

**Mortality by Reaction Type Among Hospitalized COVID-19 Patients:
An Analysis of US Electronic Medical Records**

by

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Background: Much is still unknown regarding the outcomes of symptomatic and asymptomatic COVID-19 patients.

Objective: To describe COVID-19 patients in a federated electronic medical records (EMR) network in the US and assess mortality according to COVID-19 reaction type.

Methods: This was a retrospective cohort study of COVID-19 patients hospitalized between January 21, 2020 and April 23, 2021 in the TriNetX Dataworks COVID-19 database. All data from the EMR were mapped to standard terminologies (ICD-10, LOINC, RxNorm). Reaction type and risk of mortality were examined by age, sex, race, month of index date, immunosuppressant use, dexamethasone use, and select comorbidities.

Results: There were 12,929 hospitalized COVID-19 patients identified during the study period. Of these, 8,195 patients were symptomatic. The proportion of patients was higher in the symptomatic patient group compared to the asymptomatic patient group for all investigated baseline comorbidities/characteristics, except pregnancy. After adjustment, the mean (standard deviation (SD)) time to death, in days, at day 14 was 7.05 (4.54) and 6.09 (4.76) and at day 28 was 8.28 (7.05) and 7.00 (6.79) for symptomatic and asymptomatic patients, respectively. There was an increased risk of mortality for symptomatic patients compared to asymptomatic patients at both day 14 (hazard ratio (HR)=1.89; 95% confidence interval (CI) 1.44-2.47; $p<0.001$) and day 28 (HR=1.56; 95% CI 1.26-1.94; $p<0.001$). The probability of all-cause 14-day mortality was

significantly higher in symptomatic patients (9.4%) compared to asymptomatic patients (5.9%) (log rank $p < 0.001$). The probability of all-cause 28-day mortality was also significantly higher in symptomatic patients (25.6%) compared to asymptomatic patients (22.7%) (log rank $p = 0.001$).

Conclusion: In a US-based EMR network of hospitalized COVID-19 patients, we observed an increased risk of mortality and a lower survival probability for symptomatic patients compared to asymptomatic patients at both day 14 and day 28. However, we observed that the average time to death was longer for symptomatic patients at both day 14 and day 28. These findings indicate that clinically, when allocating limited resources and treatment, it is imperative for healthcare providers to more aggressively treat symptomatic hospitalized COVID-19 patients in response to this global public health challenge.

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Preface

As an aspiring public health professional, the emergence and course of the COVID-19 pandemic has been both fascinating and devastating to watch. The goal of this work is to add to the knowledge surrounding COVID-19 to contribute to the management and control of the pandemic. The world deserves a chance to heal and learn.

I want to thank my thesis committee: Dr. Akira Sekikawa, Dr. Nancy Glynn, Dr. Jonathan Arnold, and Dr. Julius Asubonteng. The support and expertise provided by my committee truly made this project and my experience at Pitt Public Health as positive, informative, and developed as possible. To Dr. Jonathan Arnold – thank you for challenging me to be a better researcher. To Dr. Akira Sekikawa – thank you for your continued support and guidance. You have such a positive energy, and that positivity truly helped me in each aspect of this project. To Dr. Nancy Glynn – thank you for welcoming me into the Pitt Public Health community with open arms and an open door (both virtually and in-person). I am so grateful for your mentorship and your friendship. To Dr. Julius Asubonteng – thank you for facilitating such a rewarding internship experience. Because of your mentorship, I am a better student, researcher, and listener. From you, I learned that curiosity is the key to discovery.

To my family and friends – this journey has not been the easiest, but it is because of your love and endless encouragement that I can say I did it. I have the most wonderful support system, and I could never imagine navigating life without you.

1.0 Introduction

1.1 Previous Coronavirus Pandemics

Coronaviruses, most notably the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV), have caused severe illness and pathogenic outbreaks in humans for almost 20 years. SARS-CoV and MERS-CoV are believed to have originated from bats, but spillover has occurred between animal species, such as the civet and dromedary camel.¹ The SARS-CoV outbreaks occurred in 2002 and 2003 with a fatality rate estimated to be about 11%. The incubation period is two to 10 days, with an average of seven days. The reproduction number, or the average number of secondary cases produced by one initial case in a given population of susceptible individuals, is approximately 1.7 to 1.9. The MERS-CoV outbreak occurred in 2012 with a fatality rate estimated to be significantly higher at about 35%. The incubation period is two to 10 days, with an average of 5.5 days. The reproduction number is estimated to be less than one.^{2,3}

1.2 SARS-CoV-2

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged as a novel coronavirus in late 2019 as the third coronavirus with the ability to severely affect humans and is responsible for the global pandemic that we now know and refer to as COVID-19. SARS-CoV-2 was identified as the causal agent of the outbreak in Wuhan, China on January 7, 2020. Exposure

to the Huanan Seafood Wholesale Market in Wuhan was associated with the first cases of SARS-CoV-2.^{4,5} SARS-CoV-2, a betacoronavirus, and SARS-CoV share 79% of their genome sequence identity, while SARS-CoV-2 and MERS-CoV share only 50%.⁵ The incubation period for SARS-CoV-2 infection is two to 14 days, with an average of 5.2 days, which is longer than SARS-CoV and MERS-CoV. The fatality rate of SARS-CoV-2 is estimated to be about 2%, with some variability, but lower than both SARS-CoV and MERS-CoV.² However, the reproductive number of SARS-CoV-2 is approximated to be between two and four, with some variability, indicating that the transmissibility of SARS-CoV-2 is higher than that of SARS-CoV and MERS-CoV.³ Diagnosis of SARS-CoV-2 infection can occur by detection of the viral sequence through reverse transcriptase-polymerase chain reaction (RT-PCR) testing.⁶

1.3 COVID-19

COVID-19, named by the World Health Organization on February 11, 2020, is the term used to identify the disease associated with SARS-CoV-2 infection. COVID-19 is primarily spread through respiratory droplets passed from an infected person to a susceptible person when the infected person coughs or sneezes. COVID-19 patients can present a wide range of symptoms, most commonly fever, cough, myalgia or fatigue, headache, and diarrhea. For most patients, these symptoms are mild to moderate and resolve within one to two weeks. However, in severe cases, patients can develop acute respiratory distress syndrome (ARDS), which can greatly increase the risk of mortality.^{6,7}

1.3.1 Demographic Risk Factors

According to the Centers for Disease Control and Prevention (CDC) COVID-19 Data Tracker, as of October 9, 2021, race and ethnicity information was available for 22,797,175 (65%) cases out of 35,011,009 confirmed COVID-19 cases. White, non-Hispanic patients comprised 51.8% of cases, which is less than the proportion of White, non-Hispanic persons in the US. Black, non-Hispanic persons made up approximately 12% of COVID-19 cases, which is similar to the proportion of Black, non-Hispanic residents in the US. Hispanic or LatinX individuals comprise 26.6% of COVID-19 cases. This proportion is higher than the proportion of Hispanic or LatinX persons in the US, suggesting that Hispanic or LatinX persons are disproportionately affected by COVID-19 infection. However, in the 84% of deaths in which race and ethnicity information was available, the proportion of deaths in Black, non-Hispanic patients is higher than the proportion of Black, non-Hispanic persons in the US population. These data suggest that there is a disproportionate risk of COVID-19 mortality for Black, non-Hispanic individuals.⁸

Age group information was available for 98% of COVID-19 cases reported to the CDC. The 18-29 age group has the highest proportion of COVID-19 cases at about 22%, but only accounts for approximately 16% of the US population. This data suggests that young adults are disproportionately at risk for SARS-CoV-2 infection. However, children only account for about 14% of COVID-19 cases. Mortality from COVID-19 generally occurs in the older population, with 77.8% of deaths in patients 65 years or older. The proportion of deaths in each age group of older adults exceeds the proportion of people in the US population in that demographic category, indicating a severe disproportionate risk of mortality in the older population.⁸

Similar to age, information regarding sex was available for 98% of COVID-19 cases reported to the CDC, and 52.3% of infected patients are of the female sex. The proportion of

females in the US population is slightly higher than that of males. However, for the 99% of deaths in which sex information was available, 54.3% of COVID-19 deaths were in the male population, suggesting that the male sex is at higher risk for COVID-19-associated mortality.⁸

1.3.2 Reaction Types

Patients react to SARS-CoV-2 infection differently. COVID-19 can be classified into multiple categories based on presentation of the disease: asymptomatic, mild, moderate, severe, and critical.⁹ Asymptomatic patients are defined as patients with a positive RT-PCR test for SARS-CoV-2, without clinical symptoms or abnormal chest imaging findings. Two of the primary challenges of controlling COVID-19 are the transmissibility of pre-symptomatic patients and the transmissibility of asymptomatic patients. If the SARS-CoV-2 virus is in a reproductive state in the body, the virus can be spread to others. Since the incubation period is estimated to be two to 14 days, infected patients can shed the virus before showing clinical symptoms, which is often when patients first realize that they have been infected. Furthermore, asymptomatic patients can transmit the virus throughout the course of infection. However, without the indicator of clinical symptoms, many are unaware that they are infectious without the assistance of a RT-PCR test or notification of a potential exposure, which may not always be available.¹⁰

There is much uncertainty regarding the proportion of asymptomatic infection from SARS-CoV-2. A systematic review identified 43 studies that utilized PCR testing to detect current infection.¹¹ Of these, 14 studies collected longitudinal data to follow-up with patients who tested positive but were asymptomatic at the time of testing. Results showed that among these asymptomatic patients at the time of testing, 11.1% to 100% (median=72.3%; IQR 56.7% to 89.7%) remained asymptomatic throughout follow-up. In the same review, 18 studies were

identified that utilized antibody testing to retrospectively identify SARS-CoV-2 infection. Overall, the proportion of asymptomatic patients ranged from 21.7% to 85.0% (median=41.2%; IQR 32.6% to 48.1%). Among the studies that used random selection to identify a representative sample, the proportion of asymptomatic patients ranged from 21.7% to 47.3% (median=32.7%; IQR 28.7% to 43.4%). Retrospective reports require patients to correctly recall any symptoms, which could result in recall bias, leading to an underestimation or overestimation in the proportion of asymptomatic individuals. However, this research suggests that anywhere between one-third and three-quarters of SARS-CoV-2-infected patients are asymptomatic.¹¹

Symptomatic COVID-19 patients can experience a wide variety of symptoms. Fever, cough, and dyspnea are considered the most common clinical indicators of SARS-CoV-2 infection. It is estimated that fever is experienced by up to 90% of symptomatic patients. Other symptoms include myalgia or fatigue, headache, shortness of breath, sore throat, and gastrointestinal symptoms, such as diarrhea, nausea, and vomiting.⁷ Olfactory and gustatory dysfunction, or disruptions in sense of smell and taste, respectively, have also been reported as more common indicators of COVID-19. There is uncertainty regarding the proportion of patients who experience these symptoms, but it appears to be more common in younger patients and those with mild disease presentation. In a systematic review and meta-analysis of 24 studies including 8,438 patients, published in the spring of 2020, it is estimated that approximately 41% of COVID-19 patients presented olfactory dysfunction and 38% presented gustatory dysfunction.¹²

1.3.3 Hospitalization

Severe cases of COVID-19 may require hospitalization. According to case surveillance in the US from January 22 to May 30, 2020 through the Morbidity and Mortality Weekly Report

from the CDC, among 1,320,488 confirmed COVID-19 cases, 184,673 (14%) patients were hospitalized.¹³ Extensive research has investigated the demographics of patients who are at higher risk of severe disease, hospitalization, and mortality. In a cross-sectional study including 12 states and 70 counties in the US, 5,416 hospitalized adults with a confirmed COVID-19 diagnosis were analyzed. This study found at least one underlying condition, excluding hypertension, in 73% of hospitalized patients. Of the total study population, 49% of patients had hypertension, and 55% of patients were obese. Furthermore, the unadjusted rate ratio was 2.7 (95% CI 2.5-2.9) for hospitalization in adults 65 years and older compared to adults aged 18-44 years, 1.2 (95% CI 1.1-1.3) for hospitalization in males compared to females, and 3.9 (95% CI 3.7-4.2) for hospitalization in non-Hispanic Black patients compared to non-Hispanic White patients. These findings suggest that age, sex, and race are important demographic factors that impact risk of COVID-19-associated hospitalization. After adjusting for these factors, the investigators found that obesity, chronic kidney disease, diabetes, hypertension, and asthma were associated with a significantly higher risk of COVID-19-associated hospitalization.¹⁴

1.3.4 Mortality

Again referring to the case surveillance in the US from January 22 to May 30, 2020 through the Morbidity and Mortality Weekly Report from the CDC, of the 1,320,488 confirmed COVID-19 cases, 71,116 (5%) patients died.¹³ Factors that were found to increase risk of COVID-19-associated hospitalization are generally synonymous with factors that increase risk of COVID-19-associated mortality. In a systematic review and meta-analysis, 77 research studies were identified that included a total of 38,906 hospitalized COVID-19 patients. Across studies, the overall proportion of mortality among hospitalized patients was 20%. Age and sex were found to be

significant predictors of mortality, specifically patients aged 60 and above (summary relative risk [sRR]=3.61; 95% CI 2.96-4.39) and males (sRR=1.34; 95% CI 1.22-1.40). Patients with select comorbidities, namely hypertension, diabetes, cardiovascular disease, smoking, chronic obstructive pulmonary disease (COPD), chronic kidney disease, and chronic liver disease, also had a significantly higher risk of COVID-19-associated mortality.¹⁵ These results indicate that age, sex, and select comorbidities could serve as indicators for risk of severe COVID-19 presentation and mortality.

1.3.5 Immunosuppressant Use

There has been a lack of consensus regarding the effect of immunosuppressive drugs on SARS-CoV-2 infection.¹⁶ Previous research has suggested that the use of immunosuppressants could be detrimental during the early stage of COVID-19 because the host immune response is crucial in the inhibition of viral replication in the body. In the later phases of the disease, the use of immunosuppressive drugs may be beneficial due to the suppression of the cytokine storm, or the flood of inflammatory proteins, that can cause damage to the organs, specifically through acute respiratory distress syndrome (ARDS). Because of the potential interaction between immunosuppressive drugs and the cytokine storm, some studies have found that patients with COVID-19 who have been treated with immunosuppressants had a decreased risk of mortality. Thus, the use of immunosuppressive drugs is an important covariate that should be taken into account when investigating risk of mortality and time to death outcomes in COVID-19 patients.¹⁶

1.3.6 Dexamethasone Use

Similar to immunosuppressive medications, the use of dexamethasone to treat COVID-19 has been widely studied and debated. The Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial is a controlled, open-label trial involving 176 United Kingdom National Health Service organizations that explored the efficacy of multiple COVID-19 treatments among hospitalized COVID-19 patients, including dexamethasone. Among the 2,104 hospitalized COVID-19 patients randomized to receive dexamethasone and 4,321 to the control group consisting of standard care, dexamethasone treatment resulted in a significantly lower rate of 28-day mortality (age-adjusted RR=0.83; 95% CI 0.75-0.93; $p<0.001$). Thus, the use of dexamethasone should also be included as a potential covariate when evaluating risk of mortality in hospitalized COVID-19 patients.¹⁷

1.3.7 Changes in the COVID-19 Pandemic Over Time

Since the emergence of COVID-19 in the US in January 2020, the pandemic has rapidly evolved both biologically and clinically. The SARS-CoV-2 virus has mutated from its original form, introducing variants into the population and posing another challenge to researchers, healthcare providers, and public health professionals. Variants are continuously being monitored and classified based on their level of concern for the community, including important epidemiological facets, such as transmission, severity, and treatment response.¹⁸

Multiple vaccines have been developed to reduce the risk of severe COVID-19 infection. As of October 2021, the three prominent COVID-19 vaccine manufacturers circulating the United States are Pfizer-BioNTech, Moderna, and Johnson & Johnson. In August 2021, the Pfizer-

BioNTech vaccine was the first to receive Food and Drug Administration (FDA) approval for people at least 16 years of age. This vaccine was shown to be 95% effective in the initial Phase 3 trial. Moderna's vaccine was also about 95% effective in its Phase 3 clinical trial. The Johnson & Johnson vaccine was overall 72% effective, as reported by the FDA.¹⁹ These vaccines have proven to be safe and effective against COVID-19 and play an integral role in the control of the pandemic.

1.4 Knowledge Gaps

Asymptomatic patients compose a significant portion of the population infected with SARS-CoV-2. Due to the asymptomatic nature of the infection, these patients can be difficult to identify, monitor, and study. Thus, there is limited knowledge regarding the risk of mortality according to how patients react to SARS-CoV-2 infection, specifically whether patients show symptoms or have an asymptomatic presentation of COVID-19.

The role of asymptomatic infections in the COVID-19 pandemic has raised many questions and caused much confusion for public health professionals, scientists, and the general public. In early June 2020, the World Health Organization (WHO) made a statement at a press conference that transmission of COVID-19 through asymptomatic patients is very rare. Briefly after this statement and confusion from the public, the WHO released a clarification, saying that asymptomatic patients do play a role in the spread of COVID-19, but more information is needed to determine the magnitude of that role.²⁰ This is just one example of the challenges that asymptomatic infections pose to public health officials, making it particularly difficult to provide information and guidance to the community.

Many studies have reported the proportion of asymptomatic patients among their cohorts but have not examined the clinical characteristics and outcomes stratified by the type of disease presentation, or reaction type. However, a study of 1,263 COVID-19 patients conducted in India reported on the presence of symptoms stratified by disease progression. Among patients with disease progression, 92.3% were symptomatic at the time of testing or pre-symptomatic. Among patients without disease progression, 52.9% were asymptomatic throughout the course of infection.²¹ These results suggest that symptomatic presentation of COVID-19 may lead to poorer outcomes, but the magnitude of the disease progression and potentially poorer outcomes are not clearly quantified.

Furthermore, when asymptomatic disease outcomes were reported in the literature, they were often in confined, specialized settings, such as nursing facilities. In an outbreak at a skilled nursing facility in Illinois, 13/35 (37%) residents remained asymptomatic after testing positive for SARS-CoV-2. Of these 13 residents, two (20%) died. These patients were elderly (aged 96- and 89-years-old), and one patient had end-stage dementia leading up to the time of death.²² These findings indicate that the prevalence of death among asymptomatic COVID-19 patients is 20%. However, the population in this study is particularly at risk for severe disease and mortality, potentially overestimating the rate of mortality among asymptomatic patients.

In retrospective studies with broader settings, results have shown that asymptomatic patients may clear the virus more rapidly than symptomatic patients, leading to a faster recovery (9 days vs. 26 days; $p < 0.001$)²³ and potentially have better outcomes than symptomatic patients, as only 2.53% of asymptomatic patients developed severe disease.²⁴ These studies had small sample sizes of 52 and 79 asymptomatic COVID-19 patients, respectively.^{23,24} More research is needed to identify and analyze asymptomatic outcomes in large, more generalized populations.

Focusing on hospitalized patients allows for the identification of SARS-CoV-2 infection in patients with both symptomatic and asymptomatic disease presentation. Identifying a study population from a federated electronic medical record network also allows for a more comprehensive cohort of individuals, increasing the generalizability of the findings. Thus, exploring the distribution, characteristics, and risk of mortality in hospitalized COVID-19 patients in an electronic medical record system with symptomatic and asymptomatic presentation fills a substantial gap in the current knowledge regarding the clinical profile and associated outcomes of asymptomatic patients.

1.5 Public Health Significance

COVID-19 has been one of, if not the most pressing global public health concern of 2020 and 2021. As of October 7, 2021, there have been 236,132,082 confirmed cases of SARS-CoV-2 infection and 4,822,472 SARS-CoV-2-associated deaths across the globe. In the US, specifically, there have been 43,673,628 confirmed cases of SARS-CoV-2 infection and 700,773 SARS-CoV-2-associated deaths.²⁵ Due to a wide range of factors, including asymptomatic infection and public health disparities in access to testing and healthcare, these numbers are likely significant underestimations of the burden of COVID-19.

The COVID-19 pandemic has impacted all facets of life, including work, school, and recreation. Schools were closed, many businesses were forced to transition to a remote working environment, and businesses that could not withstand the economic hit permanently closed. By mid-March 2020, 3.28 million Americans filed for unemployment insurance benefits.²⁶ Patients who were hospitalized are feeling the weight of the financial burden that comes with hospital

admission. Hospital bills from COVID-19-related admission are often upwards of \$40,000 but could reach approximately \$200,000 if the patient was admitted to the intensive care unit and received invasive mechanical ventilation.²⁷

Along with the significant economic burden that coincides with a global pandemic, the allocation of limited medical resources poses an additional challenge. Hospital and ICU beds, ventilators, personal protective equipment, hospital staff, and pharmaceutical and therapeutic treatment are scarce, particularly in areas with increased rates of infection and mortality. Because of this, it can be necessary to ethically distribute resources and treatment based upon need. Ethically and effectively allocating treatment can be rationalized in multiple ways, such as treating everyone equally, prioritizing patients to preserve the highest number of life-years, prioritizing people who have the highest instrumental value, or prioritizing people at highest risk for hospitalization and mortality, and this causes debate among healthcare providers and public health leaders.²⁸ Maximizing benefits is often a necessary outlook when managing a pandemic, but how to do so ethically is a point of contention. However, many recommendations for the allocation of resources stem from scientific evidence. Thus, the continuation of research regarding COVID-19 outcomes across a wide variety of patient demographics and clinical characteristics can help guide public health decision makers and medical personnel in the task of allocating limited resources both ethically and effectively.

The role of asymptomatic infection on the transmission, hospitalization and mortality rates, and the financial burden of the COVID-19 pandemic remains unclear. To control the COVID-19 pandemic, allocate treatment and resources, and reduce economic hardship, it is imperative to investigate all facets of SARS-CoV-2, including asymptomatic infections and their respective outcomes.

2.0 Objective

To fill gaps in available research and real-world evidence, the goal of this project was to understand the possible COVID-19 reaction types and their associated outcomes in hospitalized COVID-19 patients. The first aim of this project was to characterize hospitalized patients with diagnostic evidence of COVID-19 by describing the distribution of symptomatic and asymptomatic patients and the baseline sociodemographic and clinical characteristics of patients by COVID-19 reaction type in a US healthcare database. The second aim was to assess all-cause mortality at day 14 and day 28 after the index date among these hospitalized COVID-19 patients by COVID-19 reaction type (symptomatic vs. asymptomatic). We hypothesized that hospitalized COVID-19 patients with symptomatic disease presentation will have an increased risk and probability of all-cause mortality at both day 14 and day 28 compared to hospitalized COVID-19 patients with asymptomatic disease presentation.

3.0 Methods

3.1 Study Design

This retrospective observational cohort study included 12,929 hospitalized patients with diagnosed SARS-CoV-2 and evidence of COVID-19-related symptoms during the seven days prior to or seven days after the COVID-19 diagnosis date (index date) or no evidence of COVID-19-related symptoms during the seven days prior to or seven days after the COVID-19 diagnosis date (index date). The patients were identified from the TriNetX database, a federated electronic medical record (EMR) network including 44 Healthcare Organizations in the US.

3.2 Study Population

The study population consisted of all patients who have been hospitalized with diagnosed SARS-CoV-2 through PCR testing from the date of the first confirmed COVID-19 case in the US on January 21, 2020 through April 23, 2021 in the TriNetX database. Patients were included in the study from the time of COVID-19 diagnosis (the index date), indicated by a positive PCR test, through the first of any of the following: live hospital discharge, death occurring within the facility at day 14 or day 28, or the last day of available data within the dataset, April 23, 2021.

The inclusion criteria were identified as a COVID-19 diagnosis in any position on the discharge claim record and a minimum of six months of enrollment or claims activity prior to the index date as a look-back period for establishing baseline history and status. Exclusion criteria

were children (identified as patients less than eighteen years of age), patients who were not hospitalized, patients with hospitalizations that occurred before the index date or greater than fourteen days after the index date, patients with an index date before January 21, 2020, patients without evidence of any medical bill in six months prior to the index date, patients with evidence of a prior COVID-19-associated in-patient hospitalization, patients with evidence of oxygen support within the prior three months of hospitalization, patients with evidence of post-COVID-19 conditions within the prior three months of hospitalization, and patients with evidence of prior COVID-19-related treatment before the in-patient hospitalization or index date (Figure 1). The final cohort included 12,929 hospitalized COVID-19 patients. Of which, 8,195 patients were identified as symptomatic, and 4,734 patients were identified as asymptomatic.

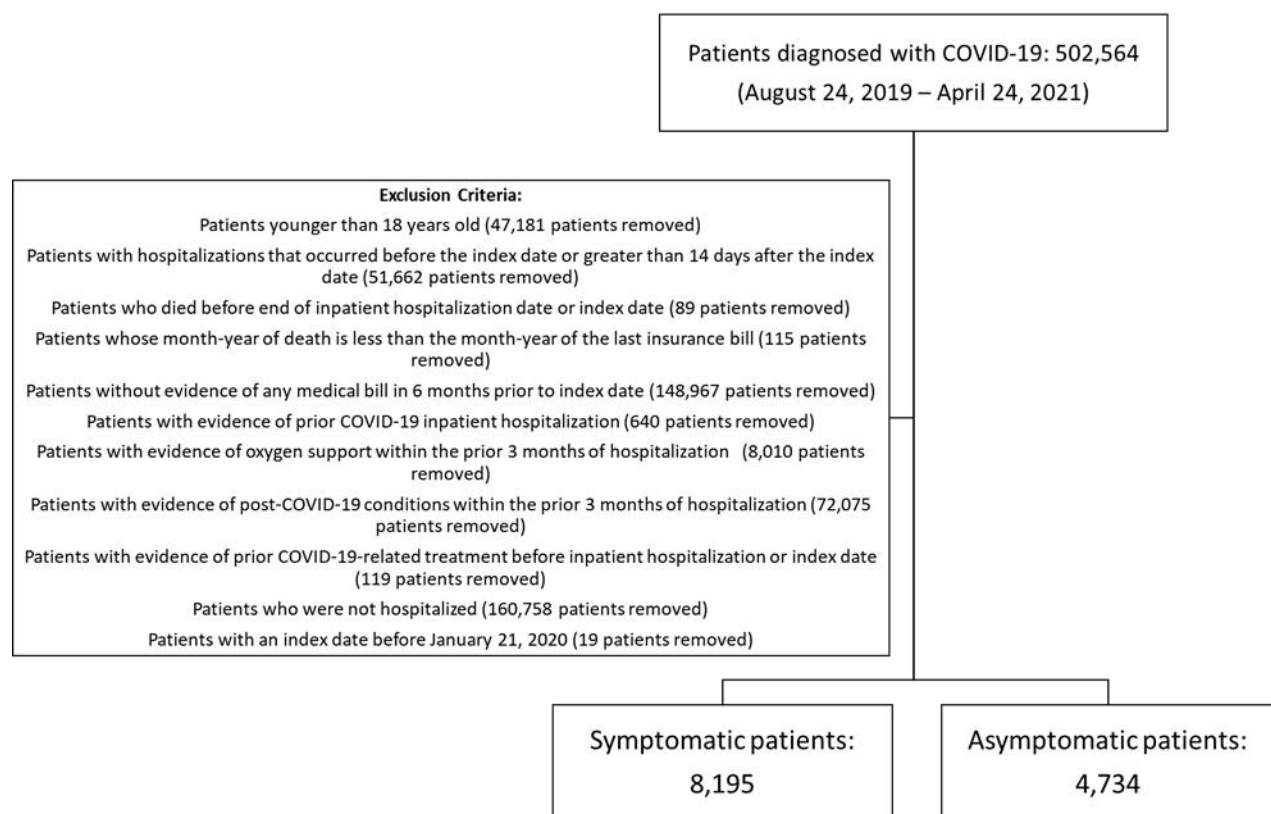


Figure 1. Cohort selection

3.3 Defining Reaction Type

Patients were identified as symptomatic if the patient presented at least one of the following symptoms, identified through ICD-10 codes, in the seven days prior to and/or the seven days after the index date and asymptomatic if the patient presented none of the following symptoms in the seven days prior to and/or the seven days after the index date: fever, headache, diarrhea, delirium or encephalopathy, cough, chest pain, sore throat, pneumonia, shortness of breath, acute bronchitis, other acute respiratory infection, acute respiratory distress syndrome, respiratory arrest, or respiratory failure, loss of taste or smell, dyspnea, malaise or fatigue, myalgia, congestion, nausea or vomiting, or acute sinusitis (Appendix Table 1).^{7,12,29}

3.4 Defining the Index Date, Baseline Comorbidities, and Primary Outcomes

The index date is defined as the date of the PCR test that resulted in a positive diagnosis of SARS-CoV-2. These data were derived from the EMR through Logical Observation Identifiers Names and Codes (LOINC).

Baseline comorbidities were derived from ICD-10 codes and present within six months of the index date. Other COVID-19 medications at baseline, specifically immunosuppressive medications and dexamethasone, derived from drug codes and/or procedure codes through RxNorm, were summarized by reaction type. Immunosuppressive medications included Abatacept, Maltose, Adalimumab, Anakinra, Azathioprine, Belatacept, Belimumab, Certolizumab pegol, Cyclophosphamide, Cyclosporine, Etanercept, Golimumab, Infliximab, Leflunomide, Methotrexate, Mycophenolate mofetil, Rituximab, Sirolimus, and Tocilizumab.

The primary outcomes in this study were all-cause mortality at day 14 and all-cause mortality at day 28.

3.5 Statistical Methods

Descriptive statistics of baseline demographic and clinical characteristics were calculated, specifically the number and proportion of patients in each category, to describe the distribution of patients according to COVID-19 reaction type both before and after propensity score matching. Prevalence of symptoms among symptomatic COVID-19 patients were reported and displayed as counts.

To reduce potential confounding, a 1:1 propensity score matching method with a caliper of 0.1 was used to identify matched pairs of patients from the symptomatic and asymptomatic groups with comparable baseline characteristics and comorbidities.³⁰ Specifically, symptomatic hospitalized COVID-19 patients will be matched 1:1 with asymptomatic hospitalized COVID-19 patients based on the following clinically relevant factors: age, sex, race, month of index date, select comorbidities (cardiovascular disease (CVD), hypertension, diabetes, obesity, asthma, chronic lung disease (CLD), cancer), immunosuppressant use, and dexamethasone use.^{14–17,31} This subgroup included 7,788 hospitalized COVID-19 patients.

The association between COVID-19 reaction type and mortality was assessed through Cox proportional hazards regression models, adjusted for various covariates. The models included were unadjusted for covariates, adjusted with propensity score, adjusted with propensity score, age, race, and sex, and adjusted with propensity score, age, race, sex, month of index date, immunosuppressant use, dexamethasone use, and history of cancer, asthma, chronic lung disease,

diabetes, hypertension, obesity, and cardiovascular disease (CVD) at baseline.^{14–17,31} To evaluate the risk of 14-day and 28-day mortality according to COVID-19 reaction type, time-to-event comparison endpoints were analyzed using Kaplan-Meier curves with log-rank tests.^{32,33} Two-sided p-values of less than 0.05 indicated statistical significance.

All analyses were performed using R version 3.5.2.

4.0 Results

4.1 Characteristics of the Study Population

From January 21, 2020 to April 23, 2021, 12,929 hospitalized COVID-19 patients were identified and included in the cohort (Figure 1). Before propensity score matching, the cohort consisted of 8,195 (63.4%) symptomatic patients and 4,734 (36.6%) asymptomatic patients. In the symptomatic patient group, 43.9% were aged 55 to 74 years, 51.7% were male, 54.5% were White, 22.4% were Black, 2.8% were Asian, 0.7% were designated as other, and 19.6% were of unknown race (Table 1). The proportion of patients diagnosed with any of the included comorbidities was generally low. Most notably, 17.2% of patients had cardiovascular disease, 6.2% had previous arrhythmias, dysrhythmia, or abnormal heartbeat, 10.4% had hypertension, 5.7% had diabetes, 5.9% had hyperlipidemia, and 7.6% had kidney disease. Seventy-one (0.9%) patients were using immunosuppressive medications, and 195 (2.4%) patients were using dexamethasone (Table 2).

In the asymptomatic patient group, patients were generally younger with 40.4% aged 18 to 44 years, most patients were female with only 39.5% male, 57.2% were White, 23.3% were Black, 3.3% were Asian, 0.6% were designated as other, and 15.6% were of unknown race (Table 1). The proportion of patients diagnosed with any of the included comorbidities was lower in the asymptomatic group compared to the symptomatic group in all the included comorbidities, except pregnancy. In the symptomatic patient group, 1.6% of patients were pregnant, while in the asymptomatic group, 14.6% of patients were pregnant. In the asymptomatic patient group, 5.7% of patients had cardiovascular disease. Forty (0.8%) patients were using immunosuppressive medications, and 127 (2.7%) patients were using dexamethasone (Table 2).

Table 1. Demographics of symptomatic and asymptomatic patients before and after propensity score

Variables n (%)	matching			
	COVID-19 Symptomatic Patients	COVID-19 Asymptomatic Patients	COVID-19 Symptomatic Patients	COVID-19 Asymptomatic Patients
	(Before Matching)	(Before Matching)	(After Matching)	(After Matching)
	N=8,195	N=4,734	N=3,894	N=3,894
Age category				
18-44	1,281 (15.6)	1,913 (40.4)	1,035 (26.6)	1,184 (30.4)
45-54	1,116 (13.6)	534 (11.3)	668 (17.2)	475 (12.2)
55-64	1,712 (20.9)	701 (14.8)	792 (20.3)	662 (17)
65-74	1,882 (23)	728 (15.4)	724 (18.6)	716 (18.4)
75-84	1,562 (19.1)	613 (12.9)	517 (13.3)	612 (15.7)
>84	642 (7.8)	245 (5.2)	158 (4.1)	245 (6.3)
Sex				
Female	3,957 (48.3)	2,865 (60.5)	2,137 (54.9)	2,154 (55.3)
Male	4,238 (51.7)	1,869 (39.5)	1,757 (45.1)	1,740 (44.7)
Race				
White	4,469 (54.5)	2,708 (57.2)	2,241 (57.6)	2,250 (57.8)
Black	1,836 (22.4)	1,105 (23.3)	918 (23.6)	903 (23.2)
Asian	226 (2.8)	155 (3.3)	116 (3)	124 (3.2)
Other	59 (0.7)	29 (0.6)	25 (0.6)	27 (0.7)
Unknown	1,605 (19.6)	737 (15.6)	594 (15.3)	590 (15.2)

Table 2. Baseline comorbidities and medications of symptomatic and asymptomatic patients before and after propensity score matching

Variables n (%)	COVID-19 Symptomatic Patients (Before Matching) N=8,195	COVID-19 Asymptomatic Patients (Before Matching) N=4,734	COVID-19 Symptomatic Patients (After Matching) N=3,894	COVID-19 Asymptomatic Patients (After Matching) N=3,894
Comorbidities				
<i>Asthma</i>	207 (2.5)	49 (1)	57 (1.5)	48 (1.2)
<i>Cancer</i>	240 (2.9)	131 (2.8)	121 (3.1)	119 (3.1)
<i>Chronic lung disease</i>	303 (3.7)	31 (0.7)	33 (0.8)	31 (0.8)
<i>Cardiovascular disease</i>	1,409 (17.2)	271 (5.7)	276 (7.1)	262 (6.7)
<i>Coronary artery disease</i>	404 (4.9)	42 (0.9)	54 (1.4)	42 (1.1)
<i>Congestive heart failure</i>	231 (2.8)	33 (0.7)	37 (1)	33 (0.8)
<i>Prior ACS, MI, stroke, coronary revascularization</i>	329 (4)	51 (1.1)	48 (1.2)	50 (1.3)
<i>Prior arrhythmias, dysrhythmias, or abnormal heartbeat</i>	512 (6.2)	99 (2.1)	113 (2.9)	97 (2.5)
<i>Hypertension</i>	852 (10.4)	62 (1.3)	69 (1.8)	62 (1.6)
<i>Diabetes</i>	466 (5.7)	31 (0.7)	39 (1)	31 (0.8)
<i>Dependence on supplemental oxygen prior to COVID-19</i>	43 (0.5)	1 (0)	4 (0.1)	1 (0)
<i>History of smoking or tobacco use</i>	343 (4.2)	71 (1.5)	87 (2.2)	58 (1.5)
<i>History of alcohol use</i>	51 (0.6)	23 (0.5)	18 (0.5)	20 (0.5)
<i>Hyperlipidemia</i>	482 (5.9)	34 (0.7)	44 (1.1)	34 (0.9)
<i>Kidney disease</i>	624 (7.6)	87 (1.8)	118 (3)	81 (2.1)
<i>Liver disease</i>	87 (1.1)	5 (0.1)	19 (0.5)	4 (0.1)

<i>Obesity</i>	356 (4.3)	43 (0.9)	43 (1.1)	42 (1.1)
<i>Pregnant</i>	129 (1.6)	689 (14.6)	114 (2.9)	388 (10)
<i>Drugs at baseline</i>				
<i>Immunosuppressive medications</i>	71 (0.9)	40 (0.8)	31 (0.8)	37 (1)
<i>Dexamethasone</i>	195 (2.4)	127 (2.7)	114 (2.9)	105 (2.7)

4.2 Symptom Profile of Symptomatic COVID-19 Patients

Among the 8,195 symptomatic patients, the most common symptom was shortness of breath, identified in 4,568 (55.7%) patients. The next most common symptoms were pneumonia (51.7%), acute respiratory distress syndrome, respiratory arrest, or respiratory failure (46.5%), dyspnea (41.5%), and congestion (33.7%). Fever was reported in 17.9% of patients, malaise or fatigue was reported in 15.6% of patients, and loss of taste or smell was only reported in 1.4% of patients (Figure 2).

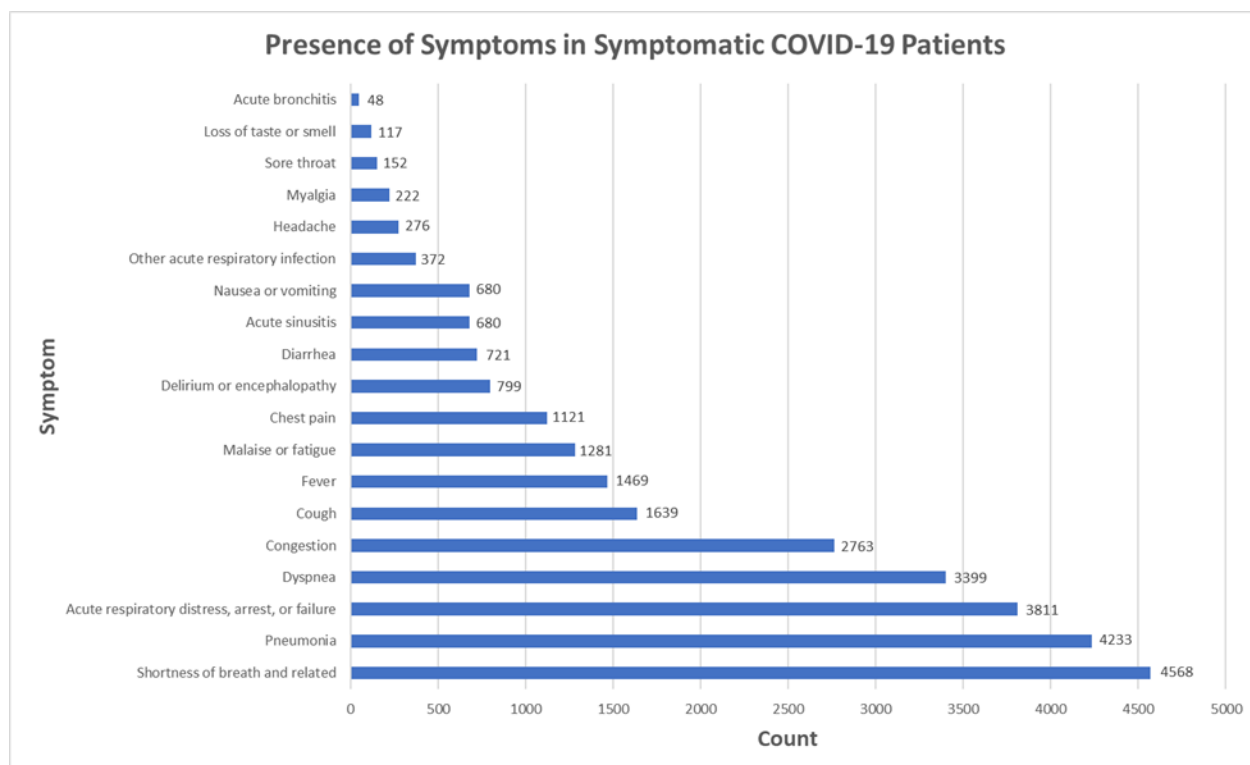


Figure 2. Symptoms reported in symptomatic COVID-19 patients

4.3 Mortality by Reaction Type at Day 14

Among symptomatic patients at day 14, 161 (4.1%) patients had died. Among asymptomatic patients at day 14, 82 (2.1%) had died. The risk of mortality was 1.70 times higher in the symptomatic patient group compared to the asymptomatic patient group (HR=1.70; 95% CI 1.30-2.21; $p<0.001$), unadjusted for any covariates. Similar findings were obtained when adjusted only for propensity score (HR=1.70; 95% CI 1.30-2.21; $p=0.001$). The risk of mortality was 1.88 times higher in the symptomatic patient group compared to the asymptomatic patient group (HR=1.88; 95% CI 1.44-2.46; $p=0.001$), adjusted for propensity score, age, race, and sex. Similar findings were reported when adjusted for propensity score, age, race, sex, month of index date,

immunosuppressant use, dexamethasone use, and history of cancer, asthma, chronic lung disease, diabetes, hypertension, obesity, and cardiovascular disease (HR=1.89; 95% CI 1.44-2.47; $p<0.001$) (Table 3).

The probability of all-cause 14-day mortality among symptomatic patients (9.4%) was significantly higher than that of asymptomatic patients (5.9%) (log rank $p<0.001$) (Figure 3). However, the average time to mortality at day 14 was shorter in asymptomatic patients compared to symptomatic patients both before and after propensity score matching. Before propensity score matching, the mean time to mortality at day 14 was 7.40 days (SD=4.55 days) and 5.76 days (SD=4.70 days) in symptomatic patients and asymptomatic patients, respectively. Similarly, after propensity score matching, the mean time to mortality at day 14 was 7.05 days (SD=4.54 days) and 6.09 days (SD=4.76 days) in symptomatic patients and asymptomatic patients, respectively (Table 5).

Table 3. Cox proportional hazard regression examining mortality at day 14

	Number of Events in Symptomatic/Asymptomatic	Hazard rate ratio (95% confidence interval)	<i>p-value</i>
Symptomatic (Mortality at day 14 †)	161/82	1.70 (1.30-2.21)	<0.001
Symptomatic (Mortality at day 14 ‡)	161/82	1.70 (1.30-2.21)	0.001
Symptomatic (Mortality at day 14 §)	161/82	1.88 (1.44-2.46)	0.001
Symptomatic (Mortality at day 14 #)	161/82	1.89 (1.44-2.47)	<0.001

† Unadjusted Cox proportional hazard regression model.

‡ Cox proportional hazard regression model adjusted with propensity score.

§ Cox proportional hazard regression model adjusted with propensity score, age, race, and sex.

Cox proportional hazard regression model adjusted with propensity score and covariates namely age, race, sex, month of index date, immunosuppressant use, dexamethasone use, and history of cancer, asthma, chronic lung disease, diabetes, hypertension, obesity, and cardiovascular disease (CVD) at baseline.

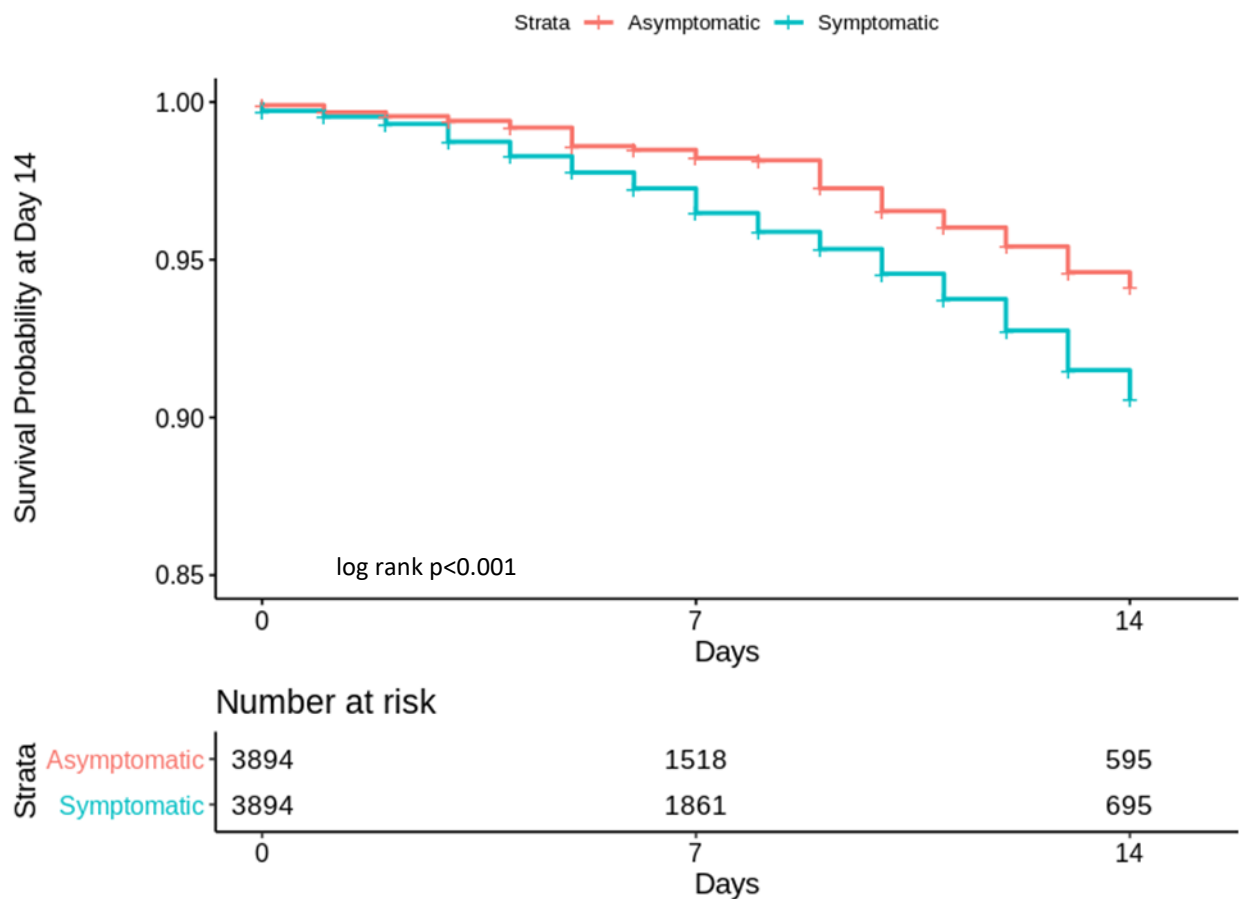


Figure 3. Kaplan-Meier curve examining time to mortality at day 14

4.4 Mortality by Reaction Type at Day 28

Among symptomatic patients at day 28, 227 (5.8%) patients had died. Among asymptomatic patients at day 28, 132 (3.4%) had died. The risk of mortality was 1.42 times higher in the symptomatic patient group compared to the asymptomatic patient group (HR=1.42; 95% CI

1.14-1.76; $p=0.001$), unadjusted for any covariates. Similar findings were obtained when adjusted only for propensity score (HR=1.40; 95% CI 1.13-1.73; $p=0.002$). The risk of mortality was 1.55 times higher in the symptomatic patient group compared to the asymptomatic patient group (HR=1.55; 95% CI 1.25-1.92; $p=0.001$), adjusted for propensity score, age, race, and sex. Similar findings were reported when adjusted for propensity score, age, race, sex, month of index date, immunosuppressant use, dexamethasone use, and history of cancer, asthma, chronic lung disease, diabetes, hypertension, obesity, and cardiovascular disease (HR=1.56; 95% CI 1.26-1.94; $p<0.001$) (Table 4).

The probability of all-cause 28-day mortality among symptomatic patients (25.6%) was also significantly higher than that of asymptomatic patients (22.7%) (log rank $p=0.001$) (Figure 4). However, similar to the average time to mortality at day 14, the mean time to mortality at day 28 was shorter in asymptomatic patients compared to symptomatic patients. Before propensity score matching, the mean time to mortality at day 28 was 8.80 days (SD=7.27 days) and 6.57 days (SD=6.58 days) in symptomatic patients and asymptomatic patients, respectively. Similarly, after propensity score matching, the mean time to mortality at day 28 was 8.28 days (SD=7.05 days) and 7.00 days (SD=6.79 days) in symptomatic patients and asymptomatic patients, respectively (Table 5).

Table 4. Cox proportional hazard regression examining mortality at day 28

	Number of Events in Symptomatic/Asymptomatic	Hazard rate ratio (95% confidence interval)	P-value
Symptomatic (Mortality at day 28 †)	227/132	1.42 (1.14-1.76)	0.001
Symptomatic (Mortality at day 28 ‡)	227/132	1.40 (1.13-1.73)	0.002

Symptomatic (Mortality at day 28 ψ)	227/132	1.55 (1.25-1.92)	0.001
Symptomatic (Mortality at day 28 #)	227/132	1.56 (1.26-1.94)	<0.001

† Unadjusted Cox proportional hazard regression model.

‡ Cox proportional hazard regression model adjusted with propensity score.

Ψ Cox proportional hazard regression model adjusted with propensity score, age, race, and sex.

Cox proportional hazard regression model adjusted with propensity score and covariates namely age, race, sex, month of index date, immunosuppressant use, dexamethasone use, and history of cancer, asthma, chronic lung disease, diabetes, hypertension, obesity, and cardiovascular disease (CVD) at baseline.

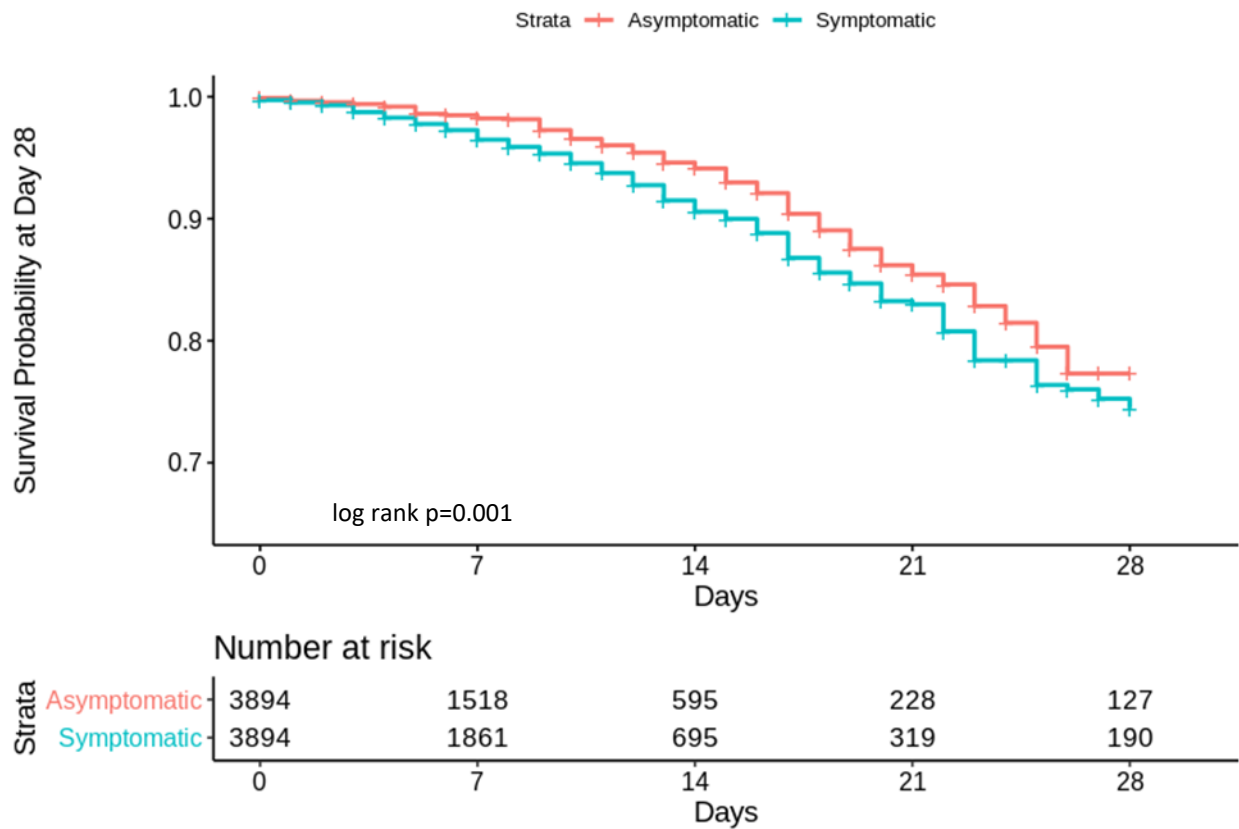


Figure 4. Kaplan-Meier curve examining time to mortality at day 28

Table 5. Time to mortality at day 14 and day 28

Variables	COVID-19 Symptomatic Patients	COVID-19 Asymptomatic Patients	COVID-19 Symptomatic Patients	COVID-19 Asymptomatic Patients
mean (SD)	(Before Matching)	(Before Matching)	(After Matching)	(After Matching)
	N=8,195	N=4,734	N=3,894	N=3,894
<i>Outcome</i>				
<i>Time to death at day 14</i>	7.40 (4.55)	5.76 (4.70)	7.05 (4.54)	6.09 (4.76)
<i>Time to death at day 28</i>	8.80 (7.27)	6.57 (6.58)	8.28 (7.05)	7.00 (6.79)

5.0 Discussion

This study showed that the proportion of asymptomatic patients was 36.6% in a cohort of hospitalized COVID-19 patients. The symptomatic patient group was generally older in age, male, and had higher proportions of all included comorbidities, except pregnancy. We hypothesized that symptomatic COVID-19 patients will have an increased risk and probability of all-cause mortality at both day 14 and day 28 compared to asymptomatic patients. Our findings supported this hypothesis, as there was a significant increased risk of mortality for symptomatic patients compared to asymptomatic patients at both day 14 (HR=1.89; 95% CI 1.44-2.47; $p<0.001$) and day 28 (HR=1.56; 95% CI 1.26-1.94; $p<0.001$). Furthermore, the probability of all-cause mortality was significantly higher in symptomatic patients (9.4%) compared to asymptomatic patients (5.9%) (log rank $p<0.001$) at day 14 and significantly higher in symptomatic patients (25.6%) compared to asymptomatic patients (22.7%) (log rank $p=0.001$) at day 28. These findings suggest that the treatment of symptomatic hospitalized COVID-19 patients is of utmost importance when presented with decisions regarding limited healthcare resources and treatment allocation.

5.1 Symptomatic and Asymptomatic Patient Profiles

The proportion of asymptomatic COVID-19 patients in this study was 36.6%, about one-third of the study population. Previous studies have suggested that between one-third and three-quarters of SARS-CoV-2 infected patients are asymptomatic.¹¹ Our findings coincide with the literature regarding the expected proportion of asymptomatic patients. Furthermore, most

asymptomatic patients were younger than symptomatic patients, as the majority of asymptomatic patients were less than 55 years of age, while the majority of symptomatic patients were aged 55 years or older. These findings can be tied to literature suggesting that older age can lead to a higher risk of hospitalization and poorer outcomes when infected with SARS-CoV-2, as symptomatic presentation of COVID-19 is a more severe disease presentation compared to asymptomatic infection.^{14,15} Similarly, a higher proportion of symptomatic patients were male (51.7%) compared to asymptomatic patients (39.5%), which can also be connected with previous literature reporting that males are at higher risk of hospitalization and poorer outcomes from COVID-19.^{14,15} However, since the cohort included a group of hospitalized patients, it is assumed that these patients are in the hospital for some medical reason. Specifically for women, pregnancy is a common cause for a medical encounter. Thus, we expected a greater number of women with an asymptomatic presentation of COVID-19 compared to men to be captured due to the methodology of this study.

Additionally, the proportion of patients was higher in the symptomatic patient group compared to the asymptomatic patient group for all investigated baseline comorbidities, except pregnancy. Patients with comorbidities also have a higher risk of hospitalization and poorer outcomes, so the findings in this study concur with those results.^{14,15} A particularly interesting finding was the higher proportion of asymptomatic patients who were pregnant (14.6%) compared to symptomatic patients (1.6%). In a meta-analysis, among obstetric patients, 59% remained asymptomatic throughout the follow-up period.³⁴ This finding suggests that the majority of pregnant patients have an asymptomatic disease presentation when infected with SARS-CoV-2, which can contribute to the understanding of the higher proportion of pregnant patients in the asymptomatic patient group in this study. We also hypothesize that the methods and study population of this research can explain the higher proportion of pregnant patients in the

asymptomatic group, as pregnant patients may be admitted to the hospital specifically for pregnancy-related reasons, and the positive PCR test confirming COVID-19 diagnosis could be a result of hospital protocol when admitted.

Among symptomatic patients, shortness of breath was the most common symptom, reported by over half of patients in this group. Shortness of breath and breathing difficulties are considered more severe symptoms of COVID-19, and current guidance suggests seeking medical attention when experiencing severe symptoms.³⁵ Since the study population consisted of hospitalized patients, we expected that the more common symptoms reported in symptomatic patients would be these more severe symptoms of COVID-19. Similarly, the next most common symptoms were pneumonia, acute respiratory distress syndrome, respiratory arrest, or respiratory failure, and dyspnea, which are also more severe conditions associated with COVID-19 disease presentation. Furthermore, the literature suggests that loss of taste or smell is more often associated with mild disease presentation, which can explain our findings that only 1.4% of the symptomatic hospitalized COVID-19 patients included in our study reported loss of taste or smell.¹² Loss of taste or smell is also a difficult symptom to capture, as loss of taste or smell is a more subjective symptom that patients may not report to their medical provider during a hospital encounter.

5.2 Symptomatic and Asymptomatic Patient Outcomes

The mortality rate among symptomatic patients at day 14 and day 28 was 4.1% and 4.8%, respectively. These rates fall into the expected range of mortality rates for COVID-19 patients but are less than the expected rate of mortality among hospitalized COVID-19 patients.^{2,13,15} Since the cohort included hospitalized patients, but patients may be hospitalized for reasons other than

COVID-19, we would expect a lower mortality rate compared to patients who are hospitalized specifically for severe COVID-19. The mortality rate among asymptomatic patients at day 14 and day 28 was 2.1% and 3.4%, respectively. This rate was lower compared to symptomatic patients at both day 14 and day 28, which was expected. In a retrospective cohort study using a COVID-19 database created by Korea Centers for Disease Control, very similar mortality rates were reported among hospitalized COVID-19 patients. In this study, among COVID-19 patients who died during hospitalization, 4.5% of patients were symptomatic and 3.3% of patients were initially asymptomatic.³⁶

The average time to death both before and after propensity score matching was shorter in asymptomatic patients compared to symptomatic patients at day 14 and day 28. The difference was about one day, but this finding is still interesting. All-cause mortality was the primary outcome in this investigation and could explain a shorter average time to death at day 14 and day 28 among asymptomatic patients, as patients were hospitalized and could have died from non-COVID-19-associated reasons.

Adjusting for propensity score and other important covariates, including age, race, sex, month of index date, immunosuppressant use, dexamethasone use, and history of cancer, asthma, chronic lung disease, diabetes, hypertension, obesity, and cardiovascular disease, the risk of mortality was 1.89 times higher in symptomatic patients compared to asymptomatic patients ($p<0.001$) at day 14 and 1.56 times higher at day 28 ($p<0.001$). Furthermore, the probability of all-cause mortality among symptomatic patients was significantly higher than that of asymptomatic patients at day 14 (log rank $p<0.001$) and day 28 (log rank $p=0.001$). We hypothesized correctly that symptomatic patients have a higher risk and probability of all-cause mortality at both day 14 and day 28. These findings align with previous research, affirming that symptomatic patients may

have poorer outcomes compared to asymptomatic patients.^{21,23,24} However, while we identified a significant difference between probability of all-cause mortality between symptomatic and asymptomatic patients, the Korean cohort study, referenced above, did not find a significant difference in mortality rate between symptomatic and initially asymptomatic patients ($p=0.17$).³⁶ Patients in this study were labeled as initially asymptomatic if they did not present any symptoms at the time of admission. Thus, patients may have become symptomatic after admission, but were identified as asymptomatic, which could explain why there was no significant difference found in mortality rate between symptomatic and initially asymptomatic patients. In our study, we used a two-week interval centered around the index date to capture and correctly identify patients who were initially asymptomatic but soon developed symptoms.

5.3 Strengths

To our knowledge, this is the first large retrospective cohort study using electronic medical record data to assess asymptomatic patient profiles and mortality by reaction type. Through the use of electronic medical records, we were able to include a variety of covariates in our analysis, including age, race, sex, month of index date, immunosuppressant use, dexamethasone use, and history of cancer, asthma, chronic lung disease, diabetes, hypertension, obesity, and cardiovascular disease, which could confound findings related to mortality if not controlled. This study included a large sample size of 12,929 hospitalized COVID-19 patients, consisting of 8,195 symptomatic patients and 4,734 asymptomatic patients. To our knowledge, this is also the first widespread US-based investigation of asymptomatic outcomes. Focusing on hospitalized patients in an electronic medical record network allowed us to identify and analyze the presence of symptoms and patients'

respective outcomes. Furthermore, using ICD-10 codes in an electronic medical record system to identify doctor-confirmed symptoms, rather than relying on patients' ability to recall symptoms, reduced potential recall bias that may occur when analyzing symptomatic COVID-19 patients.

5.4 Limitations

There are limitations that could potentially impact the findings of this study. First, as the COVID-19 pandemic is continuously changing and evolving, the study period must be discussed. The study period took place before the significant emergence of the Delta variant of SARS-CoV-2. The Delta variant was first identified in the US in March 2021 but did not become the dominant strain until the summer of 2021, which is outside of the study period for this research.³⁷ Thus, increased risk of mortality due to being infected with the Delta variant does not impact findings. However, the COVID-19 vaccines were becoming widely available toward the end of the study period. The end of the study period was April 23, 2021, which was four days after the COVID-19 vaccines became available to all adults in the United States.³⁸ Vaccination status was not considered in this investigation due to lack of availability in the data. Although, if vaccination status were included in this research, we would expect the distribution to be nondifferential and thus not bias the results of this study. Additionally, propensity score matching based on the month of the index date was used to minimize potential confounding.

Second, the classification of symptomatic and asymptomatic patients was not all-inclusive. We identified 19 more common symptoms and diagnoses to classify symptomatic and asymptomatic patients, but these symptoms did not include rarer symptoms that could be associated with COVID-19. Symptoms could also have developed outside of the 14-day window

centered around the index date that was used to capture symptomatic and asymptomatic patients. Furthermore, ICD-10 codes were used to identify symptoms to classify symptomatic and asymptomatic patients. While using ICD-10 codes reduced potential bias related to patient symptom recall, these codes may not accurately capture and reflect patients' clinical experiences. Misclassification of symptomatic and asymptomatic patients in this study was possible, which would result in a bias toward the null. In a study that evaluated the positive and negative predictive value of the use of ICD-10 codes to identify fever, cough, and dyspnea in COVID-19 patients in an electronic medical record database, results showed that ICD-10 codes may not accurately capture COVID-19 symptoms. The positive predictive value for each of the three symptoms were: for fever, 0.96 (95% CI 0.93-0.97), for cough, 0.96 (95% CI 0.95-0.97), and for dyspnea, 0.93 (95% CI 0.90-0.96). The positive predictive values were high for all symptoms included in the study, implying that a high proportion of patients who have been identified as having these symptoms truly do have these symptoms. Yet, the negative predictive values of these symptoms were low: for fever, 0.41 (95% CI 0.39-0.43), for cough, 0.18 (95% CI 0.16-0.20), and for dyspnea, 0.42 (95% CI 0.40-0.44).²⁹ These findings indicate that patients who are identified as not having these symptoms may truly have these symptoms and suggest that using ICD-10 codes to classify symptomatic and asymptomatic patients may result in an overestimation of asymptomatic patients. However, a notable limitation of this study was the data included came solely from one patient center, where most patients were evaluated in an outpatient setting, and only 3% of the sample (N = 2,201) were evaluated in an inpatient setting.²⁹ Our study included inpatient hospitalizations from multiple healthcare organizations. While the results from the study evaluating ICD-10 codes in primarily outpatient settings are informative, the differences in setting may lead to vast differences in physician reporting and documentation of symptoms. Additionally, this study only

focused on the predictive value of an individual symptom, while our study included 19 possible symptoms to capture and classify symptomatic and asymptomatic patients. Thus, identifying symptomatic patients in our study may be more accurate due to the wide breadth of symptoms included.

Third, the outcome in this analysis was all-cause mortality, not COVID-19-specific mortality. Since the cohort included hospitalized patients, it is assumed that these patients were in the hospital for a medical reason, so the risk of mortality could be higher overall in the study cohort. We used propensity score matching to reduce the potential confounding involved with increased risk of mortality from certain diseases and comorbidities in patients.

6.0 Conclusion

In this US-based EMR network of hospitalized COVID-19 patients, we observed an increased risk and probability of all-cause mortality for symptomatic patients compared to asymptomatic patients at both day 14 and day 28. These findings suggest that symptomatic presentation of COVID-19 in hospitalized patients may result in poorer outcomes compared to asymptomatic patients, and clinically, it is imperative for healthcare providers to more aggressively treat symptomatic hospitalized COVID-19 patients. More research is needed regarding the outcomes of asymptomatic patients, but this study provides a baseline framework for analyzing symptomatic and asymptomatic patient demographics, profiles, and outcomes in an electronic medical record network and scientific evidence to guide the allocation of limited resources and treatment in response to the global public health challenge of controlling and managing the COVID-19 pandemic.

Appendix A ICD-10 Codes

Appendix Table 1. ICD-10 codes to identify symptoms in symptomatic patients

COVID-19 Symptoms	ICD-10 Codes
<i>Fever</i>	R50.9
<i>Headache</i>	R51
<i>Diarrhea</i>	K59.1, R19.7
<i>Delirium or encephalopathy</i>	F05*, A81.2*, E51.2*, G04.30*, G04.31*, G04.32*, G04.39*, G92*, G93.40*, G93.41*, G93.49*, I67.3*, I67.4*, I67.83*, J10.81*, J11.81*, P91.60*, P91.61*, P91.62*, P91.63*
<i>Cough</i>	R05
<i>Chest pain</i>	R07.1, R07.8, R07.89, R07.9
<i>Sore throat</i>	J02.9
<i>Pneumonia</i>	J18.1, J18.9, J18.8, J18.0, J85.1, J12.89, J12.9, J12.81
<i>Shortness of breath</i>	R09.02, R06.0*, R06.02, R06.2
<i>Acute bronchitis</i>	J20.8
<i>Other acute respiratory infection</i>	J06.9, J22
<i>Acute respiratory distress syndrome, respiratory arrest, or respiratory failure</i>	J80, J96.0, J96.00, J96.01, J96.02, J96.2, J96.20, J96.21, J96.22, R09.2
<i>Loss of taste or smell</i>	R43*
<i>Dyspnea</i>	R06*
<i>Malaise or fatigue</i>	R53*
<i>Myalgia</i>	M79.1*
<i>Congestion</i>	R09*
<i>Nausea or vomiting</i>	R11.0*, R11.1*, R11.2*
<i>Acute sinusitis</i>	J01*

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