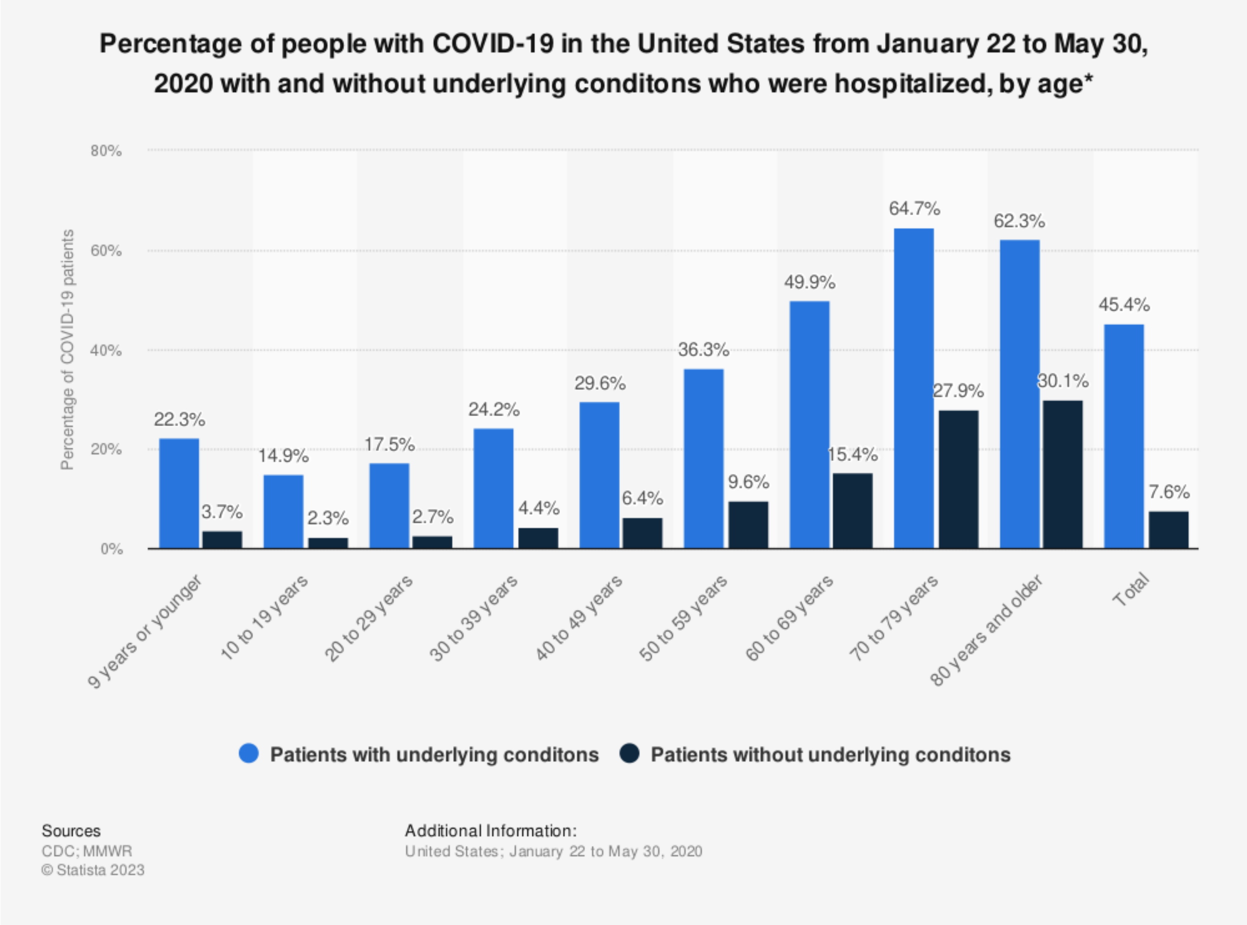
According to the NIH patients can present with mild, moderate or severe COVID-19 illness. Mild COVID-19 patients experience various signs and symptoms, such as fever, cough, sore throat, fatigue, headache, muscle pain, nausea, vomiting, diarrhea, and loss of taste and smell. They do not typically experience shortness of breath, difficulty breathing with exertion, or abnormal imaging results. Moderate COVID-19 patients exhibit lower respiratory disease findings during clinical assessment or imaging, along with oxygen saturation (SpO^2) of 94% or higher on room air. While severe COVID-19 patients exhibit an SpO2 level below 94% on room air at sea level, a PaO2/FiO2 ratio below 300 mm Hg, a respiratory rate exceeding 30 breaths per minute, or lung infiltrates exceeding 50%. (NIH, 2024)

HOSPITALIZATION

Up to 90% of subjects hospitalized from COVID-19 have comorbid conditions, yet older adults show higher hospitalization rates. (Garg, 2020; van Gerwen, 2021) Age is associated with greater COVID-19 hospitalizations in the US, with or without underlying conditions. (Figure 1.2) Studies show significant differences in cardiometabolic risk associated with COVID-19 hospitalizations by age and race/ethnicity. (O'Hearn, 2021) Multiple studies show that being male and having multimorbidity is associated with increased hospitalization. (Bergman, 2021; van Gerwen, 2021)

COVID-19 patients with chronic obstructive pulmonary disease (COPD) have shown to be susceptible to an increased severity of the disease. (Leung, 2020) Literature shows that a frequent cause of hospitalization in the COVID-19 population is respiratory failure. (Nielsen Jeschke, 2020) Higher referrals of hospitalization have been associated with COVID-19 subjects who are older, male, have a high body mass index (BMI), and have comorbid conditions, such as, obesity, hypertension or diabetes. (Cuschieri, 2020; Gupta, 2020; Lateef Ibrahim, 2022; Merzon, 2022; Vahey, 2021)

FIGURE 1.2 COVID-19 HOSPITALIZATION BY PRE-EXISTING CONDITIONS AND AGE



Source: **CDC, 2020**

* Based on 1,320,488 laboratory-confirmed COVID-19 cases individually reported to CDC during January 22–May 30, 2020. Hospitalization status was known for 600,860 (46%). Among 184,673 hospitalized patients, the presence of underlying health conditions was known for 96,884 (53%). Includes reported ICU admissions.

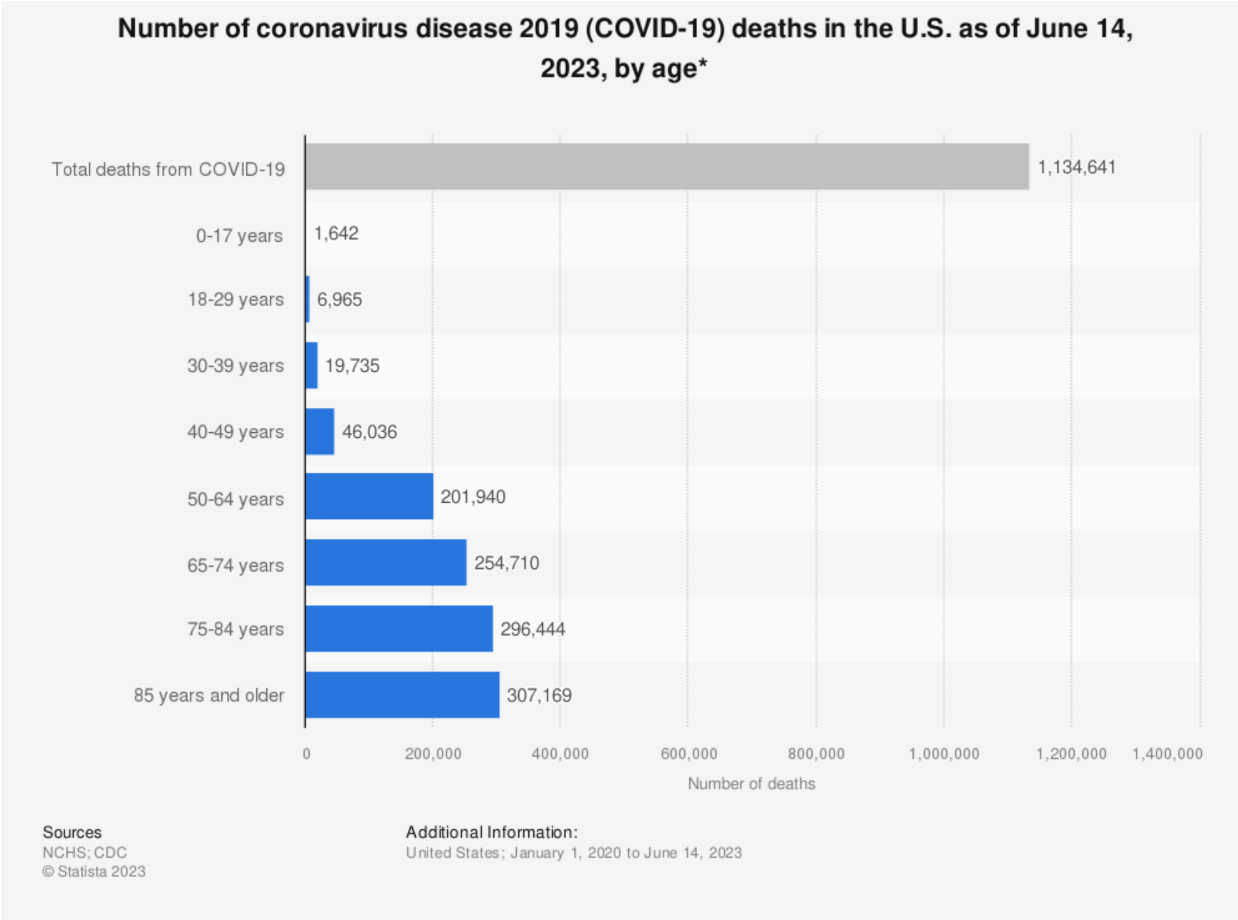
A study in Georgia of predominantly non-Hispanic Black subjects reported that non-Hispanic Blacks had a disproportionately higher hospitalization rate than other race and ethnic groups. (Racine, 2022) Within the US Military, minority ethnic groups were more likely to be hospitalized with COVID-19 than non-Hispanic Whites. (Young, 2021) Studies show that as age increases, the likelihood of in-hospital mortality also increases. (Kim, 2021; Martos Pérez, 2021)

MORTALITY RISKS RELATED TO COVID-19

Early in the pandemic, evidence showed that older adults, Hispanics, and females had a higher chance of mortality from COVID-19. (Tian, 2021) A retrospective analysis in Wuhan, China, suggests that in-hospital death of COVID-19 patients has been associated with older age. (Zhou, 2020) Multiple other studies also report that older age is associated with higher odds of mortality from COVID-19. (Takagi, 2021; Williamson, 2020; Yanez, 2020)

Males that are hospitalized for COVID-19 have a significantly higher risk of mortality than females. (Nguyen, 2021; van Gerwen, 2021) Although females had higher incidence rates in older adults (Hu, 2021), males were still more likely to die from COVID-19. (Dessie, 2021; Hu, 2021; Jin, 2020; Williamson, 2020; Yanez, 2020) Evidence shows that mortality related to sex disparities in COVID-19 are multifactorial. (Alwani, 2021) Other evidence shows that non-Hispanic Blacks with COVID-19 have higher odds of mortality than other race/ethnicity groups. (Yue, 2021) A study of COVID-19 subjects who were not admitted into the intensive care unit (ICU) showed that being older, with renal disease, or the need for supplemental oxygen was associated with mortality. (Grima, 2023) Data from the CDC, reported from the beginning of the pandemic through June 14, 2023 are shown in Figures 1.3 , 1.4, and Figure 1.5. The data show the number of US COVID-19 deaths by age group, by sex, and distribution of COVID-19 death by race and ethnicity, respectively.

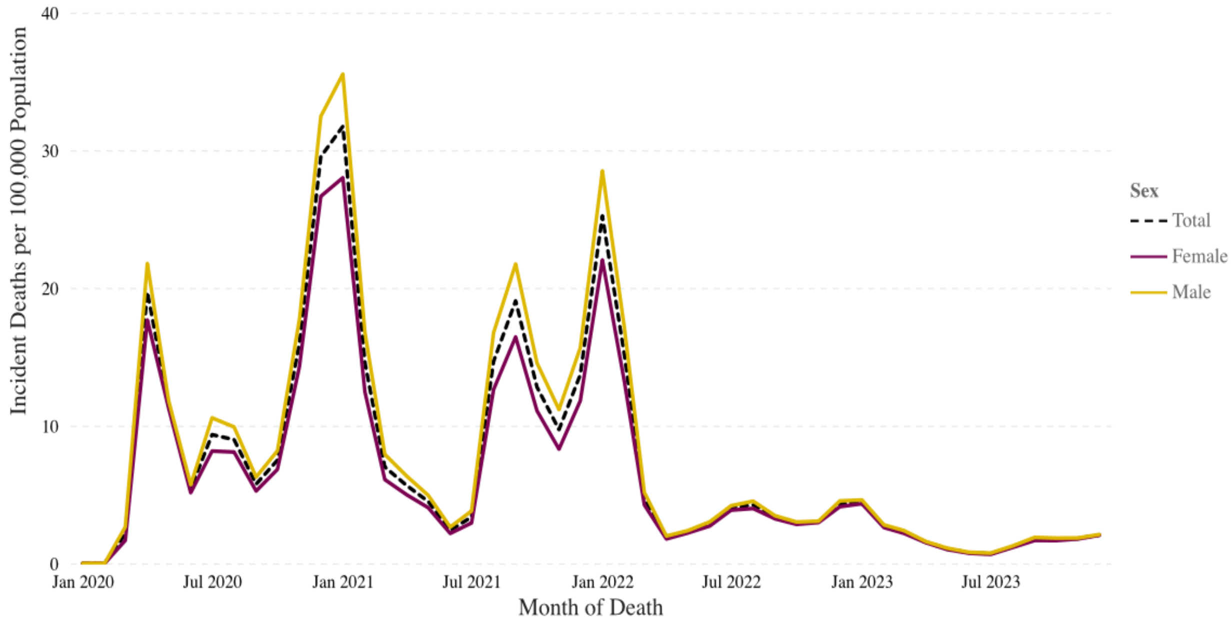
FIGURE 1.3 NUMBER OF COVID-19 DEATHS AS OF JUNE 14, 2023 BY AGE GROUP



Source: **CDC, 2023**

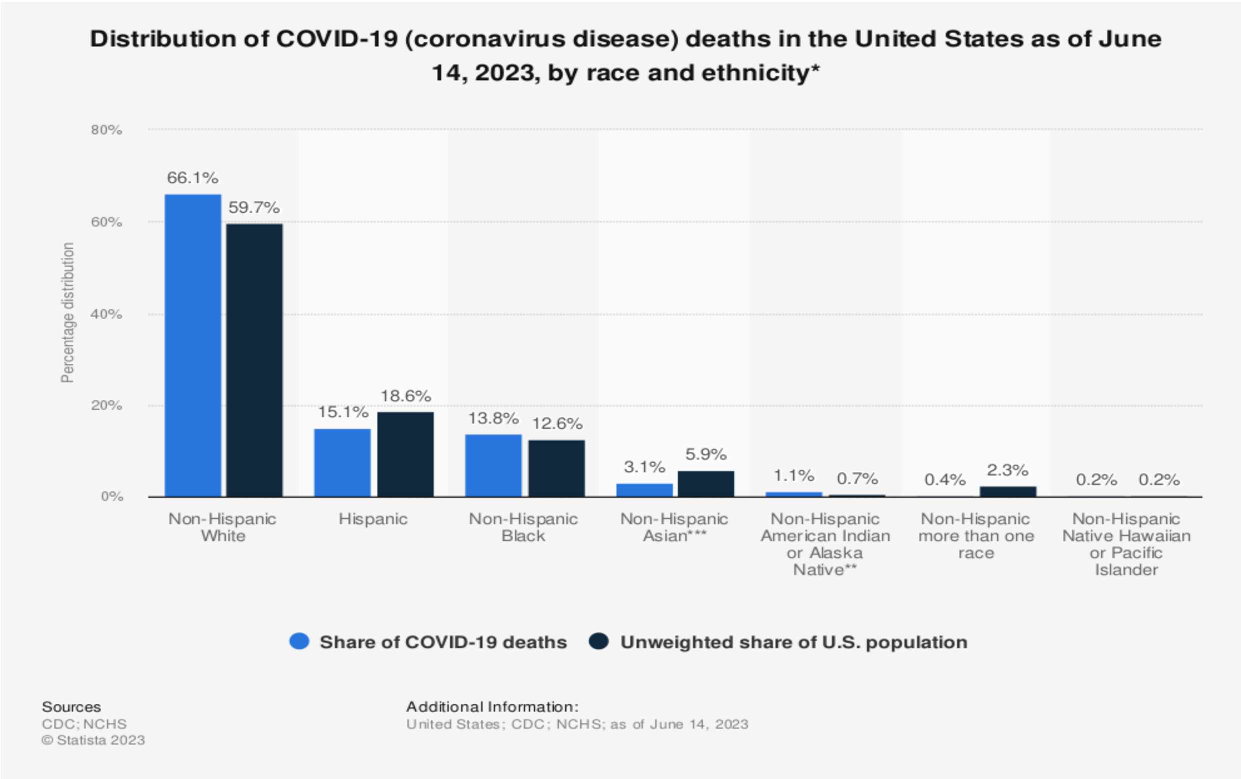
* Number of deaths reported in this table are the total number of deaths received and coded as of the date of analysis and do not represent all deaths that occurred in that period. Counts of deaths occurring before or after the reporting period are not included in the table. Data during this period are incomplete because of the lag in time between when the death occurred and when the death certificate is completed, submitted to NCHS and processed for reporting purposes. This delay can range from 1 week to 8 weeks or more, depending on the jurisdiction and cause of death. Deaths with confirmed or presumed COVID-19, coded to ICD–10 code U07.1

FIGURE 1.4 COVID-19 MONTHLY DEATH RATES PER 100,000 POPULATION BY SEX



Source: **[CDC, 2024]**

FIGURE 1.5 DISTRIBUTION OF COVID-19 DEATHS IN THE US AS OF JUNE 14, 2023 BY RACE AND ETHNICITY



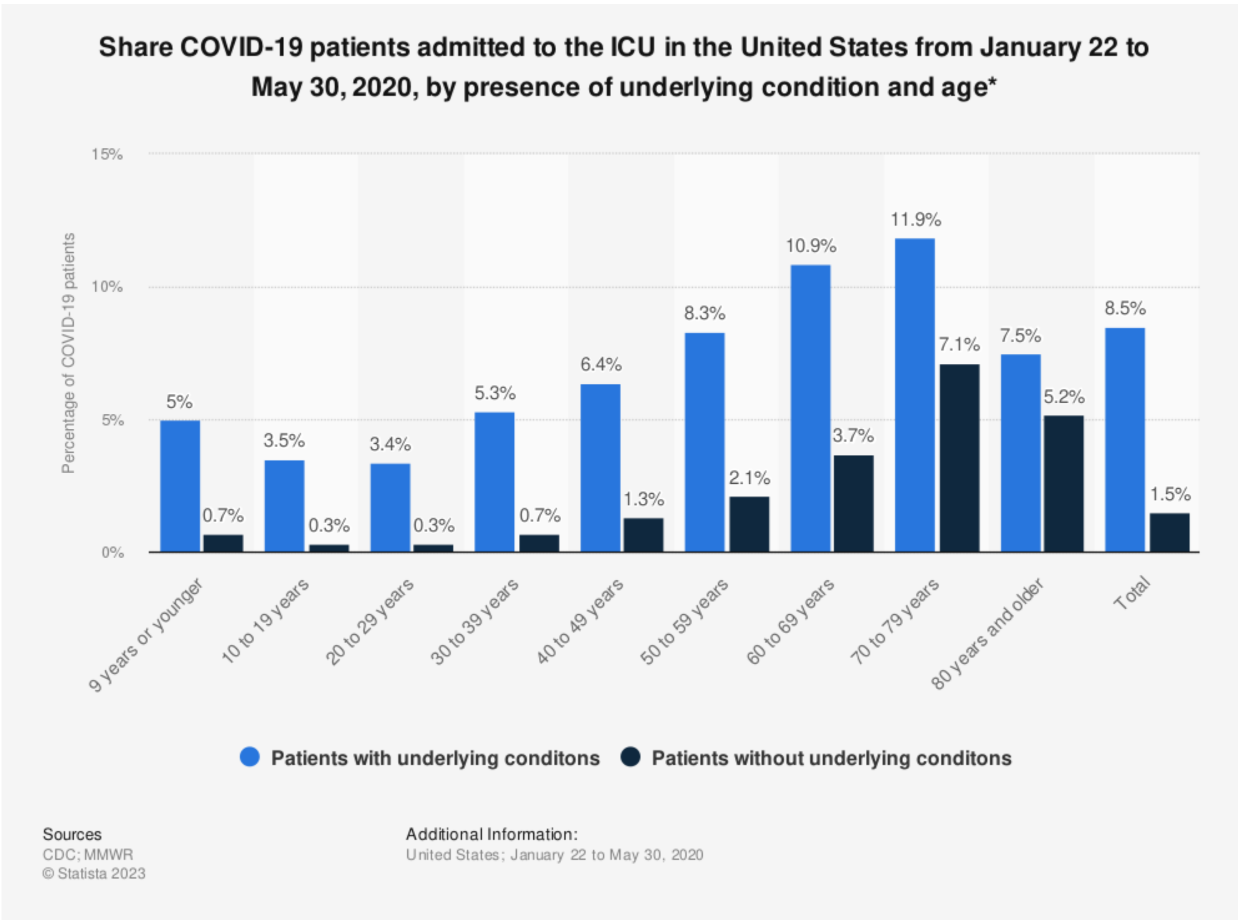
Source: **CDC, 2023**

* The percent of deaths reported in this table represent all deaths received and coded as of the date of analysis and do not represent all deaths that occurred in that period. Data are incomplete because of the lag in time between when the death occurred and when the death certificate is completed, submitted to NCHS and processed for reporting purposes. Provisional counts reported here track approximately 1–2 weeks behind other published data sources on the number of COVID-19 deaths in the U.S. COVID-19 deaths are defined as having confirmed or presumed COVID-19.
** Includes persons having origins in any of the original peoples of North and South America
*** Includes persons having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent.

Critically ill subjects who are older, obese, or require mechanical ventilation were also at risk for higher mortality. (Cedano, 2021) In a study of subjects admitted to the emergency department (ED), Wiley et al. found minorities to have a higher mortality risk than non-Hispanic Whites. (Wiley, 2022) However, Casillas et al. reported that Hispanic/Latino subjects had lower mortality rates than non-Hispanics. (Casillas, 2021) Several studies in the US found racial disparities, socioeconomic status, and health inequities associated with mortality. (Abedi, 2021; Isath, 2022; Jain, 2020; Williamson, 2020) COVID-19 has the potential to cause death in subjects who have comorbid conditions, such as COPD, chronic heart failure (CHF), diabetes mellitus (DM), and kidney failure. (Dessie, 2021; Rahmani, 2021) In China, COVID-19 subjects with hypertension and diabetes have an increased risk of ARDS and death. (Wu, 2020) However, in Italy, there is evidence that hypertension, as well as COPD and diabetes also were associated with mortality. (Grasselli, 2020)

Studies have shown COVID-19 patients require extended periods of mechanical ventilation. (Angel, 2020) Numerous studies have highlighted the adverse outcomes associated with mechanical ventilation in the COVID-19 population, including increased mortality (Butler, 2023; Silva, 2022) and elevated hospital readmission rates. (Butler, 2023) Subjects with more than two comorbid conditions are at an increased risk of mechanical ventilation and death. (van Gerwen, 2021) The compliance of a patient's respiratory system during intubation is linked to ICU outcomes and tends to decrease after initiation of mechanical ventilation. (Li Bassi, 2021) The necessity for mechanical ventilation arises in cases of severe respiratory failure caused by COVID-19. (Moretti, 2021; Robba, 2020) Certain demographic factors, such as being male, (Mughal, 2020; Osawa, 2022; Regina, 2020) older, obesity, (Monteiro, 2020; Mughal, 2020; Osawa, 2022) or having chronic diseases like coronary artery disease or diabetes, (Mughal, 2020) increase the likelihood of requiring mechanical ventilation. CDC data from the first wave of the pandemic in the US reported in Figures 1.6 and 1.7 present the percentage of people with COVID-19 who were admitted to the ICU with and without underlining conditions, by age group and gender, respectively. Patients admitted to the ICU were older, more likely to be male, and present with comorbid conditions.

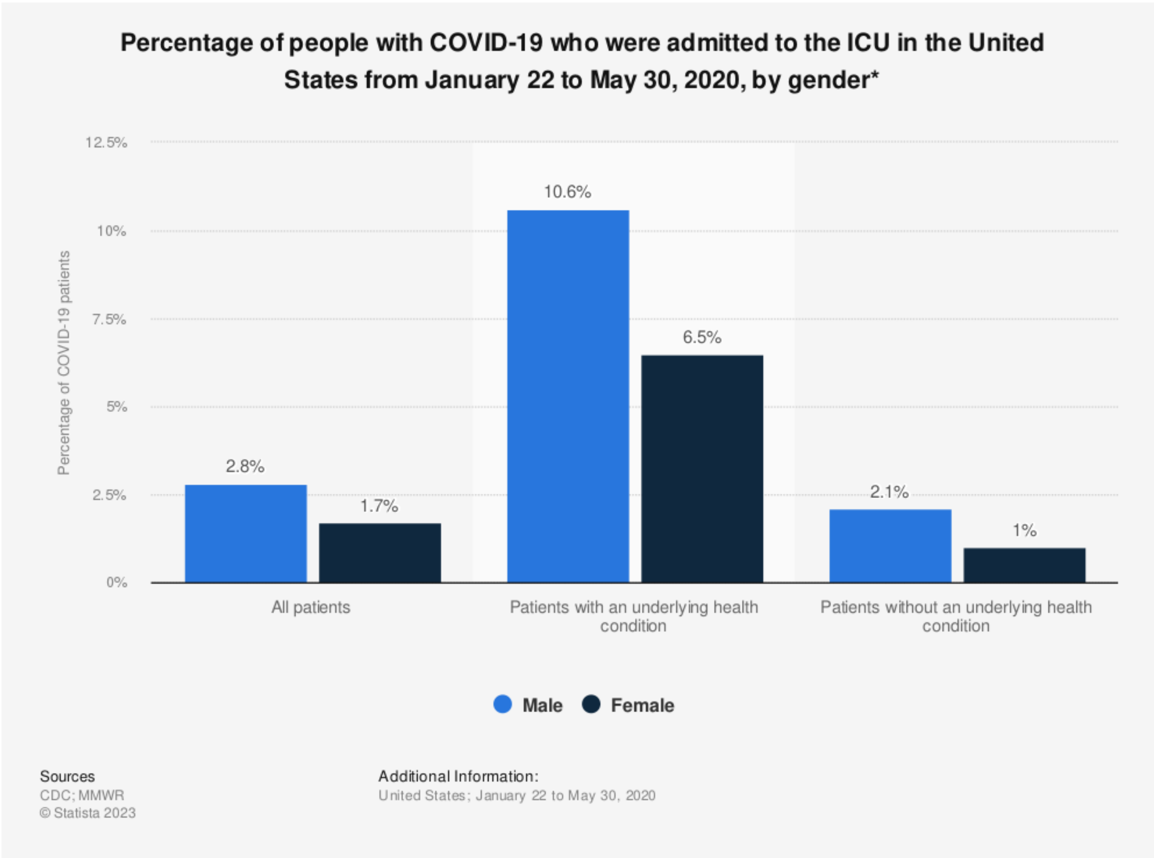
FIGURE 1.6 COVID-19 SUBJECTS ADMITTED INTO THE ICU BY PRE-EXISTING CONDITIONS AND AGE GROUP



Source: **CDC, 2020**

* Based on 1,320,488 laboratory-confirmed COVID-19 cases individually reported to CDC during January 22–May 30, 2020. Hospitalization status was known for 600,860 (46%). Among 184,673 hospitalized patients, the presence of underlying health conditions was known for 96,884 (53%). Includes reported ICU admissions.

FIGURE 1.7 COVID-19 SUBJECTS ADMITTED INTO THE ICU BY GENDER



Source: **CDC, 2020**

* Based on 1,320,488 laboratory-confirmed COVID-19 cases individually reported to CDC during January 22–May 30, 2020. Hospitalization status was known for 600,860 (46%). Among 184,673 hospitalized patients, the presence of underlying health conditions was known for 96,884 (53%). Includes reported ICU admissions.

In a retrospective study by Nada et al., which examined subjects succumbing to COVID-19 infection, 85% of deaths were directly attributed to COVID-19, and 62% of those patients who died required mechanical ventilation. (Nada, 2021) Age, BMI, and low PF ratios are considered significant risk factors for mortality in critically ill, mechanically ventilated COVID-19 patients. (Osawa, 2022) The odds of mortality are higher for COVID-19 patients who require mechanical ventilation, particularly if they are older, (Hirayama, 2021; King, 2020) male, and have preexisting comorbid conditions. (Grasselli, 2020; Patel, 2020) Mortality rates for COVID-19 patients requiring mechanical ventilation range from 50% to 80%. (Arentz, 2020; Bhatraju, 2020; Tu, 2021) Studies consistently show that older age (Krause, 2021; King, 2020) and male gender increase the mortality risk for mechanically ventilated COVID-19 patients. (Hirayama, 2021; van Gerwen, 2021)

Differences in respiratory mechanics and gas exchange have been associated with early mortality in COVID-19 patients compared to those successfully extubated from mechanical ventilation. (Schenck, 2020) Liberation from mechanical ventilation is less likely in COVID-19 patients with increasing age and low C_{RS}. (Gamberini, 2020) Prolonged ICU hospitalization and decreased lung compliance may also contribute to ventilator-associated bacterial pneumonia in mechanically ventilated COVID-19 patients, ultimately leading to mortality. (Moretti, 2021)

PHARMACOLOGICAL INTERVENTIONS FOR COVID-19

Remdesivir, initially studied as a potential treatment during the 2014 Ebola outbreak, is a type of medicine that interferes with viral replication and is changed into an active form inside the body. (Eastman, 2020) Early remdesivir treatment in COVID-19 patients who were not hospitalized can prevent hospitalization and mortality. (Gottlieb, 2022) The literature shows that remdesivir treatments can decrease the length of stay of hospitalized COVID-19 subjects. (Beigel, 2020) Of COVID-19 patients who are not mechanically ventilated, multiple studies shows that remdesivir has the capability to reduce mortality rates (Amstutz, 2023; Lee, 2022; WHO, 2022) and prevent mechanical ventilation. (WHO, 2022) Granted, the literature shows that remdesivir is not clinically beneficial once a COVID-19 subject has been placed on mechanical ventilation. (WHO, 2022) Wang et al. further state that remdesivir does show promising results in clinical improvement of subjects with severe COVID-19 compared to a placebo, although not statistically significant. (Wang, 2020)

Dexamethasone is an anti-inflammatory glucocorticoid frequently used to manage chronic inflammatory conditions and severe allergies. (Ghosh, 2009) There are conflicted results in the literature regarding dexamethasone and COVID-19. While some studies show that dexamethasone reduces mortality rates (Águas, 2021; Horby, 2021; Noreen, 2021) in hospitalized COVID-19 subjects whether they were mechanically ventilated or on supplemental oxygen. (Horby, 2021) Gragueb-Chatti et al. suggest that dexamethasone may have a positive impact on reducing ICU stay and days on the ventilator of mechanically ventilated COVID-19 subjects. (Gragueb-Chatti, 2021) Other studies state that dexamethasone had no impact on survival of COVID-19 subjects in the ICU, nor diminish risk of being mechanically ventilated for those requiring supplemental oxygen. (Bouadma, 2022)

LONG COVID

The term Long COVID, also known as post-acute sequelae of COVID-19 (PASC), has been adopted to represent the population of people infected with COVID-19, experiencing long-term effects. (Thaweethai, 2023) Long COVID has been associated with various clinical manifestations that may create lasting morbidity. (Chippa, 2023; Niyatiwatchanchai, 2022) Subjects recovering from COVID-19 present with a wide range of persistent symptoms up to 12 weeks after hospitalization. (Leth, 2021; Singh, 2023)

Age, (Cabrera Martimbianco, 2021; Notarte, 2022) sex, (Cabrera Martimbianco, 2021; Maglietta, 2022; Munblit, 2021; Notarte, 2022; Paradowska-Nowakowska, 2023) multimorbidity, (Cabrera Martimbianco, 2021; Notarte, 2022) disease severity and hospitalization are reported to be potential risk factors of Long COVID. (Cabrera Martimbianco, 2021; Maglietta, 2022) Maglietta et al., also reports mental health symptoms to be associated with higher risks of Long COVID. (Maglietta, 2022)

After being discharged from the hospital, many survivors continue to experience muscle weakness, sleep difficulties, and anxiety or depression. (Almeida, 2022) Some severe COVID-19 patients continue to have impaired respiratory function, functional capacity, quality of life (QoL) and fatigue 6 months after ICU discharge. (Sirayder, 2022) Han et al. report physical, cognitive and mental health symptoms persist at least a year after recovery in a large proportion of COVID-19 survivors. (Han, 2022)

Literature shows that symptoms also continue to persist even after mild COVID-19 infection in a substantial number of patients. (van Kessel, 2022) A proportion of non-hospitalized COVID-19 patients present with impaired health-related quality of life, cognitive and psychological function, and pulmonary and physical function at long-term follow-up. (Del Corral, 2024) The literature reports Long COVID to be associated with poor QoL, with particular persistent symptoms including fatigue, dyspnea, sleep disturbances and mental health issues. (Malik, 2022)

Long COVID has been significantly associated with increased depression, anxiety, and post-traumatic stress disorder (PTSD). (Bonazza, 2022; Goodman, 2023) Studies show a high prevalence of clinically significant psychological distress exist of COVID-19 survivors and the need for long-term follow-up psychiatric assessment should be highlighted. (Imran, 2021) COVID-19 subjects have consistently reported mental health symptoms, such as, PTSD, anxiety and depression, up to 6 months after COVID-19 diagnosis. (Houben-Wilke, 2022) Mazza et al. reveals that psychological stressors, specifically, post-traumatic stress disorder (PTSD), insomnia, and anxiety decreases over time. (Mazza, 2021) Other literature show that symptoms of anxiety, depression and poor sleep quality actually recover slowly over the 5 years following COVID-19 hospitalization for survivors. (Fernández-de-las-Peñas, 2022)

A study of more than 300 hospitalized subjects in the United Kingdom (UK) reports breathlessness, lower scores in QoL measures, and worsened mobility months after hospital discharge. (Sigfrid, 2021) Multiple other studies suggest that previously hospitalized COVID-19 subjects may present with reduced pulmonary function and continued breathlessness. (Mumoli, 2021; Nalbandian, 2021) A systematic review reports a potential risk for residual lung injury and long-term respiratory sequela in survivors of COVID-19, including decreased respiratory muscle strength and pulmonary function. (Akbarialiabad, 2021) Several studies examining pulmonary function of ICU hospitalized COVID-19 subjects found a decrease in pulmonary function months after discharge, (Bellan, 202; Blanco, 2021; Compagnone, 2022; Huang, 2020) and pulmonary symptoms are a target for long-term recovery interventions. (George, 2020)

DYSPNEA, PULMONARY FUNCTION AND LONG COVID

A systematic review including more than 5,000 participants with Long COVID, suggests that dyspnea was one of the most reported clinical conditions associated with Long COVID. (Cabrera Martimbianco, 2021) Dyspnea is a prominent symptom and cause of disability in subjects with pulmonary disease, including Long COVID-19. (Demir, 2003; Singh, 2023) Although most hospitalized COVID-19 patients recover, a substantial proportion continue to experience fatigue and dyspnea, (Froidure, 2021) which plays an intricate role and is related to decreased QoL measures in other disease conditions, such as COPD and idiopathic pulmonary fibrosis (IPF). (Jacobsen, 2012; Martinez, 2000; Okutan, 2013) Some COVID-19 patients continue to experience these dyspneic symptoms up to 6 months after hospital discharge, suggesting persistent lung abnormalities and diffusion capacity alterations. (Fortini, 2021)

Although some evidence suggests that dyspnea following COVID-19 is not related cardiopulmonary impairment and pulmonary function parameters remain normal. (Beaudry, 2022) Impaired pulmonary function persisting a year after hospital discharge was reported in a single-center ICU study in Belgium, a Chinese study of severe but non-mechanically ventilated COVID-19 subjects, as well as in a meta-analysis. (Torres-Castro, 2021; Truffaut, 2021; Wu, 2021)

Valid measures of dyspnea and physical function exist, with two of the most common being The University of California – San Diego Shortness of Breath Questionnaire (UCSD) and the 6-minute walking distance (6MWD), respectively. (Blanco, 2010; Kupferberg, 2005) Studies show that 6MWD largely depends on the degree of restrictive disease in other pulmonary-diseased populations. (Porteous, 2016) Current evidence-based interventions for dyspnea include cognitive-behavioral strategies, such as yoga and slow-breathing exercises, may help relieve dyspnea and related distress in COPD patients. (Norweg, 2013)

PHYSICAL FUNCTION AND LONG COVID

Long COVID patients face challenges in managing physical activity and coping with their continuing symptoms, highlighting the need for tailored advice and support to resume activities important to their well-being. (Humphreys, 2020) Although, pulmonary function and symptoms have been shown to improve over time, impairments in physical function continue to persist for months in some cases. (Erber, 2021) Huang et al. examined physical function of 57

COVID-19 subjects with non-severe and severe COVID-19 and reported decreases in 6MWD. (Huang, 2020)

Gautam et al. performed a multicenter UK study of COVID-19 survivors with comorbid conditions and abnormal pulmonary function, and these subjects were more likely to experience breathlessness and a reduced QoL for months. (Gautam, 2022) Critically ill survivors in an Italian study continued to experience persistent symptoms of decreased physical function. (Latronico, 2022) A more recent descriptive study of death certificate data in the US, indicated Long COVID-19 as an underlying or contributing cause of death. (Ahmad, 2022)

Anxiety and Depression

Uzunova et al. reveals that long-term follow up for at least one month after COVID-19 should be required to assess for anxiety. (Uzunova, 2021) Survivors of COVID-19 have shown persistent depression symptoms three months after being discharged from the hospital. (Mazza, 2022) Depression has been significantly associated with complications of COVID-19 infection. (Bucciarelli, 2022) Long COVID subjects with depression and those of female sex are particularity more likely to experience fatigue and dyspnea. (Paradowska-Nowakowska, 2023) Literature shows that depression is associated with delaying recovery following COVID-19 infection, impacting physical recovery. (Liyanage-Don, 2021)

Post-Traumatic Stress Disorder

Being admitted to the ICU is shown to be a potential predictor of PTSD within the COVID-19 population. (Horn, 2020) Literature shows that PTSD is associated with delaying recovery following COVID-19 infection, impacting physical recovery. (Liyanage-Don, 2021)

Being female and of lower socioeconomic status are shown to be potential predictors of PTSD during the COVID-19 pandemic. (Di Crosta, 2020) COVID-19 survivors with PTSD are more likely to experience persistent respiratory symptoms, insomnia, anxiety and decreased quality of life up to 6-months after being discharged. (Huang, 2021) A study in China reports that rates of PTSD in COVID-19 patients increase with age and poor health, although subjects older than 60 were less likely to be impacted. (Shen, 2021)

PULMONARY REHABILITATION

Exercise training is a potential intervention to improve exercise capacity in COVID-19 survivors, (Dun, 2021; Jimeno-Almazán, 2023) and may help combat the respiratory and functional sequelae of the disease. Pulmonary rehabilitation is a well-established intervention that includes respiratory muscle training, self-management education, exercise training, and breathing techniques (Dun, 2021; Holland, 2021) that improve lung function, exercise capacity, and QoL in other pulmonary-diseased populations, such as COPD, (McCarthy, 2015; Reis, 2013) and sarcoidosis. (Wallaert, 2020)

Some literature supports the use of pulmonary rehabilitation (PR) in Long COVID subjects. (Akbarialiabad, 2021) However, limited studies have examined the effect of PR on pulmonary capacity in the Long COVID-19 population.

Evidence suggests that PR should be considered in reducing prolonged disability in survivors of COVID-19. (Besnier, 2022; Wang, 2020) There are reports that PR has potential benefits beyond just reducing respiratory symptoms. (Gloeckl, 2021) Improvement in respiratory function, exercise endurance, self-care in daily activities and psychological support have been shown in COVID-19 patients who participate in PR. (Li, 2020) Other reports show PR does improve respiratory function, reducing fatigue and dyspnea, but does not improve depression or anxiety. (Kołodziej, 2021)

Multidisciplinary rehabilitation programs, including physical training (aerobic, resistance, and breathing exercises), education, and group psychotherapy have also shown to improve body composition, dyspnea, fatigue and physical capacity in the Long COVID population. (Ostrowska, 2023) Studies show that although completing just two weeks of PR, showed improvement in daily activity participation and QoL, longer PR programs may be more beneficial. (Postolache, 2023) A single-center study in Austria completing six weeks of PR improved Long COVID subject's dyspnea, fatigue, exercise capacity, functional status, and QoL. (Nopp, 2022)

Reports show that PR is safe, feasible, and effective for COVID-19 survivors, (Hermann, 2020; Santus, 2013; Zampogna, 2021) as well as potentially accelerating their recovery in 6MWD and pulmonary function values. (Zhu, 2021) PR is beneficial in the short and long term (Ochmann, 2012) for subjects with pulmonary disease (Holland, 2013; van Ranst, 2011) regardless of their sociodemographic condition. (Trappenburg, 2005) Although PR improves independence in subjects by decreasing dyspnea, reducing hospital utilization, (Nici, 2011; Raskin, 2006) and enhancing their overall QoL, (Postolache, 2013; Santus, 2013) PR is still relatively underutilized compared to other rehabilitation interventions. (Holland, 2013; Sundh, 2017)

SUMMARY

Gaps in comprehensive understanding of the complete nature of COVID-19 and Long COVID persist, hindering effective clinical practices and public health decision-making within these populations. The National Institutes of Health (NIH) states that more work is needed to understand and diminish disparities in advanced pulmonary care. (NIH, 2023)

The overall objective of this study proposal is to (1) determine whether respiratory mechanics, oxygenation impairment, social demographics, and multimorbidity of mechanically ventilated COVID-19 subjects are associated with survival; (2) determine the factors associated with physical function after completing six weeks of pulmonary rehabilitation (PR) of COVID-19 subjects with persisting pulmonary symptoms; and (3) investigate the impact of socioeconomic disparities on participation in pulmonary rehabilitation and morbidity of the Long COVID population.

CHAPTER 2

The Effect of Oxygenation Impairment and Compliance on Survival of Subjects with COVID-19 Requiring Mechanical Ventilation[1]

Specific Aim 1

To determine whether respiratory mechanics, oxygenation impairment, social demographics, and comorbid conditions are associated with survival of mechanically ventilated subjects with COVID-19 infection.

Hypothesis 1a. Mechanically ventilated COVID-19 subjects with lower respiratory compliance and/or higher airway resistance will have lower odds of survival than mechanically ventilated COVID-19 subjects with higher respiratory compliance and/or lower airway resistance.

Hypothesis 1b. Mechanically ventilated COVID-19 subjects with severe oxygenation impairment will have lower odds of survival than mechanically ventilated COVID-19 subjects without any oxygenation impairment.

Hypothesis 1c. Mechanically ventilated COVID-19 subjects who are younger, female sex, non-Hispanic White, use dexamethasone and/or remdesivir, or without multimorbidity will have higher odds of survival than mechanically ventilated COVID-19 subjects who are older, male sex, Hispanic or non-Hispanic Black, without use of dexamethasone and/or remdesivir, or with multimorbidity.

[1] Micheals, K., Lee, M. J., Al Snih, S., Walsh, B. K., & Rojas, J. D. (2023). The Effect of Oxygenation Impairment and Compliance on Mortality Among Subjects With COVID-19 Requiring Mechanical Ventilation. *Respir Care*, *68*(11), 1565-1568. https://doi.org/10.4187/respcare.10776

METHODS

Data Source

This scientific research used data from the electronic health record (EHR) from our academic care facility from the University of Texas Medical Branch (UTMB) in Galveston, Texas. In pulmonary diseased population, such as asthma, data derived from the EHR can be leveraged to improve clinical practice by facilitating studies and interventions. (Edwards, 2008; Greenblatt, 2019; Landeo-Gutierrez, 2023) Studies show that EHR data can be used as an element to develop best medical practice because of its capabilities (Ghazisaeedi, 2014) Epic Systems Corporation (EPIC) includes computerized provider order entry, electronic prescribing, integrated documentation, test result tracking, and active medication and problem lists, classifying it as a complete system by the Office of the National Coordinator. (Makam, 2014) In the US, EPIC continuously ranks as the largest EHR, accounting for more than a third of the market. (Definitive Healthcare, 2022)

Measures

Outcome Variable

SURVIVAL

Survival was dichotomized into (1) survived, if the subject was discharged alive or (2) deceased, if the subject died during hospitalization.

Independent Variables

Oxygenation Impairment

Oxygenation impairment was assessed and categorized by PaO2/FiO2 (PF ratio). Categories were: (1) Subjects with PF ratios of more than 300 were considered not impaired, (2) subjects with PF ratios between 200-300 were considered mildly impaired (3) PF ratios between 100-200 were considered moderately impaired, and (4) PF ratios less than 100 were considered severely impaired.

Pulmonary Static Compliance

Static compliance (C_{STAT}) was calculated as {tidal volume (V_T) / [plateau pressure (P_{PLAT}) – positive end-expiratory pressure (PEEP)]} (Desai, 2022; Hess, 2014) C_{STAT} is the compliance at a given fixed volume when there is no airflow, and muscles are relaxed. (Desai, 2022) It is determined by the compliance in the lungs and chest wall with normal ranges for patients receiving mechanical ventilation being 50-100 mL/cmH2O. (Hess, 2014) We will compute C_{STAT} using the initial measured V_T, airway P_{PLAT} and PEEP values, within 48 h of mechanical ventilation commencement for the first 5 days after being intubated. C_{STAT} has long been accepted as a prognostic factor in subjects with respiratory failure and provides insight on pulmonary diseases. (Mancebo, 1988; Desai, 2022) Evidence notes that dynamic compliance (C_{DYN}) and C_{STAT} reflect different clinical implications, although they show linear correlation. (Durack, 2021; Lucangelo, 2005; Marini, 2021; Popow, 1988)

Pulmonary Dynamic Compliance

Dynamic compliance (C_{DYN}) was calculated as [tidal volume (V_T) / (peak inspiratory pressure – PEEP)]. (Aşar, 2021; Lucangelo, 2005; Zingg, 2022) C_{DYN} is a continuous measurement of lung compliance calculated at each time point representing changes made during rhythmic breathing. (Desai, 2022) C_{DYN} can give insight on alveolar collapse. (Hanson, 2009; Suarez-Sipmann, 2007)

Airway Resistance

Airway resistance (R_{AW}) was calculated as the difference between C_{STAT} and C_{DYN} which is attributed to airway resistance (R_{AW}). (Kock, 2018) In mechanically ventilated subjects, R_{AW} should be less than 10 cmH2O/L/sec to be acceptable. (Hess, 2014) R_{AW} is the resistance to flow imposed by the airways and resistance to tissue deformation due to the viscoelastic forces within the lungs, mediastinum and chest wall. (Henderson, 2012) Measurement of the resistance of the respiratory system can clarify the cause and severity of disease. (Henderson, 2012)

Covariates

Socio-demographics

Socio-demographics included age (total age in years), sex assigned at birth (male or female), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic/Latino, or Other).

Comorbid Conditions

Comorbid conditions included were asthma, history of stroke, diabetes, hypertension, liver disease, coronary artery disease (CAD), congestive heart failure, COPD, obesity, end-stage renal disease (ESRD), chronic kidney disease (CKD), and history of cancer based on prior literature.

Comorbid conditions were further examined as **multimorbidity** and dichotomized into (1) having less than two comorbid conditions or (2) multimorbidity, when a subject had two or more comorbid conditions.

Medication Usage

Medication use was categorized into (1) none (2) use of dexamethasone, (3) use of remdesivir, or (4) use of both, dexamethasone and remdesivir.

Statistical Analysis

Statistical Methods: Descriptive statistics of the sample were performed. Generalized estimating equation (GEE) regression models with a binomial distribution was performed to estimate the odds ratio (OR) and 95 % Confidence Interval (CI) of factors associated with survival. GEE accounts for the effects of the repeated measures on our analysis. The GEE is an extension of traditional linear models and uses generalized linear models to model longitudinal data by estimating population average regression coefficients as a function of covariates. (Friedel, 2019) This approach explains correlation in clustered data since each patient can have multiple observations and missing values. The model estimation excludes missing value observations. Models will fit for survival with yes or no as the outcome.

RESULTS

We hypothesized that mechanically ventilated COVID-19 subjects with lower respiratory compliance and/or higher airway resistance would have lower odds of survival than mechanically ventilated COVID-19 subjects with higher respiratory compliance and/or lower airway resistance. We also hypothesized that mechanically ventilated COVID-19 subjects with severe oxygenation impairment would have lower odds of survival than mechanically ventilated COVID-19 subjects without any oxygenation impairment. Lastly, we hypothesized that mechanically ventilated COVID-19 subjects who are younger, female sex, non-Hispanic White, with dexamethasone and/or remdesivir use, or without multimorbidity would have higher odds of survival than mechanically ventilated COVID-19 subjects who are older, male sex, Hispanic or non-Hispanic Black, without dexamethasone and/or remdesivir use, or with multimorbidity.

ANALYSES FOR OVERALL SAMPLE

Four hundred fifteen subjects met our criterion and were included in the study. Descriptive characteristics of the overall sample are provided in (Tables 2.1 and 2.2A and 2.2B). There were 250 (60%) males and 165 (40%) females. The overall average age was 59 ± 14 years old. Most of the population 252 (60.7%) did not survive, while 163 (39%) did survive. The majority of the subjects were Hispanic/Latino 175 (42%), followed by Non-Hispanic White 163 (39%), Non-Hispanic Black 56 (13%), and Other races/ethnicities 21 (5%). Most of the subjects 238 (57%) subjects had less than two comorbid conditions, whereas 177 (43%) had multimorbidity. More than a third 148 (36%) of the subjects did not take dexamethasone and/or remdesivir, while 128 (31%) took dexamethasone, 30 (7%) took remdesivir and 109 (27%) took both, dexamethasone and remdesivir. The average C_{DYN} was 26 ± 13 ml/cmH20 and the average C_{STAT} was 37 ± 48 ml/cmH2O. On average, PF ratios were 117 ± 74 mmHg and R_{AW} was 13 ± 42 cmH2O/L/sec. More than half of the subjects had severe oxygenation impairment 149 (51%), while 115 (40%) had moderate oxygenation impairment, 17 (6%) had mild oxygenation impairment and 8 (3%) did not have oxygenation impairment.

TABLE 2.1A DESCRIPTIVE BASELINE CHARACTERISTICS FOR CONTINUOUS VARIABLES OF MECHANICALLY VENTILATED COVID-19 SUBJECTS (N=415).[1]

Variable	n	(% miss)	mean ± SD	median (IQR)
Age in years	415	0.0%	59 ± 14	60 (50-69)
Dynamic compliance ml/cmH2O	415	0.8%	26 ± 13	24 (19-31)
Static compliance ml/cmH2O	415	17.0%	37 ± 48	27 (20-36)
PaO2/FiO2 mmHg	415	30.2%	117 ± 74	98 (72-136)
Airway resistance ml/cmH2O	415	17%	13 ± 42	4 (2-8)

[1] Micheals, K., Lee, M. J., Al Snih, S., Walsh, B. K., & Rojas, J. D. (2023). The Effect of Oxygenation Impairment and Compliance on Mortality Among Subjects With COVID-19 Requiring Mechanical Ventilation. *Respir Care*, *68*(11), 1565-1568. https://doi.org/10.4187/respcare.10776

TABLE 2.2A DESCRIPTIVE BASELINE CHARACTERISTICS FOR CATEGORICAL VARIABLES OF MECHANICALLY VENTILATED COVID-19 SUBJECTS (N=415).[1]

Variable	(% missing)	n (%)
Sex	0 (0.0)	
Female		165 (39.8)
Male		250 (60.2)
Survival	0 (0.0)	
No		252 (60.7)
Yes		163 (39.3)
Race and ethnicity	0 (0.0)	
Non-Hispanic White		163 (39.3)
Hispanic or Latino		175 (42.2)
Non-Hispanic Black		56 (13.5)
Other		21 (5.1)
Medication	0 (0.0)	
None		147 (35.7)
Dexamethasone		128 (30.7)
Remdesivir		29 (7.1)
Both		109 (26.5)
Oxygenation Impairment	30.2%	
None		8 (3.0)
Mild		17 (5.9)
Moderate		115 (39.8)
Severe		149 (51.3)

[1] Micheals, K., Lee, M. J., Al Snih, S., Walsh, B. K., & Rojas, J. D. (2023). The Effect of Oxygenation Impairment and Compliance on Mortality Among Subjects With COVID-19 Requiring Mechanical Ventilation. *Respir Care*, *68*(11), 1565-1568. https://doi.org/10.4187/respcare.10776

TABLE 2.2B DESCRIPTIVE BASELINE CHARACTERISTICS FOR COMORBID CONDITIONS OF MECHANICALLY VENTILATED COVID-19 SUBJECTS (N=415).

Variable	Missing (%)	n (%)
Asthma	0 (0.0)	
No		404 (97.3)
Yes		11 (2.7)
Stroke	0 (0.0)	
No		390 (94.0)
Yes		25 (6.0)
Liver Disease	0 (0.0)	
No		400 (96.4)
Yes		15 (3.6)
Diabetes	0 (0.0)	
No		314 (75.7)
Yes		101 (24.3)
Hypertension	0 (0.0)	
No		284 (68.4)
Yes		131 (31.6)
Coronary Artery Disease	0 (0.0)	
No		378 (91.1)
Yes		37 (8.9)
Congestive Heart Failure	0 (0.0)	
No		386 (93.0)
Yes		29 (7.0)
Chronic Obstructive Pulmonary Disease	0 (0.0)	
No		406 (97.8)
Yes		9 (2.2)
Obesity	0 (0.0)	
No		167 (40.2)
Yes		248 (59.8)
End-Stage Renal Disease	0 (0.0)	
No		398 (95.9)
Yes		17 (4.1)
Chronic Kidney Disease	0 (0.0)	
No		374 (90.1)
Yes		41 (9.9)
Cancer	0 (0.0)	
No		384 (92.5)
Yes		31 (7.5)
Multimorbidity	0 (0.0)	
Less than comorbid conditions		238 (57.3)
Multimorbid		177 (42.7)

ANALYSES FOR SURVIVAL

Tables 2.3A illustrates the descriptive baseline characteristics of the mechanically ventilated COVID-19 sample by survival. The majority 61% (252) of the subjects did not survive, and 163 (39%) survived during their hospital stay. Subjects who survived were significantly younger (56 ± 15 years) than those who did not survive (62 ± 13 years). Regarding sex, 37.2% of males survived (93/250), compared to 42.4% of the females (70/165), showing a statistically significant difference ($p = 0.02$).

In terms of race and ethnicity 41.1% (67) non-Hispanic White subjects, 30.8% (54) Hispanic or Latino subjects, 57.1% (32) non-Hispanic Black subjects, and 47.6% (10) subjects from other races survived, with significant differences of the groups ($p < 0.001$). Dexamethasone and/or remdesivir use was also associated with survival, as 38.8% (57/147) subjects not on dexamethasone or remdesivir, 32.0% (41/128) of the subjects on dexamethasone, 37.9% (11/29) subjects on remdesivir, and 48.6% (53/109) of the subjects on both dexamethasone and remdesivir survived, with significant differences noted ($p < 0.001$).

Additionally, the mean C_{DYN} was 28 ± 14 ml/cmH2O for survivors and 26 ± 12 ml/cmH2O for non-survivors, with a significant difference ($p < 0.001$). However, there was no significant difference in C_{STAT} between survivors (37 ± 36 ml/cmH2O) and non-survivors (37 ± 54 ml/cmH2O; $p = 0.78$). The PF ratio was significantly higher of survivors (143 ± 95 mm Hg) compared to non-survivors (103 ± 53 mm Hg; $p < 0.001$). There was no significant difference in R_{AW} between survivors (12 ± 29 cm/H2O/L/sec) and non-survivors (14 ± 49 cm/H2O/L/sec; $p = 0.13$).

Regarding multimorbidity, 33.6% (80/238) of the subjects with less than two comorbidities survived, while 46.9% (83/177) of the subjects with two or more comorbidities survived, showing a significant difference ($p < 0.001$).

Tables 2.3B presents the descriptive baseline comorbid conditions of the mechanically ventilated COVID-19 sample by survival. Patients with asthma had significantly lower survival rates compared to those without asthma ($p < 0.001$), as did stroke patients ($p < 0.001$). Liver disease did not significantly impact survival ($p = 0.90$). Diabetes was associated with lower survival rates ($p = 0.02$), as was hypertension ($p < 0.001$). While CAD did not significantly affect survival ($p = 0.71$), CHF was linked to significantly lower survival rates ($p < 0.001$). COPD showed a strong association with lower survival rates ($p < 0.001$). Obesity did not significantly impact survival ($p = 0.47$). ESRD was associated with significantly lower survival rates ($p = 0.01$), while CKD did not significantly affect survival ($p = 0.15$). There was a trend towards lower survival among patients with Cancer, although this did not reach statistical significance ($p = 0.06$).

These results highlight the importance of managing comorbidities such as Asthma, Stroke, Diabetes, Hypertension, CHF, COPD, ESRD, and potentially Cancer to improve survival outcomes in this population.

TABLE 2.3A DESCRIPTIVE BASELINE CHARACTERISTICS BY SURVIVAL OF MECHANICALLY VENTILATED COVID-19 SUBJECTS (N=415).[1]

Characteristics		Survival n (%)		p-value
		Yes	**No**	
Total	415	163 (39.3)	252 (60.7)	
Age in years (mean ± SD)	415	56 ± 15	62 ± 13	**<0.001**
Sex				**0.02**
Male	250	93 (37.2)	157 (62.8)	
Female	165	70 (42.4)	95 (57.5)	
Race and Ethnicity				**<0.001**
Non-Hispanic White	163	67 (41.1)	96 (58.9)	
Hispanic or Latino	175	54 (30.8)	121 (69.1)	
Non-Hispanic Black	56	32 (57.1)	24 (42.9)	
Other	21	10 (47.6)	11 (52.4)	
Medication				**<0.001**
None	147	57 (38.8)	90 (61.2)	
Dexamethasone	128	41 (32.0)	87 (68.0)	
Remdesivir	29	11 (37.9)	18 (62.1)	
Both	109	53 (48.6)	56 (51.4)	
C_{DYN} (mean ± SD) ml/cmH2O	403	28 ± 14	26 ± 12	**<0.001**
C_{STAT} (mean ± SD) ml/cmH2O	410	37 ± 36	37 ± 54	**0.78**
PF ratio (mean ± SD)	292	143 ± 95	103 ± 53	**<0.001**
R_{AW} (mean ± SD) mm Hg	347	12 ± 29	14 ± 49	**0.13**
Multimorbidity				**<0.001**
< 2 comorbidities	238	80 (33.6)	158 (66.4)	
2 or more comorbidities	177	83 (46.9)	94 (53.1)	
SD – standard deviation; C_{DYN} – Dynamic compliance; C_{STAT} – Static compliance; PF ratio – PaO2/FiO2; R_{AW} – Airway resistance				

[1] Micheals, K., Lee, M. J., Al Snih, S., Walsh, B. K., & Rojas, J. D. (2023). The Effect of Oxygenation Impairment and Compliance on Mortality Among Subjects With COVID-19 Requiring Mechanical Ventilation. *Respir Care*, *68*(11), 1565-1568. https://doi.org/10.4187/respcare.10776

TABLE 2.3B DESCRIPTIVE BASELINE COMORBID CONDITIONS BY SURVIVAL OF MECHANICALLY VENTILATED COVID-19 SUBJECTS (N=415).

Characteristics	Survival		p-value
	Yes	**No**	
Total	163 (39.3)	252 (60.7)	
Asthma			**<0.001**
No	156 (44.4)	195 (55.6)	
Yes	44 (43.6)	57 (56.4)	
Stroke			**<0.001**
No	149 (38.2)	241 (61.8)	
Yes	14 (56.0)	11 (44.0)	
Liver Disease			0.90
No	157 (39.3)	243 (60.7)	
Yes	6 (40.0)	9 (60.0)	
Diabetes			**0.02**
No	119 (37.9)	195 (62.1)	
Yes	44 (43.6)	57 (56.4)	
Hypertension			**<0.001**
No	101 (35.5)	183 (64.5)	
Yes	62 (47.3)	69 (52.7)	
CAD			0.71
No	148 (39.1)	230 (60.9)	
Yes	15 (40.5)	22 (59.5)	
CHF			**<0.001**
No	146 (47.8)	240 (52.2)	
Yes	17 (58.6)	12 (41.4)	
COPD			**<0.001**
No	156 (38.4)	250 (61.6)	
Yes	7 (77.8)	2 (22.2)	
Obesity			0.47
No	54 (34.4)	103 (65.6)	
Yes	99 (39.9)	149 (60.1)	
ESRD			**0.01**
No	154 (38.7)	244 (61.3)	
Yes	9 (52.9)	8 (47.1)	
CKD			0.15
No	145 (38.8)	229 (61.2)	
Yes	18 (43.9)	23 (56.1)	
Cancer			**0.06**
No	153 (39.9)	231 (60.1)	
Yes	10 (32.3)	21 (67.7)	

CAD – coronary artery disease; CHF – congestive heart failure; COPD – chronic obstructive pulmonary disease; ESRD – end-stage renal disease; CKD – chronic kidney disease

Multivariate Analyses For Survival

Table 2.4A presents the results from the multivariate analysis of the mechanically ventilated COVID-19 sample for survival. The multivariate analysis revealed several significant factors associated with survival of the mechanically ventilated COVID-19 population. Older age was associated with lower odds of survival, with each year increase in age corresponding to a 5% decrease in the odds of survival (OR 0.95, 95% CI 0.94-0.96, $p < 0.001$). Males had a 30% lower odds of survival compared to females (OR 0.70, 95% CI 0.52-0.93, $p = 0.01$).

Regarding race and ethnicity, Hispanic subjects had a 43% lower odds of survival (OR 0.57, 95% CI 0.42-0.8, $p < 0.001$) compared to Non-Hispanic Whites. Surprisingly, Non-Hispanic Black subjects had nearly twice the odds of survival (OR 1.91, 95% CI 1.25-2.90, $p = 0.002$) compared to Non-Hispanic Whites.

Dexamethasone and/or remdesivir use was not significantly associated with survival, except for subjects who received both dexamethasone and remdesivir, who had 61% higher odds of survival (OR 1.61, 95% CI 1.15-2.26, $p = 0.005$) compared to those who received no medication.

Shockingly, multimorbidity was associated with 46% higher odds of survival (OR 1.46, 95% CI 1.11-1.93, $p = 0.006$) compared to subjects without multimorbidity. Oxygenation impairment showed a significant association with survival, with subjects having mild, moderate, and severe impairment showing lower odds of survival compared to those with no impairment ($p < 0.05$ for all categories).

Dynamic compliance was positively associated with survival, with a 3% increase in the odds of survival for each unit increase in dynamic compliance (OR 1.03, 95% CI 1.01-1.05, p <

0.001). However, static compliance and airway resistance were not significantly associated with survival.

Table 2.4B present the results from the multivariate analysis examining variables of interest with comorbid conditions individually on survival of mechanically ventilated COVID-19 subjects. The multivariate analysis revealed several significant factors associated with survival of the studied population. Older age was associated with lower odds of survival, with each year increase in age corresponding to a 6% decrease in the odds of survival (OR 0.94, 95% CI 0.93-0.95, $p < 0.001$).

Surprisingly, sex was not significantly associated with survival. (OR 0.79, 95% CI 0.58-1.06, $p = 0.11$). Regarding race and ethnicity, Hispanic subjects had a 44% lower odds of survival (OR 0.56, 95% CI 0.41-0.78, $p < 0.001$) compared to Non-Hispanic Whites. In contrast, Non-Hispanic Black subjects had nearly twice the odds of survival (OR 1.81, 95% CI 1.15-2.85, $p = 0.01$).

Of the medication categories, only the group receiving both dexamethasone and remdesivir had a significantly higher odds of survival (OR 1.66, 95% CI 1.17-2.37, $p = 0.005$) compared to those receiving no medication.

Oxygenation impairment showed a significant association with survival, with subjects having mild, moderate, and severe impairment showing lower odds of survival compared to those with no impairment ($p < 0.05$ for all categories). Dynamic compliance was positively associated with survival, with a 3% increase in the odds of survival for each unit increase in dynamic compliance (OR 1.03, 95% CI 1.01-1.05, $p < 0.001$).

Of the comorbidities, having hypertension (OR 1.55, 95% CI 1.11-2.18, $p = 0.01$), CHF (OR 2.58, 95% CI 1.43-4.66, $p = 0.001$) and COPD (OR 8.87, 95% CI 3.06-25.8, $p < 0.001$)

were significantly associated with survival. Those with cancer (OR 0.55, 95% CI 0.31-0.98, p = 0.04) were significantly associated with lower survival, while asthma, diabetes, stroke, ESRD, obesity showed no significant association with survival.

Figures 2.1, 2.2, 2.3, 2.4, 2.5 and 2.6 illustrate age, sex, race/ethnicity, dexamethasone and/or remdesivir use, oxygenation impairment, and C_{DYN} by survival of mechanically ventilated COVID-19 subjects, respectively.

TABLE 2.4A FACTORS ASSOCIATED WITH SURVIVAL OF MECHANICALLY VENTILATED COVID-19 SUBJECTS (N=415).[1]

Characteristics	Odds Ratio (95% CI)	*p*-value
Age	0.95 (0.94 – 0.96)	**<0.001**
Sex (reference: Female)	0.70 (0.52 – 0.93)	**0.01**
Race/Ethnicity (reference: Non-Hispanic White)		
Hispanic	0.57 (0.42 – 0.80)	**<0.001**
Non-Hispanic Black	1.91 (1.25 – 2.90)	**0.002**
Other	1.02 (0.54 – 1.91)	0.96
Medication Use (reference: None)		
Dexamethasone	0.87 (0.62 – 1.23)	0.43
Remdesivir	0.84 (0.49 – 1.45)	0.53
Both	1.61 (1.15 – 2.26)	**0.005**
Multimorbidity (reference: <2 comorbid conditions)	1.46 (1.11 – 1.93)	**0.006**
Oxygenation Impairment (reference: None)		
Mild	0.34 (0.13 – 0.89)	**0.03**
Moderate	0.25 (0.11 – 0.57)	**<0.001**
Severe	0.09 (0.04 – 0.21)	**<0.001**
Dynamic Compliance	1.03 (1.01 – 1.05)	**<0.001**
Static Compliance	1.00 (0.98 – 1.02)	0.86
Airway Resistance	1.00 (0.98 – 1.02)	0.91

[1] Micheals, K., Lee, M. J., Al Snih, S., Walsh, B. K., & Rojas, J. D. (2023). The Effect of Oxygenation Impairment and Compliance on Mortality Among Subjects With COVID-19 Requiring Mechanical Ventilation. *Respir Care*, *68*(11), 1565-1568. https://doi.org/10.4187/respcare.10776

TABLE 2.4B FACTORS ASSOCIATED WITH SURVIVAL OF MECHANICALLY VENTILATED COVID-19 SUBJECTS BY INDIVIDUAL COMORBID CONDITIONS (N=415).

Characteristics	Odds Ratio (95% CI)	p-value
Age	0.94 (0.93 – 0.95)	< **0.001**
Sex (reference: Female)	0.79 (0.58 – 1.06)	0.11
Race/Ethnicity (reference: Non-Hispanic		
Hispanic	0.56 (0.41 – 0.78)	< **0.001**
Non-Hispanic Black	1.81 (1.15 – 2.85)	**0.01**
Other	1.02 (0.55 – 2.04)	0.86
Medication Use (reference: None)		
Dexamethasone	0.86 (0.60 – 1.22)	0.39
Remdesivir	0.75 (0.42 – 1.33)	0.33
Both	1.66 (1.17 – 2.37)	**0.005**
Oxygenation Impairment (reference:		
Mild	0.37 (0.14 – 0.97)	**0.04**
Moderate	0.28 (0.12 – 0.64)	**0.003**
Severe	0.10 (0.04 - 0.23)	< **0.001**
Dynamic Compliance	1.03 (1.01 – 1.05)	< **0.001**
Static Compliance	0.99 (0.98 – 1.01)	0.63
Airway Resistance	1.00 (0.98 – 1.02)	0.92
Asthma	1.75 (0.69 – 4.46)	0.23
Diabetes	0.97 (0.68 – 1.39)	0.86
Stoke	1.18 (0.56 – 2.45)	0.66
Hypertension	1.55 (1.11 – 2.18)	**0.01**
CHF	2.58 (1.43 – 4.66)	**0.001**
COPD	8.87 3.06 – 25.8)	< **0.001**
ESRD	0.54 (0.25 – 1.19)	0.12
Obesity	0.72 (0.51 – 1.01)	0.06
Cancer	0.55 (0.31 – 0.98)	**0.04**

FIGURE 2.1 AGE BY SURVIVAL OF MECHANICALLY VENTILATED COVID-19 SUBJECTS

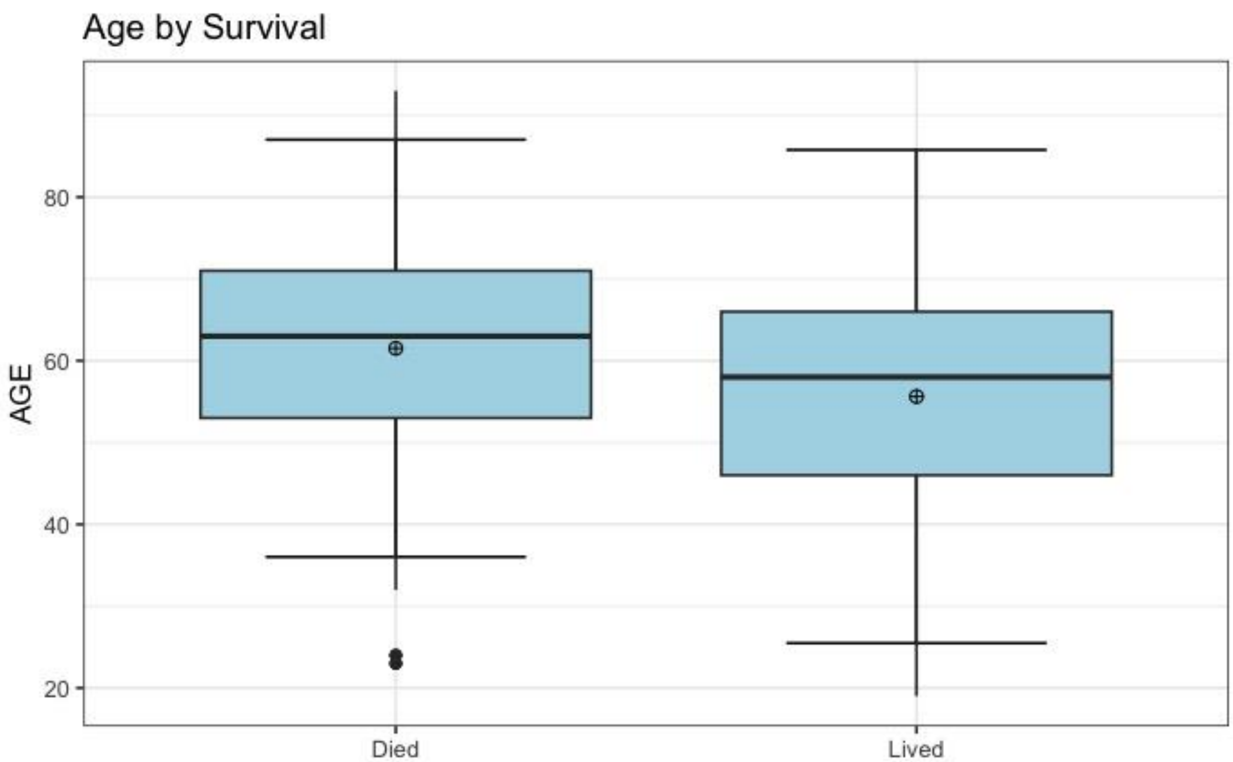


FIGURE 2.2 SEX BY SURVIVAL OF MECHANICALLY VENTILATED COVID-19 SUBJECTS

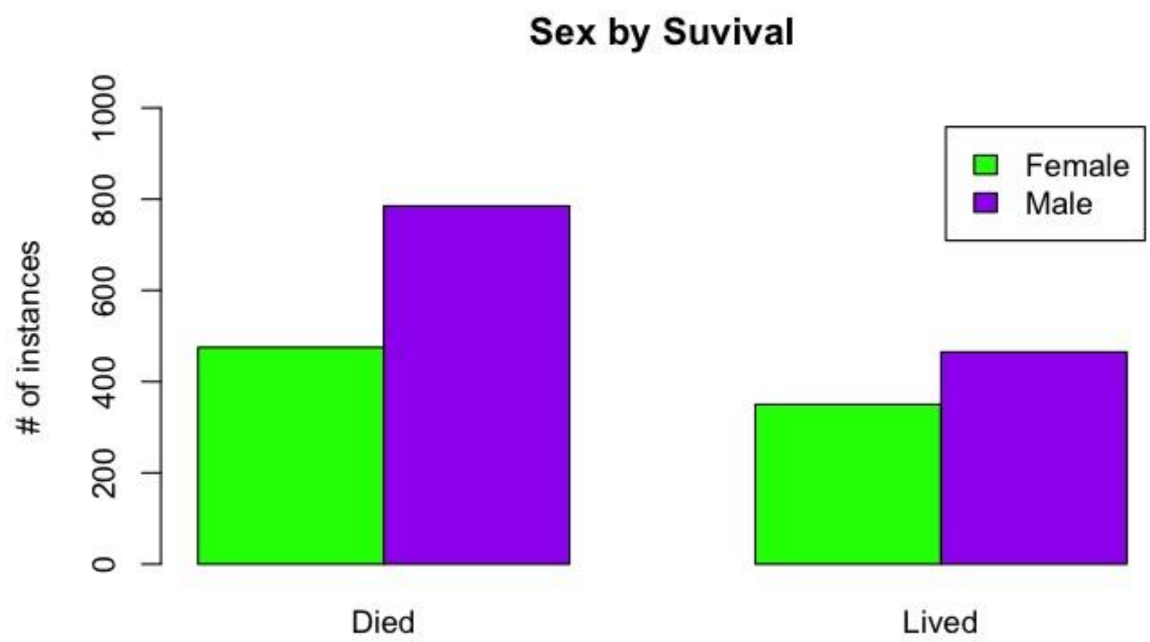


FIGURE 2.3 RACE/ETHNICITY BY SURVIVAL OF MECHANICALLY VENTILATED COVID-19 SUBJECTS

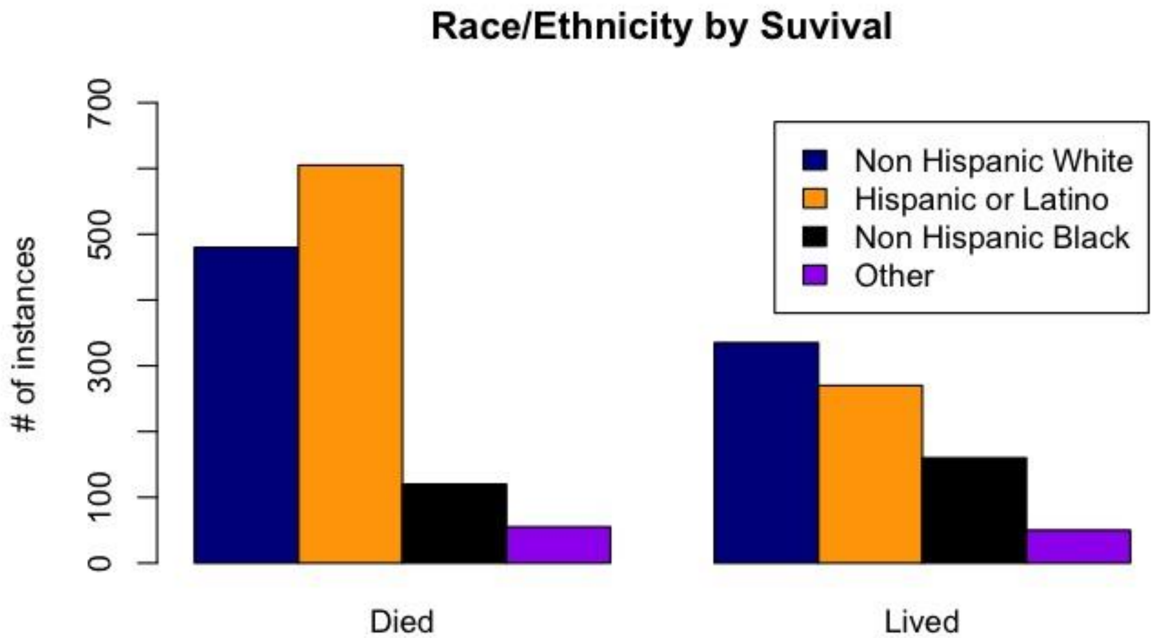
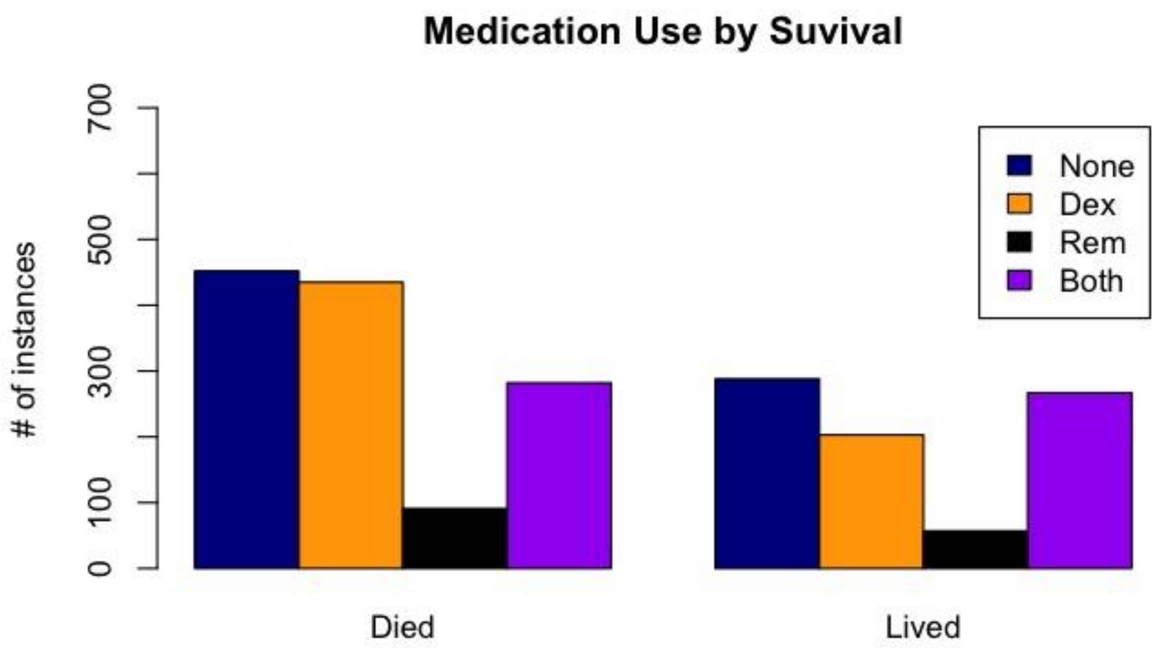
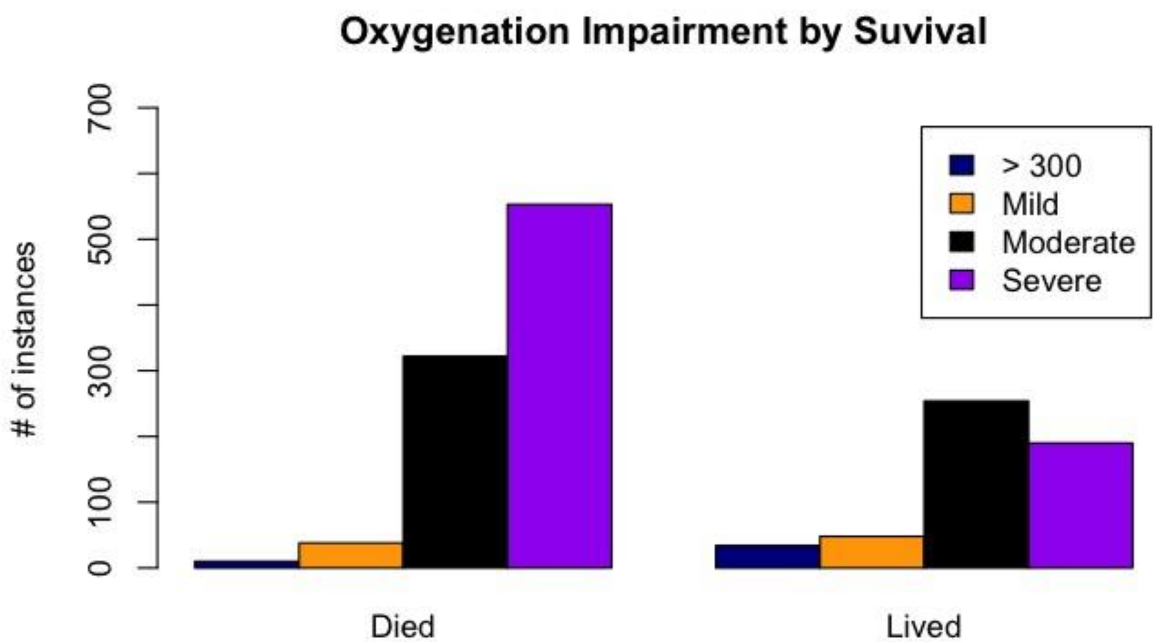


FIGURE 2.4 MEDICATION USE BY SURVIVAL OF MECHANICALLY VENTILATED COVID-19 SUBJECTS



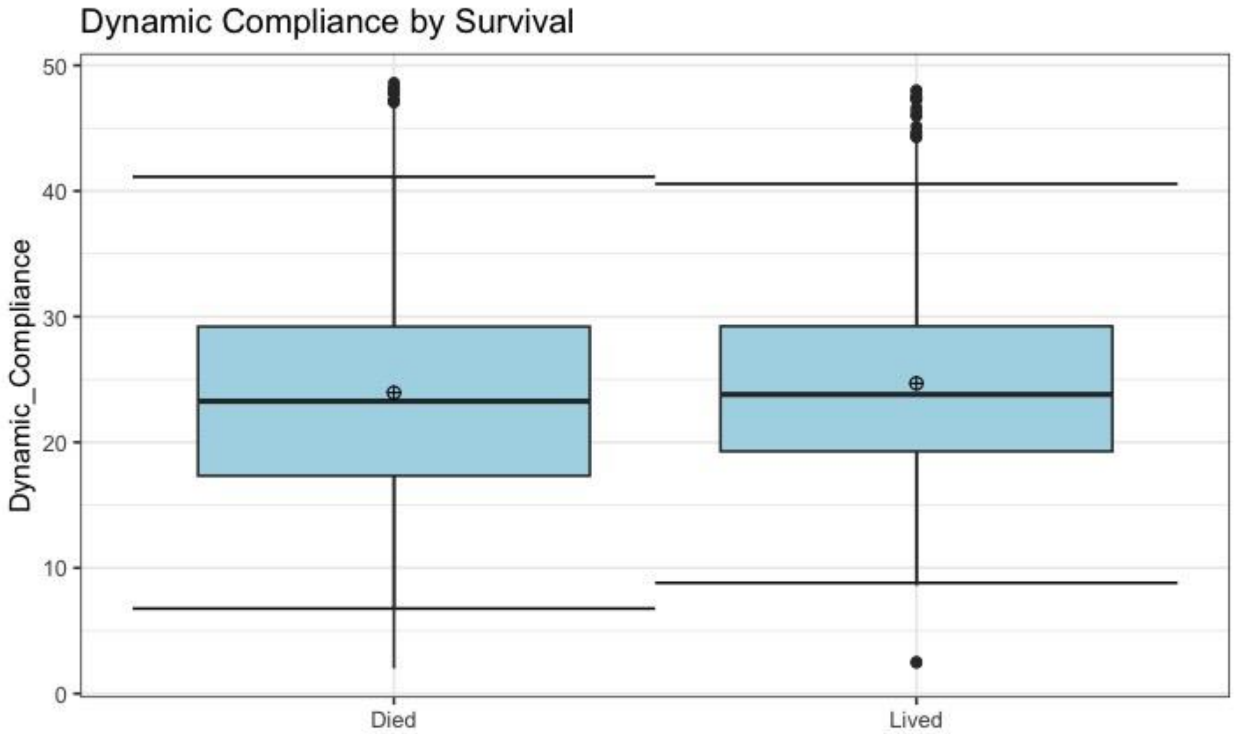
Abbreviations: Dex – dexamethasone; Rem – remdesivir; Both – dexamethasone and remdesivir

FIGURE 2.5 OXYGENATION IMPAIRMENT BY SURVIVAL OF MECHANICALLY VENTILATED COVID-19 SUBJECTS



Abbreviations: > 300 – normal lung function; mild – mild oxygenation impairment; moderate – moderate oxygenation impairment; severe – severe oxygenation impairment

FIGURE 2.6 DYNAMIC COMPLIANCE BY SURVIVAL OF MECHANICALLY VENTILATED COVID-19 SUBJECTS



CHAPTER 3

Dyspnea, Physical Function and Pulmonary Rehabilitation of Long COVID Subjects

Specific Aim 2

To determine the factors associated with physical function after completing six weeks of pulmonary rehabilitation (PR) of COVID-19 subjects with persistent pulmonary symptoms.

Hypothesis 2a. COVID-19 subjects with persistent pulmonary symptoms who complete six weeks of PR that have mild dyspnea will have higher odds of improved physical function than COVID-19 subjects with persistent pulmonary symptoms who complete six weeks of PR with moderate/severe dyspnea.

Hypothesis 2b. COVID-19 subjects with persistent pulmonary symptoms who complete six weeks of PR that have depressive symptoms will have lower odds of improved physical function than COVID-19 subjects with persistent pulmonary symptoms who complete six weeks of PR without depressive symptoms.

Hypothesis 2c. COVID-19 subjects with persistent pulmonary symptoms who complete six weeks of PR that have anxiety will have lower odds of improved physical function than COVID-19 subjects with persistent pulmonary symptoms who complete six weeks of PR without anxiety.

Hypothesis 2d. COVID-19 subjects with persistent pulmonary symptoms who complete six weeks of PR that have PTSD will have lower odds of improved physical function than COVID-19 subjects with persistent pulmonary symptoms who complete six weeks of PR without PTSD.

METHODS

<u>Data Source</u>

This scientific research used data from the electronic health record (EHR) from our university-associated hospital systems, Post-COVID-19 Health Clinic in the Houston, TX region. UTMB Health's Post-COVID Recovery Clinic potentially leads participants to resume life as they lived it before COVID-19, returning to their daily routines and favorite activities. Post-COVID Recovery Clinic offers a patient-focused, comprehensive, clinic-based program with virtual visit capabilities. As participants recover from COVID-19, a team of physicians, practitioners, and mental health professionals can support them. Participants are evaluated on their condition and helped with recovery strategies to support their rehabilitation needs. Inclusion criteria were subjects 18 years or older, positively diagnosed with COVID-19 with persistent symptoms, who completed six weeks of PR at The University of Texas Medical Branch (UTMB) Post-COVID-19 Clinic between June 1, 2020, and February 1, 2022. Sixty-eight subjects were reviewed, and 64 met the study's inclusion criteria.

<u>Measures</u>

Outcome Variables

PHYSICAL FUNCTION

6-Minute Walking Distance (6MWD) evaluates an individual's functional capacity and endurance by measuring the distance a person can walk in 6 minutes.

6MWD difference [after pulmonary rehabilitation (post-PR) – before pulmonary rehabilitation (pre-PR)] was examined as a continuous variable.

6MWD post-PR was examined as a continuous variable.

Minimal Clinically Important Difference (MCID) in 6MWD was dichotomized into (1) achieving MCID or (2) not achieving MCID.

The 6MWD provides detailed information regarding COPD subjects' exacerbations, hospitalizations, and deaths. (Celli, 2016) 6MWD is reliable and valid in assessing disease severity (Casanova, 2007; du Bois, 2011), functional capacity (Starobin, 2006), and respiratory function. (Rick, 2014) The 6MWD is also used to measure the outcomes of PR programs. (Spencer, 2008) A 6-minute walk test (6-MWT) is appropriate for predicting mortality (Karanth, 2017; Pinto-Plata, 2004) and measuring maximal effort (Blanco, 2010) and mobility. (Harada, 1999) The outcome variable measures the distance a patient can walk over 6 minutes (6MWD). (ATS, 2002)

The 6-MWT measures a subject's total distance walked over 6 minutes and records occurrences of fatigue and dyspnea. (Enright, 2003; Spencer, 2008) The 6MWD is a measure considered reliable and valid in assessing disease severity (Casanova, 2007; du Bois, 2011), functional capacity, (Enright, 2003; Starobin, 2006) maximal effort, (Blanco, 2010) mobility, (Enright, 2003; Harada, 1999) respiratory function, (Rick, 2014) and mortality. (Celli, 2016; Enright, 2003; Karanth, 2017; Pinto-Plata, 2004)

In a systematic review, Bohannon et al. consider a change of 14-30.5m in 6MWD clinically important in various pathological patient populations. (Bohannon, 2017) In pulmonary diseased populations, a 29-34m change in the distance would be considered a clinically significant change. (Holland, 2009) The outcome measure 6MWD was evaluated pre and post-six weeks of PR. Some studies report that a 24 to 45m change in 6MWD in pulmonary diseased populations would be considered clinically significant (du Bois, 2011; Holland, 2009), with a 30m decrease in distance representing a worsening clinical status. (Polkey, 2013) A study of older patients with COPD reported that a change of 50m-54m represents MCID. (Redelmeier, 1997; Rasekaba, 2009) However, other studies have shown a range of 54-80m being clinically significant. (Wise, 2005)

To determine the MCID in our sample, we employed the receiver operating characteristic curve (ROC) to estimate the cut-point that best predicts MCID. (Hajian-Tilaki, 2013) Our analysis used several cut points (30m, 35m, 40m, 45m, 50m, 54m, 80m, 108m and 120m). The area under the curve (AUC) values were 0.64, 0.64, 0.67, 0.67, 0.58, 0.58, 0.55, 0.57, and 0.55, respectively. Cut points of 30m (AUC; 64), 80m (AUC: 55), and 108m (AUC: 0.57) were used for our analysis.

Independent Variables

PULMONARY RESTRICTION

Pulmonary Restriction was categorized using forced vital capacity (FVC) percent of predicted from spirometry results into (1) normal lung function or mild restriction if subjects had FVC more than 80% of predicted, or (2) moderate to severe restriction if subjects had FVC less than 80% of predicted. Subjects were considered to have abnormal lung function if their FEV1/FVC was less than the lower limit of normal (LLN) or when the FVC was less than 80% of predicted values. (Ranu, 2011) We also evaluated the diffusion capacity of the lungs for carbon monoxide (DLCO) when available, but not all subjects who participated in PR had diffusion studies done.

UNIVERSITY OF CALIFORNIA – SAN DIEGO SHORTNESS OF BREATH QUESTIONNAIRE (UCSD)

University of California – San Diego Shortness of Breath Questionnaire (UCSD) was collected as a continuous variable, then dichotomized into (1) mild dyspnea if values were < 34 or (2) moderate/severe dyspnea if values were ≥ 34. UCSD is a tool designed to assess and measure the severity and impact of shortness of breath (SOB) by summing responses across a 24-series of items that the individual rates based on their experience and perception of SOB. Items are scored 0-5, with 0 being no difficulty and 5 being the most difficult, forming a total score ranging from 0 to 120. The UCSD is recognized as a reliable and valid assessment tool to measure the severity of dyspnea and exercise tolerance during activities of daily living (ADL) or following a 6-minute walk test (6MWT). (Chen, 2021; Eakin, 1998; Gries, 2013; Kupferberg, 2005) The questions asked are listed in Appendix A.

HOSPITALIZATION STATUS

Hospitalization status was dichotomized and presented as (1) previously hospitalized due to COVID-19 infection or (2) not hospitalized due to COVID-19 infection.

ANXIETY DISORDER

General Anxiety Disorder Screener – (GAD-7) is a reliable and valid tool that measures anxiety in clinical research (Hinz, 2017) by summing responses across a seven-item questionnaire. Items are scored 0-3, with 0 being not at all and 3 being nearly daily. The total summary score ranges from 0 to 21. A cutoff score of 10 or greater is acceptable for classifying GAD. GAD was dichotomized into having anxiety disorder or not. (Spitzer, 2006) The questions asked are listed in Appendix B.

Depression

The Patient Health Questionnaire – (PHQ-9) is a valid and reliable tool used for screening, diagnosing, monitoring, and measuring the severity of depression by summing responses across a nine-item questionnaire. Items are scored 0-3, with 0 being not at all and 3 being nearly daily. The total summary score ranges from 0 to 27. (Levis, 2019) Depression was categorized using the PHQ-9 score, with cutoff scores being 5, 10, 15, and 20, reflecting levels of mild, moderate, moderately severe, and severe depression, respectively. (Kroenke, 2021) We categorized our population by PHQ-9 score, with a score of (1) less than 10 being none or mild depression; (2) greater than or equal to 10 being moderate to severe depression. The questions asked are listed in Appendix C.

Post-Traumatic Stress Disorder (PTSD)

Impact of Event Scale-6 (IES-6) is a valid and reliable tool used to screen for post-traumatic stress disorder (PTSD) in COVID-19 patients (Jeong, 2022) by calculating responses across a six-item questionnaire. Items are scored 0-4, with 0 being not at all and 4 being "extremely." The total summary score ranges from 0 to 24. (Hosey, 2019) We categorized PTSD by quartiles of IES-6 score, being (1) < 6 as none or mild PTSD, (2) between 6 to 15 as moderate PTSD, or (3) > 15 as severe PTSD, respectively. The questions asked are in Appendix D.

Covariates

Socio-demographic Factors

Socio-demographics included in the study were age (total age in years), sex (male or female), and race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic/Latino, or Other).

BODY MASS INDEX

Body Mass Index (BMI) was computed by dividing weight (kilograms) by height (meters^2) and was used as a continuous variable.

MULTIMORBIDITY

Multimorbidity included comorbid conditions of interest: asthma, history of stroke, diabetes, hypertension, liver disease, coronary artery disease (CAD), congestive heart failure, COPD, obesity, end-stage renal disease (ESRD), chronic kidney disease (CKD), and history of cancer. Multimorbidity was dichotomized into (1) less than two comorbid conditions or (2) multimorbidity, if subjects had two or more comorbidities.

Statistical Analysis

Statistical Methods: All data were visually and statistically examined for normal distribution using Shapiro–Wilk's test. Outliers were replaced using their respective interquartile ranges' lower and upper bounds. Descriptive statistics were performed to test the descriptive characteristics of the sample by physical function. Continuous variables were presented as means and standard deviations if they were normally distributed and medians and interquartile ranges if they were not. Categorical variables were presented as frequencies and percentages. Logistic regression analysis was performed to estimate the odds ratio (OR) and 95 % Confidence Interval

(CI) of achieving MCID in 6MWD difference (before and after PR) for COVID-19 patients with persistent symptoms that complete PR, controlling for all variables. Linear regression analysis was performed to estimate the coefficients of 6MWD pre- and post-PR and change of 6MWD (post-PR – pre-PR), controlling for all variables. A <0.05 level of significance was used. All analyses were performed in RStudio.

In our analysis, 6MWD was gathered as a continuous variable and examined as the value of 6MWD post-PR, followed by the difference in 6MWD (post-PR – pre-PR).

To test hypothesis 2a. Logistic regression model using binomial distribution to estimate the odds of achieving MCID in 6MWD as a function of dyspnea, controlling for sociodemographic and health factors of COVID-19 subjects with persistent symptoms who completed PR.

To test hypothesis 2b. Logistic regression model using binomial distribution was used to estimate the odds of achieving MCID in 6MWD as a function of depressive symptoms, controlling for sociodemographic and health factors of COVID-19 subjects with persistent symptoms who completed PR.

To test hypothesis 2c. Logistic regression model using binomial distribution to estimate the odds of achieving MCID in 6MWD as a function of anxiety, controlling for sociodemographic and health factors of COVID-19 subjects with persistent symptoms who completed PR.

To test hypothesis 2d. Logistic regression model using binomial distribution to estimate the odds of achieving MCID in 6MWD as a function of PTSD, controlling for sociodemographic and health factors of COVID-19 subjects with persistent symptoms who completed PR.

RESULTS

This purpose of this aim was to determine the factors associated with physical function after completing six weeks of pulmonary rehabilitation (PR) of COVID-19 subjects with persistent pulmonary symptoms. The outcomes examined were achieving MCID in 6MWD as a function of dyspnea, depressive symptoms, anxiety, and PTSD, controlling for sociodemographic and health factors of COVID-19 subjects with persistent symptoms who completed PR.

First, we hypothesized that Long COVID subjects with mild dyspnea would have higher odds of achieving minimal clinically important differences (MCID) in 6MWD than those with moderate/severe dyspnea. We also hypothesized that Long COVID subjects with depressive symptoms will have lower odds of achieving MCID in 6MWD than those without depressive symptoms. We further hypothesized that Long COVID subjects with anxiety will have lower odds of achieving MCID in 6MWD than those without anxiety. Lastly, we hypothesized that Long COVID subjects with PTSD will have lower odds of achieving MCID in 6MWD than those without PTSD.

ANALYSES FOR OVERALL SAMPLE

Table 3.1A presents the baseline characteristics of 64 subjects with Long COVID in the study sample. Participants had a mean age of 56 ± 13.1 years. The majority were female (64.1%), with Non-Hispanic White being the most common race/ethnicity (54.7%), followed by Hispanic (28.1%) and Non-Hispanic Black (17.2%). The overall average BMI was 35 ± 8.5 Kg/m^2.

Regarding hospitalization, 68.8% of participants were previously hospitalized due to COVID-19. Most participants had less than two comorbid conditions (76.6%) compared to those with multimorbidity (23.4%). Anxiety was absent in the majority (80%), while 20% were classified as anxious. Most participants had none to mild depression (71.1%), while 28.9% experienced moderate to severe depressive symptoms. Mild PTSD was reported by more than half (52.2%) of participants, with 21.7% and 26.1% reporting moderate and severe PTSD, respectively.

Table 3.1B presents the baseline pulmonary characteristics of the sample. The median 6MWD before PR (pre-PR) was 1083 meters (IQR 900 – 1259). After PR (post-PR), the median 6MWD increased to 1349 meters (IQR 1000 – 1482), improving overall physical function. The median difference in 6MWD (post-PR – pre-PR) was 261 meters (IQR 100 – 421).

Regarding subjects achieving MCID in 6MWD post-PR, the majority of participants achieved improvements of at least 30 meters (92.2%), 80 meters (79.7%), and 108 meters (76.6%) post-PR.

Regarding dyspnea severity, 29.7% of participants reported mild dyspnea, while 70.3% reported moderate to severe dyspnea. Moderate pulmonary restriction was present in about a third (32.8%) of participants, while 67.2% had mild restriction or normal lung function.

TABLE 3.1A DESCRIPTIVE BASELINE CHARACTERISTICS OF LONG COVID SUBJECTS (N=64).

Characteristics	Missing (%)	Overall N (%)
Age (years), mean ± SD	0 (0)	56 ± 13.1
Sex	0 (0)	
Male		23 (35.9)
Female		41 (64.1)
Race/Ethnicity	0 (0)	
Non-Hispanic White		35 (54.7)
Non-Hispanic Black		11(17.2)
Hispanic or Latino		18 (28.1)
BMI (Kg/m2), mean ± SD	3 (5)	35 ± 8.5
Hospitalized	0 (0)	
Yes		44 (68.8)
No		20 (31.2)
Multimorbidity	0 (0)	
< 2 comorbid conditions		49 (76.6)
≥ 2 comorbid conditions		15 (23.4)
Anxiety	19 (29.7)	
Not anxious		36 (80)
Anxious		9 (20)
Depression	19 (29.7)	
None or Mild		32 (71.1)
Moderate to Severe		13 (28.9)
PTSD	18 (28.1)	
Mild		24 (52.2)
Moderate		10 (21.7)
Severe		12 (26.1)

Abbreviations: BMI – body mass index; PTSD – post-traumatic stress disorder

TABLE 3.1B DESCRIPTIVE BASELINE PULMONARY CHARACTERISTICS OF LONG COVID SUBJECTS (N=64).

Characteristics	Missing (%)	Overall N (%)
6MWD pre-PR (meters), median (IQR)	0 (0)	1083 (900 – 1259)
6MWD post-PR (meters), median (IQR)	0 (0)	1349 (1000 – 1482)
6MWD difference (meters), median (IQR)	0 (0)	261 (100 – 421)
6MWD MCID 30m	0 (0)	
Yes		59 (92.2)
No		5 (7.8)
6MWD MCID 80m	0 (0)	
Yes		51 (79.7)
No		13 (20.3)
6MWD MCID 108m	0 (0)	
Yes		49 (76.6)
No		15 (23.4)
Dyspnea	0 (0)	
Mild		19 (29.7)
Moderate/Severe		45 (70.3)
Pulmonary restriction	3 (4.7)	
Normal lung function or mild restriction		41 (67.2)
Moderate to Severe		20 (32.8)

PR – pulmonary rehabilitation; 6MWD – Six Minute Walk Distance; MCID – minimum clinically important difference; 6MWD difference = (post-PR – pre-PR)

ANALYSES FOR 6-MINUTE WALKING DISTANCE

6-Minute Walking Distance Post-Pulmonary Rehabilitation

Table 3.2A presents the results of univariate analysis examining the association between various predictor variables and the 6-minute walk distance (6MWD) post-pulmonary rehabilitation (post-PR) of long COVID subjects. The analysis included 64 participants.

Age was found to have a significant negative association with 6MW post-PR (coefficient = -5.416, p = 0.04), indicating that older age is associated with a shorter 6MWD. BMI showed a non-significant negative association with 6MW post-PR (coefficient = -6.562, p = 0.12), suggesting that higher BMI may be associated with a shorter 6MWD, although this result did not reach statistical significance.

Baseline 6MWD before pulmonary rehabilitation (pre-PR) was significantly positively associated with 6MWD post-PR (coefficient = 0.676, p < 0.001), indicating that a longer baseline walk distance is associated with a longer walk distance post-PR.

Of demographic variables, only race/ethnicity showed significant associations. Non-Hispanic Black participants had a significantly lower 6MWD post-PR compared to Non-Hispanic White participants (coefficient = -271.49, p = 0.004), while Hispanic or Latino participants also showed a lower 6MWD, although not statistically significant (coefficient = -110.61, p = 0.15).

Regarding comorbidities, participants with multimorbidity had a significantly lower 6MWD post-PR compared to those with less than two comorbid conditions (coefficient = -216.03, p = 0.007). Other variables, including sex, hospitalization status, anxiety, depression, PTSD, pulmonary restriction severity, and dyspnea severity, did not show significant associations with 6MWD post-PR.

TABLE 3.2 UNIVARIATE ANALYSIS FOR 6-MINUTE WALKING DISTANCE POST-PULMONARY REHABILITATION OF LONG COVID SUBJECTS (N=64).

Predictor Variable	Coefficient	Std. Error	*p*-value
Age	-5.416	2.606	0.0418
BMI (Kg/m^2)	-6.562	4.138	0.118
6MWD pre-PR	0.676	0.092	<0.001
6MWD difference	0.641	0.138	<0.001
Sex	(reference: female)		
Male	78.53	72.10	0.28
Race/Ethnicity	(reference: Non-Hispanic White)		
Non-Hispanic Black	-271.49	90.65	0.00396
Hispanic or Latino	-110.61	76.07	0.15105
Multimorbidity	(reference: less than two comorbid conditions)		
Multimorbid	-216.03	77.74	0.00721
Hospitalization status	(reference: not hospitalized from COVID-19)		
Hospitalized	-58.11	74.98	0.441
Anxiety	(reference: not anxious)		
Anxious	107.63	100.93	0.292
Depression	(reference: none or mild depression)		
Moderate to severe depression	42.61	90.01	0.638
PTSD	(reference: none or mild PTSD)		
Moderate PTSD	31.04	101.64	0.762
Severe PTSD	113.78	95.47	0.240
Pulmonary Restriction	(reference: none or mild pulmonary restriction)		
Moderate to severe restriction	8.985	76.256	0.907
Dyspnea	(reference: mild dyspnea)		
Moderate to severe dyspnea	-136.74	74.44	0.071

Abbreviations: BMI – body mass index; 6MWD – 6-minute walking distance; PR – pulmonary rehabilitation; PTSD – post-traumatic stress disorder

6-Minute Walking Distance Difference before and after Pulmonary Rehabilitation

Table 3.3 presents the results of univariate regression analysis examining the association between various predictor variables and the change in 6MWD difference (post-pulmonary rehabilitation – pre-pulmonary rehabilitation) of Long COVID subjects. The analysis included 64 participants.

Age did not show a significant association with 6MWD difference (coefficient = -1.137, p = 0.60), indicating that age was not a significant predictor of the change in 6MWD difference. BMI showed a trend towards a negative association with 6MWD difference, although it did not reach statistical significance (coefficient = -5.542, p = 0.09), suggesting that higher BMI may be associated with a smaller improvement in 6MWD difference.

A higher baseline 6MWD (pre-PR) was found to correlate with a smaller increase in the 6MWD difference (coefficient = -0.199, p = 0.04), indicating that individuals with greater initial walking abilities showed less improvement. Conversely, an increase in the 6MWD post-PR was strongly associated to a larger improvement in the 6MWD difference (coefficient = 0.400, p < 0.001), suggesting that the post-rehabilitation walking distance is a significant predictor of PR success. Essentially, while patients starting with a higher pre-PR 6MWD tend to show smaller gains, those who improve their walking distance post-PR demonstrate significant enhancements in their physical function.

Of demographic variables, only race/ethnicity showed significant associations. Non-Hispanic Black and Hispanic or Latino participants had significant lower 6MWD differences compared to Non-Hispanic White participants (coefficient = -168.63, p = 0.02; coefficient = -130.30, p = 0.04), respectively. Regarding comorbidities, participants with multimorbidity did not show a significant association with 6MWD difference compared to those with less than two comorbid conditions (coefficient = -89.74, p = 0.17).

Other variables, including sex, hospitalization status, anxiety, depression, PTSD, pulmonary restriction severity, and dyspnea severity, did not show significant associations with 6MWD difference.

TABLE 3.3 UNIVARIATE REGRESSION ANALYSIS FOR 6-MINUTE WALKING DISTANCE DIFFERENCE OF LONG COVID SUBJECTS (N=64).

Predictor Variable	Coefficient	Std. Error	*p*-value
Age	-1.137	2.125	0.60
BMI (Kg/m^2)	-5.542	3.248	0.09
6MWD pre-PR	-0.19943	0.09632	**0.04**
6MWD post-PR	0.40033	0.08655	**<0.001**
Sex	(reference: female)		
Male	3.946	57.525	0.95
Race/Ethnicity	(reference: Non-Hispanic White)		
Non-Hispanic Black	-168.63	72.46	**0.02**
Hispanic or Latino	-130.30	60.80	**0.04**
Multimorbidity	(reference: less than two comorbid conditions)		
Multimorbid	-89.74	64.16	0.17
Hospitalization status	(reference: not hospitalized from COVID-19)		
Hospitalized	75.49	58.77	0.20
Anxiety	(reference: not anxious)		
Anxious	73.53	90.82	0.42
Depression	(reference: none or mild depression)		
Moderate to severe depression	68.92	80.08	0.39
PTSD	(reference: none or mild PTSD)		
Moderate PTSD	36.22	93.25	0.70
Severe PTSD	29.88	87.59	0.74
Pulmonary Restriction	(reference: none or mild pulmonary restriction)		
Moderate to severe restriction	92.69	60.19	0.13
Dyspnea	(reference: mild dyspnea)		
Moderate to Severe dyspnea	-71.02	59.74	0.24
Abbreviations: BMI – body mass index; 6MWD – 6-minute walking distance; PR – pulmonary rehabilitation; PTSD – post-traumatic stress disorder			

Minimal Clinically Important Difference at 30 meters

Table 3.4A presents baseline characteristics of Long COVID subjects based on achieving Minimal Clinically Important Difference (MCID) 6MWD at 30m. Sixty-four subjects were included, with 59 (92.2%) achieving MCID and 5 (7.8%) not achieving MCID at 30m.

The mean age was similar between the two groups (56 ±13 years for achieved vs. 58 ±14) years for those who did not achieve MCID, p=0.77). Regarding sex, the majority of males achieved MCID (22, 95.7%) compared to those who did not (1, 4.3%), but this difference was not statistically significant (p=0.65). There were similar results for females, with most of them achieving an MCID (37, 90.2%) and a small portion who did not (4, 9.8%). Significant differences were observed in terms of race/ethnicity (p=0.01). All non-Hispanic White participants achieved MCID at 30m (35, 100.0%), while there were more participants of Non-Hispanic Black (11, 84.6%) and Hispanic or Latino (18, 85.7%) participants who achieved MCID than those who did not achieve MCID.

The mean BMI was similar between the groups [34 ±8 Kg/m2) for those who achieved MCID vs. 37 ±10 Kg/m2) for those who did not achieve MCID at 30m p=0.67). There were no significant differences in hospitalization rates between the groups (p=0.64). Regarding multimorbidity, most participants had less than two comorbid conditions, with similar proportions in both groups (92.5% for those who achieved MCID vs. 7.5% for those who did not achieve MCID at 30m, p=1.00). Similarly, there were no significant differences in anxiety, depression, or PTSD between the groups (p=0.57, p=1.00, and p=0.80, respectively).

Table 3.4B describes baseline pulmonary characteristics of Long COVID subjects based on achieving MCID in 6MWD at 30m. The median 6MWD pre-PR was 1033 meters (IQR 860-1254) for those who achieved MCID and 1073 meters (IQR 1158-1275) for those who did not, with no significant difference (p=0.82). However, the median 6MWD post-PR was 1352 meters (IQR 1232-1487) for achievers of MCID and 1107 meters (IQR 1120-1218) for non-achievers, with a trend towards significance (p=0.056). The median 6MWD difference was significantly higher for achievers of MCID at 30m (310 meters, IQR 156-439) compared to non-achievers (-30 meters, IQR -80-4, p<0.001).

Regarding dyspnea, most participants had mild dyspnea, with 18 (94.7%) achieving MCID and 1 (5.3%) not achieving MCID at 30m. Similarly, for moderate/severe dyspnea, 41 (91.1%) achieved MCID at 30m, and 4 (8.9%) did not (p=1.00). Regarding pulmonary restriction, the majority had normal lung function or mild restriction, with 41 (91.1%) achieving MCID at 30m and 4 (8.9%) not. For moderate to severe restriction, 20 (95.2%) subjects achieved MCID at 30m, and 1 (4.8%) did not (p=1.00).

TABLE 3.4A DESCRIPTIVE BASELINE CHARACTERISTICS BY MCID OF 30M OF LONG COVID SUBJECTS (N=64).

Characteristics	MCID 30m		*p*-value
	Yes	**No**	
Total	59 (92.2%)	5 (7.8%)	
Age (years), mean ± SD	56 ± 13	58 ± 14	0.77
Sex			0.65*f*
Male	22 (95.7%)	1 (4.3%)	
Female	37 (90.2%)	4 (9.8%)	
Race/Ethnicity			**0.01** *f*
Non-Hispanic White	35 (100.0%)	0 (0.0%)	
Non-Hispanic Black	11 (84.6%)	2 (15.4%)	
Hispanic or Latino	18 (85.7%)	3 (14.3%)	
BMI (Kg/m^2), mean ± SD	34 ± 8	37 ± 10	0.67
Hospitalized			0.64 *f*
Yes	44 (93.6%)	3 (6.4%)	
No	20 (90.9%)	2 (9.1%)	
Multimorbidity			1 *f*
< 2 comorbid conditions	49 (92.5%)	4 (7.5%)	
≥ 2 comorbid conditions	15 (93.8%)	1 (6.3%)	
Anxiety			0.57 *f*
Not anxious	36 (90.0%)	4 (10.0%)	
Anxious	9 (100.0%)	0 (0.0%)	
Depression			1 *f*
None or Mild	32 (91.4%)	3 (8.6%)	
Moderate to Severe	13 (92.9%)	1 (7.1%)	
PTSD			0.80 *f*
Mild	24 (88.9%)	3 (11.1%)	
Moderate	12 (92.3%)	1 (7.7%)	
Severe	12 (92.3%)	1 (7.7%)	

Abbreviations: MCID – minimal clinically important difference; BMI - body mass index; PTSD – post-traumatic stress disorder; Kg – kilograms; m – meters; *f* – Fisher's exact test

TABLE 3.4B DESCRIPTIVE BASELINE PULMONARY CHARACTERISTICS BY MCID OF 30M OF LONG COVID SUBJECTS (N=64).

Characteristics	MCID 30m		*p*-value
	Yes	**No**	
Total	59 (92.2%)	5 (7.8%)	
6MWD pre-PR (meters) median (IQR)	1033 (860-1254)	1073 (1158-1275)	0.82
6MWD post-PR (meters) median (IQR)	1352 (1232-1487)	1107 (1120-1218)	0.056
6MWD difference (meters) median (IQR)	310 (156 439)	-30 (-80-4)	**<0.001**
Dyspnea			1 *f*
Mild	18 (94.7%)	1 (5.3%)	
Moderate/Severe	41 (91.1%)	4 (8.9%)	
Pulmonary restriction			1 *f*
Normal lung function or mild restriction	41 (91.1%)	4 (8.9%)	
Moderate to Severe	20 (95.2%)	1 (4.8%)	

Abbreviations: PR – pulmonary rehabilitation; 6MWD – Six Minute Walk Distance; MCID – minimum clinically important difference; 6MWD difference = (post-PR – pre-PR); *f* – Fisher's exact test

Minimal Clinically Important Difference at 80 meters

Table 3.5A presents the baseline characteristics of Long COVID subjects based on achieving MCID in 6MWD at 80m. Of the 64 subjects included, 51 (79.7%) achieved MCID, while 13 (20.3%) did not achieve MCID.

The mean age was similar between those who achieved MCID (56 ± 13 years) and those who did not achieve MCID (57 ± 14 years) (p=0.85). Regarding sex, a majority of both males and females achieved MCID (82.6% and 78%, respectively) compared to their counterparts who did not achieve MCID (17.4% and 22%, respectively) (p=0.76). Significant differences in race/ethnicity were observed (p=0.002), with a higher proportion of non-Hispanic White participants achieving MCID (94.3%) compared to non-Hispanic Blacks (54.5%) and Hispanic or Latino (66.7%) subjects.

The mean BMI was similar between participants who achieved MCID (34 Kg/m^2) compared to those who did not (37 Kg/m^2) (p=0.29). There were no significant differences in hospitalization rates between those who achieved MCID and those who did not (p=0.31). Regarding multimorbidity, most participants had less than two comorbid conditions, 83.7% for those who achieved MCID vs. 16.3% for those who did not achieve MCID at 80m. Although two-thirds of 10 (66.7%) subjects with multimorbidity achieved MCID at 80m, there was no significant difference between the groups p=0.16). Similarly, there were no significant differences in anxiety, depression, or PTSD between the groups (p=1.00, p=1.00, and p=0.61, respectively).

Table 3.5B provides an overview of baseline pulmonary characteristics of Long COVID subjects based on achieving the MCID in 6MWD at 80m.

The median 6MWD pre-PR was 1052 meters (IQR 850-1191) for those who achieved MCID and 1254 meters (IQR 1158-1284) for those who did not, with no significant difference observed ($p=0.38$). However, post-PR, the median 6MWD was significantly higher for those who achieved MCID (1429m, IQR 1232-1560) compared to those who did not (1262m, IQR 1162-1311) ($p=0.02$). Similarly, the median 6MWD difference was significantly higher for achievers (293m, IQR 199-458) of MCID at 80m compared to non-achievers (39m, IQR 4-59) ($p<0.001$).

Regarding dyspnea, a higher proportion of subjects with mild dyspnea achieved MCID (90%) than those with moderate/severe dyspnea (78%). However, this difference was not statistically significant ($p=0.31$). Regarding pulmonary restriction, 77% of subjects with normal lung function or mild restriction achieved MCID, while 86% of those with moderate to severe restriction achieved MCID. Again, the difference was not statistically significant ($p=0.52$).

TABLE 3.5A DESCRIPTIVE BASELINE CHARACTERISTICS BY MCID OF 80M OF LONG COVID SUBJECTS (N=64).

Characteristics	MCID 80m		*p*-value
	Yes	**No**	
Total	51 (79.7%)	13 (20.3%)	
Age (years), mean ± SD	56 ± 13	57 ± 14	0.85
Sex			0.76 *f*
Male	19 (82.6%)	4 (17.4%)	
Female	32 (78%)	9 (22%)	
Race/Ethnicity			**0.002** *f*
Non-Hispanic White	33 (94.3%)	2 (5.7%)	
Non-Hispanic Black	6 (54.5%)	5 (45.5%)	
Hispanic or Latino	12 (66.7%)	6 (33.3%)	
BMI (Kg/m2), mean ± SD	34 ± 9	37 ± 7	0.29
Hospitalized			0.31 *f*
Yes	37 (84.1%)	7 (15.9%)	
No	14 (70.0%)	6 (30.0%)	
Multimorbidity			0.16 *f*
< 2 comorbid conditions	41 (83.7%)	8 (16.3%)	
≥ 2 comorbid conditions	10 (66.7%)	5 (33.3%)	
Anxiety			1 *f*
Not anxious	27 (75.0%)	9 (25.0%)	
Anxious	7 (77.8%)	2 (22.2%)	
Depression			1 *f*
None or mild	26 (76.5%)	8 (23.5%)	
Moderate to severe	12 (80.0%)	3 (20.0%)	
PTSD			0.61 *f*
Mild	18 (69.2%)	8 (30.8%)	
Moderate	10 (83.3%)	2 (16.7%)	
Severe	10 (83.3%)	2 (16.7%)	

Abbreviations: MCID – minimal clinically important difference; BMI – body mass index; PTSD – post-traumatic stress disorder; Kg – kilograms; m – meters; *f* – Fisher's exact test

TABLE 3.5B DESCRIPTIVE BASELINE PULMONARY CHARACTERISTICS BY MCID OF 80M OF LONG COVID SUBJECTS (N=64).

Characteristics	MCID 80m		*p*-value
	Yes	**No**	
Total	51 (79.7%)	13 (20.3%)	
6MWD pre-PR (meters) median (IQR)	1052 (850 – 1191)	1254 (1158 – 1284)	0.38
6MWD post-PR (meters) median (IQR)	1429 (1232 – 1560)	1262 (1162 – 1311)	**0.02**
6MWD difference (meters) median (IQR)	293 (199 – 458)	39 (4 – 59)	**<0.001**
Dyspnea			0.31 *f*
Mild	18 (90%)	2 (10%)	
Moderate/Severe	37 (78%)	11 (23%)	
Pulmonary restriction			0.52 *f*
Normal lung function or mild restriction	34 (77%)	10 (23%)	
Moderate to severe restriction	18 (86%)	3 (14%)	

Abbreviations: PR – pulmonary rehabilitation; 6MWD – Six-Minute Walking Distance; MCID – minimum clinically important difference; 6MWD difference = (post-PR – pre-PR); *f* – Fisher's exact test

Minimal Clinically Important Difference at 108 meters

Table 3.6A provides an overview of baseline characteristics of Long COVID subjects based on achieving MCID in 6MWD at 108m. Of the 64 subjects, 49 (76.6%) achieved MCID, while 15 (23.4%) did not achieve MCID.

The mean age was similar between subjects who achieved MCID at 108m (56 ± 13 years) and those who did not achieve MCID (58 ± 13 years) (p=0.61). Regarding sex, no significant differences were observed (p=0.81), with 78.3% of males and 75.6% of females achieving MCID. Significant differences were observed in terms of race/ethnicity (p=0.02). A higher proportion of non-Hispanic White subjects achieved MCID (88.6%) compared to non-Hispanic Black (54.5%) and Hispanic or Latino (66.7%) subjects.

The mean BMI was similar between the subjects who achieved MCID at 108m (34 ± 9 Kg/m^2) and those who did not achieve MCID (35 ± 8 Kg/m^2) (p=0.66). There were no significant differences in hospitalizations between subjects who achieved MCID at 108m and those who did not (p=0.53). Regarding multimorbidity, a significantly higher proportion of subjects with less than two comorbid conditions achieved MCID (83.7%) compared to those with multimorbidity (53.3%) (p=0.03). However, there were no significant differences in anxiety, depression, or PTSD between the groups (p=1.00, p=1.00, and p=0.38, respectively).

Table 3.6B provides an overview of Long COVID subjects' baseline pulmonary characteristics based on their MCID achievement in 6MWD at 108m.

There was no significant difference in the median 6MWD pre-PR between those who achieved MCID at 108m compared to those who did not (p=0.51), with a median of 1052 meters for those who achieved the MCID and 1216 meters for those who did not. However, post-PR, the median 6MWD was significantly higher for those who achieved the MCID (1434 meters, p=0.006) than those who did not (1262 meters). Similarly, the median 6MWD difference was significantly higher for achievers (296 meters) compared to non-achievers (46 meters) ($p<0.001$).

In terms of dyspnea, a higher proportion of participants with mild dyspnea achieved the MCID (84.2%) compared to those with moderate/severe dyspnea (73.3%), although this difference was not statistically significant (p=0.52). Regarding pulmonary restriction, there was no significant difference in the proportion of participants with normal lung function or mild restriction between the two groups (p=0.34), with 70.7% of those who achieved the MCID and 29.3% of those who did not. However, a higher proportion of participants with moderate to severe restriction achieved the MCID (85.0%) compared to those who did not achieve the MCID (15.0%).

TABLE 3.6A DESCRIPTIVE BASELINE CHARACTERISTICS BY MCID OF 108M OF LONG COVID SUBJECTS (N = 64).

Characteristics	MCID 108m		*p*-value
	Yes	**No**	
Total	49 (76.6%)	15 (23.4%)	
Age (years), mean ± SD	56 ± 13	58 ± 13	0.61
Sex			0.81
Male	18 (78.3%)	5 (21.7%)	
Female	31 (75.6%)	10 (24.4%)	
Race/Ethnicity			**0.02** *f*
Non-Hispanic White	31 (88.6%)	4 (11.4%)	
Non-Hispanic Black	6 (54.5%)	5 (45.5%)	
Hispanic or Latino	12 (66.7%)	6 (33.3%)	
BMI (kg/m^2), mean ± SD	34 ± 9	35 ± 8	0.66
Hospitalized			0.53 *f*
Yes	35 (79.5%)	9 (20.5%)	
No	14 (70.0%)	6 (30.0%)	
Multimorbidity			**0.03** *f*
< 2 comorbid conditions	41 (83.7%)	8 (16.3%)	
≥ 2 comorbid conditions	8 (53.3%)	7 (46.7%)	
Anxiety			1.00 *f*
Not anxious	26 (72.2%)	10 (27.8%)	
Anxious	7 (77.8%)	2 (22.2%)	
Depression			1.00 *f*
None or Mild	23 (71.9%)	9 (28.1%)	
Moderate to Severe	10 (76.9%)	3 (23.1%)	
PTSD			0.38 *f*
Mild	15 (65.2%)	9 (34.8%)	
Moderate	8 (80.0%)	2 (20.0%)	
Severe	10 (83.3%)	2 (16.7%)	

Abbreviations: MCID – minimal clinically important difference; BMI – body mass index; PTSD – post-traumatic stress disorder; Kg – kilograms; m – meters; *f* – Fisher's exact test

TABLE 3.6B DESCRIPTIVE BASELINE PULMONARY CHARACTERISTICS BY MCID OF 108M OF LONG COVID SUBJECTS (N = 64).

Characteristics	MCID 108m		*p*-value
	Yes	**No**	
Total	49 (76.6%)	15 (23.4%)	
6MWD pre-PR (meters), median (IQR)	1052 (850 – 1182)	1216 (1148 – 1280)	0.51
6MWD post-PR (meters), median (IQR)	1434 (1232 – 1562)	1262 (1141 – 1317)	**0.006**
6MWD difference (meters), median (IQR)	296 (211 – 460)	46 (7 – 66)	**<0.001**
Dyspnea			0.52 *f*
Mild	16 (84.2%)	3 (15.8%)	
Moderate/Severe	33 (73.3%)	12 (26.7%)	
Pulmonary restriction			0.34 *f*
Normal lung function or mild restriction	29 (70.7%)	12 (29.3%)	
Moderate to severe restriction	17 (85.0%)	3 (15.0%)	
Abbreviations: PR – pulmonary rehabilitation; 6MWD – Six Minute Walk Distance; MCID – minimum clinically important difference; 6MWD difference = (post-PR – pre-PR); *f* – Fisher's exact test			

Multivariate Analysis for 6MWD difference

No factors included in the linear regression model were shown to be associated with 6MWD difference.

Multivariate Analysis for 6MWD post-PR

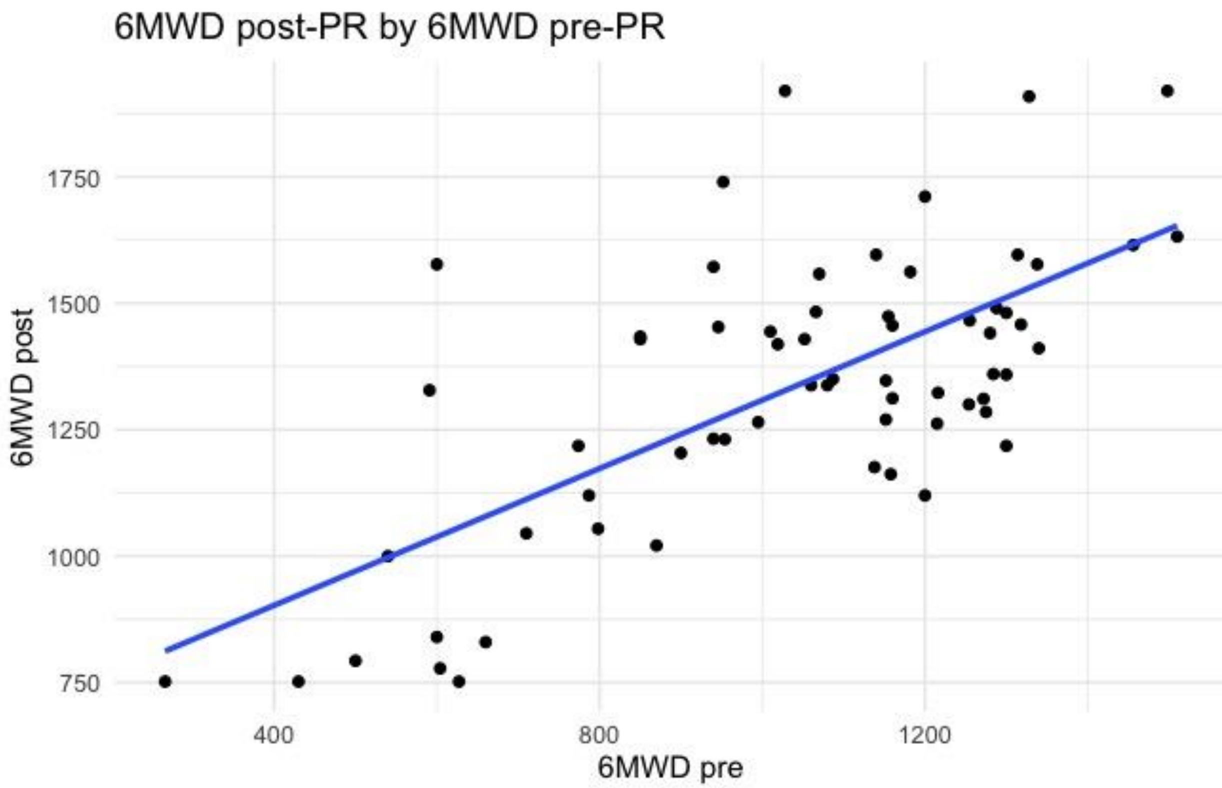
Table 3.7 presents the results of the linear regression analysis examining factors associated with 6- 6MWD post-PR. The primary predictor, 6MWD pre-PR, showed a significant positive association with 6MWD post-PR (OR = 0.57, 95% CI 0.36 – 0.77, $p < 0.001$), indicating that for every additional meter walked in the pre-PR assessment, there was an expected increase of 0.57 meters in the post-PR 6MWD. Other factors, such as age, BMI, race and ethnicity, sex, dyspnea at baseline, multimorbidity, and hospitalization status, did not show statistically significant associations with 6MWD post-PR. However, on average, subjects with moderate/severe restriction had a 126-meter higher 6MWD post-PR compared to those without (OR = 126.0, 95% CI 2.14 – 250.0, $p = 0.046$). The interaction term for age and BMI was also non-significant (OR = -0.47, 95% CI -0.91 – 0.02, $p = 0.06$), indicating that the combined effect of age and BMI on 6MWD post-PR was insignificant in this analysis.

Figures 3.1A and 3.1B illustrate 6MWD post-PR by 6MWD pre-PR and pulmonary restriction, respectively. These results suggest that while 6MWD pre-PR strongly predicts 6MWD post-PR, other demographic and clinical factors may not independently predict post-PR 6MWD in this population.

TABLE 3.7 FACTORS ASSOCIATED WITH 6-MINUTE WALKING DISTANCE POST-PULMONARY REHABILITATION FOR LONG COVID SUBJECTS (N = 64)

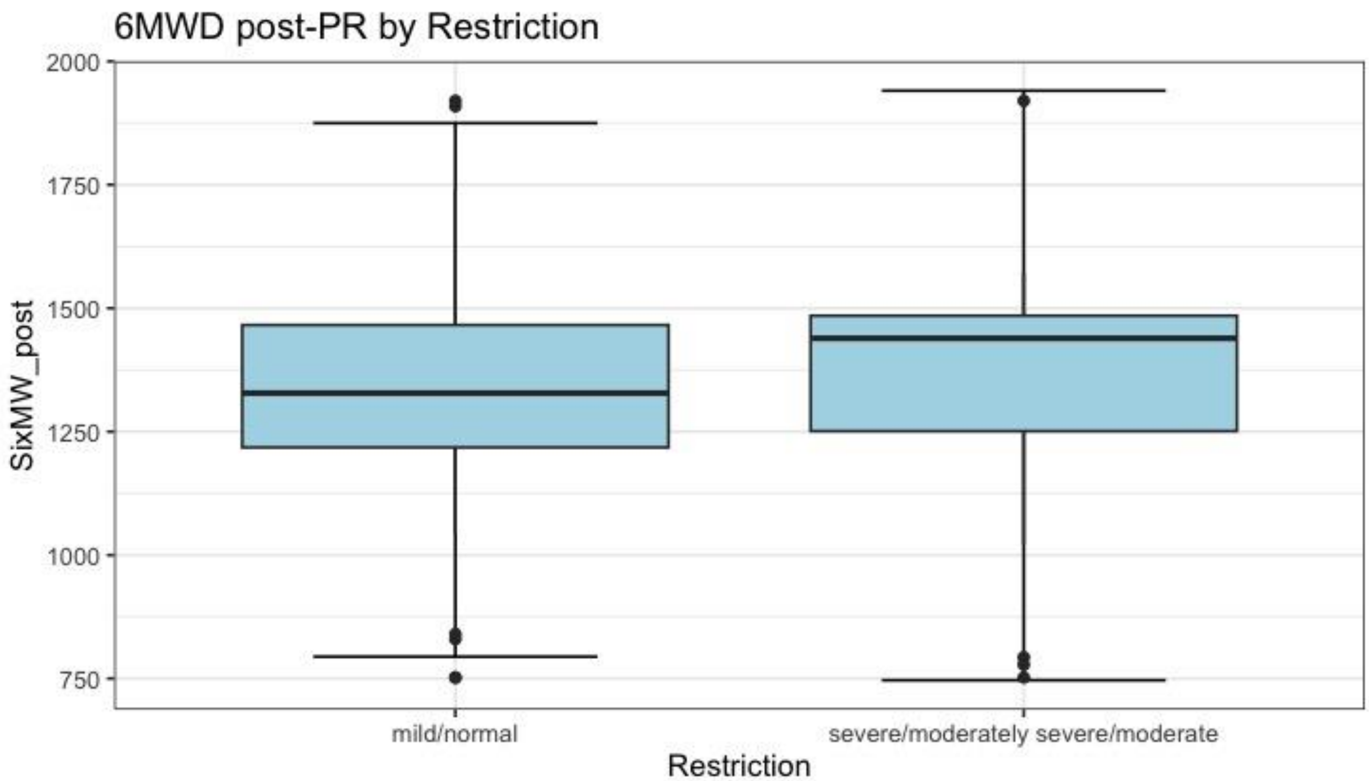
Characteristics	OR (95% CI)	*p*-value
Age (years)	12.8 [(-4.55) – 30.2]	0.145
BMI (Kg/m^2)	18.3 [(-6.17) – 42.8]	0.139
Race and ethnicity		
Non-Hispanic White	Reference	
Non-Hispanic Black	-132 [(-284.0) – 20.2]	0.088
Hispanic/Latino	-27.2 [(-160.0) – 106.0]	0.683
Sex		
Female	Reference	
Male	-68.2 [(-197) – 60.4]	0.292
Dyspnea at baseline		
Mild Dyspnea	Reference	
Moderate/Severe Dyspnea	-68.2 [(-160.0) – 106.0]	0.261
Pulmonary Restriction		
Normal lung function or mild	Reference	
Moderate to severe	**126.0 (2.14 – 250.0)**	**0.046**
Multimorbidity		
< 2 comorbid conditions	Reference	
≥ 2 comorbid conditions	- 109.0 [(-231.0) – 24.3]	0.107
Hospitalization Status		
Not Hospitalized	Reference	
Hospitalized	-3.63 [(-129.0) – 122.0]	
6MWD pre-PR	**0.57 (0.36 – 0.77)**	**<0.001**
Age (years):BMI(Kg/m^2)	-0.47 [(-0.91) – 0.02]	0.06

FIGURE 3.1A 6-MINUTE WALKING DISTANCE (6MWD) POST-PULMONARY REHABILITATION (PR) BY 6MWD PRE-PR (P = < 0.001)



Abbreviations: 6MWD pre – 6-minute walking distance before pulmonary rehabilitation; 6MWD post – 6-minute walking distance after pulmonary rehabilitation

FIGURE 3.1B 6-MINUTE WALKING DISTANCE (6MWD) POST-PULMONARY REHABILITATION (PR) BY PULMONARY RESTRICTION (*P* = 0.046)



Abbreviations: 6MWD pre – 6-minute walking distance before pulmonary rehabilitation; 6MWD post – 6-minute walking distance after pulmonary rehabilitation; mild/normal – normal lung function or mild pulmonary restriction; severe/moderately severe/moderate – moderate to severe pulmonary restriction

Multivariate Analysis for MCID in 6MWD at 30m

No factors included in the multivariate analysis for achieving MCID at 30m were shown to be significant.

Multivariate Analysis for MCID in 6MWD at 80m

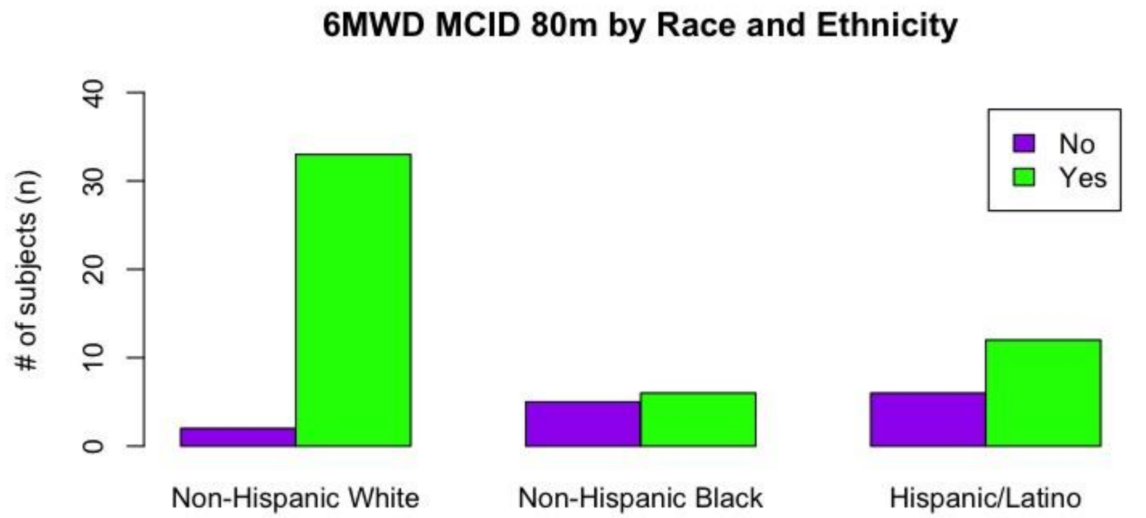
Table 3.8 presents the multivariate analysis of factors associated with achieving MCID at 80m for Long COVID patients who completed six weeks of pulmonary rehabilitation, revealing interesting insights. Age, sex, BMI, dyspnea, pulmonary restriction, hospitalization, and multimorbidity showed no significant association with achieving the MCID. However, race/ethnicity played a significant role. Non-Hispanic Black participants were significantly less likely to achieve the MCID than Non-Hispanic Whites, with an odds ratio of 0.048 (95% CI: 0.003 – 0.418, p = 0.012). Hispanic/Latino participants showed a trend towards lower likelihood, although not statistically significant, with an odds ratio of 0.132 (95% CI: 0.012 – 0.994, p = 0.064).

Figure 3.2 illustrates the MCID of 6MWD at 80m by race and ethnicity. No factors included in the multivariable analysis for MCID at 80, with depression, anxiety, or PTSD as the primary predictors, were shown to be significant.

TABLE 3.8 FACTORS ASSOCIATED WITH MCID AT 80 OF FOR LONG COVID SUBJECTS WHO COMPLETED 6-WEEKS OF PULMONARY REHABILITATION

Characteristic	OR (95% CI)	*p*-value
Age	0.991 (0.922 – 1.060)	0.794
Race/Ethnicity		
Non-Hispanic White	Reference	
Non-Hispanic Black	**0.048 (0.003 – 0.418)**	**0.012**
Hispanic or Latino	0.132 (0.012 – 0.994)	0.064
Sex		
Female	Reference	
Male	0.395 (0.050 – 2.740)	0.351
BMI	1.030 (0.939 – 1.150)	0.516
Dyspnea		
Mild	Reference	
Moderate to Severe	0.241 (0.018 – 1.830)	0.206
Pulmonary Restriction		
Normal lung function or mild	Reference	
Moderate to severe	2.130 (0.323 – 17.800)	0.447
Hospitalization Status		
Not Hospitalized	Reference	
Hospitalized	2.070 (0.374 – 12.800)	0.407
Multimorbidity		
< 2 comorbid conditions	Reference	
≥ 2 comorbid conditions	0.531 (0.074 – 3.570)	0.511
Abbreviations: BMI – body mass index		

FIGURE 3.2 MINIMAL CLINICALLY IMPORTANT DIFFERENCE IN 6-MINUTE WALKING DISTANCE AT 80 METERS BY RACE AND ETHNICITY ($p = 0.012$)



Multivariate Analysis for MCID in 6MWD at 108m

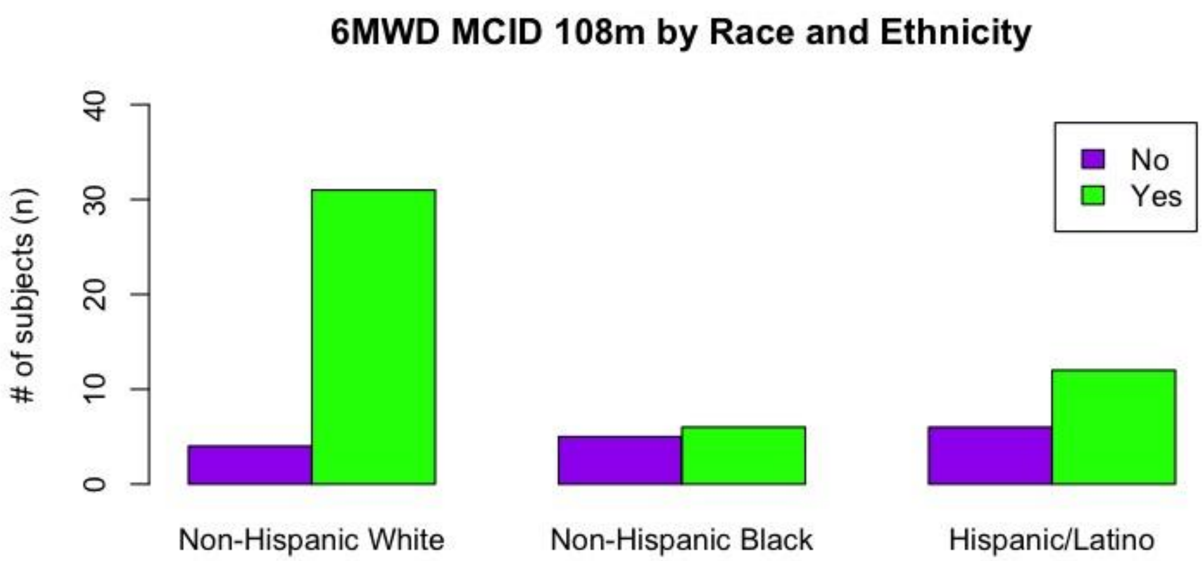
Table 3.9 presents the multivariate analysis of factors associated with achieving MCID at 108m for Long COVID patients who completed six weeks of PR, with dyspnea as the primary predictor, revealing some notable findings. Age, sex, BMI, restriction, hospitalization, and dyspnea severity did not show significant associations with achieving the MCID at 108m. However, race/ethnicity played a significant role. Non-Hispanic Black participants were significantly less likely to achieve MCID than Non-Hispanic White participants, with an odds ratio of 0.099 (95% CI: 0.010 - 0.718, p = 0.029). Hispanic/Latino participants also showed a lower likelihood of achieving the MCID, although not statistically significant, with an odds ratio of 0.473 (95% CI: 0.071 - 3.120, p = 0.427). These results suggest that race/ethnicity may be a crucial factor in the rehabilitation outcomes of Long COVID patients, particularly at the 108m distance, highlighting the importance of culturally sensitive interventions in this population.

Figure 3.3 illustrates the MCID of 6MWD at 108m by race and ethnicity. No factors included in the multivariable analysis for MCID at 108m, with depression, anxiety, or PTSD as the primary predictors, were shown to be significant.

TABLE 3.9 FACTORS ASSOCIATED WITH MCID AT 108 OF FOR LONG COVID SUBJECTS WHO COMPLETED 6-WEEKS OF PULMONARY REHABILITATION BY DYSPNEA

Characteristic	OR (95% CI)	*p*-value
Age	0.998 (0.933 - 1.070)	0.945
Race/Ethnicity		
Non-Hispanic White	Reference	
Non-Hispanic Black	**0.099 (0.010 - 0.718)**	**0.029**
Hispanic or Latino	0.473 (0.071 - 3.120)	0.427
Sex		
Female	Reference	
Male	0.453 (0.065 - 2.870)	0.401
BMI	1.040 (0.944 - 1.150)	0.474
Dyspnea		
Mild	Reference	
Moderate to severe	0.333 (0.034 - 2.170)	0.284
Pulmonary Restriction		
Normal lung function or mild	Reference	
Moderate to severe	5.330 (0.891 - 47.100)	0.091
Hospitalization Status		
Not Hospitalized	Reference	
Hospitalized	1.040 (0.212 - 5.130)	0.957
Multimorbidity		
< 2 comorbid conditions	Reference	
≥ 2 comorbid conditions	0.171 (0.023 - 0.975)	0.058
Abbreviations: BMI – body mass index		

FIGURE 3.3 MINIMAL CLINICALLY IMPORTANT DIFFERENCE IN 6-MINUTE WALKING DISTANCE AT 108 METERS BY RACE AND ETHNICITY (P = 0.029)



CHAPTER 4

Long COVID and Social Determinants of Health on Pulmonary Rehabilitation, Hospital Readmissions and Mortality

Specific Aim 3

To investigate the impact of socioeconomic disparities on participation in pulmonary rehabilitation and morbidity of Long COVID patients.

Hypothesis 3a. Long COVID patients with socioeconomic disparities are less likely to participate in pulmonary rehabilitation programs compared to patients without socioeconomic disparities.

Hypothesis 3b. Long COVID patients with socioeconomic disparities will have a lower likelihood of outpatient resources following Long COVID compared to patients without socioeconomic disparities, due to limited access to post-discharge care and resources.

Hypothesis 3c. Long COVID patients with socioeconomic disparities will exhibit a higher frequency of emergency room visits compared to those with without socioeconomic disparities, as socioeconomic barriers may hinder access to timely primary care and disease management resources, leading to exacerbations and complications.

Hypothesis 3d. Long COVID patients with socioeconomic disparities will have a higher rate of inpatient hospital admissions compared to those without socioeconomic disparities, potentially due to barriers in accessing preventive care and disease management resources.

METHODS

Data Source

Data were collected in February 2024 from the TriNetX Global Collaborative Network, which provided access to electronic health records (diagnoses, procedures, medications, laboratory values, genomic information) from approximately 90 million patients from 73 healthcare organizations. TriNetX, LLC complies with the Health Insurance Portability and Accountability Act (HIPAA), the US federal law protecting health care data's privacy and security, and any additional data privacy regulations applicable to the contributing healthcare organization (HCO). TriNetX is certified to the International Organization for Standardization (ISO) 27001:2013 standard and maintains an information security management system to ensure the protection of the healthcare data to which it has access and to meet the requirements of the HIPAA security rule. Any data displayed on the TriNetX platform in aggregate form or any patient-level data provided in a data set generated by the TriNetX platform only contains deidentified data, as per the deidentification standard defined in Section §164.514(a) of the HIPAA privacy rule. The process by which the data is deidentified is certified through a formal determination by a qualified expert as defined in Section §164.514(b)(1) of the HIPAA privacy rule. Because only deidentified patient records were used in this study and the study did not involve collecting, using, or transmitting individually identifiable data, this study did not require institutional review board approval. (Arranz-Herrero, 2023)

Measures

Outcome Variables

Pulmonary Rehabilitation Participation

Pulmonary rehabilitation participation was defined by the following code set shown in Table 4.1a**.**

Table 4.1a Code sets for Outcome Variables - Pulmonary Rehabilitation Participation

Description	Code	Standardized Vocabulary
pulmonary rehabilitation	UMLS:SNOMED:15081005	SNOMED
pulmonary rehabilitation program, non-physician provider, per diem	UMLS:HCPCS:S9473	HCPCS
physician or other qualified health care professional services for outpatient pulmonary rehabilitation; without continuous oximetry monitoring (per session)	UMLS:CPT:94625	CPT
physician or other qualified health care professional services for outpatient pulmonary rehabilitation; with continuous oximetry monitoring (per session)	UMLS:CPT:94626	CPT
pulmonary diagnostic testing, rehabilitation, and therapies	UMLS:CPT:1015099	CPT
physician or other qualified health care professional services for outpatient pulmonary rehabilitation	UMLS:CPT:1036835	CPT
Abbreviations: CPT - Current Procedural Terminology; HCPCS - Healthcare Common Procedure Coding System; SNOMED - Systematized Nomenclature of Medicine Clinical Terms		

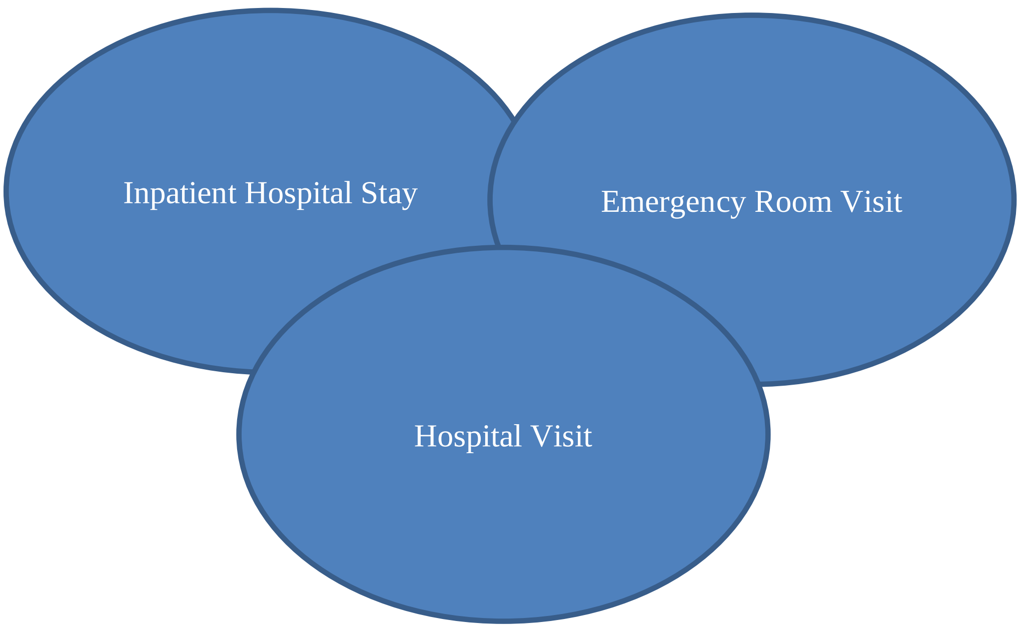
Morbidity

Morbidity was defined by hospital visits, emergency room visits and inpatient hospital stays using the following code sets shown in Table 4.1b. Figure 4.1 is a Venn diagram to illustrate that the cohorts of morbidity, including hospital visit, ER visit, and inpatient hospital stay could overlap with one another, indicating that a single hospital visit could involve an ER visit, an inpatient hospital stay, or both.

TABLE 4.1B CODE SETS FOR OUTCOME VARIABLES ON MORBIDITY

Variable	Description	Code	Standardized Vocabulary
Hospital Visit	visit	TNX:Visit	TNX
Emergency Room Visit	visit: emergency	UMLS:HL7V3.0:VisitType:EMER	UMLS
Inpatient Hospital Stay	visit: inpatient encounter	UMLS:HL7V3.0:VisitType:IMP	UMLS
Abbreviations: TNX – TriNetX coding; ULMS - Unified Medical Language System			

FIGURE 4.1 VENN DIAGRAM OF OUTCOME VARIABLES - MORBIDITY



Independent Variables

LONG COVID AND SOCIOECONOMIC DISPARITIES

Long COVID and socioeconomic disparities were defined by the following code sets shown in Table 4.2a**.**

TABLE 4.2A CODE SETS FOR INDEPENDENT VARIABLES - LONG COVID AND SOCIOECONOMIC DISPARITIES

Variable	Description	Code	Standardized Vocabulary
Long COVID			
	post COVID-19 condition	UMLS:ICD10CM:U09	ICD10
	post COVID-19 condition, unspecified	UMLS:ICD10CM:U09.9	ICD10
Socioeconomic Disparities			
	encounter for counseling for socioeconomic factors	UMLS:ICD10CM:Z71.88	ICD10
	extreme poverty	UMLS:ICD10CM:Z59.5	ICD10
	other problems related to housing and economic circumstances	UMLS:ICD10CM:Z59.89	ICD10
	problem related to housing and economic circumstances, unspecified	UMLS:ICD10CM:Z59.9	ICD10
	transportation insecurity	UMLS:ICD10CM:Z59.82	ICD10
	Food insecurity	UMLS:ICD10CM:Z59.41	ICD10
	financial insecurity	UMLS:ICD10CM:Z59.86	ICD10
	problems related to housing and economic circumstances	UMLS:ICD10CM:Z59	ICD10
	other problems related to housing and economic circumstances	UMLS:ICD10CM:Z59.8	ICD10
	persons with potential health hazards related to socioeconomic and psychosocial circumstances	UMLS:ICD10CM:Z55-Z65	ICD10
Abbreviations: ICD10 - International Classification of Diseases, Tenth Revision			

DIAGNOSIS AND MEDICATION USAGE

Diagnosis and medication usage were defined by the following code sets shown in Table 4.2b**.**

TABLE 4.2B CODE SETS FOR INDEPENDENT VARIABLES – DIAGNOSIS AND MEDICATION USAGE

Variable	Description	Code	Standardized Vocabulary
Diagnosis			
	factors influencing health status and contact with health services	Z00-Z99	ICD10
	overweight, obesity and other hyperalimentation	E65-E68	ICD10
	diabetes mellitus	E08-E13	ICD10
	asthma	J45	ICD10
	other chronic obstructive pulmonary disease	J44	ICD10
	other respiratory disorders	J98	ICD10
	other diseases of the respiratory system	J96-J99	ICD10
Medication Usage			
	antiasthma/bronchodilators	RE100	ICD10
	dexamethasone	3264	ICD10
	remdesivir	2284718	ICD10
Abbreviations: ICD10 - International Classification of Diseases, Tenth Revision			

Covariates

SOCIO-DEMOGRAPHICS

Socio-demographics included were age, sex, race and ethnicity, and were defined by the following code sets shown in Table 4.3**.**

TABLE 4.3 CODE SETS FOR SOCIO-DEMOGRAPHICS

Variable	Description	Code	Standardized Vocabulary
Age			
	age at index	49042-0	LOINC
Sex			
	male	76690-7	LOINC
	female	76689-9	LOINC
Race			
	White	2106-3	LOINC
	Black or African American	2054-5	LOINC
	Asian	2028-9	LOINC
	Other Race	2131-1	LOINC
Ethnicity			
	Hispanic or Latino	2135-2	LOINC
	Not Hispanic or Latino	2186-5	LOINC

Abbreviations: LOINC - Logical Observation Identifiers Names and Codes

Cohort Definition

Two cohorts were defined for this analysis: Long COVID with Socioeconomic Disparities and Long COVID without Socioeconomic Disparities.

Long COVID with Socioeconomic Disparities included patients who met the following criteria. At least age 18 years or older at the time of the event, a positive diagnosis of Post COVID-19 condition, as well as the occurrence of any socioeconomic disparity issues within 5 years before or up to 5 years after the first instance of Long COVID. The specific diagnoses related to socioeconomic factors, were, extreme poverty, housing and economic circumstances, transportation insecurity, food insecurity, financial insecurity, and other related issues.
Long COVID without Socioeconomic Disparities included patients who met the following criteria. At least age 18 years or older at the time of the event, a positive diagnosis of Post COVID-19 condition, with no occurrence of socioeconomic disparities within 5 years before or up to 5 years after the first instance of Long COVID. The specific diagnoses related to socioeconomic factors that were excluded were, extreme poverty, housing and economic circumstances, transportation insecurity, food insecurity, financial insecurity, and other related issues.

Patients were excluded from the study if they had cancer, defined by a positive diagnosis of Neoplasms (UMLS:ICD10CM:C00-D49) in the TriNetX database. This exclusion was implemented to ensure that the study focused specifically on outcomes related to Long COVID and PR, without the potential confounding effects of cancer and its treatments. Cancer patients often have unique health considerations and may undergo treatments that could significantly impact their health status and outcomes, making it important to study Long COVID outcomes in a more homogenous population.

Propensity Score Matching

Propensity score matching was performed on all listed characteristics, including diagnosis, medication use, and socio-demographics, to balance the cohorts.

Statistical Analysis

Analysis Setup

We exclusively utilized statistical packages available within the TriNetX version 9.0 database for propensity score matching and cohort balancing, leveraging the platform's integrated tools for comprehensive data analysis.

The analysis process included defining the index event and outcomes criteria and setting up and running the analysis. The index event for each patient was defined as the first instance of meeting the criteria for Long COVID. The outcomes were analyzed within a time window starting one day after the index event and ending 1095 days after the index event.

The index event for Long COVID patients with socioeconomic disparities was defined as when the following terms in this group occurred at any time. Patients had to have (1) Post COVID-19 condition (at least 18 years old at the time of the event); or (2) Post COVID-19 condition, unspecified (at least 18 years old at the time of the event).

They also had to have any instance of a socioeconomic disparity that occurred within five years before or up to 5 years after the first instance of Long COVID.

Analyses Specifications in TriNetX

The Compare Outcomes Analytic TriNetX function, supports four types of analyses: Measure of Association, Survival, Number of Instances, and Lab result distribution. The first three analyses support the "exclude patients with outcomes prior to the window" setting. This option can exclude patients from the analysis if they are not at risk for an outcome (e.g. if the outcome is a chronic disease). When "exclude patients with the outcome prior to the time window" is not checked, all patients in the cohort are included in the analysis, regardless of whether they had the outcome prior to the time window. When "exclude patients with the outcome prior to the time window" is checked, patients are excluded from the analysis if their record includes the outcome prior to the beginning of the time window. This selection will exclude all patients with the outcome prior to the index event. If the start of the time window for the analysis falls some days after the index event, patients will also be excluded if they have the outcome between the index event and the start of the time window.

Measure of Association Analysis in TriNetX

The Measure of Association Analysis TriNetX function, calculates and compares the fraction of patients with the selected outcome. The output summary includes: Patients in each Cohort (count of patients meeting query criteria); Patients with Outcome in each Cohort (of the patients in the cohort, count of patients that had the outcome in the time window); and Risk (the fraction of patients in the cohort that have the outcome in the time window, i.e. Patients with Outcome / Patients in Cohort). In addition, Risk Difference (the difference in the risks in Cohort 1 and Cohort 2), Risk Ratio (the ratio of the risks in Cohort 1 and Cohort 2), and Odds Ratio (the ratio of the odds in Cohort 1 and Cohort 2). The bar chart shows the risk of the outcome for both cohorts.

Survival Analysis in TriNetX

The Kaplan-Meier Analysis TriNetX function, estimates probability of the outcome at a respective time interval (daily time interval is used in this analysis). In order to account for the patients who exited the cohort during the analysis period, and therefore should not be included in the analysis, censoring is applied. In this analysis, patients are removed from the analysis (censored) after the last fact in their record.

The output summary includes: Patients in each Cohort (count of patients meeting query criteria); Patients with Outcome (of the patients in the cohort, count of patients that had the outcome in the time window); Median Survival (the number of days when the survival drops below 50%; the "-" indicates that survival does not drop below 50% during the time window); and Survival Probability at End of Time Window (the % survival at the end of the time window). In addition, Log-Rank test, Hazard Ratio and test for Proportionality.

Number of Instances Analysis in TriNetX

The Number of Instances Analysis calculates how many times the outcome occurred in the time window. The output summary includes: Patients in Cohort (count of patients meeting query criteria); Patients with Outcome (of the patients in the cohort, count of patients that had the outcome in the time window); Mean (mean of the counts); Standard Deviation (standard deviation of the counts); Median (median of the counts); and Median (1+ instances) when patients with zero instances included in the analysis. In addition, T-Test statistics testing for the difference between the cohorts is included.

RESULTS

Before propensity score matching, the cohort of Long COVID patients with socioeconomic disparities consisted of 4,396 patients, while the cohort without disparities consisted of 59,487 patients. After matching, both cohorts were reduced to 4,388 patients each.

Propensity Score Density Function: The propensity score density function before and after matching showed a shift in the distribution for both groups. Before matching, the density function for Long COVID patients with socioeconomic disparities was more spread out compared to Long COVID patients without socioeconomic disparities. After matching, the density functions became more aligned, indicating better balance between the two groups.

Characteristics Before Propensity Score Matching: Before matching, the two groups differed in several demographic and diagnostic characteristics. Long COVID patients with socioeconomic disparities were slightly younger (mean age 49.4 ± 16.4 years) compared to those without disparities (mean age 50.2 ± 16.6 years). The distribution of race and ethnicity also differed, with the disparity group having higher proportions of Black or African American, Hispanic or Latino, and Asian subjects compared to the non-disparity group.

In terms of diagnosis, the disparity group had higher proportions of various health conditions, including factors influencing health status and contact with health services, overweight, obesity, diabetes mellitus, asthma, other chronic obstructive pulmonary disease, other respiratory disorders, and other diseases of the respiratory system compared to the non-disparity group.

Characteristics After Propensity Score Matching: After propensity score matching, the demographic and diagnostic characteristics between the two groups were more balanced. The mean age, sex distribution, and racial and ethnic composition were similar between the two groups. The proportions of various health conditions were also comparable after matching, indicating improved balance between the groups. Table 4.4 presents the patient count for the Long COVID sample analyzed within our study before and after propensity score matching. Figure 4.2 illustrates the propensity score density function - before and after matching for each cohort (with or without socioeconomic disparities). Table 4.5A presents the baseline characteristics for each cohort before propensity score matching. Table 4.5B presents each cohorts' baseline characteristics after propensity score matching.

TABLE 4.4 COHORT 1 (LONG COVID PATIENTS WITH SOCIOECONOMIC DISPARITIES) AND COHORT 2 (LONG COVID PATIENTS WITHOUT SOCIOECONOMIC DISPARITIES) PATIENT COUNT BEFORE AND AFTER PROPENSITY SCORE MATCHING

	Cohort	Patient count before matching	Patient count after matching
1	Long COVID w SES disparities	4,396	4,388
2	Long COVID w/o SES disparities	59,487	4,388

FIGURE 4.2 PROPENSITY SCORE DENSITY FUNCTION – BEFORE (A) AND AFTER (B) MATCHING (LONG COVID WITH SES DISPARITIES - PURPLE, LONG COVID W/O SES DISPARITIES - GREEN)

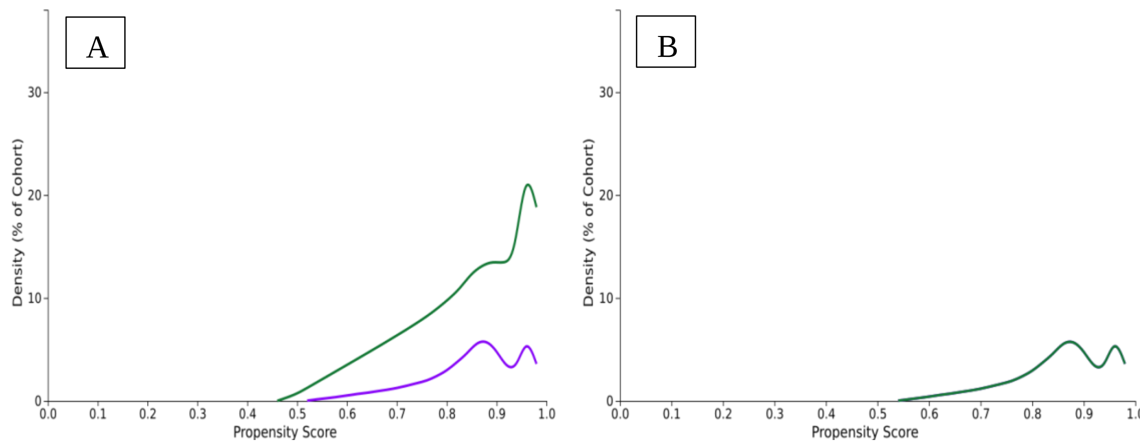


TABLE 4.5A COHORT 1 (N = 4,396) AND COHORT 2 (N = 59,487) BASELINE CHARACTERISTICS BEFORE PROPENSITY SCORE MATCHING

Demographics

Cohort			Mean ± SD	Patients	% of Cohort	*p*-value	Std diff.
1 2	AI	Age at Index	49.4 ± 16.4 50.2 ± 16.6	4,396 59,486	100% 100%	0.003	0.047
1 2	2106-3	White		2,929 40,455	66.6% 68.0%	0.059	0.029
1 2	F	Female		2,857 36,584	65.0% 61.5%	<0.001	0.072
1 2	2186-5	Not Hispanic or Latino		3,387 40,427	77.0% 68.0%	<0.001	0.205
1 2	2135-2	Hispanic or Latino		470 4,642	10.7% 7.8%	<0.001	0.100
1 2	2054-5	Black or African American		661 5,598	15.0% 9.4%	<0.001	0.172
1 2	M	Male		1,520 22,417	34.6% 37.7%	<0.001	0.065
1 2	2131-1	Other Race		168 2,540	3.8% 4.3%	0.155	0.023
1 2	2028-9	Asian		109 2,353	2.5% 4.0%	<0.001	0.084

Diagnosis

Cohort			Patients	% of Cohort	*p*-value	Std diff.
1 2	Z00- Z99	Factors influencing health status and contact with health services	3,530 24,406	80.3% 41.0%	<0.001	0.878
1 2	E65- E68	Overweight, obesity and other hyperalimentation	981 5,855	22.3% 9.8%	<0.001	0.345
1 2	E08- E13	Diabetes mellitus	930 5,668	21.2% 9.5%	<0.001	0.327
1 2	J45	Asthma	677 4,512	15.4% 7.6%	<0.001	0.247

1 2	J44	Other chronic obstructive pulmonary disease	348 1,859	7.9% 3.1%	<0.001	0.211
1 2	J98	Other respiratory disorders	454 2,084	10.3% 3.5%	<0.001	0.271
1 2	J96- J99	Other diseases of the respiratory system	802 4,915	18.2% 8.3%	<0.001	0.298
Medication						
Cohort			Patients	% of Cohort	*p*-value	Std diff.
1 2	RE100	Antiasthma/ Bronchodilators	1,829 15,656	41.6% 26.3%	<0.001	0.327
1 2	3264	Dexamethasone	659 5,491	15.0% 9.2%	<0.001	0.177
1 2	22847 18	Remdesivir	276 1,984	6.3% 3.3%	<0.001	0.138

TABLE 4.5B COHORT 1 (N = 4,388) AND COHORT 2 (N = 4,388) BASELINE CHARACTERISTICS AFTER PROPENSITY SCORE MATCHING

Demographics

Cohort			Mean ± SD	Patients	% of Cohort	*p*-value	Std diff.
1 2	AI	Age at Index	49.4 ± 16.4 49.7 ± 16.4	4,388 4,388	100% 100%	0.373	0.019
1 2	2106-3	White		2,928 2,980	66.7% 67.9%	0.237	0.025
1 2	F	Female		2,851 2,857	65.0% 65.1%	0.893	0.003
1 2	2186-5	Not Hispanic or Latino		3,380 3,523	77.0% 80.3%	<0.001	0.080
1 2	2135-2	Hispanic or Latino		469 433	10.7% 9.9%	0.206	0.027
1 2	2054-5	Black or African American		655 687	14.9% 15.7%	0.343	0.020
1 2	M	Male		1,518 1,515	34.6% 34.5%	0.946	0.001
1 2	2131-1	Other Race		168 147	3.8% 3.4%	0.228	0.026
1 2	2028-9	Asian		109 99	2.5% 2.3%	0.483	0.015

Diagnosis

Cohort			Mean ± SD	Patients	% of Cohort	*p*-value	Std diff.
1 2	Z00-Z99	Factors influencing health status and contact with health services		3,522 3,514	80.3% 80.1%	0.830	0.005
1 2	E65-E68	Overweight, obesity and other hyperalimentation		974 923	22.2% 21.0%	0.186	0.028
1 2	E08-E13	Diabetes mellitus		922 895	21.0% 20.4%	0.477	0.015
1 2	J45	Asthma		672 701	15.3% 16.0%	0.394	0.018

1 2	J44	Other chronic obstructive pulmonary disease		342 326	7.8% 7.4%	0.520	0.014
1 2	J98	Other respiratory disorders		446 401	10.2% 9.1%	0.104	0.035
1 2	J96- J99	Other diseases of the respiratory system		794 726	18.1% 16.5%	0.055	0.041
Medication							
Cohort			Mean ± SD	Patients	% of Cohort	*p*-value	Std diff.
1 2	RE100	Antiasthma/ Bronchodilators		1,821 1,776	41.5% 40.5%	0.329	0.021
1 2	3264	Dexamethasone		655 585	14.9% 13.3%	0.032	0.046
1 2	22847 18	Remdesivir		274 230	6.2% 5.2%	0.044	0.043

Pulmonary Rehabilitation

Pulmonary rehabilitation participation indicates that a patient went to pulmonary rehabilitation at least on one occasion. Table 4.6 presents the results of participation in pulmonary rehabilitation of Long COVID patients with and without socioeconomic disparities.

Risk Analysis: In the risk analysis for pulmonary rehabilitation, Long COVID patients with socioeconomic disparities had 4,388 patients, of which 952 had the outcome of interest, resulting in a risk of 0.217. Long COVID patients without socioeconomic disparities also had 4,388 patients, with 886 experiencing the outcome, resulting in a risk of 0.202. The risk difference between the two cohorts was 0.015 (95% CI -0.002 to 0.032), with a risk ratio of 1.074 (95% CI 0.991 to 1.166) and an odds ratio of 1.095 (95% CI 0.988 to 1.214). While the risk difference was not statistically significant ($p = 0.083$), there may be a trend toward higher risk in the socioeconomic disparity group. Table 4.6a presents the risk analysis results comparing the participation in pulmonary rehabilitation (PR) across Long COVID patients with socioeconomic disparities and those without socioeconomic disparities. Figure 4.3a illustrates the risk of pulmonary rehabilitation visits of Long COVID patients with and without socioeconomic disparities.

Kaplan-Meier Analysis: Both cohorts had 4,388 patients, with 952 Long COVID patients with socioeconomic disparities and 886 Long COVID patients without socioeconomic disparities experiencing the outcome. The median survival time was not calculable, but the probability of not experiencing the outcome (PR) by the end of the study period is 66.80% for patients with socioeconomic disparities and 67.39% for patients without socioeconomic disparities. These findings suggest a slightly lower probability of PR in the group with socioeconomic disparities, but the difference is minimal. The log rank compares the curves of the groups. The test statistic is $\chi 2 = 3.332$ with 1 degree of freedom and a p-value of 0.068. This p-value suggests no statistically significant difference in the PR outcomes between the two cohorts, although it is close to the significance level of 0.05. The hazard ratio (HR) measures how quickly participation in PR is likely to happen in one group compared to another. The HR was 1.089 (95% CI 0.994 to 1.193), with no evidence of a significant difference in hazard between the two groups (p = 0.201).Table 4.6b presents the Kaplan-Meier analysis results comparing the outcomes of participating in pulmonary rehabilitation (PR) of Long COVID patients with and without socioeconomic disparities. Figure 4.3b illustrates the Kaplan-Meier curve of pulmonary rehabilitation visits of Long COVID patients with and without socioeconomic disparities.

Number of Instances Analysis: For Long COVID patients with socioeconomic disparities, the mean number of PR instances is 4.881, with a standard deviation of 11.088. This finding means that, on average, patients in this group underwent PR about 4.881 times, but the variation is relatively high. Meanwhile, the mean number of PR instances for patients without socioeconomic disparities is 4.030, with a standard deviation of 7.545.

Similarly, on average, patients without socioeconomic disparities underwent PR about 4.030 times, with less variation than those with socioeconomic disparities. The median number of PR instances for patients with socioeconomic disparities is 2, indicating that half of the patients in this group underwent PR twice or fewer times. The median number of PR instances for the patients without socioeconomic disparities is 1, indicating that half of the patients in this group underwent PR once or twice. The t-test statistic is 1.909 with 1836 degrees of freedom and a p-value of 0.056.

Table 4.6c presents the number of instances of pulmonary rehabilitation (PR) of Long COVID patients with and without socioeconomic disparities. Figure 4.3c illustrates a histogram of the number of pulmonary rehabilitation visits of Long COVID patients with and without socioeconomic disparities.

TABLE 4.6 PARTICIPATION IN PULMONARY REHABILITATION OF LONG COVID PATIENTS WITH AND WITHOUT SOCIOECONOMIC DISPARITIES.

TABLE 4.6A RISK ANALYSIS RESULTS COMPARING THE PARTICIPATION IN PULMONARY REHABILITATION ACROSS LONG COVID PATIENTS WITH SOCIOECONOMIC DISPARITIES AND THOSE WITHOUT SOCIOECONOMIC DISPARITIES

Cohort	Patients in cohort	Patients with outcome	Risk
1 Long COVID with Socioeconomic Disparities	4,388	952	0.217
2 Long COVID without Socioeconomic Disparities	4,388	886	0.202

		95% CI	z	*p*
Risk Difference	0.015	(-0.002, 0.032)	1.731	0.083
Risk Ratio	1.074	(0.991, 1.166)	N/A	N/A
Odds Ratio	1.095	(0.988, 1.214)	N/A	N/A

FIGURE 4.3A RISK OF PULMONARY REHABILITATION PARTICIPATION ACROSS LONG COVID PATIENTS WITH (PURPLE) AND WITHOUT (GREEN) SOCIOECONOMIC DISPARITIES

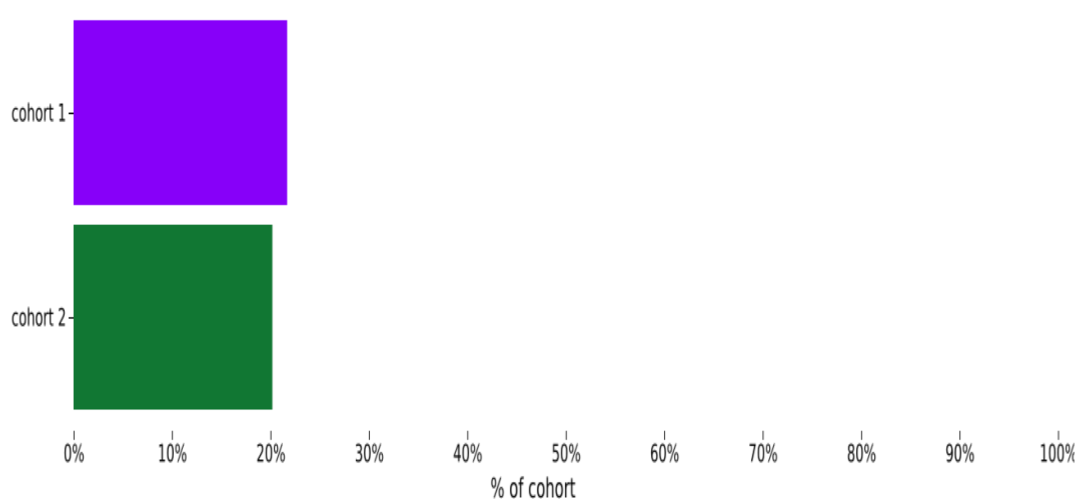


TABLE 4.6B KAPLAN-MEIER ANALYSIS RESULTS COMPARING THE OUTCOMES OF PARTICIPATING IN PULMONARY REHABILITATION OF LONG COVID PATIENTS WITH AND WITHOUT SOCIOECONOMIC DISPARITIES

Cohort	Patients in cohort	Patients with outcome	Median (days)	Probability at end of time window
1 Long COVID with Socioeconomic Disparities	4,388	952	--	66.80%
2 Long COVID without Socioeconomic Disparities	4,388	886	--	67.39%

	χ^2	df	*p*
Log-Rank Test	3.332	1	0.068

	Hazard Ratio	95% CI	χ^2	df	*p*
Hazard Ratio and Proportionality	1.089	(0.994, 1.193)	1.633	1	0.201

FIGURE 4.3B: KAPLAN-MEIER CURVE ON PULMONARY REHABILITATION PARTICIPATION ACROSS LONG COVID PATIENTS WITH (PURPLE) AND WITHOUT (GREEN) SOCIOECONOMIC DISPARITIES

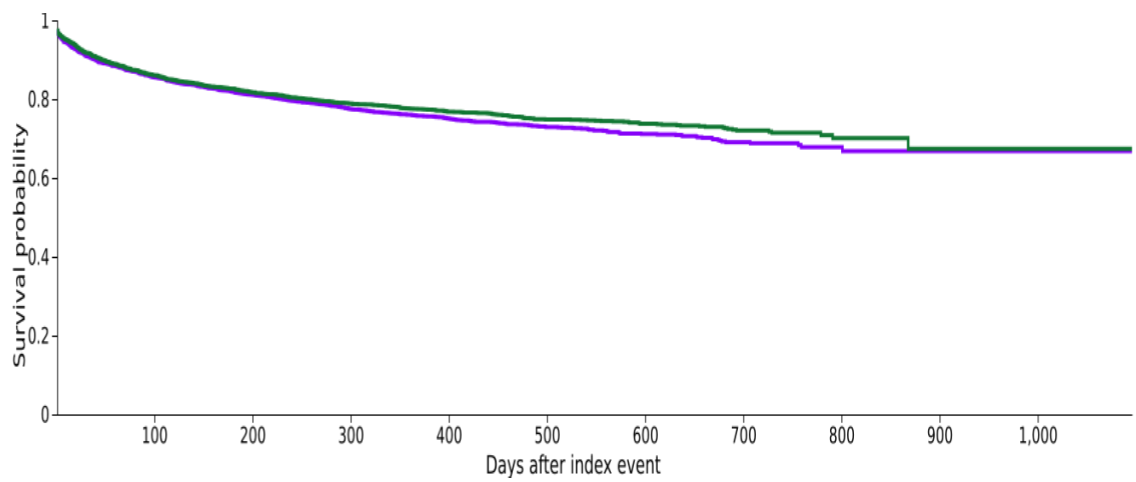
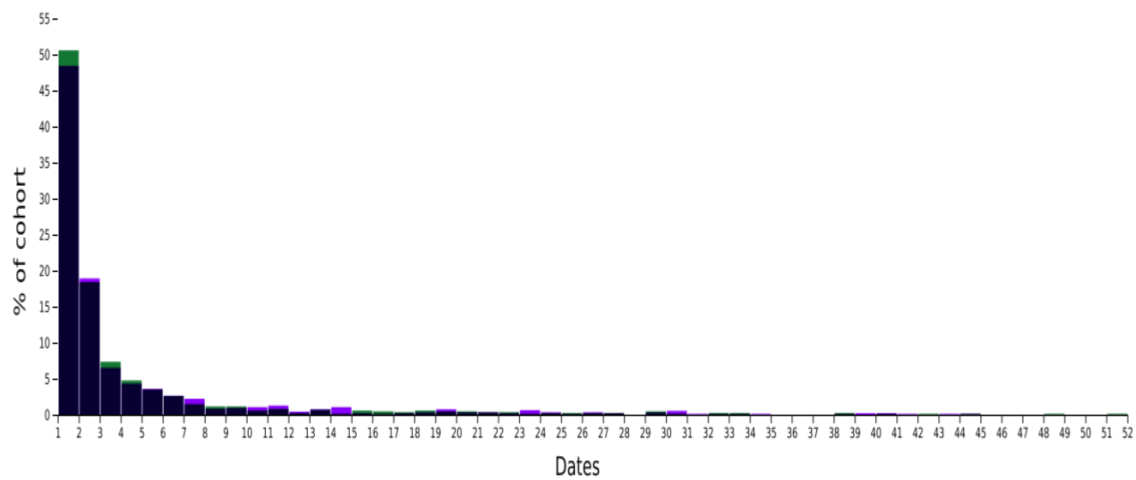


TABLE 4.6C NUMBER OF INSTANCES OF PULMONARY REHABILITATION OF LONG COVID PATIENTS WITH AND WITHOUT SOCIOECONOMIC DISPARITIES

Cohort	Patients in cohort	Patients with outcome	Mean	SD	Median
1 Long COVID with Socioeconomic Disparities	4,388	952	4.881	11.088	2
2 Long COVID without Socioeconomic Disparities	4,388	886	4.030	7.545	1

	t	df	*p*
Test Statistics	1.909	1836	0.056

FIGURE 4.3C: NUMBER OF INSTANCES OF PULMONARY REHABILITATION PARTICIPATION ACROSS LONG COVID PATIENTS WITH (PURPLE) AND WITHOUT (GREEN) SOCIOECONOMIC DISPARITIES



10 data points for Cohort 1 and 4 data points for Cohort 2 were omitted for display purposes.

Hospital Visits

Hospital visits indicate that patients presented themselves at the hospital. Table 4.7 presents the results of hospital visits of Long COVID patients with and without socioeconomic disparities.

Risk Analysis: The risk difference between the two cohorts is 0.022, which means that the absolute difference in the proportion of patients with hospital visits between the two groups is 2.2 percentage points. The risk ratio has a value of 1.023 for Long COVID patients with socioeconomic disparities, meaning that the risk of hospital visits is 2.3% higher in Long COVID patients with socioeconomic disparities than those without socioeconomic disparities. The odds ratio is 1.507, meaning that the odds of hospital visits are 50.7% higher for Long COVID patients with socioeconomic disparities than those without socioeconomic disparities. All values were statistically significant, indicating a higher risk of hospital visits in Long COVID patients with socioeconomic disparities. Table 4.7a presents the risk analysis results comparing the hospital visits of Long COVID patients with and without socioeconomic disparities. Figure 4.4a illustrates the risk of hospital visits of Long COVID patients with and without socioeconomic disparities.

Kaplan-Meier Survival Analysis: For Long COVID patients with socioeconomic disparities, the median time to hospital visit was seven days. This finding means that half of the patients in this group experienced a hospital visit within seven days. For those without socioeconomic disparities, the median time to hospital visit was ten days, indicating that half experienced a hospital visit within ten days. The probability of not experiencing a hospital visit by the end of the study period is 0.00% for both cohorts, suggesting that all patients in both groups experienced a hospital visit within three years. The log-rank test statistic is $\chi2 = 76.226$ with 1 degree of freedom and a p-value of <0.001, indicating a significant difference in the time to a hospital visit between Long COVID patients with and without socioeconomic disparities. A hazard ratio (HR) of 1.208 (95% CI 1.157, 1.261) suggests that, on average, the risk of experiencing a hospital visit is 20.8% higher in the group with socioeconomic disparities than in the group without. Table 4.7b presents the Kaplan-Meier analysis comparing the outcomes of hospital visits of Long COVID patients, with and without socioeconomic disparities. Figure 4.4b illustrates a Kaplan-Meier curve of hospital visits of Long COVID patients with and without socioeconomic disparities.

Number of Instances Analysis: Long COVID patients with socioeconomic disparities had a mean number of hospital visits of 33.091 ± 43.967, meaning, on average, patients in this group had about 33 hospital visits, but there is a wide variation in the number of visits. The mean number of hospital visits for patients without socioeconomic disparities is 25.589 ± 33.254. Similarly, on average, these patients had about 26 hospital visits, with less variation. The median number of hospital visits for those with socioeconomic disparities was 17, indicating that half of this group had 17 or fewer hospital visits. Meanwhile, the median number of hospital visits for patients without socioeconomic disparities is 14, indicating that half of this group had 14 or fewer hospital visits. The t-test statistic is 8.739 with 8272 degrees of freedom and a p-value of <0.001, suggesting a significantly higher number of hospital visits on average for Long COVID with socioeconomic disparities than those without. Table 4.7c presents the number of hospital visits of Long COVID patients with and without socioeconomic disparities. Figure 4.4c illustrates a histogram of the number of instances of hospital visits across Long COVID Patients with (Purple) and without (Green) Socioeconomic Disparities.

Table 4.7 Hospital Visits

Table 4.7a Risk Analysis Results comparing Hospital Visits across Long COVID Patients with Socioeconomic Disparities and those without Socioeconomic Disparities

Cohort	Patients in cohort	Patients with outcome	Risk
1 Long COVID with Socioeconomic Disparities	4,388	4,185	0.954
2 Long COVID without Socioeconomic Disparities	4,388	4,089	0.932

		95% CI	z	*p*
Risk Difference	0.022	(0.012, 0.032)	4.413	< 0.001
Risk Ratio	1.023	(1.013, 1.034)	N/A	N/A
Odds Ratio	1.507	(1.255, 1.811)	N/A	N/A

Figure 4.4a Risk of Hospital Visits across Long COVID Patients with (Purple) and without (Green) Socioeconomic Disparities

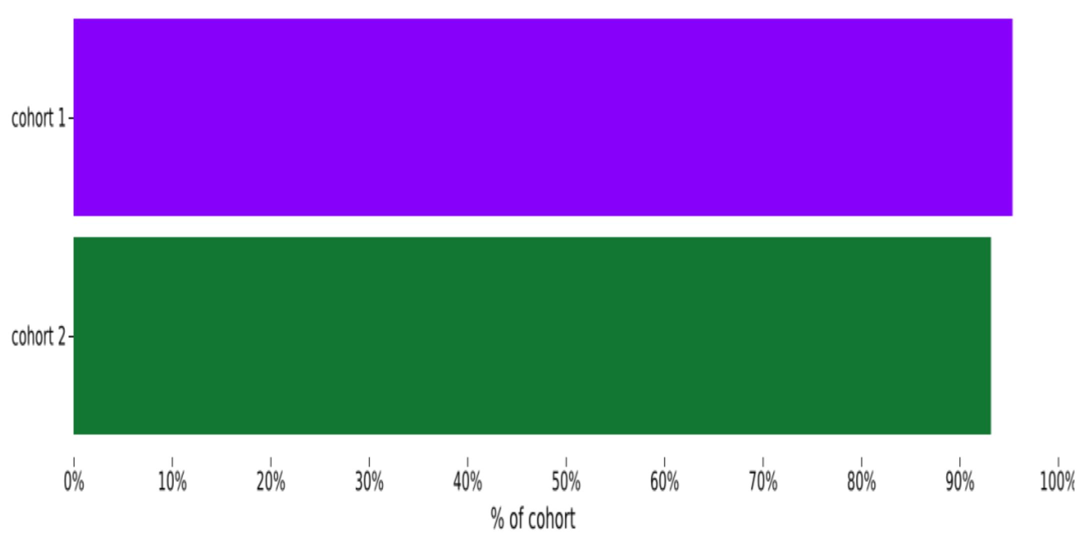


TABLE 4.7B KAPLAN-MEIER ANALYSIS RESULTS COMPARING THE OUTCOMES OF A HOSPITAL VISIT OF LONG COVID PATIENTS WITH AND WITHOUT SOCIOECONOMIC DISPARITIES

Cohort	Patients in cohort	Patients with outcome	Median (days)	Probability at end of time window
1 Long COVID with Socioeconomic Disparities	4,388	4,185	7	0.00%
2 Long COVID without Socioeconomic Disparities	4,388	4,089	10	0.00%

	χ^2	df	*p*
Log-Rank Test	76.226	1	< 0.001

	Hazard Ratio	95% CI	χ^2	df	*p*
Hazard Ratio and Proportionality	1.208	(1.157, 1.261)	5.237	1	0.022

FIGURE 4.4B KAPLAN-MEIER CURVE ON HOSPITAL VISITS ACROSS LONG COVID PATIENTS WITH (PURPLE) AND WITHOUT (GREEN) SOCIOECONOMIC DISPARITIES

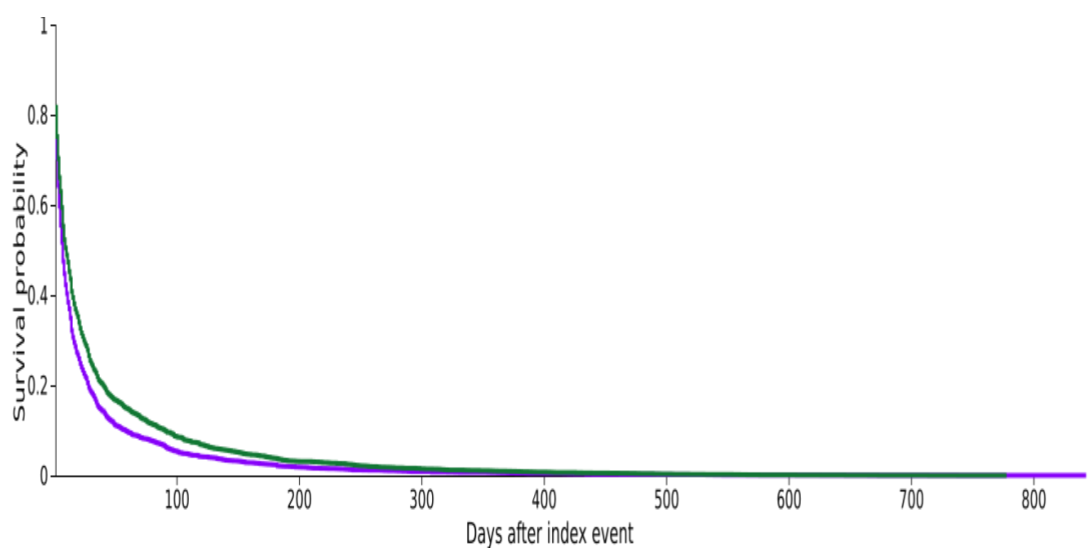
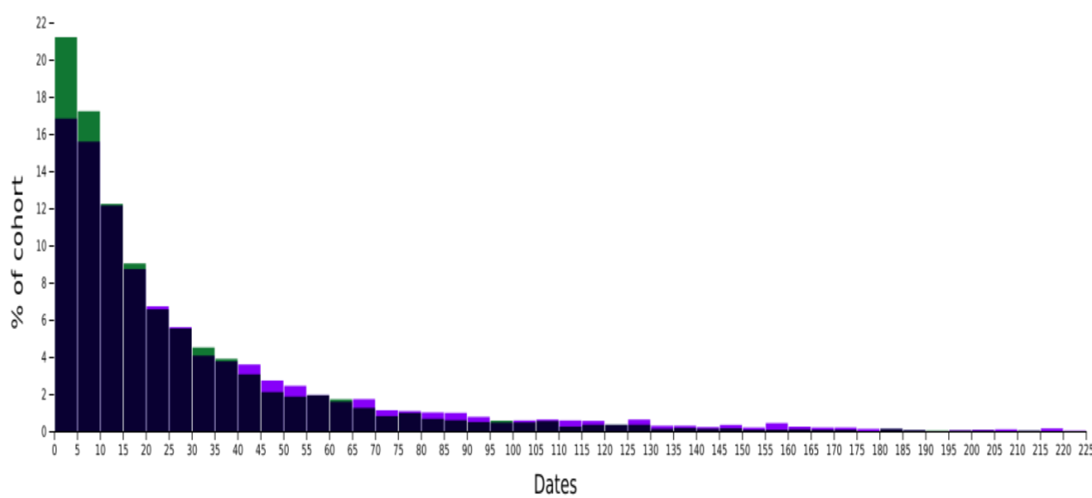


TABLE 4.7C NUMBER OF INSTANCES OF HOSPITAL VISITS OF LONG COVID PATIENTS WITH AND WITHOUT SOCIOECONOMIC DISPARITIES

Cohort	Patients in cohort	Patients with outcome	Mean	SD	Median
1 Long COVID with Socioeconomic Disparities	4,388	4,185	33.091	43.967	17
2 Long COVID without Socioeconomic Disparities	4,388	4,089	25.589	33.254	14

	t	df	*p*
Test Statistics	8.739	8272	< 0.001

FIGURE 4.4C NUMBER OF INSTANCES OF HOSPITAL VISITS ACROSS LONG COVID PATIENTS WITH (PURPLE) AND WITHOUT (GREEN) SOCIOECONOMIC DISPARITIES



38 data points for Cohort 1 and 15 data points for Cohort 2 were omitted for display purposes.

Emergency Room Visits

Emergency room visit indicates that a patient presented themselves to an emergency room at some point in time. Table 4.8 presents the results of emergency room (ER) visits of Long COVID patients with and without socioeconomic disparities.

Risk Analysis: The risk difference between the two cohorts is 0.070 (95% CI 0.051, 0.088), which means that the absolute difference in the proportion of patients with ER visits between the groups is 7.0. The risk ratio has a value of 1.294 (95% CI 1.207, 1.386), which means that the risk of ER visits is 29.4% higher in the group with socioeconomic disparities than in the group without. The odds ratio is 1.424 (95% CI 1.295, 1.565), meaning the odds of ER visits are 42.4% higher in Long COVID patients with socioeconomic disparities than those without. Table 4.8a presents the risk analysis results comparing the ER visits of Long COVID patients with and without socioeconomic disparities. Figure 4.5a illustrates the risk of ER visits across Long COVID patients with and without socioeconomic disparities.

Kaplan-Meier Survival Analysis: For Long COVID patients with socioeconomic disparities, the median time to an ER visit is 724 days, meaning that half of the patients experienced an ER visit within 724 days. For those without socioeconomic disparities, the median time to an ER visit is 953 days, indicating that half of the patients in this group experienced an ER visit within 953 days. The probability of not experiencing an ER visit by the end of the study period is 45.81% for patients with socioeconomic disparities and 49.79% for those without socioeconomic disparities. The test statistic is $\chi 2 = 70.958$ with 1 degree of freedom and a p-value of <0.001, indicating a significant difference in the time to an ER visit between Long COVID patients with and without socioeconomic disparities. An HR of 1.413 (95% CI 1.304, 1.533) suggests that, on average, the risk of experiencing an ER visit is 41.3%

higher in the group with socioeconomic disparities than in the group without. Table 4.8b presents the Kaplan-Meier curve results comparing the outcomes of ER visits of Long COVID patients with and without socioeconomic disparities. Figure 4.5b illustrates the Kaplan-Meier curve for ER visits across Long COVID patients with and without socioeconomic disparities.

Number of Instances Analysis: For Long COVID patients with socioeconomic disparities, the mean number of ER visits is 3.114 ± 4.546, meaning, on average, patients in this group had about 3.114 ER visits, with a relatively high variation in the number of visits. The mean number of ER visits for those without socioeconomic disparities is 2.321 ± 2.648. Similarly, on average, these patients had about 2.321 ER visits, with less variation. The median number of ER visits for Long COVID patients with socioeconomic disparities is two, indicating that half had two or fewer ER visits. Meanwhile, the median number of ER visits for Long COVID patients without socioeconomic disparities is one, indicating that half of this group had one or fewer ER visits. The t-test statistic is 5.012 with 2388 degrees of freedom and a p-value of <0.001. Table 4.8c presents the number of hospital visits of Long COVID patients with and without socioeconomic disparities. Figure 4.5c illustrates a histogram of the number of instances of ER visits across Long COVID patients with and without socioeconomic disparities.

Table 4.8 Emergency Room Visits

Table 4.8a Risk Analysis Results comparing Emergency Room Visits across Long COVID patients with and without Socioeconomic Disparities

Cohort	Patients in cohort	Patients with outcome	Risk
1 Long COVID with Socioeconomic Disparities	4,388	1,348	0.307
2 Long COVID without Socioeconomic Disparities	4,388	1,042	0.237

		95% CI	z	*p*
Risk Difference	0.070	(0.051, 0.088)	7.338	< 0.001
Risk Ratio	1.294	(1.207, 1.386)	N/A	N/A
Odds Ratio	1.424	(1.295, 1.565)	N/A	N/A

Figure 4.5a Risk of Emergency Room Visits across Long COVID Patients with (purple) and without (green) Socioeconomic Disparities

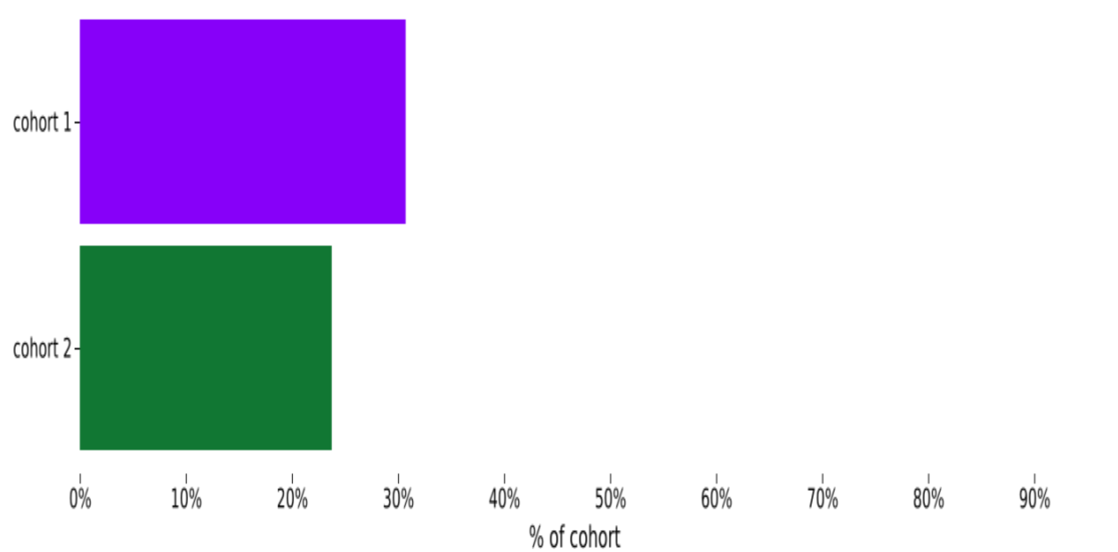


TABLE 4.8B KAPLAN-MEIER ANALYSIS RESULTS COMPARING THE OUTCOMES OF AN EMERGENCY ROOM VISIT OF LONG COVID PATIENTS WITH AND WITHOUT SOCIOECONOMIC DISPARITIES

Cohort	Patients in cohort	Patients with outcome	Median (days)	Probability at end of time window
1 Long COVID with Socioeconomic Disparities	4,388	1,348	724	45.81%
2 Long COVID without Socioeconomic Disparities	4,388	1,042	953	49.79%

	χ^2	df	*p*
Log-Rank Test	70.958	1	< 0.001

	Hazard Ratio	95% CI	χ^2	df	p
Hazard Ratio and Proportionality	1.413	(1.304, 1.533)	0.645	1	0.422

FIGURE 4.5B KAPLAN-MEIER CURVE ON EMERGENCY ROOM VISITS ACROSS LONG COVID PATIENTS WITH (PURPLE) AND WITHOUT (GREEN) SOCIOECONOMIC DISPARITIES

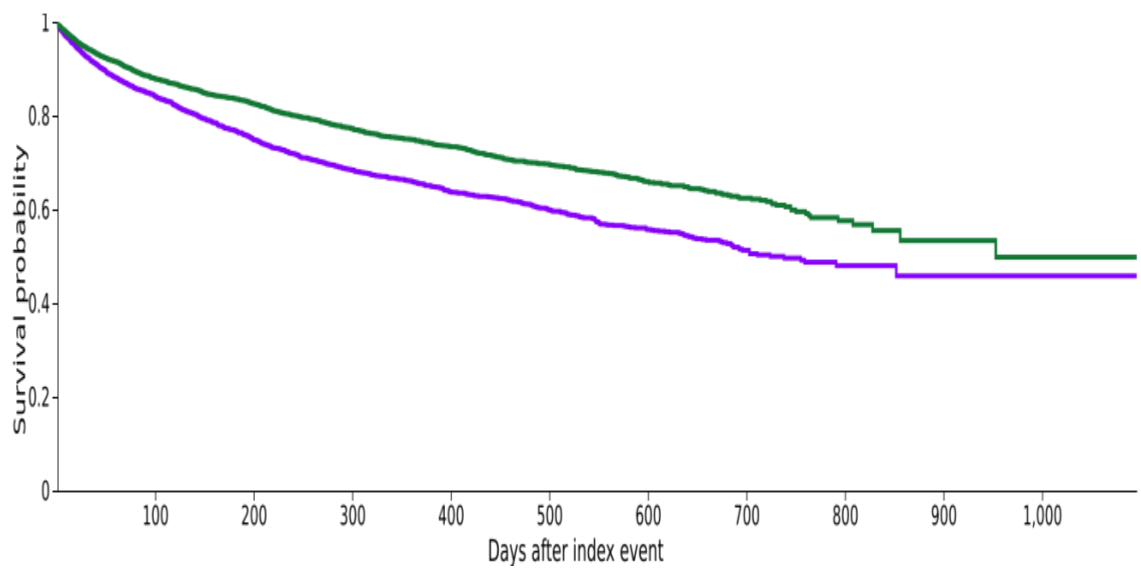
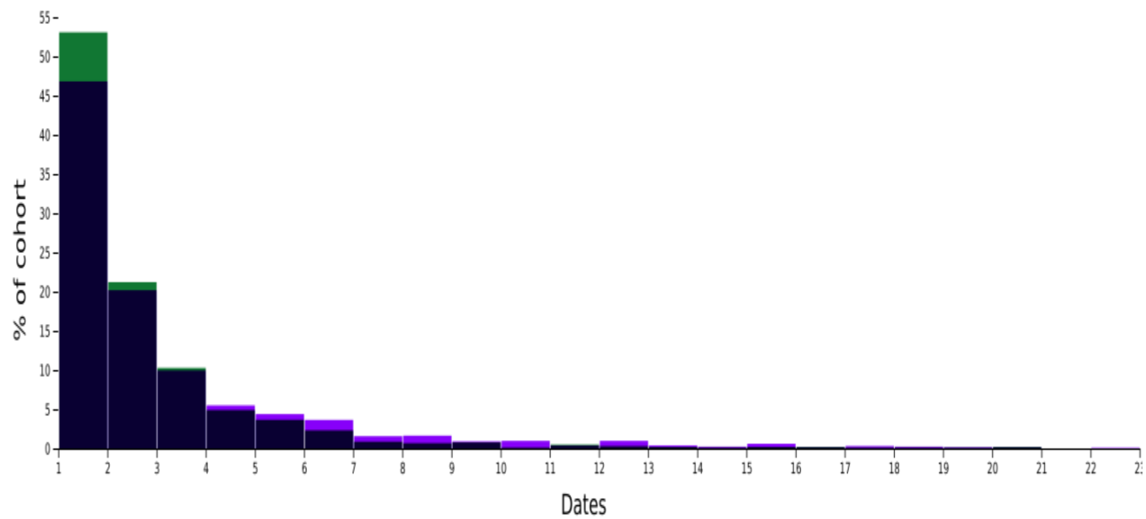


TABLE 4.8C NUMBER OF INSTANCES OF EMERGENCY ROOM VISITS OF LONG COVID PATIENTS WITH AND WITHOUT SOCIOECONOMIC DISPARITIES

Cohort	Patients in cohort	Patients with outcome	Mean	SD	Median
1 Long COVID with Socioeconomic Disparities	4,388	1,348	3.114	4.546	2
2 Long COVID without Socioeconomic Disparities	4,388	1,042	2.321	2.648	1

	t	df	p
Test Statistics	5.012	2388	< 0.001

FIGURE 4.5C NUMBER OF INSTANCES ON EMERGENCY ROOM VISITS ACROSS LONG COVID PATIENTS WITH (PURPLE) AND WITHOUT (GREEN) SOCIOECONOMIC DISPARITIES



13 data points for Cohort 1 and 3 data points for Cohort 2 were omitted for display purposes.

Inpatient Hospital Visits

Inpatient hospital visit indicates a patient stayed overnight at the hospital. Table 4.9 presents the results of inpatient hospital visits of Long COVID patients with and without socioeconomic disparities.

Risk Analysis: The risk difference between Long COVID patients with and without socioeconomic disparities is 0.074 (95% CI 0.056, 0.091), meaning the absolute difference in the proportion of patients with inpatient hospital visits between the two groups is 7.4 percentage points. A risk ratio value of 1.387 (95% CI 1.282, 1.500) means that the risk of inpatient hospital visits is 38.7% higher in Long COVID with socioeconomic disparities than those without. An odds ratio of 1.526 (95% CI 1.380, 1.688) means that the odds of inpatient hospital visits are 52.6% higher for Long COVID patients with socioeconomic disparities than those without. All of these differences were statistically significant ($p < 0.001$). Table 4.9a presents the risk analysis results comparing the inpatient hospital visits of Long COVID patients with and without socioeconomic disparities. Figure 4.6a illustrates the risk of inpatient hospital visits across Long COVID Patients with and without socioeconomic disparities.

Kaplan-Meier Survival Analysis: The median time for patients to experience an inpatient hospital visit had yet to be reached by the end of the study period. The probability of not experiencing an inpatient hospital visit by the end of the study period is 58.88% for Long COVID patients with socioeconomic disparities and 71.93% for those without socioeconomic disparities. This finding suggests that patients without socioeconomic disparities had a higher probability of avoiding an inpatient hospital visit by the end of the study period. The log-rank test statistic is $\chi 2 = 73.854$ with 1 degree of freedom and a p-value of <0.001, indicating a significant difference in the time to an inpatient hospital visit between Long COVID patients with and without socioeconomic disparities. Granted, a hazard ratio of 1.471 (1.346, 1.608) suggests that, on average, the risk of experiencing an inpatient hospital visit is 47.1% higher in Long COVID patients with socioeconomic disparities than those without. However, there is no statistically significant difference. Table 4.9b presents the results of the Kaplan-Meier analysis, comparing the outcomes of inpatient hospital visits of Long COVID patients with and without socioeconomic disparities. Figure 4.6b illustrates the Kaplan-Meier curve on inpatient hospital visits across Long COVID Patients with and without socioeconomic disparities.

Number of Instances Analysis: For Long COVID patients with socioeconomic disparities, the mean number of inpatient hospital visits is 6.064 ± 16.897, meaning, on average, patients with socioeconomic disparities had about 6.064 inpatient hospital visits, but there is a wide variation in the number of visits. The mean number of inpatient hospital visits for patients without socioeconomic disparities is 4.822 ± 7.290. Similarly, on average, this group had about 4.822 inpatient hospital visits, with less variation. The median number of inpatient hospital visits for Long COVID patients with and without socioeconomic disparities is two, indicating that half of each group had two or fewer inpatient hospital visits. The t-test statistic of 1.997 with 1998 degrees of freedom and a p-value of 0.046, suggests that there is a significant difference in the number of inpatient hospital visits between the two groups, with patients who have socioeconomic disparities having a higher number of inpatient hospital visits on average compared to those without socioeconomic disparities. Table 4.9c presents the number of inpatient hospital visits of Long COVID patients with and without socioeconomic disparities. Figure 4.6c illustrates a histogram of the number of instances of inpatient hospital visits across Long COVID patients with and without socioeconomic disparities.

Table 4.9 Inpatient Hospital Visits

Table 4.9a Risk Analysis Results comparing Inpatient Hospital Visits across Long COVID patients with and without Socioeconomic Disparities

Cohort	Patients in cohort	Patients with outcome	Risk
1 Long COVID with Socioeconomic Disparities	4,388	1,162	0.265
2 Long COVID without Socioeconomic Disparities	4,388	838	0.191

		95% CI	z	p
Risk Difference	0.074	(0.056, 0.091)	8.245	< 0.001
Risk Ratio	1.387	(1.282, 1.500)	N/A	N/A
Odds Ratio	1.526	(1.380, 1.688)	N/A	N/A

Figure 4.6a Risk of Inpatient Hospital Visit across Long COVID Patients with (Purple) and without (Green) Socioeconomic Disparities

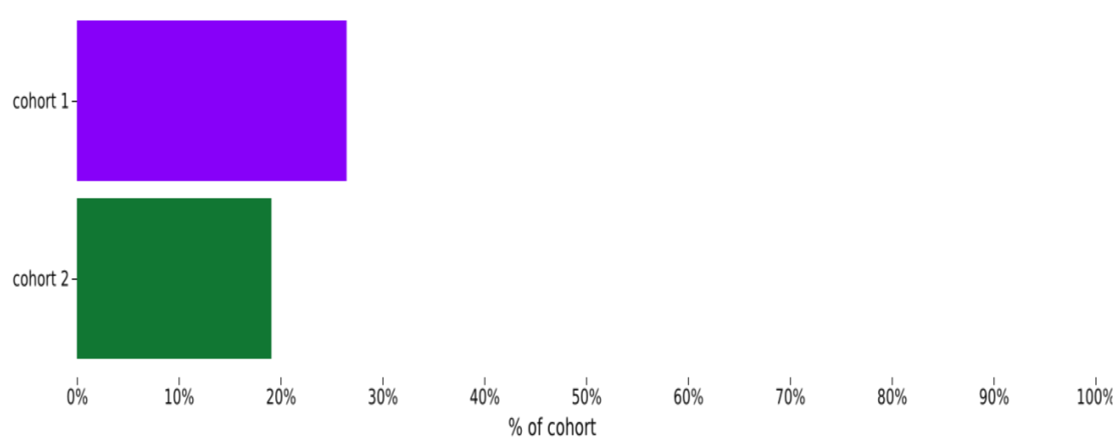


TABLE 4.9B KAPLAN-MEIER ANALYSIS RESULTS COMPARING THE OUTCOMES OF AN INPATIENT HOSPITAL VISIT OF LONG COVID PATIENTS WITH AND WITHOUT SOCIOECONOMIC DISPARITIES

Cohort	Patients in cohort	Patients with outcome	Median (days)	Probability at end of time window
1 Long COVID with Socioeconomic Disparities	4,388	1,162	--	58.88%
2 Long COVID without Socioeconomic Disparities	4,388	838	--	71.93%

	χ^2	df	*p*
Log-Rank Test	73.854	1	< 0.001

	Hazard Ratio	95% CI	χ^2	df	*p*
Hazard Ratio and Proportionality	1.471	(1.346, 1.608)	1.719	1	0.190

FIGURE 4.6B KAPLAN-MEIER CURVE ON INPATIENT HOSPITAL VISITS ACROSS LONG COVID PATIENTS WITH (PURPLE) AND WITHOUT (GREEN) SOCIOECONOMIC DISPARITIES

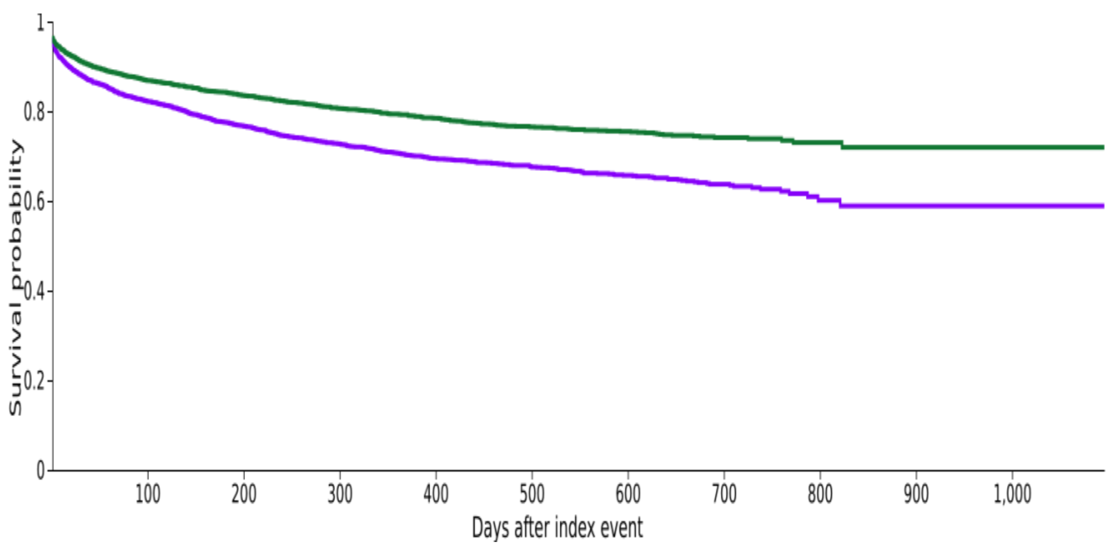
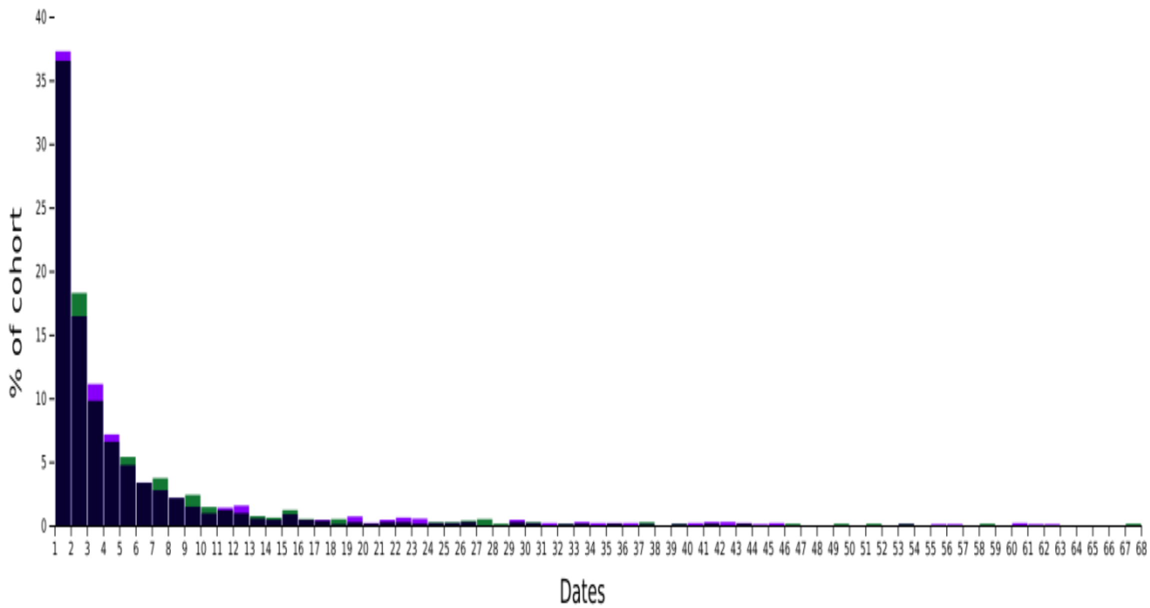


TABLE 4.9C NUMBER OF INSTANCES OF INPATIENT HOSPITAL VISITS OF LONG COVID PATIENTS WITH AND WITHOUT SOCIOECONOMIC DISPARITIES

Cohort	Patients in cohort	Patients with outcome	Mean	SD	Median
1 Long COVID with Socioeconomic Disparities	4,388	1,162	6.064	16.897	2
2 Long COVID without Socioeconomic Disparities	4,388	838	4.822	7.290	2

	t	df	*p*
Test Statistics	1.997	1998	0.046

FIGURE 4.6C NUMBER OF INSTANCES OF INPATIENT HOSPITAL VISITS ACROSS LONG COVID PATIENTS WITH (PURPLE) AND WITHOUT (GREEN) SOCIOECONOMIC DISPARITIES



5 data points for Cohort 1 and 0 data points for Cohort 2 were omitted for display purposes.

Chapter 5

Discussion

In our research study, we aimed to (1) determine whether respiratory mechanics, oxygenation impairment, social demographics, and comorbid conditions are associated with survival of mechanically ventilated subjects with COVID-19 infection (2) determine the factors associated with physical function after completing six weeks of pulmonary rehabilitation (PR) of COVID-19 subjects with persistent pulmonary symptoms, and (3) investigate the impact of socioeconomic disparities on participation in pulmonary rehabilitation and morbidity of Long COVID patients.

Aim 1

The COVID-19 pandemic has posed unprecedented challenges globally, impacting millions of lives and overwhelming healthcare systems. Understanding the factors associated with COVID-19 severity and outcomes is crucial for improving clinical care and public health strategies. This study investigated the associations between respiratory mechanics, oxygenation impairment, social demographics, medication use, comorbid conditions, and survival of mechanically ventilated COVID-19 subjects.

GEE modeling was performed to obtain the OR and 95% CI of survival of mechanically ventilated COVID-19 subjects. We found that age, sex, race/ethnicity, medication use, multimorbidity, oxygenation impairment, and dynamic compliance were significantly associated with the survival of the mechanically ventilated COVID-19 population. However, we did not find a significant effect of static compliance or airway resistance on the survival of the mechanically ventilated COVID-19 population.

Compared to a small (49 subjects) retrospective study of critically ill COVID-19 patients in Belgium on mechanical ventilation, our study's mortality rate of 60% is slightly higher than theirs of 55%. (de Terwangne, 2021) Our mortality rate was also similar to the mortality rates of other COVID-19 subjects who required mechanical ventilation. (Arentz, 2020; Bhatraju, 2020; Tu, 2021) Our mortality rate is also higher than that reported for subjects with traditional (non-COVID-19)

Our findings are similar to previous studies that found older age negatively associated with survival in the mechanically ventilated COVID-19 population. (Chang, 2021; Tan, 2021; Tian, 2021) When examining the literature on COVID-19 patients who required mechanical ventilation, we also found consistency with prior literature in that the odds of survival were lower if subjects were older. (Hirayama, 2021; King, 2020) Our study agreed with prior literature that reported significant associations between race/ethnicity and survival (Abedi, 2021; Isath, 2022; Wiley, 2022). Our study agreed with Tian et al. that Hispanics had higher mortality from COVID-19 but disagreed with their statement that females have a higher chance of mortality than males. (Tian, 2021) Regarding sex, we found that males had lower odds of survival than females, in agreement with previous studies that concluded males were most likely to die from COVID-19. Dessie, 2021; Hu, 2021; Jin, 2020; Williamson, 2020; Yanez, 2020)

When examining populations with a majority of Hispanic/Latino subjects like our population, our findings differed from Hidalgo et al., where outcomes were not influenced by race (Hidalgo, 2022) and agreed with Casillas et al. that outcomes of COVID-19 subjects were influenced by race. (Casillas, 2021) Both studies examined COVID-19 subjects overall rather than only mechanically ventilated subjects, which may conclude that the subjects in our study had a more severe disease. Also, our surprising finding that Non-Hispanic Black subjects were associated with higher odds of survival than non-Hispanic whites may have been because, in our sample, Non-Hispanic Blacks were significantly younger than non-Hispanic whites. Our finding that subjects with multimorbidity were more likely to survive than subjects with less than two comorbid conditions could be because they frequent hospitals more often. These findings may be contributed to the subjects with multimorbidity having higher PF ratios, while those with less than two comorbid conditions were mostly severely oxygenation impaired. The multimorbid cohort also included mostly Non-Hispanic Black subjects, who were, in turn, younger, in our study sample.

Regarding medication usage, our study agreed that dexamethasone (Bouadma, 2022) and remdesivir (WHO, 2022) neither had an impact on critically ill COVID-19 subjects, yet we did find using both dexamethasone and remdesivir to be significantly associated with survival compared to neither in our study In agreement with other studies, we found an association between respiratory compliance and survival. (Longino, 2021) We also found mild, moderate, and severe oxygenation impairment decreased survival odds compared to no oxygenation impairment, in agreement with Osawa et al. who found low PF ratios to be considered a significant risk factor for mortality. (Osawa, 2022) Airway resistance and static compliance were not significantly associated with survival in our analysis.

These findings emphasize the need for individualized treatment approaches based on respiratory status and comorbid conditions.

Aim 2

This aim contributes to the growing literature on COVID-19 outcomes and highlights the multifactorial nature of disease severity and survival. We aimed to determine if PR clinically improves physical function for subjects with continuing dyspnea post-COVID-19 infection by increasing 6MWD. In agreement with other literature on COVID-19 subjects with persistent symptoms who attended PR, we found that completing six weeks of PR improves physical function values in subjects with continuing symptoms from COVID-19.(Nopp, 202; Zampogna, 2021) Our main finding was that regardless of health characteristics, most subjects improved 6MWD after six weeks of PR.

Linear regression models were performed to retrieve coefficients 6MWD difference and 6MWD post-PR after completing six weeks of PR of COVID-19 subjects with persistent pulmonary symptoms to assess physical function. Logistic were regression models were performed to retrieve OR and 95% CI of ability to achieve MCID at 6MWD of 30m, 80m, and 108m after completing six weeks of PR of COVID-19 subjects with persistent pulmonary symptoms to also assess for physical function. No significant findings were found when examining 6MWD difference (post-PR – pre-PR), MCID at 6MWD of 30m, nor when using depression, anxiety, or PTSD as the primary predictor in our analysis.

We found a significant association between 6MWD pre-PR and 6MWD post-PR, suggesting that the initial 6MWD before rehabilitation predicts the walk distance after rehabilitation. Participants with higher 6MWD-pre may have had better baseline fitness levels or exercise tolerance, indicating that subjects with better initial fitness are more likely to improve or maintain their fitness levels after PR. Participants with higher 6MWD pre-PR may respond more positively to the rehabilitation program, leading to more significant improvements in 6MWD post-PR.

The literature shows that subjects with Long COVID-19 may benefit from PR, similar to subjects with other pulmonary diseased processes, such as sarcoidosis (Wallaert, 2020) and COPD. (Corhay, 2014) Our study agreed that participants with moderate to severe pulmonary restriction had benefits in physical function measures after completing PR. Participants with moderate to severe pulmonary restriction had a significantly greater 6MWD post-PR compared to those with normal lung function or mild pulmonary restriction. These findings could be because these participants are more accustomed to adapting to their impaired lung function than those with normal or mild restriction.

There were conflicting reports in the literature on whether PR results differ across genders. A study including 80 subjects in a tertiary care facility with and without COPD suggests that PR improves QoL outcomes regardless of gender. (Nguyen, 2017) In contrast, a study of 246 subjects hospitalized with COVID-19 suggests differences in recovery rates between genders. (Lindahl, 2022) In agreement with Nguyen et al., our study found no differences associated with gender and PR benefit. (Nguyen, 2017) In our study, we found that non-Hispanic Blacks were less likely to achieve MCID of 80m and 108m in 6MWD compared to non-Hispanic Whites. These findings suggest that race/ethnicity may be an important factor to consider in the rehabilitation of long COVID patients, with tailored interventions potentially needed for different ethnic groups to achieve optimal outcomes. We found no associations between hospitalization status and benefits in physical function measures after completing PR. However, subjects with moderate to severe pulmonary restriction had greater 6MWD post-PR than subjects with mild pulmonary restriction or normal lung function.

Despite the minimal statistical significance of our study, the trends shown make it evident that most of our population had improvements after completing six weeks of PR. Our results may also lack statistical significance since our population presented with higher mobility scores on average than those in predetermined populations of MCID in 6MWD, in disease, and in healthy populations. (Bohannon, 2017; Camarri, 2006; McKay, 2017; Rasekaba, 2009; Wise, 2005)

Although we cannot say that PR should be used in all subjects hospitalized with COVID-19 (Wang, 2020), our findings support a possible beneficial effect that PR should be considered in COVID-19 subjects who present with persistent symptoms after hospital discharge, due to the majority of participants achieving MCID regardless of other factors.

By evaluating the effectiveness of this intervention, the findings of this analysis could have significant implications on how Long COVID-19 subjects are managed and cared for by providing evidence-based recommendations for using PR as a treatment option. This research could improve Long COVID subjects' long-term health outcomes and provide an alternative criterion for MCID in 6MWD for this population.

Aim 3

The analysis of Long COVID patients with and without socioeconomic disparities provides valuable insights into the impact of socioeconomic factors on healthcare outcomes. After propensity score matching, both cohorts were included 4,388 patients each, ensuring comparability between the groups.

The propensity score density function showed a shift in distribution for both groups, indicating improved balance after matching. Before matching, patients with socioeconomic disparities were slightly younger and had a different racial and ethnic composition than those without disparities. There were also differences in the prevalence of various health conditions between the two groups. However, these differences were mitigated after matching, resulting in a better balance in demographic and diagnostic characteristics.

Regarding participation in PR, the risk analysis showed a trend towards higher participation rates in Long COVID patients without socioeconomic disparities, but the difference was not statistically significant. Kaplan-Meier analysis and the hazard ratio also did not show a significant difference in PR outcomes between the two groups, with both groups showing low participation in PR.

Regarding hospital visits, the risk analysis revealed a significantly higher risk of hospital visits in Long COVID patients with socioeconomic disparities. Kaplan-Meier analysis showed a significant difference in the time to a hospital visit between the two groups, with patients with socioeconomic disparities experiencing hospital visits sooner. The number of instances analysis further supported these findings, showing a higher mean number of hospital visits in the disparities group.

For emergency room (ER) visits, the risk analysis indicated a significantly higher risk of ER visits in Long COVID patients with socioeconomic disparities. Kaplan-Meier analysis also showed a significant difference in the time to an ER visit between the two groups. The findings suggest that patients without socioeconomic disparities had a slightly higher probability of avoiding an ER visit by the end of the study period. However, the two groups have no statistically significant difference in the hazard of ER visits. The number of instances analysis confirmed these results, showing a higher mean number of ER visits in the disparities group. There was a significant difference in the number of ER visits between the two groups, with Long COVID patients with socioeconomic disparities having a higher number of ER visits on average compared to those without socioeconomic disparities.

Regarding inpatient hospital visits, the risk analysis revealed a higher risk of inpatient visits in Long COVID patients with socioeconomic disparities. While the Kaplan-Meier analysis did not show a significant difference in the time to an inpatient visit between the two groups, the number of instances analysis showed a higher mean number of inpatient visits in the disparities group.

The findings from the analysis of Long COVID patients with and without socioeconomic disparities across various healthcare outcomes provide valuable insights into the impact of socioeconomic factors on disease management and healthcare utilization. Understanding these disparities is crucial for designing effective interventions and improving outcomes for all patients, especially those from vulnerable populations. These findings highlight the importance of considering socioeconomic disparities in managing Long COVID patients. Addressing these disparities through targeted interventions and support programs may help improve healthcare outcomes and reduce long-term healthcare system burdens.

LIMITATIONS OF THE STUDY

The present study has some limitations. In aim 1, the study was conducted in a single academic health center limiting the generalizability of the data. EHR data is liable to the quality, consistency, and completeness of documentation by the clinician. Plateau pressures were not gathered consistently throughout the studied population, effecting the estimates of static compliance and airway resistance.

In aim 2, the study's data may have limitations in being generalizable to the US population because it was also drawn from a single medical center and included a relatively small sample size of 64 subjects. Second, subjects did not perform pulmonary function testing after completing PR, so the extent to which their pulmonary function improved is not known. Our study lacked a comparative group (no PR), so it’s not clearly understood if PR is the sole factor in our outcomes. Lastly, we classify pulmonary restriction based on spirometry data and not actual lung volumes. Restriction was considered based on the FVC% of predicted and a normal FEV1/FVC.

In aim 3, we utilized basic statistical methods provided within the TriNetX database and did not conduct multivariate analysis, which limits our ability to effectively control for variables of interest. It's important to note that TriNetX may not encompass a representative sample of the population, as it primarily comprises data from healthcare providers and institutions using the TriNetX platform. This limitation can introduce selection bias and restrict the generalizability of study findings. Furthermore, the quality and completeness of data in TriNetX may vary. Missing data or inaccuracies in coding could impact the validity of analyses and the conclusions drawn from the data. Lastly, as researchers using TriNetX, we have limited control over how data is collected and recorded, which could affect the quality and consistency of the data, despite undergoing transformative data quality reviews.

STRENGTHS OF THE STUDY

There are many strengths of this study. First, our study is unique in that we observed subjects who did not survive the COVID-19 pandemic and observed outcomes and potential treatment measures for survivors who still experience persistent symptoms.

Aim two includes several strengths, such as using the EHR, which is a reliable and comprehensive source of information on subjects included in the study. Also, the statistical methods were performed to account for confounding variables while identifying the independent effects of the intervention on the outcome variables. We also attempted to identify an appropriate cut point in MCID in this population using ROC. Lastly, this study addresses a critical gap in the current literature and adds to the understanding of Long COVID management.

Aim three includes several strengths as well. First, it uses TriNetX, an extensive global database that creates generalizability to the entire world and large sample sizes for studies. It also has the advantage of using propensity score matching to ensure that cohorts are adequately balanced before making conclusions about a study.

Future Research Implications

Future research is recommended to determine whether therapeutically improving dynamic compliance or oxygenation impairment will improve the survival of the mechanically ventilated COVID-19 population. Further studies are required to longitudinally examine pulmonary impairment and the quality of life for survivors of COVID-19 who have been mechanically ventilated. Ethnic/racial, economic, and health inequities concerning survival in the COVID-19 population warrant further research. This research will likely require a meta-analysis from studies like ours, with a single large minority (Hispanic/Latino) population, and other studies that include differing minority populations, such as Non-Hispanic Blacks, that may be found in different areas of the US. Future research should focus on validating these findings in larger cohorts and exploring additional factors that may influence outcomes in this population. Additionally, efforts to address health disparities and improve access to care for underserved populations are critical for mitigating the impact of COVID-19 and future pandemics.

Future research is also needed to determine if PR clinically improves physical function for subjects with continuing dyspnea post-COVID-19 infection, since we only examined 6MWD. More extensive cohort studies are required to longitudinally examine if PR is beneficial in QoL and physical function measures for survivors of COVID-19. At our facility, 768 subjects were referred to the post-COVID-19 clinic for PR, yet only 68 (11.3%) subjects completed the six weeks. Sociodemographic, socioeconomic, and health inequities concerning PR participation and completion in the COVID-19 population warrant future research.

Future research should also focus on developing and implementing effective strategies to mitigate the impact of socioeconomic factors on Long COVID outcomes. Due to the underutilization of PR regardless of socioeconomic status, future research should also examine morbidity differences between groups that complete PR compared to those that do not.

CHAPTER 6

Conclusions

Specific aim one found that for every 1mL/cmH2O increase in dynamic compliance, the odds of survival increased by 3% when controlling for covariates. Severe, moderate, and mild oxygenation impairment significantly decreased the odds of survival compared to not having oxygenation impairment when controlling for covariates. We also concluded that as age increased, the odds of survival for mechanically ventilated COVID-19 patients significantly decreased. Being Hispanic was also associated with lower odds of survival compared to being Non-Hispanic White. We deem it crucial to evaluate respiratory mechanics and their association with the survival of mechanically ventilated COVID-19 subjects. Sociodemographics, oxygenation impairment, and dynamic compliance should be considered for prognostic benefits in managing the mechanically ventilated COVID-19 population.

Our specific aim 2 found that most subjects had a clinical improvement in physical function after completing six weeks of PR. However, validation with a larger PR population is warranted. We also found that Non-Hispanic Blacks are less likely to show improvement in physical function measures than Non-Hispanic Whites after completing six weeks of PR when controlling for age, sex, BMI, being hospitalized, comorbid conditions, and pulmonary function. A greater 6MWD at baseline is associated with a greater 6MWD post-PR. Subjects with moderate to severe pulmonary restriction have a greater post-PR 6MWD compared to subjects with normal lung function or mild pulmonary restriction. Lastly, we observed that the majority of participants (92.2% for 30m, 79.7% for 80m, and 76.6% for 108m) who completed six weeks of pulmonary rehabilitation achieved minimal clinically important differences (MCID) in 6-minute walk distance (6MWD). Granted non-Hispanic Black subjects have lower odds of showing improvement in physical function that non-Hispanic Whites. In conclusion, completing six weeks of PR has benefits when using 6MWD to show improvement of physical function in subjects with continuing dyspnea post-COVID-19 infection.

Regarding our third aim of investigating the impact of socioeconomic disparities on participation in pulmonary rehabilitation and morbidity of Long COVID patients, the results of our study demonstrate the significant impact of socioeconomic disparities on morbidity outcomes of Long COVID patients. Addressing these disparities through targeted interventions and support services could help improve outcomes and reduce healthcare utilization in this population. We also found that regardless of socioeconomic status, Long COVID patients did not have high utilization of PR.

Summary for:

AIM 1:

Factors associated with survival of mechanically ventilated COVID-19 subjects:

- For every 1-year increase in age, the odds of survival decrease by 5%.
- For every 1-unit increase in dynamic compliance, survival increases by 3%
- Males have 30% lower odds of survival compared to females
- Hispanics have 43% lower odds of survival than Non-Hispanic Whites
- Using dexamethasone and remdesivir increases odds of survival 61% compared to using neither.
- Mild, moderate and severe oxygenation impairment decreases the odds of survival compared to not having oxygenation impairment

The findings suggest, given the significant impact of dynamic compliance, age, sex, race, medication use, and oxygenation impairment on survival of mechanically ventilated COVID-19 patients, clinicians should carefully monitor these factors and consider them in treatment decisions. Tailoring treatment strategies based on individual patient characteristics, such as age, sex, race, and respiratory mechanics, could improve outcomes in mechanically ventilated COVID-19 patients. This may include adjusting medication regimens or ventilation strategies based on these factors. We should develop prognostic tools that incorporate sociodemographic factors, oxygenation impairment, and dynamic compliance to better predict outcomes in mechanically ventilated COVID-19 patients. This could help clinicians identify high-risk patients early and intervene appropriately. We should also, educate healthcare providers about the impact of sociodemographic factors, oxygenation impairment, and dynamic compliance on survival in mechanically ventilated COVID-19 patients. This could lead to more informed decision-making and improved patient outcomes.

AIM 2:

Factors associated with physical function after completing six weeks of pulmonary rehabilitation (PR) of COVID-19 subjects with persistent pulmonary symptoms.

- The majority of participants that completed six weeks of PR had positive physical function outcomes.
- Non-Hispanic Blacks are less likely to have positive outcomes in physical function compared to Non-Hispanic Whites after completing six weeks of PR.

- Participants with moderate to severe pulmonary restriction are more likely to have positive outcomes in physical function compared to those with normal lung function or mild pulmonary restriction after completing six weeks of PR.

These findings suggest that PR can be effective in improving physical function in subjects with persistent pulmonary symptoms after COVID-19. The majority of participants completing six weeks of PR experienced positive outcomes in physical function, indicating the potential benefits of this intervention. However, a concerning racial disparity was observed, with Non-Hispanic Blacks being less likely to have positive outcomes compared to Non-Hispanic Whites. This highlights a need to address potential barriers or differences in care that may contribute to this disparity. Additionally, the study found that participants with moderate to severe pulmonary restriction were more likely to have positive physical function outcomes compared to those with normal lung function or mild restriction. This suggests that the severity of pulmonary restriction may influence the effectiveness of PR, with more impaired subjects potentially benefiting more from the intervention. These findings underscore the importance of equitable access to and tailoring of PR programs to individual needs, particularly in diverse populations affected by COVID-19.

AIM 3:

Impact of socioeconomic disparities on participation in pulmonary rehabilitation and morbidity of Long COVID patients.

- Regardless of socioeconomic status, PR is underutilized amongst Long COVID patients.

- Long COVID patients with socioeconomic disparities are more likely to visit the hospital than those without socioeconomic disparities.
- Long COVID patients with socioeconomic disparities are more likely to visit the emergency room than those without socioeconomic disparities.
- Long COVID patients with socioeconomic disparities are more likely to have an inpatient hospital visit than those without socioeconomic disparities.

The findings suggest that we should implement targeted interventions aimed at improving participation of PR for Long COVID patients regardless of socioeconomic status. This could include providing financial assistance for rehabilitation programs or offering transportation services for those who may face barriers in attending. We could also, establish community support services that specifically cater to Long COVID patients with socioeconomic disparities. This could involve creating support groups, providing educational resources, and offering guidance on navigating the healthcare system. We could implement care coordination programs that help Long COVID patients with socioeconomic disparities better manage their health. This could involve coordinating care between different healthcare providers and ensuring patients have access to necessary resources and support. Lastly, we could advocate for policy changes that address socioeconomic disparities in healthcare. This could involve supporting legislation that improves access to healthcare services for vulnerable populations and promotes health equity.

APPENDICES

APPENDIX A: UNIVERSITY OF CALIFORNIA – SAN DIEGO QUESTIONNAIRE

When I do, or if I were to do, the following tasks, I would rate my shortness of breath as:

1. At rest
2. Walking on a level at your own pace
3. Walking on a level with others your age
4. Walking up a hill
5. Walking up stairs
6. While rating
7. Standings up from a chair
8. Brushing teeth
9. Shaving

When I do, or if I were to do, the following tasks, I would rate my shortness of breath as:

10. Showering/bathing
11. Dressing
12. Picking up and straightening
13. Doing dishes
14. Sweeping/vacuuming
15. Making bed
16. Shopping
17. Doing laundry
18. Washing car
19. Mowing lawn
20. Watering lawn
21. Sexual activities

How much do these limit you in your daily life?

22. Shortness of breath
23. Fear of "hurting myself" by overexerting
24. Fear of shortness of breath

APPENDIX B: GENERAL ANXIETY DISORDER SCREENER

Over the last 2 weeks, how often have you been bothered by the following problems?

1. Feeling nervous, anxious or on edge
2. Not being able to stop or control worrying
3. Worrying too much about different things
4. Trouble relaxing
5. Being so restless that it is hard to sit still
6. Becoming easily annoyed or irritable
7. Feeling afraid as if something awful might happen

APPENDIX C: THE PATIENT HEALTH QUESTIONNAIRE

Over the last 2 weeks, how often have you been bothered by the following problems?

1. Little interest or pleasure in doing things
2. Feeling down, depressed or hopeless
3. Trouble falling asleep, staying asleep, or sleeping too much
4. Feeling tired or having little energy
5. Poor appetite or overeating
6. Feeling bad about yourself - or that you're a failure or have let yourself or your family down
7. Trouble concentrating on things, such as reading the newspaper or watching television
8. Moving or speaking so slowly that other people could have noticed, or the opposite, being so fidgety or restless that you have been moving around a lot more than usual
9. Thoughts that you would be better off dead or of hurting yourself in some way

APPENDIX D: IMPACT OF EVENT SCALE-6

1. Thought about it when I did not mean to
2. I felt watchful or on-guard
3. Other things kept making me think about it
4. I was aware that I still had a lot of feelings about it, but I didn't deal with them
5. I tried not to think about it
6. I had trouble concentrating

REFERENCES

Abedi, V., Olulana, O., Avula, V., Chaudhary, D., Khan, A., Shahjouei, S., . . . Zand, R. (2021). Racial, Economic, and Health Inequality and COVID-19 Infection in the United States. J Racial Ethn Health Disparities, 8(3), 732-742. https://doi.org/10.1007/s40615-020-00833-4

Águas, R., Mahdi, A., Shretta, R., Horby, P., Landray, M., White, L., & Consortium, C. (2021). Author Correction: Potential health and economic impacts of dexamethasone treatment for patients with COVID-19. Nat Commun, 12(1), 1596. https://doi.org/10.1038/s41467-021-22038-x

Ahmad, F. B., Anderson, R. N., Cisewski, J. A., & Sutton, P. D. (2022). Identification of Deaths With Post-acute Sequelae of COVID-19 From Death Certificate Literal Text: United States, January 1, 2020–June 30, 2022. *NCHS Vital Statistics Rapid Release*, *25*. https://doi.org/dx.doi. org/10.15620/cdc:121968 .

Akbarialiabad, H., Taghrir, M. H., Abdollahi, A., Ghahramani, N., Kumar, M., Paydar, S., . . . Bastani, B. (2021). Long COVID, a comprehensive systematic scoping review. *Infection*, *49*(6), 1163-1186. https://doi.org/10.1007/s15010-021-01666-x

Almeida, L. V., Garcia-Araujo, A., Lopez, M., Rocha, D. S., Mendes, R. G., Borghi-Silva, A., . . . Dibai, D. B. (2022). Results and effects of patients who have recovered from COVID-19: identifying the relationship with risk factors and comorbidities. *Cien Saude Colet*, *27*(8), 2963-2972. https://doi.org/10.1590/1413-81232022278.18672021

Alwani, M., Yassin, A., Al-Zoubi, R. M., Aboumarzouk, O. M., Nettleship, J., Kelly, D., . . . Shabsigh, R. (2021). Sex-based differences in severity and mortality in COVID-19. *Rev Med Virol*, *31*(6), e2223. https://doi.org/10.1002/rmv.2223

Amstutz, A., Speich, B., Mentré, F., Rueegg, C. S., Belhadi, D., Assoumou, L., . . . Briel, M. (2023). Effects of remdesivir in patients hospitalised with COVID-19: a systematic review and individual patient data meta-analysis of randomised controlled trials. *Lancet Respir Med*,*11*(5), 453-464. https://doi.org/10.1016/S2213-2600(22)00528-8

Angel, L., Kon, Z. N., Chang, S. H., Rafeq, S., Palasamudram Shekar, S., Mitzman, B., . . . Cerfolio, R. J. (2020). Novel Percutaneous Tracheostomy for Critically Ill Patients With COVID-19. *Ann Thorac Surg*, *110*(3), 1006-1011. https://doi.org/10.1016/j.athoracsur.2020.04.010

Arentz, M., Yim, E., Klaff, L., Lokhandwala, S., Riedo, F. X., Chong, M., & Lee, M. (2020). Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. *JAMA*, *323*(16), 1612-1614. https://doi.org/10.1001/jama.2020.4326

Arranz-Herrero, J., Presa, J., Rius-Rocabert, S., Utrero-Rico, A., Arranz-Arija, J., Lalueza, A., . . . Nistal-Villan, E. (2023). Determinants of poor clinical outcome in patients with influenza pneumonia: A systematic review and meta-analysis. *Int J Infect Dis*, *131*, 173-179. https://doi.org/10.1016/j.ijid.2023.04.003

Baradaran, A., Ebrahimzadeh, M. H., & Kachooei, A. R. (2020). Prevalence of Comorbidities in COVID-19 Patients: A Systematic Review and Meta-Analysis. *Arch Bone Jt Surg*, *8*(Suppl 1), 247-255. https://doi.org/10.22038/abjs.2020.47754.2346

Beaudry, R. I., Brotto, A. R., Varughese, R. A., de Waal, S., Fuhr, D. P., Damant, R. W., . . . Stickland, M. K. (2022). Persistent dyspnea after COVID-19 is not related to cardiopulmonary impairment; a cross-sectional study of persistently dyspneic COVID-19, non-dyspneic COVID-19 and controls. *Front Physiol*, *13*, 917886. https://doi.org/10.3389/fphys.2022.917886

Beigel, J. H., Tomashek, K. M., Dodd, L. E., Mehta, A. K., Zingman, B. S., Kalil, A. C., . . . Members, A.-S. G. (2020). Remdesivir for the Treatment of Covid-19 - Final Report. *N Engl J Med*, *383*(19), 1813-1826. https://doi.org/10.1056/NEJMoa2007764

Bellan, M., Soddu, D., Balbo, P. E., Baricich, A., Zeppegno, P., Avanzi, G. C., . . . Pirisi, M. (2021). Respiratory and Psychophysical Sequelae Among Patients With COVID-19 Four Months After Hospital Discharge. *JAMA Netw Open*, *4*(1), e2036142. https://doi.org/10.1001/jamanetworkopen.2020.36142

Bergman, J., Ballin, M., Nordström, A., & Nordström, P. (2021). Risk factors for COVID-19 diagnosis, hospitalization, and subsequent all-cause mortality in Sweden: a nationwide study. *Eur J Epidemiol*, *36*(3), 287-298. https://doi.org/10.1007/s10654-021-00732-w

Besnier, F., Bérubé, B., Malo, J., Gagnon, C., Grégoire, C. A., Juneau, M., . . . Bherer, L. (2022). Cardiopulmonary Rehabilitation in Long-COVID-19 Patients with Persistent Breathlessness and Fatigue: The COVID-Rehab Study. *Int J Environ Res Public Health*, *19*(7). https://doi.org/10.3390/ijerph19074133

Bhatraju, P. K., Ghassemieh, B. J., Nichols, M., Kim, R., Jerome, K. R., Nalla, A. K., . . . Mikacenic, C. (2020). Covid-19 in Critically Ill Patients in the Seattle Region - Case Series. *N Engl J Med*, *382*(21), 2012-2022. https://doi.org/10.1056/NEJMoa2004500

Blanco, J. R., Cobos-Ceballos, M. J., Navarro, F., Sanjoaquin, I., Arnaiz de Las Revillas, F., Bernal, E., . . . Ugedo, J. (2021). Pulmonary long-term consequences of COVID-19 infections after hospital discharge. *Clin Microbiol Infect*, *27*(6), 892-896. https://doi.org/10.1016/j.cmi.2021.02.019

Bohannon, R. W., & Crouch, R. (2017). Minimal clinically important difference for change in 6-minute walk test distance of adults with pathology: a systematic review. *J Eval Clin Pract*, *23*(2), 377-381. https://doi.org/10.1111/jep.12629

Bonazza, F., Luridiana Battistini, C., Fior, G., Bergamelli, E., Wiedenmann, F., D'Agostino, A., . . . Lamiani, G. (2022). Recovering from COVID-19: psychological sequelae and post-traumatic growth six months after discharge. *Eur J Psychotraumatol*, *13*(1), 2095133. https://doi.org/10.1080/20008198.2022.2095133

Bouadma, L., Mekontso-Dessap, A., Burdet, C., Merdji, H., Poissy, J., Dupuis, C., . . . Group, C. S. (2022). High-Dose Dexamethasone and Oxygen Support Strategies in Intensive Care Unit Patients With Severe COVID-19 Acute Hypoxemic Respiratory Failure: The COVIDICUS Randomized Clinical Trial. *JAMA Intern Med*, *182*(9), 906-916. https://doi.org/10.1001/jamainternmed.2022.2168

Bucciarelli, V., Nasi, M., Bianco, F., Seferovic, J., Ivkovic, V., Gallina, S., & Mattioli, A. V. (2022). Depression pandemic and cardiovascular risk in the COVID-19 era and long COVID syndrome: Gender makes a difference. *Trends Cardiovasc Med*, *32*(1), 12-17. https://doi.org/10.1016/j.tcm.2021.09.009

Butler, M. J., Best, J. H., Mohan, S. V., Jonas, J. A., Arader, L., & Yeh, J. (2023). Mechanical ventilation for COVID-19: Outcomes following discharge from inpatient treatment. *PLoS One*, *18*(1), e0277498. https://doi.org/10.1371/journal.pone.0277498

Cabrera Martimbianco, A. L., Pacheco, R. L., Bagattini, Â., & Riera, R. (2021). Frequency, signs and symptoms, and criteria adopted for long COVID-19: A systematic review. *Int J Clin Pract*, *75*(10), e14357. https://doi.org/10.1111/ijcp.14357

Cascella, M., Rajnik, M., Aleem, A., Dulebohn, S. C., & Napoli, R. D. (2023). Features, Evaluation, and Treatment of Coronavirus (COVID-19). *StatPearls*. https://doi.org/NBK554776

Casillas, E., Wu, G., Iantorno, S., Ning, W. V., Choi, J., Chan, P., & Lee, M. M. (2021). COVID-19: Highlighting Health Disparities in the Los Angeles Latinx Community. *Clin Med Res*, *19*(4), 161-168. https://doi.org/10.3121/cmr.2021.1654

Cedano, J., Fabian Corona, E., Gonzalez-Lara, M., Santana, M., Younes, I., Ayad, S., . . . Pullatt, R. (2021). Characteristics and outcomes of patients with COVID-19 in an intensive care unit of a community hospital; retrospective cohort study. *J Community Hosp Intern Med Perspect*, *11*(1), 27-32. https://doi.org/10.1080/20009666.2020.1830516

Cereda, M., & Deutschman, C. S. (2020). Coronavirus Disease 2019 and Acute Respiratory Distress Syndrome: Why the Intensivist Is More Important Than Ever. *Crit Care Med*, *48*(12), 1838-1840. https://doi.org/10.1097/CCM.0000000000004663

Chippa, V., Aleem, A., & Anjum , F. (2023). Post-Acute Coronavirus (COVID-19) Syndrome. *StatPearls*. https://doi.org/NBK570608

Chiumello, D., Busana, M., Coppola, S., Romitti, F., Formenti, P., Bonifazi, M., . . . Gattinoni, L. (2020). Physiological and quantitative CT-scan characterization of COVID-19 and typical ARDS: a matched cohort study. *Intensive Care Med*, *46*(12), 2187-2196. https://doi.org/10.1007/s00134-020-06281-2

Compagnone, N., Palumbo, D., Cremona, G., Vitali, G., De Lorenzo, R., Calvi, M. R., . . . Group, C.-B. S. (2022). Residual lung damage following ARDS in COVID-19 ICU survivors. *Acta Anaesthesiol Scand*, *66*(2), 223-231. https://doi.org/10.1111/aas.13996

Consortium, W. S. T. (2022). Remdesivir and three other drugs for hospitalised patients with COVID-19: final results of the WHO Solidarity randomised trial and updated meta-analyses. *Lancet*, *399*(10339), 1941-1953. https://doi.org/10.1016/S0140-6736(22)00519-0

Cucinotta, D., & Vanelli, M. (2020). WHO Declares COVID-19 a Pandemic. *Acta Biomed*, *91*(1), 157-160. https://doi.org/10.23750/abm.v91i1.9397

Cuschieri, S., & Grech, S. (2020). COVID-19 and diabetes: The why, the what and the how. *J Diabetes Complications*, *34*(9), 107637. https://doi.org/10.1016/j.jdiacomp.2020.107637

Dai, C. L., Kornilov, S. A., Roper, R. T., Cohen-Cline, H., Jade, K., Smith, B., . . . Hadlock, J. J. (2021). Characteristics and Factors Associated With Coronavirus Disease 2019 Infection, Hospitalization, and Mortality Across Race and Ethnicity. *Clin Infect Dis*, *73*(12), 2193-2204. https://doi.org/10.1093/cid/ciab154

Dalsania, A. K., Fastiggi, M. J., Kahlam, A., Shah, R., Patel, K., Shiau, S., . . . DallaPiazza, M. (2022). The Relationship Between Social Determinants of Health and Racial Disparities in COVID-19 Mortality. *J Racial Ethn Health Disparities*, *9*(1), 288-295. https://doi.org/10.1007/s40615-020-00952-y

de Terwangne, C., Sorgente, A., Tortora, R., Cheung, D., Duprez, F., Place, S., . . . Mashayekhi, S. (2021). Mortality Rate and Predictors Among Patients with COVID-19 Related Acute Respiratory Failure Requiring Mechanical Ventilation: a Retrospective Single Centre

Study. *J Crit Care Med (Targu Mures)*, *7*(1), 21-27. https://doi.org/10.2478/jccm-2020-0043

Del Corral, T., Menor-Rodríguez, N., Fernández-Vega, S., Díaz-Ramos, C., Aguilar-Zafra, S., & López-de-Uralde-Villanueva, I. (2024). Longitudinal study of changes observed in quality of life, psychological state cognition and pulmonary and functional capacity after COVID-19 infection: A six- to seven-month prospective cohort. *J Clin Nurs*, *33*(1), 89-102. https://doi.org/10.1111/jocn.16352

Demir, G., Akkoca, O., Doğan, R., Saryal, S., & Karabiyikoğlu, G. (2003). [The evaluation of dyspnea and quality of life in COPD]. *Tuberk Toraks*, *51*(4), 365-372.

Dessie, Z. G., & Zewotir, T. (2021). Mortality-related risk factors of COVID-19: a systematic review and meta-analysis of 42 studies and 423,117 patients. *BMC Infect Dis*, *21*(1), 855. https://doi.org/10.1186/s12879-021-06536-3

Di Crosta, A., Palumbo, R., Marchetti, D., Ceccato, I., La Malva, P., Maiella, R., . . . Di Domenico, A. (2020). Individual Differences, Economic Stability, and Fear of Contagion as Risk Factors for PTSD Symptoms in the COVID-19 Emergency. *Front Psychol*, *11*, 567367. https://doi.org/10.3389/fpsyg.2020.567367

Dmytriw, A. A., Chibbar, R., Chen, P. P. Y., Traynor, M. D., Kim, D. W., Bruno, F. P., . . . Keesari, P. R. (2021). Outcomes of acute respiratory distress syndrome in COVID-19 patients compared to the general population: a systematic review and meta-analysis. *Expert Rev Respir Med*, *15*(10), 1347-1354. https://doi.org/10.1080/17476348.2021.1920927

Dun, Y., Liu, C., Ripley-Gonzalez, J. W., Liu, P., Zhou, N., Gong, X., . . . Liu, S. (2021). Six-month outcomes and effect of pulmonary rehabilitation among patients hospitalized with

COVID-19: a retrospective cohort study. *Ann Med*, *53*(1), 2099-2109. https://doi.org/10.1080/07853890.2021.2001043

Eastman, R. T., Roth, J. S., Brimacombe, K. R., Simeonov, A., Shen, M., Patnaik, S., & Hall, M. D. (2020). Remdesivir: A Review of Its Discovery and Development Leading to Emergency Use Authorization for Treatment of COVID-19. *ACS Cent Sci*, *6*(5), 672-683. https://doi.org/10.1021/acscentsci.0c00489

Erber, J., Wießner, J. R., Zimmermann, G. S., Barthel, P., Burian, E., Lohöfer, F., . . . Lahmer, T. (2021). Longitudinal Assessment of Health and Quality of Life of COVID-19 Patients Requiring Intensive Care-An Observational Study. *J Clin Med*, *10*(23). https://doi.org/10.3390/jcm10235469

Fang, X., Li, S., Yu, H., Wang, P., Zhang, Y., Chen, Z., . . . Ma, X. (2020). Epidemiological, comorbidity factors with severity and prognosis of COVID-19: a systematic review and meta-analysis. *Aging (Albany NY)*, *12*(13), 12493-12503. https://doi.org/10.18632/aging.103579

Fernández-de-Las-Peñas, C., Martín-Guerrero, J. D., Cancela-Cilleruelo, I., Moro-López-Menchero, P., Rodríguez-Jiménez, J., & Pellicer-Valero, O. J. (2023). Trajectory curves of post-COVID anxiety/depressive symptoms and sleep quality in previously hospitalized COVID-19 survivors: the LONG-COVID-EXP-CM multicenter study. *Psychol Med*, *53*(9), 4298-4299. https://doi.org/10.1017/S003329172200006X

Ferreira, J. C., Ho, Y. L., Besen, B. A. M. P., Malbouisson, L. M. S., Taniguchi, L. U., Mendes, P. V., . . . Group, E. S. (2021). Protective ventilation and outcomes of critically ill patients with COVID-19: a cohort study. *Ann Intensive Care*, *11*(1), 92. https://doi.org/10.1186/s13613-021-00882-w

Fortini, A., Torrigiani, A., Sbaragli, S., Lo Forte, A., Crociani, A., Cecchini, P., . . . Faraone, A. (2021). COVID-19: persistence of symptoms and lung alterations after 3-6 months from hospital discharge. *Infection*, *49*(5), 1007-1015. https://doi.org/10.1007/s15010-021-01638-1

Friedel, J. E., DeHart, W. B., Foreman, A. M., & Andrew, M. E. (2019). A Monte Carlo method for comparing generalized estimating equations to conventional statistical techniques for discounting data. *J Exp Anal Behav*, *111*(2), 207-224. https://doi.org/10.1002/jeab.497

Froidure, A., Mahsouli, A., Liistro, G., De Greef, J., Belkhir, L., Gérard, L., . . . Ghaye, B. (2021). Integrative respiratory follow-up of severe COVID-19 reveals common functional and lung imaging sequelae. *Respir Med*, *181*, 106383. https://doi.org/10.1016/j.rmed.2021.106383

Galbadage, T., Peterson, B. M., Awada, J., Buck, A. S., Ramirez, D. A., Wilson, J., & Gunasekera, R. S. (2020). Systematic Review and Meta-Analysis of Sex-Specific COVID-19 Clinical Outcomes. *Front Med (Lausanne)*, *7*, 348. https://doi.org/10.3389/fmed.2020.00348

Gamberini, L., Tonetti, T., Spadaro, S., Zani, G., Mazzoli, C. A., Capozzi, C., . . . Collaboration, I.-R. C.-. (2020). Factors influencing liberation from mechanical ventilation in coronavirus disease 2019: multicenter observational study in fifteen Italian ICUs. *J Intensive Care*, *8*, 80. https://doi.org/10.1186/s40560-020-00499-4

Garg, S., Kim, L., Whitaker, M., O'Halloran, A., Cummings, C., Holstein, R., . . . Fry, A. (2020). Hospitalization Rates and Characteristics of Patients Hospitalized with Laboratory-Confirmed Coronavirus Disease 2019 - COVID-NET, 14 States, March 1-30,

2020. *MMWR Morb Mortal Wkly Rep*, *69*(15), 458-464. https://doi.org/10.15585/mmwr.mm6915e3

Gattinoni, L., Chiumello, D., Caironi, P., Busana, M., Romitti, F., Brazzi, L., & Camporota, L. (2020). COVID-19 pneumonia: different respiratory treatments for different phenotypes? *Intensive Care Med*, *46*(6), 1099-1102. https://doi.org/10.1007/s00134-020-06033-2

Gautam, N., Madathil, S., Tahani, N., Bolton, S., Parekh, D., Stockley, J., . . . Geberhiwot, T. (2022). Medium-Term Outcomes in Severely to Critically Ill Patients With Severe Acute Respiratory Syndrome Coronavirus 2 Infection. *Clin Infect Dis*, *74*(2), 301-308. https://doi.org/10.1093/cid/ciab341

George, P. M., Barratt, S. L., Condliffe, R., Desai, S. R., Devaraj, A., Forrest, I., . . . Spencer, L. G. (2020). Respiratory follow-up of patients with COVID-19 pneumonia. *Thorax*, *75*(11), 1009-1016. https://doi.org/10.1136/thoraxjnl-2020-215314

Ghosh, M. C., Baatar, D., Collins, G., Carter, A., Indig, F., Biragyn, A., & Taub, D. D. (2009). Dexamethasone augments CXCR4-mediated signaling in resting human T cells via the activation of the Src kinase Lck. *Blood*, *113*(3), 575-584. https://doi.org/10.1182/blood-2008-04-151803

Gilissen, V. J. H. S., Koning, M. V., & Klimek, M. (2022). The Influence of Hypercapnia and Atmospheric Pressure on the Pao2/Fio2 Ratio-Pathophysiologic Considerations, a Case Series, and Introduction of a Clinical Tool. *Crit Care Med*, *50*(4), 607-613. https://doi.org/10.1097/CCM.0000000000005316

Gloeckl, R., Leitl, D., Jarosch, I., Schneeberger, T., Nell, C., Stenzel, N., . . . Koczulla, A. R. (2021). Pulmonary rehabilitation in long COVID: more than just natural recovery!? *ERJ Open Res*, *7*(3). https://doi.org/10.1183/23120541.00454-2021

Goodman, M. L., Molldrem, S., Elliott, A., Robertson, D., & Keiser, P. (2023). Long COVID and mental health correlates: a new chronic condition fits existing patterns. *Health Psychol Behav Med*, *11*(1), 2164498. https://doi.org/10.1080/21642850.2022.2164498

Gottlieb, R. L., Vaca, C. E., Paredes, R., Mera, J., Webb, B. J., Perez, G., . . . Investigators, G.-U.-.-P. (2022). Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients. *N Engl J Med*, *386*(4), 305-315. https://doi.org/10.1056/NEJMoa2116846

Gragueb-Chatti, I., Lopez, A., Hamidi, D., Guervilly, C., Loundou, A., Daviet, F., . . . Hraiech, S. (2021). Impact of dexamethasone on the incidence of ventilator-associated pneumonia and blood stream infections in COVID-19 patients requiring invasive mechanical ventilation: a multicenter retrospective study. *Ann Intensive Care*, *11*(1), 87. https://doi.org/10.1186/s13613-021-00876-8

Grant, T., Croce, E., & Matsui, E. C. (2022). Asthma and the social determinants of health. *Ann Allergy Asthma Immunol*, *128*(1), 5-11. https://doi.org/10.1016/j.anai.2021.10.002

Grasselli, G., Greco, M., Zanella, A., Albano, G., Antonelli, M., Bellani, G., . . . Network, C.-L. I. (2020). Risk Factors Associated With Mortality Among Patients With COVID-19 in Intensive Care Units in Lombardy, Italy. *JAMA Intern Med*, *180*(10), 1345-1355. https://doi.org/10.1001/jamainternmed.2020.3539

Grasselli, G., Tonetti, T., Protti, A., Langer, T., Girardis, M., Bellani, G., . . . collaborators. (2020). Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study. *Lancet Respir Med*, *8*(12), 1201-1208. https://doi.org/10.1016/S2213-2600(20)30370-2

Green, H., Fernandez, R., & MacPhail, C. (2021). The social determinants of health and health outcomes among adults during the COVID-19 pandemic: A systematic review. *Public Health Nurs*, *38*(6), 942-952. https://doi.org/10.1111/phn.12959

Grima, P., Guido, M., & Zizza, A. (2023). Clinical characteristics and risk factors associated with COVID-19 mortality in a non-Intensive Care Unit. *J Prev Med Hyg*, *64*(1), E3-E8. https://doi.org/10.15167/2421-4248/jpmh2023.64.1.2828

Guan, W. J., Ni, Z. Y., Hu, Y., Liang, W. H., Ou, C. Q., He, J. X., . . . Covid-19, C. M. T. E. G. f. (2020). Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*, *382*(18), 1708-1720. https://doi.org/10.1056/NEJMoa2002032

Guimarães, R. M., & Pastura, D. C. L. D. (2023). Impact of sociodemographic factors on COVID-19 survival: a nationwide 2,000,000 in-patients' cohort in Brazil. *Rev Bras Epidemiol*, *26*, e230050. https://doi.org/10.1590/1980-549720230050

Gupta, A., Madhavan, M. V., Sehgal, K., Nair, N., Mahajan, S., Sehrawat, T. S., . . . Landry, D. W. (2020). Extrapulmonary manifestations of COVID-19. *Nat Med*, *26*(7), 1017-1032. https://doi.org/10.1038/s41591-020-0968-3

Han, Q., Zheng, B., Daines, L., & Sheikh, A. (2022). Long-Term Sequelae of COVID-19: A Systematic Review and Meta-Analysis of One-Year Follow-Up Studies on Post-COVID Symptoms. *Pathogens*, *11*(2). https://doi.org/10.3390/pathogens11020269

Health, N. I. o. (2023). *Disparities identified among patients receiving advanced pulmonary support*

Health, N. I. o. (2024, February 29, 2024). *Clinical Spectrum of SARS-CoV-2 Infection*. https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/#:~:text=Patients%20with%20COVID%2D19%20are,given%20oxygen%20therapy%20and%20hospitalized.

Hermann, M., Pekacka-Egli, A. M., Witassek, F., Baumgaertner, R., Schoendorf, S., & Spielmanns, M. (2020). Feasibility and Efficacy of Cardiopulmonary Rehabilitation After COVID-19. *Am J Phys Med Rehabil*, *99*(10), 865-869. https://doi.org/10.1097/PHM.0000000000001549

Hirayama, A., Masui, J., Murayama, A., Fujita, S., Okamoto, J., Tanaka, J., . . . Asada, R. (2021). The characteristics and clinical course of patients with COVID-19 who received invasive mechanical ventilation in Osaka, Japan. *Int J Infect Dis*, *102*, 282-284. https://doi.org/10.1016/j.ijid.2020.10.051

Holland, A. E., Cox, N. S., Houchen-Wolloff, L., Rochester, C. L., Garvey, C., ZuWallack, R., . . . Singh, S. J. (2021). Defining Modern Pulmonary Rehabilitation. An Official American Thoracic Society Workshop Report. *Ann Am Thorac Soc*, *18*(5), e12-e29. https://doi.org/10.1513/AnnalsATS.202102-146ST

Holland, A. E., & Nici, L. (2013). The return of the minimum clinically important difference for 6-minute-walk distance in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*, *187*(4), 335-336. https://doi.org/10.1164/rccm.201212-2191ED

Holland, A. E., Wadell, K., & Spruit, M. A. (2013). How to adapt the pulmonary rehabilitation programme to patients with chronic respiratory disease other than COPD. *Eur Respir Rev*, *22*(130), 577-586. https://doi.org/10.1183/09059180.00005613

Horby, P., Lim, W. S., Emberson, J. R., Mafham, M., Bell, J. L., Linsell, L., . . . Group, R. C. (2021). Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med*, *384*(8), 693-704. https://doi.org/10.1056/NEJMoa2021436

Horn, M., Wathelet, M., Fovet, T., Amad, A., Vuotto, F., Faure, K., . . . Henry, M. (2020). Is COVID-19 Associated With Posttraumatic Stress Disorder? *J Clin Psychiatry*, *82*(1). https://doi.org/10.4088/JCP.20m13641

Houben-Wilke, S., Goërtz, Y. M., Delbressine, J. M., Vaes, A. W., Meys, R., Machado, F. V., . . . Janssen, D. J. (2022). The Impact of Long COVID-19 on Mental Health: Observational 6-Month Follow-Up Study. *JMIR Ment Health*, *9*(2), e33704. https://doi.org/10.2196/33704

Hu, D., Lou, X., Meng, N., Li, Z., Teng, Y., Zou, Y., & Wang, F. (2021). Influence of age and gender on the epidemic of COVID-19 : Evidence from 177 countries and territories-an exploratory, ecological study. *Wien Klin Wochenschr*, *133*(7-8), 321-330. https://doi.org/10.1007/s00508-021-01816-z

Huang, L., Xu, X., Zhang, L., Zheng, D., Liu, Y., Feng, B., . . . Zhang, Z. (2021). Post-traumatic Stress Disorder Symptoms and Quality of Life of COVID-19 Survivors at 6-Month Follow-Up: A Cross-Sectional Observational Study. *Front Psychiatry*, *12*, 782478. https://doi.org/10.3389/fpsyt.2021.782478

Huang, Y., Tan, C., Wu, J., Chen, M., Wang, Z., Luo, L., . . . Liu, J. (2020). Impact of coronavirus disease 2019 on pulmonary function in early convalescence phase. *Respir Res*, *21*(1), 163. https://doi.org/10.1186/s12931-020-01429-6

Humphreys, H., Kilby, L., Kudiersky, N., & Copeland, R. (2021). Long COVID and the role of physical activity: a qualitative study. *BMJ Open*, *11*(3), e047632. https://doi.org/10.1136/bmjopen-2020-047632

Imran, J., Nasa, P., Alexander, L., Upadhyay, S., & Alanduru, V. (2021). Psychological distress among survivors of moderate-to-critical COVID-19 illness: A multicentric prospective cross-sectional study. *Indian J Psychiatry*, *63*(3), 285-289. https://doi.org/10.4103/psychiatry.IndianJPsychiatry_1074_20

Isath, A., Malik, A. H., Goel, A., Gupta, R., Shrivastav, R., & Bandyopadhyay, D. (2022). Nationwide Analysis of the Outcomes and Mortality of Hospitalized COVID-19 Patients. *Curr Probl Cardiol*, *48*(2), 101440. https://doi.org/10.1016/j.cpcardiol.2022.101440

Jacobsen, R., Frølich, A., & Godtfredsen, N. S. (2012). Impact of exercise capacity on dyspnea and health-related quality of life in patients with chronic obstructive pulmonary disease. *J Cardiopulm Rehabil Prev*, *32*(2), 92-100. https://doi.org/10.1097/HCR.0b013e31823be107

Jagan, N., Morrow, L. E., Walters, R. W., Plambeck, R. W., Ng, I., Chovatiya, J. J., . . . Malesker, M. A. (2023). A Retrospective Analysis of the Effects of Time on Compliance and Driving Pressures in ARDS. *Respir Care*, *68*(1), 52-59. https://doi.org/10.4187/respcare.10080

Jain, V. K., Iyengar, K., Vaish, A., & Vaishya, R. (2020). Differential mortality in COVID-19 patients from India and western countries. *Diabetes Metab Syndr*, *14*(5), 1037-1041. https://doi.org/10.1016/j.dsx.2020.06.067

Jimeno-Almazán, A., Buendía-Romero, Á., Martínez-Cava, A., Franco-López, F., Sánchez-Alcaraz, B. J., Courel-Ibáñez, J., & Pallarés, J. G. (2023). Effects of a concurrent training, respiratory muscle exercise, and self-management recommendations on recovery from post-COVID-19 conditions: the RECOVE trial. *J Appl Physiol (1985)*, *134*(1), 95-104. https://doi.org/10.1152/japplphysiol.00489.2022

Jin, J. M., Bai, P., He, W., Wu, F., Liu, X. F., Han, D. M., . . . Yang, J. K. (2020). Gender Differences in Patients With COVID-19: Focus on Severity and Mortality. *Front Public Health*, *8*, 152. https://doi.org/10.3389/fpubh.2020.00152

Karmakar, M., Lantz, P. M., & Tipirneni, R. (2021). Association of Social and Demographic Factors With COVID-19 Incidence and Death Rates in the US. *JAMA Netw Open*, *4*(1), e2036462. https://doi.org/10.1001/jamanetworkopen.2020.36462

Kaufman, B. G., Whitaker, R., Pink, G., & Holmes, G. M. (2020). Half of Rural Residents at High Risk of Serious Illness Due to COVID-19, Creating Stress on Rural Hospitals. *J Rural Health*, *36*(4), 584-590. https://doi.org/10.1111/jrh.12481

Khanijahani, A., Iezadi, S., Gholipour, K., Azami-Aghdash, S., & Naghibi, D. (2021). A systematic review of racial/ethnic and socioeconomic disparities in COVID-19. *Int J Equity Health*, *20*(1), 248. https://doi.org/10.1186/s12939-021-01582-4

Kim, L., Garg, S., O'Halloran, A., Whitaker, M., Pham, H., Anderson, E. J., . . . Langley, G. E. (2021). Risk Factors for Intensive Care Unit Admission and In-hospital Mortality Among Hospitalized Adults Identified through the US Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET). *Clin Infect Dis*, *72*(9), e206-e214. https://doi.org/10.1093/cid/ciaa1012

King, C. S., Sahjwani, D., Brown, A. W., Feroz, S., Cameron, P., Osborn, E., . . . Nathan, S. (2020). Outcomes of mechanically ventilated patients with COVID-19 associated respiratory failure. *PLoS One*, *15*(11), e0242651. https://doi.org/10.1371/journal.pone.0242651

Kolifarhood, G., Aghaali, M., Mozafar Saadati, H., Taherpour, N., Rahimi, S., Izadi, N., & Hashemi Nazari, S. S. (2020). Epidemiological and Clinical Aspects of COVID-19; a Narrative Review. *Arch Acad Emerg Med*, *8*(1), e41.

Koppurapu, V. S., Puliaiev, M., Doerschug, K. C., & Schmidt, G. A. (2021). Ventilated Patients With COVID-19 Show Airflow Obstruction. *J Intensive Care Med*, *36*(6), 696-703. https://doi.org/10.1177/08850666211000601

Kołodziej, M., Wyszyńska, J., & Bal-Bocheńska, M. (2021). COVID-19: A New Challenge for Pulmonary Rehabilitation? *J Clin Med*, *10*(15). https://doi.org/10.3390/jcm10153361

Krause, M., Douin, D. J., Kim, K. K., Fernandez-Bustamante, A., & Bartels, K. (2021). Characteristics and Outcomes of Mechanically Ventilated COVID-19 Patients-An Observational Cohort Study. *J Intensive Care Med*, *36*(3), 271-276. https://doi.org/10.1177/0885066620954806

Kupferberg, D. H., Kaplan, R. M., Slymen, D. J., & Ries, A. L. (2005). Minimal clinically important difference for the UCSD Shortness of Breath Questionnaire. *J Cardiopulm Rehabil*, *25*(6), 370-377. https://doi.org/10.1097/00008483-200511000-00011

Lateef Ibrahim, S., Alkhakany, A. J., & Falih Mizil, Z. (2022). Investigation of Risk Factors for Hospitalization of COVID-19 Patients with Diabetes in Najaf, Iraq. *Arch Razi Inst*, *77*(5), 1639-1645. https://doi.org/10.22092/ARI.2022.357995.2133

Latronico, N., Peli, E., Calza, S., Rodella, F., Novelli, M. P., Cella, A., . . . Investigators, L. (2022). Physical, cognitive and mental health outcomes in 1-year survivors of COVID-19-associated ARDS. *Thorax*, *77*(3), 300-303. https://doi.org/10.1136/thoraxjnl-2021-218064

Lee, T. C., Murthy, S., Del Corpo, O., Senécal, J., Butler-Laporte, G., Sohani, Z. N., . . . McDonald, E. G. (2022). Remdesivir for the treatment of COVID-19: a systematic review and meta-analysis. *Clin Microbiol Infect*, *28*(9), 1203-1210. https://doi.org/10.1016/j.cmi.2022.04.018

Leth, S., Gunst, J. D., Mathiasen, V., Hansen, K., Søgaard, O., Østergaard, L., . . . Agergaard, J. (2021). Persistent Symptoms in Patients Recovering From COVID-19 in Denmark. *Open Forum Infect Dis*, *8*(4), ofab042. https://doi.org/10.1093/ofid/ofab042

Leung, J. M., Yang, C. X., Tam, A., Shaipanich, T., Hackett, T. L., Singhera, G. K., . . . Sin, D. D. (2020). ACE-2 expression in the small airway epithelia of smokers and COPD patients: implications for COVID-19. *Eur Respir J*, *55*(5). https://doi.org/10.1183/13993003.00688-2020

Li Bassi, G., Suen, J. Y., Dalton, H. J., White, N., Shrapnel, S., Fanning, J. P., . . . Consortium, C.-C. C. (2021). An appraisal of respiratory system compliance in mechanically ventilated covid-19 patients. *Crit Care*, *25*(1), 199. https://doi.org/10.1186/s13054-021-03518-4

Li, J. (2020). Rehabilitation management of patients with COVID-19: lessons learned from the first experience in China. *Eur J Phys Rehabil Med*, *56*(3), 335-338. https://doi.org/10.23736/S1973-9087.20.06292-9

Liu, B., Spokes, P., He, W., & Kaldor, J. (2021). High risk groups for severe COVID-19 in a whole of population cohort in Australia. *BMC Infect Dis*, *21*(1), 685. https://doi.org/10.1186/s12879-021-06378-z

Liyanage-Don, N. A., Winawer, M. R., Hamberger, M. J., Agarwal, S., Trainor, A. R., Quispe, K. A., & Kronish, I. M. (2022). Association of depression and COVID-induced PTSD with cognitive symptoms after COVID-19 illness. *Gen Hosp Psychiatry*, *76*, 45-48. https://doi.org/10.1016/j.genhosppsych.2022.02.006

Longino, A., Riveros, T., Risa, E., Hebert, C., Krieger, J., Coppess, S., . . . Johnson, N. J. (2021). Respiratory Mechanics in a Cohort of Critically Ill Subjects With COVID-19 Infection. *Respir Care*, *66*(10), 1601-1609. https://doi.org/10.4187/respcare.09064

Magesh, S., John, D., Li, W. T., Li, Y., Mattingly-App, A., Jain, S., . . . Ongkeko, W. M. (2021). Disparities in COVID-19 Outcomes by Race, Ethnicity, and Socioeconomic Status: A Systematic-Review and Meta-analysis. *JAMA Netw Open*, *4*(11), e2134147. https://doi.org/10.1001/jamanetworkopen.2021.34147

Maglietta, G., Diodati, F., Puntoni, M., Lazzarelli, S., Marcomini, B., Patrizi, L., & Caminiti, C. (2022). Prognostic Factors for Post-COVID-19 Syndrome: A Systematic Review and Meta-Analysis. *J Clin Med*, *11*(6). https://doi.org/10.3390/jcm11061541

Malik, P., Patel, K., Pinto, C., Jaiswal, R., Tirupathi, R., Pillai, S., & Patel, U. (2022). Post-acute COVID-19 syndrome (PCS) and health-related quality of life (HRQoL)-A systematic review and meta-analysis. *J Med Virol*, *94*(1), 253-262. https://doi.org/10.1002/jmv.27309

Marini, J. J., & Gattinoni, L. (2020). Management of COVID-19 Respiratory Distress. *JAMA*, *323*(22), 2329-2330. https://doi.org/10.1001/jama.2020.6825

Mart, M. F., & Ely, E. W. (2020). Coronavirus Disease 2019 Acute Respiratory Distress Syndrome: Guideline-Driven Care Should Be Our Natural Reflex. *Crit Care Med*, *48*(12), 1835-1837. https://doi.org/10.1097/CCM.0000000000004627

Martinez, T. Y., Pereira, C. A., dos Santos, M. L., Ciconelli, R. M., Guimarães, S. M., & Martinez, J. A. (2000). Evaluation of the short-form 36-item questionnaire to measure health-related quality of life in patients with idiopathic pulmonary fibrosis. *Chest*, *117*(6), 1627-1632. https://doi.org/10.1378/chest.117.6.1627

Martos Pérez, F., Luque Del Pino, J., Jiménez García, N., Mora Ruiz, E., Asencio Méndez, C., García Jiménez, J. M., . . . Núñez Rodríguez, M. V. (2021). Comorbidity and prognostic factors on admission in a COVID-19 cohort of a general hospital. *Rev Clin Esp (Barc)*, *221*(9), 529-535. https://doi.org/10.1016/j.rceng.2020.05.010

Mazza, M. G., Palladini, M., De Lorenzo, R., Magnaghi, C., Poletti, S., Furlan, R., . . . group, C.-B. O. C. S. (2021). Persistent psychopathology and neurocognitive impairment in COVID-19 survivors: Effect of inflammatory biomarkers at three-month follow-up. *Brain Behav Immun*, *94*, 138-147. https://doi.org/10.1016/j.bbi.2021.02.021

Mazza, M. G., Palladini, M., Poletti, S., & Benedetti, F. (2022). Post-COVID-19 Depressive Symptoms: Epidemiology, Pathophysiology, and Pharmacological Treatment. *CNS Drugs*, *36*(7), 681-702. https://doi.org/10.1007/s40263-022-00931-3

McCarthy, B., Casey, D., Devane, D., Murphy, K., Murphy, E., & Lacasse, Y. (2015). Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*(2), CD003793. https://doi.org/10.1002/14651858.CD003793.pub3

Merzon, E., Weiss, M. D., Cortese, S., Rotem, A., Schneider, T., Craig, S. G., . . . Manor, I. (2022). The Association between ADHD and the Severity of COVID-19 Infection. *J Atten Disord*, *26*(4), 491-501. https://doi.org/10.1177/10870547211003659

Micheals, K., Lee, M. J., Al Snih, S., Walsh, B. K., & Rojas, J. D. (2023). The Effect of Oxygenation Impairment and Compliance on Mortality Among Subjects With COVID-19 Requiring Mechanical Ventilation. *Respir Care*, *68*(11), 1565-1568. https://doi.org/10.4187/respcare.10776

Monteiro, A. C., Suri, R., Emeruwa, I. O., Stretch, R. J., Cortes-Lopez, R. Y., Sherman, A., . . . Qadir, N. (2020). Obesity and smoking as risk factors for invasive mechanical ventilation in COVID-19: A retrospective, observational cohort study. *PLoS One*, *15*(12), e0238552. https://doi.org/10.1371/journal.pone.0238552

Moretti, M., Van Laethem, J., Minini, A., Pierard, D., & Malbrain, M. L. N. G. (2021). Ventilator-associated bacterial pneumonia in coronavirus 2019 disease, a retrospective monocentric cohort study. *J Infect Chemother*, *27*(6), 826-833. https://doi.org/10.1016/j.jiac.2021.01.011

Mughal, M. S., Kaur, I. P., Jaffery, A. R., Dalmacion, D. L., Wang, C., Koyoda, S., . . . Granet, K. M. (2020). COVID-19 patients in a tertiary US hospital: Assessment of clinical course and predictors of the disease severity. *Respir Med*, *172*, 106130. https://doi.org/10.1016/j.rmed.2020.106130

Mumoli, N., Bonaventura, A., Colombo, A., Vecchié, A., Cei, M., Vitale, J., . . . Dentali, F. (2021). Lung Function and Symptoms in Post-COVID-19 Patients: A Single-Center Experience. *Mayo Clin Proc Innov Qual Outcomes*, *5*(5), 907-915. https://doi.org/10.1016/j.mayocpiqo.2021.08.002

Munblit, D., Bobkova, P., Spiridonova, E., Shikhaleva, A., Gamirova, A., Blyuss, O., . . . Team, S. S. R. (2021). Incidence and risk factors for persistent symptoms in adults previously hospitalized for COVID-19. *Clin Exp Allergy*, *51*(9), 1107-1120. https://doi.org/10.1111/cea.13997

Nada, K. M., Hsu, E. S., Seashore, J., Zaidan, M., Nishi, S. P., Duarte, A., & Sharma, G. (2021). Determining Cause of Death During Coronavirus Disease 2019 Pandemic. *Crit Care Explor*, *3*(4), e0419. https://doi.org/10.1097/CCE.0000000000000419

Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M. V., McGroder, C., Stevens, J. S., . . . Wan, E. Y. (2021). Post-acute COVID-19 syndrome. *Nat Med*, *27*(4), 601-615. https://doi.org/10.1038/s41591-021-01283-z

Nasiri, M. J., Haddadi, S., Tahvildari, A., Farsi, Y., Arbabi, M., Hasanzadeh, S., . . . Mirsaeidi, M. (2020). COVID-19 Clinical Characteristics, and Sex-Specific Risk of Mortality: Systematic Review and Meta-Analysis. *Front Med (Lausanne)*, *7*, 459. https://doi.org/10.3389/fmed.2020.00459

Nguyen, N. T., Chinn, J., De Ferrante, M., Kirby, K. A., Hohmann, S. F., & Amin, A. (2021). Male gender is a predictor of higher mortality in hospitalized adults with COVID-19. *PLoS One*, *16*(7), e0254066. https://doi.org/10.1371/journal.pone.0254066

Nici, L., & Zuwallack, R. (2011). Scope, background and definition of pulmonary rehabilitation. *Eur J Phys Rehabil Med*, *47*(3), 465-474.

Nielsen Jeschke, K., Bonnesen, B., Hansen, E. F., Jensen, J. S., Lapperre, T. S., Weinreich, U. M., & Hilberg, O. (2020). Guideline for the management of COVID-19 patients during hospital admission in a non-intensive care setting. *Eur Clin Respir J*, *7*(1), 1761677. https://doi.org/10.1080/20018525.2020.1761677

Niyatiwatchanchai, N., Deesomchok, A., Chaiwong, W., Duangjit, P., Pothirat, C., Liwsrisakun, C., . . . Srisuwan, T. (2022). Comparative Study of Early Impacts of Post-COVID-19 Pneumonia on Clinical Manifestations, Pulmonary Function, and Chest Radiographs. *Medicina (Kaunas)*, *58*(2). https://doi.org/10.3390/medicina58020216

Nopp, S., Moik, F., Klok, F. A., Gattinger, D., Petrovic, M., Vonbank, K., . . . Zwick, R. H. (2022). Outpatient Pulmonary Rehabilitation in Patients with Long COVID Improves Exercise Capacity, Functional Status, Dyspnea, Fatigue, and Quality of Life. *Respiration*, *101*(6), 593-601. https://doi.org/10.1159/000522118

Noreen, S., Maqbool, I., & Madni, A. (2021). Dexamethasone: Therapeutic potential, risks, and future projection during COVID-19 pandemic. *Eur J Pharmacol*, *894*, 173854. https://doi.org/10.1016/j.ejphar.2021.173854

Norweg, A., & Collins, E. G. (2013). Evidence for cognitive-behavioral strategies improving dyspnea and related distress in COPD. *Int J Chron Obstruct Pulmon Dis*, *8*, 439-451. https://doi.org/10.2147/COPD.S30145

Notarte, K. I., de Oliveira, M. H. S., Peligro, P. J., Velasco, J. V., Macaranas, I., Ver, A. T., . . . Fernández-de-Las-Peñas, C. (2022). Age, Sex and Previous Comorbidities as Risk Factors Not Associated with SARS-CoV-2 Infection for Long COVID-19: A Systematic Review and Meta-Analysis. *J Clin Med*, *11*(24). https://doi.org/10.3390/jcm11247314

O'Hearn, M., Liu, J., Cudhea, F., Micha, R., & Mozaffarian, D. (2021). Coronavirus Disease 2019 Hospitalizations Attributable to Cardiometabolic Conditions in the United States: A Comparative Risk Assessment Analysis. *J Am Heart Assoc*, *10*(5), e019259. https://doi.org/10.1161/JAHA.120.019259

Ochmann, U., Jörres, R. A., & Nowak, D. (2012). Long-term efficacy of pulmonary rehabilitation: a state-of-the-art review. *J Cardiopulm Rehabil Prev*, *32*(3), 117-126. https://doi.org/10.1097/HCR.0b013e3182467194

Okutan, O., Tas, D., Demirer, E., & Kartaloglu, Z. (2013). Evaluation of quality of life with the chronic obstructive pulmonary disease assessment test in chronic obstructive pulmonary disease and the effect of dyspnea on disease-specific quality of life in these patients. *Yonsei Med J*, *54*(5), 1214-1219. https://doi.org/10.3349/ymj.2013.54.5.1214

Organization, W. H. *WHO Coronavirus (COVID-19) Dashboard*

Osawa, E. A., & Maciel, A. T. (2022a). An algorithm to predict the need for invasive mechanical ventilation in hospitalized COVID-19 patients: the experience in Sao Paulo. *Acute Crit Care*, *37*(4), 580-591. https://doi.org/10.4266/acc.2022.00283

Osawa, E. A., & Maciel, A. T. (2022b). Characteristics and Risk Factors for Mortality in Critically Ill Patients with COVID-19 Receiving Invasive Mechanical Ventilation: The Experience of a Private Network in Sao Paulo, Brazil. *J Crit Care Med (Targu Mures)*, *8*(3), 165-175. https://doi.org/10.2478/jccm-2022-0015

Ostrowska, M., Rzepka-Cholasińska, A., Pietrzykowski, Ł., Michalski, P., Kosobucka-Ozdoba, A., Jasiewicz, M., . . . Kubica, A. (2023). Effects of Multidisciplinary Rehabilitation Program in Patients with Long COVID-19: Post-COVID-19 Rehabilitation (PCR SIRIO 8) Study. *J Clin Med*, *12*(2). https://doi.org/10.3390/jcm12020420

Pan, C., Chen, L., Lu, C., Zhang, W., Xia, J. A., Sklar, M. C., . . . Qiu, H. (2020). Lung Recruitability in COVID-19-associated Acute Respiratory Distress Syndrome: A Single-Center Observational Study. *Am J Respir Crit Care Med*, *201*(10), 1294-1297. https://doi.org/10.1164/rccm.202003-0527LE

Pan, S. Y., Ding, M., Huang, J., Cai, Y., & Huang, Y. Z. (2021). Airway resistance variation correlates with prognosis of critically ill COVID-19 patients: A computational fluid dynamics study. *Comput Methods Programs Biomed*, *208*, 106257. https://doi.org/10.1016/j.cmpb.2021.106257

Paradowska-Nowakowska, E., Łoboda, D., Gołba, K. S., & Sarecka-Hujar, B. (2023). Long COVID-19 Syndrome Severity According to Sex, Time from the Onset of the Disease, and Exercise Capacity-The Results of a Cross-Sectional Study. *Life (Basel)*, *13*(2). https://doi.org/10.3390/life13020508

Patel, U., Malik, P., Usman, M. S., Mehta, D., Sharma, A., Malik, F. A., . . . Sacks, H. (2020). Age-Adjusted Risk Factors Associated with Mortality and Mechanical Ventilation Utilization Amongst COVID-19 Hospitalizations-a Systematic Review and Meta-Analysis. *SN Compr Clin Med*, *2*(10), 1740-1749. https://doi.org/10.1007/s42399-020-00476-w

Pearce, A. K., McGuire, W. C., & Malhotra, A. (2021). Lung and chest wall mechanics in COVID-19 acute respiratory distress syndrome. *J Thorac Dis*, *13*(11), 6214-6216. https://doi.org/10.21037/jtd-21-1567

Pennington, A. F., Kompaniyets, L., Summers, A. D., Danielson, M. L., Goodman, A. B., Chevinsky, J. R., . . . Gundlapalli, A. V. (2021). Risk of Clinical Severity by Age and Race/Ethnicity Among Adults Hospitalized for COVID-19-United States, March-September 2020. *Open Forum Infect Dis*, *8*(2), ofaa638. https://doi.org/10.1093/ofid/ofaa638

Porteous, M. K., Rivera-Lebron, B. N., Kreider, M., Lee, J., & Kawut, S. M. (2016). Determinants of 6-minute walk distance in patients with idiopathic pulmonary fibrosis undergoing lung transplant evaluation. *Pulm Circ*, *6*(1), 30-36. https://doi.org/10.1086/685022

Postolache, P., & Cojocaru, D. C. (2013). Pulmonary rehabilitation--from guidelines to practice. *Rev Med Chir Soc Med Nat Iasi*, *117*(2), 380-387.

Postolache, P. A., Nechifor, A., Buculei, I., Soare, I., Mocanu, H., & Petrariu, F. D. (2023). Clinical Features and Paraclinical Findings in Patients with SARS CoV-2 Pneumonia and the Impact of Pulmonary Rehabilitation on the Instrumental Activities of Daily Living in POST-COVID-19 Patients. *J Pers Med*, *13*(2). https://doi.org/10.3390/jpm13020182

Racine, R., Shah, P., Moore, J. X., Kenerly, J., Owens, J., & Hess, D. C. (2022). Profound racial disparities in COVID-19 associated hospitalizations in rural Southwest Georgia. *Am J Med Sci*, *364*(1), 1-6. https://doi.org/10.1016/j.amjms.2021.10.013

Rahmani, A. M., & Mirmahaleh, S. Y. H. (2021). Coronavirus disease (COVID-19) prevention and treatment methods and effective parameters: A systematic literature review. *Sustain Cities Soc*, *64*, 102568. https://doi.org/10.1016/j.scs.2020.102568

Raskin, J., Spiegler, P., McCusker, C., ZuWallack, R., Bernstein, M., Busby, J., . . . Youngson, L. (2006). The effect of pulmonary rehabilitation on healthcare utilization in chronic obstructive pulmonary disease: The Northeast Pulmonary Rehabilitation Consortium. *J Cardiopulm Rehabil*, *26*(4), 231-236. https://doi.org/10.1097/00008483-200607000-00006

Regina, J., Papadimitriou-Olivgeris, M., Burger, R., Le Pogam, M. A., Niemi, T., Filippidis, P., . . . Lhopitallier, L. (2020). Epidemiology, risk factors and clinical course of SARS-CoV-2 infected patients in a Swiss university hospital: An observational retrospective study. *PLoS One*,*15*(11), e0240781. https://doi.org/10.1371/journal.pone.0240781

Reis, L. F., Guimarães, F. S., Fernandes, S. J., Cantanhede, L. A., Dias, C. M., Lopes, A. J., & De Menezes, S. L. (2013). A long-term pulmonary rehabilitation program progressively improves exercise tolerance, quality of life and cardiovascular risk factors in patients with COPD. *Eur J Phys Rehabil Med*, *49*(4), 491-497.

Robba, C., Battaglini, D., Ball, L., Patroniti, N., Loconte, M., Brunetti, I., . . . Pelosi, P. (2020). Distinct phenotypes require distinct respiratory management strategies in severe COVID-19. *Respir Physiol Neurobiol*, *279*, 103455. https://doi.org/10.1016/j.resp.2020.103455

Ronderos Botero, D. M., Omar, A. M. S., Sun, H. K., Mantri, N., Fortuzi, K., Choi, Y., . . . Chilimuri, S. (2020). COVID-19 in the Healthy Patient Population: Demographic and Clinical Phenotypic Characterization and Predictors of In-Hospital Outcomes. *Arterioscler Thromb Vasc Biol*, *40*(11), 2764-2775. https://doi.org/10.1161/ATVBAHA.120.314845

Salzberger, B., Buder, F., Lampl, B., Ehrenstein, B., Hitzenbichler, F., Holzmann, T., . . . Hanses, F. (2021). Epidemiology of SARS-CoV-2. *Infection*, *49*(2), 233-239. https://doi.org/10.1007/s15010-020-01531-3

Santus, P., Bassi, L., Radovanovic, D., Airoldi, A., Raccanelli, R., Triscari, F., . . . Spanevello, A. (2013). Pulmonary Rehabilitation in COPD: A Reappraisal (2008-2012). *Pulm Med*, *2013*, 374283. https://doi.org/10.1155/2013/374283

Schenck, E. J., Hoffman, K., Goyal, P., Choi, J., Torres, L., Rajwani, K., . . . Berlin, D. A. (2020). Respiratory Mechanics and Gas Exchange in COVID-19-associated Respiratory Failure. *Ann Am Thorac Soc*, *17*(9), 1158-1161. https://doi.org/10.1513/AnnalsATS.202005-427RL

Shen, X., Yan, S., Jiang, H., Cao, H., Dowling, R., Feng, J., . . . Gan, Y. (2021). Post-traumatic Stress Disorder and Associated Factors 1 Year After the Beginning of the COVID-19 Pandemic Among Chinese Residents. *Front Psychiatry*, *12*, 766127. https://doi.org/10.3389/fpsyt.2021.766127

Sigfrid, L., Drake, T. M., Pauley, E., Jesudason, E. C., Olliaro, P., Lim, W. S., . . . investigators, I. C. (2021). Long Covid in adults discharged from UK hospitals after Covid-19: A prospective, multicentre cohort study using the ISARIC WHO Clinical Characterisation Protocol. *Lancet Reg Health Eur*, *8*, 100186. https://doi.org/10.1016/j.lanepe.2021.100186

Silva, E. C. G. E., Schmitt, A. C. B., Godoy, C. G., Gambeta, A. C., Carvalho, C. R. F., Fu, C., . . . Pompeu, J. E. (2022). Ambulation capacity, age, immunosuppression, and mechanical ventilation are risk factors of in-hospital death in severe COVID-19: a cohort study. *Clinics (Sao Paulo)*, *77*, 100075. https://doi.org/10.1016/j.clinsp.2022.100075

Sinatti, G., Santini, S. J., Tarantino, G., Picchi, G., Cosimini, B., Ranfone, F., . . . Balsano, C. (2022). PaO. *Intern Emerg Med*, *17*(3), 665-673. https://doi.org/10.1007/s11739-021-02840-7

Singh, S. J., Baldwin, M. M., Daynes, E., Evans, R. A., Greening, N. J., Jenkins, R. G., . . . Brightling, C. E. (2023). Respiratory sequelae of COVID-19: pulmonary and extrapulmonary origins, and approaches to clinical care and rehabilitation. *Lancet Respir Med*. https://doi.org/10.1016/S2213-2600(23)00159-5

Sirayder, U., Inal-Ince, D., Kepenek-Varol, B., & Acik, C. (2022). Long-Term Characteristics of Severe COVID-19: Respiratory Function, Functional Capacity, and Quality of Life. *Int J Environ Res Public Health*, *19*(10). https://doi.org/10.3390/ijerph19106304

Stanojevic, S. (2021). Socioeconomic disadvantage and lung health: accumulating evidence to support health policy. *Eur Respir J*, *57*(3). https://doi.org/10.1183/13993003.04025-2020

Sundh, J., Lindgren, H., Hasselgren, M., Montgomery, S., Janson, C., Ställberg, B., & Lisspers, K. (2017). Pulmonary rehabilitation in COPD - available resources and utilization in Swedish primary and secondary care. *Int J Chron Obstruct Pulmon Dis*, *12*, 1695-1704. https://doi.org/10.2147/COPD.S135111

Takagi, H., Kuno, T., Yokoyama, Y., Ueyama, H., Matsushiro, T., Hari, Y., & Ando, T. (2021). Meta-regression of COVID-19 prevalence/fatality on socioeconomic characteristics of data from top 50 U.S. large cities. *J Med Virol*, *93*(2), 595-598. https://doi.org/10.1002/jmv.26335

Thaweethai, T., Jolley, S. E., & Karlson, E. W. (2023). Development of a Definition of Postacute Sequelae of SARS-CoV-2 Infection. *JAMA Network*. https://doi.org/10.1001/jama.2023.8823

Tian, T., Zhang, J., Hu, L., Jiang, Y., Duan, C., Li, Z., . . . Zhang, H. (2021). Risk factors associated with mortality of COVID-19 in 3125 counties of the United States. *Infect Dis Poverty*, *10*(1), 3. https://doi.org/10.1186/s40249-020-00786-0

Tisminetzky, M. (2022). Decline in Ventilatory Ratio as a Predictor of Mortality in Adults With ARDS Receiving Prone Positioning. *Respiratory Care*, *67*(9), 1067-1074. https://doi.org/10.4187/respcare.09783

Torres-Castro, R., Vasconcello-Castillo, L., Alsina-Restoy, X., Solis-Navarro, L., Burgos, F., Puppo, H., & Vilaró, J. (2021). Respiratory function in patients post-infection by COVID-19: a systematic review and meta-analysis. *Pulmonology*, *27*(4), 328-337. https://doi.org/10.1016/j.pulmoe.2020.10.013

Trappenburg, J. C., Troosters, T., Spruit, M. A., Vandebrouck, N., Decramer, M., & Gosselink, R. (2005). Psychosocial conditions do not affect short-term outcome of multidisciplinary rehabilitation in chronic obstructive pulmonary disease. *Arch Phys Med Rehabil*, *86*(9), 1788-1792. https://doi.org/10.1016/j.apmr.2005.03.030

Truffaut, L., Demey, L., Bruyneel, A. V., Roman, A., Alard, S., De Vos, N., & Bruyneel, M. (2021). Post-discharge critical COVID-19 lung function related to severity of radiologic lung involvement at admission. *Respir Res*, *22*(1), 29. https://doi.org/10.1186/s12931-021-01625-y

Tu, Y., Yang, P., Zhou, Y., Wen, X., Li, Q., Zhou, J., . . . Gao, F. (2021a). Risk factors for mortality of critically ill patients with COVID-19 receiving invasive ventilation. *Int J Med Sci*, *18*(5), 1198-1206. https://doi.org/10.7150/ijms.50039

Tu, Y., Yang, P., Zhou, Y., Wen, X., Li, Q., Zhou, J., . . . Gao, F. (2021b). Risk factors for mortality of critically ill patients with COVID-19 receiving invasive ventilation. *Int J Med Sci*, *18*(5), 1198-1206. https://doi.org/10.7150/ijms.50039

Upshaw, T. L., Brown, C., Smith, R., Perri, M., Ziegler, C., & Pinto, A. D. (2021). Social determinants of COVID-19 incidence and outcomes: A rapid review. *PLoS One*, *16*(3), e0248336. https://doi.org/10.1371/journal.pone.0248336

Uzunova, G., Pallanti, S., & Hollander, E. (2021). Presentation and management of anxiety in individuals with acute symptomatic or asymptomatic COVID-19 infection, and in the post-COVID-19 recovery phase. *Int J Psychiatry Clin Pract*, *25*(2), 115-131. https://doi.org/10.1080/13651501.2021.1887264

Vahey, G. M., McDonald, E., Marshall, K., Martin, S. W., Chun, H., Herlihy, R., . . . Team, C. I. (2021). Risk factors for hospitalization among persons with COVID-19-Colorado. *PLoS One*, *16*(9), e0256917. https://doi.org/10.1371/journal.pone.0256917

van Gerwen, M., Alsen, M., Little, C., Barlow, J., Genden, E., Naymagon, L., & Tremblay, D. (2021). Risk factors and outcomes of COVID-19 in New York City; a retrospective cohort study. *J Med Virol*, *93*(2), 907-915. https://doi.org/10.1002/jmv.26337

van Kessel, S. A. M., Olde Hartman, T. C., Lucassen, P. L. B. J., & van Jaarsveld, C. H. M. (2022). Post-acute and long-COVID-19 symptoms in patients with mild diseases: a systematic review. *Fam Pract*, *39*(1), 159-167. https://doi.org/10.1093/fampra/cmab076

van Ranst, D., Otten, H., Meijer, J. W., & van 't Hul, A. J. (2011). Outcome of pulmonary rehabilitation in COPD patients with severely impaired health status. *Int J Chron Obstruct Pulmon Dis*, *6*, 647-657. https://doi.org/10.2147/COPD.S24579

Wallaert, B., Kyheng, M., Labreuche, J., Stelianides, S., Wemeau, L., & Grosbois, J. M. (2020). Long-term effects of pulmonary rehabilitation on daily life physical activity of patients with stage IV sarcoidosis: A randomized controlled trial. *Respir Med Res*, *77*, 1-7. https://doi.org/10.1016/j.resmer.2019.10.003

Wang, Y., Zhang, D., Du, G., Du, R., Zhao, J., Jin, Y., . . . Wang, C. (2020). Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet*, *395*(10236), 1569-1578. https://doi.org/10.1016/S0140-6736(20)31022-9

Wiley, Z., Ross-Driscoll, K., Wang, Z., Smothers, L., Mehta, A. K., & Patzer, R. E. (2022). Racial and Ethnic Differences and Clinical Outcomes of Patients With Coronavirus

Disease 2019 (COVID-19) Presenting to the Emergency Department. *Clin Infect Dis*, *74*(3), 387-394. https://doi.org/10.1093/cid/ciab290

Williamson, E. J., Walker, A. J., Bhaskaran, K., Bacon, S., Bates, C., Morton, C. E., . . . Goldacre, B. (2020). Factors associated with COVID-19-related death using OpenSAFELY. *Nature*, *584*(7821), 430-436. https://doi.org/10.1038/s41586-020-2521-4

Wu, C., Chen, X., Cai, Y., Xia, J., Zhou, X., Xu, S., . . . Song, Y. (2020a). Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med*, *180*(7), 934-943. https://doi.org/10.1001/jamainternmed.2020.0994

Wu, C., Chen, X., Cai, Y., Xia, J., Zhou, X., Xu, S., . . . Song, Y. (2020b). Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med*, *180*(7), 934-943. https://doi.org/10.1001/jamainternmed.2020.0994

Wu, C., Chen, X., Cai, Y., Xia, J., Zhou, X., Xu, S., . . . Song, Y. (2020c). Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med*, *180*(7), 934-943. https://doi.org/10.1001/jamainternmed.2020.0994

Wu, X., Liu, X., Zhou, Y., Yu, H., Li, R., Zhan, Q., . . . Wang, Y. (2021). 3-month, 6-month, 9-month, and 12-month respiratory outcomes in patients following COVID-19-related hospitalisation: a prospective study. *Lancet Respir Med*, *9*(7), 747-754. https://doi.org/10.1016/S2213-2600(21)00174-0

Yanez, N. D., Weiss, N. S., Romand, J. A., & Treggiari, M. M. (2020). COVID-19 mortality risk for older men and women. *BMC Public Health*, *20*(1), 1742. https://doi.org/10.1186/s12889-020-09826-8

Young, J. M., Stahlman, S. L., Clausen, S. S., Bova, M. L., & Mancuso, J. D. (2021). Racial and Ethnic Disparities in COVID-19 Infection and Hospitalization in the Active Component US Military. *Am J Public Health*, *111*(12), 2194-2201. https://doi.org/10.2105/AJPH.2021.306527

Yue, H., & Hu, T. (2021). Geographical Detector-Based Spatial Modeling of the COVID-19 Mortality Rate in the Continental United States. *Int J Environ Res Public Health*, *18*(13). https://doi.org/10.3390/ijerph18136832

Zampogna, E., Paneroni, M., Belli, S., Aliani, M., Gandolfo, A., Visca, D., . . . Vitacca, M. (2021). Pulmonary Rehabilitation in Patients Recovering from COVID-19. *Respiration*, *100*(5), 416-422. https://doi.org/10.1159/000514387

Zhang, X., Smith, N., Spear, E., & Stroustrup, A. (2021). Neighborhood characteristics associated with COVID-19 burden-the modifying effect of age. *J Expo Sci Environ Epidemiol*, *31*(3), 525-537. https://doi.org/10.1038/s41370-021-00329-1

Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., . . . Cao, B. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*, *395*(10229), 1054-1062. https://doi.org/10.1016/S0140-6736(20)30566-3

Zhu, P., Wang, Z., Guo, X., Feng, Z., Chen, C., Zheng, A., . . . Cai, Y. (2021). Pulmonary Rehabilitation Accelerates the Recovery of Pulmonary Function in Patients With

COVID-19. *Front Cardiovasc Med*, *8*,

691609. https://doi.org/10.3389/fcvm.2021.691609

VITA

Khamron Micheals was born January 21, 1992, to Randy Robertson and Michelle Rivers, in Houston, TX. Khamron completed his schooling up to high school at Mirabeau Lamar High School in Houston, TX. He completed his Bachelor of Science degree in Respiratory Care at University of Texas Medical Branch in Galveston, Texas, in the year 2016. Upon graduation, he worked as a critical care respiratory therapist at Houston Methodist Hospital within the Texas Medical Center. Khamron simultaneously completed his Master of Science degree in Healthcare Administration at Texas Southern University in Houston, Texas, in the year 2020. After the commencement of his master's degree, in 2020, Khamron decided to pursue his Ph.D. in Rehabilitation Sciences at the University of Texas Medical Branch in Galveston, Texas to enhance his skills as a scientific and rehabilitation researcher. Khamron is graduating from his PhD in Rehabilitation Science in spring, 2024.

Permanent Address: 4717 Independence Heights Ln.
Houston, Texas 77018