

University of Nevada, Reno

**The Impact of the COVID-19 Pandemic on Cancer Patients: From
Mortality Patterns to Long-term Sequelae**

A dissertation submitted in partial fulfillment of the requirements for the degree
of Doctor of Philosophy in Epidemiology

By

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Abstract

The COVID-19 pandemic has constituted one of the most significant public health challenges of this century, profoundly impacting global mortality patterns and healthcare systems. In addition to the immediate consequences of acute infection, a considerable proportion of individuals experience persistent symptoms that extend well beyond the acute phase. Cancer patients are particularly vulnerable to pandemic-related changes, as they are already burdened by chronic illness, immunosuppression, and complex treatment needs. Although previous research has documented an increased risk of severe COVID-19 outcomes among individuals with cancer, there remains a notable lack of population-level studies examining its real-world impact on cancer mortality. Simultaneously, there is an urgent need for large-scale, nationally representative research to evaluate the long-term consequences of COVID-19 among cancer survivors. Furthermore, in modern clinical contexts, the co-occurrence of multiple chronic health conditions—including cancer—has become increasingly common, raising concerns about whether individuals with multimorbidity face elevated risks of developing long COVID.

This dissertation aimed to investigate the multifaceted consequences of the COVID-19 pandemic on cancer patients, focusing on changes in mortality patterns and long-term health outcomes:

The first study examined cancer-related mortality changes in the state of Nevada during the first two years of the pandemic (2020–2021), comparing

observed deaths to expected values based on pre-pandemic data from 2015 to 2019. The findings showed that overall cancer-related mortality—defined as deaths where cancer was listed as either the underlying or a contributing cause—experienced a modest decline during the pandemic. More specifically, deaths with cancer as the underlying cause declined relative to expectations, while deaths listing cancer as a contributing cause increased. These shifts may be attributed to the mortality shifting from cancer to COVID-19, reduced diagnosis during the pandemic, and potential omissions or misclassification on death certificates.

The second study utilized nationally representative data from the 2022 Behavioral Risk Factor Surveillance System (BRFSS) to assess the prevalence of long COVID among cancer survivors. The results indicated that cancer survivors had significantly higher odds of experiencing long COVID compared to individuals without a cancer history, with the disparity being most pronounced among younger adults. Additionally, the study found that cancer survivors required a higher number of COVID-19 vaccine doses to achieve a significant association with reduced odds of long COVID, compared to those without cancer.

The third study, based on 2023 BRFSS data, explored the relationship between chronic health conditions (CHCs) and long COVID across three dimensions: individual CHCs, cumulative CHC burden, and multimorbidity patterns. All CHCs tested were significantly associated with elevated odds of

long COVID. A clear dose-response relationship was observed between the number of CHCs and the odds of long COVID. Furthermore, multimorbidity clusters identified through latent class analysis (LCA) were significantly associated with increased odds of long COVID, with the Severe Multimorbidity Cluster showing the strongest association. In most multimorbidity groups, COVID-19 vaccination was not significantly associated with a reduction in long COVID odds.

Collectively, these studies provide new insights into changes in mortality patterns during the COVID-19 pandemic and the long-term consequences of infection among populations with cancer. The findings highlight the importance of enhancing long-term surveillance, implementing targeted follow-up and supportive care strategies, and promoting COVID-19 vaccination to reduce pandemic-related health disparities in this high-risk population.

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Chapter 1: Introduction

Introduction and the Gap in Literature

The COVID-19 pandemic has constituted one of the most far-reaching public health crises in modern times, with widespread and lasting effects on mortality patterns and the global healthcare landscape (Weinberger et al., 2020; Woolf et al., 2020). Since it first emerged in late 2019, the virus has spread across continents, resulting in over 770 million documented cases and more than 7 million officially reported deaths, according to World Health Organization (WHO) estimates as of 2025 (WHO, 2025). The clinical course of acute SARS-CoV-2 infection is highly variable, encompassing asymptomatic cases as well as severe outcomes such as pneumonia, respiratory failure, and dysfunction of multiple organ systems (Chilamakuri & Agarwal, 2021).

In addition to the immediate consequences of acute infection, an increasing body of evidence has highlighted that a significant subset of individuals continue to suffer from ongoing symptoms well beyond the acute phase (Fang et al., 2024; Koc et al., 2022). This post-viral condition, often referred to as “long COVID” or post-acute sequelae of SARS-CoV-2 infection (PASC), can involve persistent manifestations including fatigue, dyspnea, and cognitive disturbances, and may last for weeks or even several months (Dagher et al., 2023; Soriano et al., 2022).

The pandemic’s overall impact has not been limited to the biological effects

of viral infection; it has also resulted in widespread indirect consequences that have shifted healthcare priorities and altered patient outcomes. These include disruptions in routine medical services, increased strain on hospital systems, and psychosocial burdens arising from prolonged isolation and economic uncertainty—factors that have all contributed to substantial changes in the healthcare environment (Alexander et al., 2022; Schneider et al., 2023).

Cancer, a prevalent and often life-threatening chronic illness, has been particularly susceptible to these pandemic-related changes (Al-Quteimat & Amer, 2020; Moraliyage et al., 2021). Individuals diagnosed with cancer, who already carry a significant disease burden, have encountered layered vulnerabilities in the context of COVID-19 (Schneider et al., 2023). On the one hand, their risk of experiencing severe illness from COVID-19 is elevated due to compromised immunity resulting both from the malignancy itself and from treatments such as chemotherapy and radiotherapy (Kamboj & Sepkowitz, 2009; Liu et al., 2020). On the other hand, these patients have also borne the consequences of interrupted cancer care delivery systems (Keim-Malpass et al., 2023). Delays in cancer screening, postponed or modified therapeutic regimens, and irregular follow-up schedules have raised major concerns about more frequent late-stage diagnoses and reduced efficacy in disease management (Keim-Malpass et al., 2023; London et al., 2020; Moraliyage et al., 2021).

A growing number of studies have documented that cancer patients are

more likely to experience adverse outcomes after contracting COVID-19, including greater risk of hospitalization, intensive care unit (ICU) admission, and death (H. J. Han et al., 2021; Liang et al., 2020). At the same time, the longer-term consequences of COVID-19 for cancer patients raise significant concern, particularly due to their complex clinical profiles and persistent medical needs (Aboueshia et al., 2021; Schneider et al., 2023). Cancer-associated immunosuppression—either intrinsic to the disease or a consequence of ongoing treatment—may increase susceptibility to developing long COVID symptoms in this population (Corey et al., 2021; Su et al., 2022). Furthermore, cancer commonly coexists with other chronic health conditions. This presence of multimorbidity not only complicates the treatment and monitoring of cancer itself but may also amplify the total burden of illness in individuals recovering from COVID-19 (Song & Giuriato, 2023).

Although it is well established that COVID-19 poses an immediate and serious threat to individuals with cancer, there remains a notable lack of research examining its real-world impact on cancer mortality at the population level. The interpretation of mortality data during the pandemic is further complicated by overlapping causes of death, especially in cases where COVID-19 interacts with pre-existing conditions such as cancer. These complexities highlight the need for more detailed analyses to accurately assess the burden of COVID-19 on cancer mortality. At the same time, research on the long-term consequences of COVID-19 among cancer survivors remains limited and

inconclusive. Although some studies have begun to investigate cancer patients' vulnerability to long COVID, their results are often inconsistent. A major limitation of the current evidence base is that it primarily derives from single-center studies or samples that lack population-level representativeness. These methodological constraints underscore the need for large-scale, nationally representative investigations that can offer more generalizable insights into long COVID risk in cancer populations. Moreover, most existing studies on long COVID risk factors have focused on the role of individual chronic diseases—such as cancer, chronic obstructive pulmonary disease (COPD), and diabetes—examined in isolation. However, in reality, a large and growing proportion of individuals live with multiple chronic health conditions (CHCs) simultaneously, rather than a single disease. Despite this, there remains a substantial knowledge gap regarding how the co-occurrence of multiple CHCs may compound the risk of long COVID. Even less is known about whether specific patterns or clusters of multimorbidity are associated with particularly high vulnerability to persistent post-COVID symptoms. Addressing this gap is critical for advancing precision public health approaches to long COVID prevention and management.

Specific Aims

This dissertation sets out to investigate the multifaceted impact of the COVID-19 pandemic on cancer patients, with a particular focus on mortality

patterns and long COVID. Specifically, it aims to:

1. Examine changes in cancer-related mortality during the COVID-19 pandemic by comparing observed cancer-related deaths during the pandemic (2020-2021) to expected deaths based on pre-pandemic data (2015-2019).
2. Assess whether prevalence of long COVID is higher among cancer survivors compared to individuals without a history of cancer, using nationally representative survey data from the United States.
3. Investigate the association between pre-existing chronic health conditions (CHCs) and long COVID, evaluated across three dimensions: individual CHCs, cumulative CHC burden, and distinct multimorbidity patterns.

Organization of the Dissertation

This dissertation is structured into six chapters. Chapter 1 provides an overview of existing knowledge, identifies key gaps in literature, and outlines the study aims. Chapter 2 presents a comprehensive background on the biological, epidemiological, and clinical intersections among cancer, COVID-19, long COVID, and multimorbidity. Chapters 3 through 5 comprise the three research studies, each formatted as a standalone manuscript. Finally, Chapter 6 offers an integrative discussion of the findings, emphasizing their implications for research, clinical practice, and public health in the post-pandemic era.

Chapter 2: Background and Significance

1. The Impact of the COVID-19 Pandemic

The coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been one of the most disruptive global health crises in modern history. It profoundly affected mortality patterns and healthcare systems worldwide, with the United States among the most severely impacted countries (Weinberger et al., 2020; Woolf et al., 2020).

Since emerging in late 2019, the virus has led to over 770 million confirmed cases and more than 7 million deaths officially reported to the World Health Organization (WHO) as of 2025 (WHO, 2025). However, these figures likely underestimate the true mortality burden. WHO estimated that at least 3 million deaths occurred globally in 2020 due to the pandemic—1.2 million more than officially reported—underscoring significant undercounting of both direct and indirect deaths attributable to COVID-19 (WHO, 2021). Beyond direct fatalities, the pandemic exerted a broad spectrum of indirect effects, including disruptions to routine care, overburdened healthcare infrastructure, and heightened psychosocial stress linked to prolonged social isolation and economic hardship. Together, these consequences have profoundly reshaped public health priorities and clinical outcomes across populations (Alexander et al., 2022; Schneider et al., 2023).

The clinical manifestations of acute COVID-19 range from asymptomatic infection to severe pneumonia, acute respiratory failure, and multi-organ dysfunction (Chilamakuri & Agarwal, 2021). Pulmonary injury is among the most prominent features of severe disease, with studies indicating that the lungs are the most commonly and severely affected organ (Torres-Castro et al., 2021). Acute respiratory distress syndrome (ARDS) is a hallmark complication in critical COVID-19 cases. The pathogenesis of severe illness involves dysregulated immune activation, characterized by excessive cytokine release and systemic hyperinflammation—commonly referred to as a cytokine storm—which contributes to tissue injury and multi-organ failure (Tay et al., 2020; B. Zhang et al., 2020). In addition to pulmonary complications, SARS-CoV-2 infection has been associated with extrapulmonary manifestations including myocardial injury, arrhythmias, thromboembolic events, acute kidney injury, and various neurologic sequelae (Gupta et al., 2020).

Several risk factors for severe COVID-19 have been identified. Age remains one of the most important risk factors for adverse COVID-19 outcomes. Older adults experience decreased efficacy of the immune system, which impairs the body's ability to mount an effective response to infections. Age-related chronic pro-inflammatory status of the immune system with persistent low-grade innate immune activation may exacerbate tissue damage caused by infections in the elderly (Shaw et al., 2010; Zhang et al., 2023). As a result, older individuals consistently face higher risks of hospitalization, ICU admission, and mortality,

with case fatality rates rising sharply with age (Verity et al., 2020; Zhang et al., 2023). In addition to advanced age, pre-existing chronic conditions are well-established risk factors for both increased susceptibility to SARS-CoV-2 infection and progression to severe disease (Jordan et al., 2020; Singh et al., 2021). These include chronic obstructive pulmonary disease (COPD), cardiovascular disease, diabetes, chronic kidney disease, cancer, etc. For instance, individuals with pre-existing respiratory conditions may experience worsening of underlying disease following COVID-19 infection due to further compromise of lung function (Chiner-Vives et al., 2022). Patients with diabetes and hypertension are often in a state of stress for a long time and exhibit impaired immune responses, which may increase vulnerability to infection and the risk of developing severe illness (Zheng et al., 2020). Patients with cardiovascular disease are more likely to become infected due to weakened heart function, and heart damage is a common symptom in people infected with SARS-CoV-2 and a comorbidity that is highly associated with the severity of COVID-19 (Muller-Wieland et al., 2022). Immunocompromised populations, such as individuals undergoing active cancer treatment or living with hematologic malignancies, also face elevated risk due to impaired immune surveillance and reduced vaccine responsiveness (Lee et al., 2020). In addition to age and chronic health conditions, some other risk factors for severe COVID-19 include male, obesity, and smoking (Jordan et al., 2020; Zhang et al., 2023).

2. Long COVID: Definition, Symptoms, and Public Health Relevance

As the COVID-19 pandemic progressed, it became increasingly apparent that a considerable proportion of individuals infected with SARS-CoV-2 experienced a range of persistent symptoms long after the resolution of acute infection (Fang et al., 2024; Koc et al., 2022). This condition, now widely recognized as long COVID or post-acute sequelae of SARS-CoV-2 infection (PASC), encompasses symptoms such as fatigue, shortness of breath, and cognitive dysfunction that can persist for weeks to months after infection (Dagher et al., 2023; Soriano et al., 2022). The U.S. Centers for Disease Control and Prevention (CDC) defines long COVID as a chronic condition that occurs after SARS-CoV-2 infection and persists for at least three months (CDC, 2025a). The symptom profile of long COVID is heterogeneous and affects multiple organ systems. Commonly reported symptoms include fatigue, shortness of breath, cough, chest pain, cognitive impairment (“brain fog”), anosmia, sleep disturbances, and myalgia (Carfi et al., 2020; Davis et al., 2021). These symptoms may fluctuate over time, worsen with physical or mental exertion, and often interfere with daily functioning and quality of life. For some individuals, long COVID results in substantial disability, work limitations, or prolonged financial burden, severely impacting overall well-being (Carlile et al., 2024; Greenhalgh et al., 2022).

Long COVID was poorly understood in the early stages of the pandemic. Some patients may not have received timely or appropriate treatment in the

initial phases (Rushforth et al., 2021). Nevertheless, long COVID has now emerged as a major public health concern due to its widespread prevalence and persistent impact. A meta-analysis suggests that depending on region, approximately 25–50% of individuals who contract SARS-CoV-2 may experience long COVID (C. Chen et al., 2022). It is increasingly recognized that this condition imposes a significant burden not only on individuals but also on healthcare systems and national economies (Greenhalgh et al., 2024).

While the precise pathophysiology of long COVID remains under investigation, several mechanisms have been proposed. These include the persistence of SARS-CoV-2 virus or its components, dysregulated immune response, endothelial inflammation and immune thrombosis (B. Chen et al., 2023; Greenhalgh et al., 2024; Santoro et al., 2023; Sherif et al., 2023). However, diagnostic biomarkers are still lacking, and the wide variety of symptom presentations poses significant challenges for diagnosis and treatment. Current clinical practice is largely symptom-based, with the primary goals of rehabilitation focused on symptom relief and functional restoration (Greenhalgh et al., 2024; Koc et al., 2022).

Given its far-reaching impact on individuals, social productivity, and healthcare systems, long COVID represents a new and evolving dimension of disease burden in the ongoing pandemic. Understanding its risk factors is essential for developing effective prevention and management strategies. Several risk factors for long COVID have been identified. First, disease severity

during the acute phase is strongly associated with the likelihood of long COVID. Studies have shown that individuals who required ICU admission or mechanical ventilation are more likely to report long-term symptoms (Halpin et al., 2021; Koc et al., 2022). Second, pre-existing chronic health conditions not only increase the risk of severe acute COVID-19 outcomes but also appear to be associated with the development of long COVID. Conditions such as chronic obstructive pulmonary disease (COPD), diabetes, asthma, cardiovascular disease, and stroke have been reported as predictors of persistent symptoms (Erinoso et al., 2024; Hejazian et al., 2024; Hung et al., 2024; Steenblock et al., 2022; Tsampasian et al., 2024). In addition, older age may be associated with long COVID risk, although current evidence on this association remains mixed (Davis et al., 2021; C. Wang et al., 2023). While men are more likely to experience severe acute COVID-19 outcomes, several studies suggest that women are at higher risk of developing long COVID (Koc et al., 2022; C. Wang et al., 2023).

3. Cancer Patients as a High-Risk Population

Cancer, as a prevalent and often life-threatening chronic disease, has been severely impacted by the COVID-19 pandemic and its associated healthcare disruptions (Al-Quteimat & Amer, 2020; Moraliyage et al., 2021). Cancer patients represent a key immunocompromised subgroup within the general population and have consistently been identified as one of the most vulnerable

groups throughout the pandemic. Their elevated risk for adverse outcomes is multifactorial, resulting from both the disease itself and its associated treatments. The immune system plays a central role in defending against SARS-CoV-2 infection (Mohseni Afshar et al., 2022). In addition to the immunosuppressive effects of cancer progression itself, many cancer therapies—such as chemotherapy, radiation therapy, and immunotherapy—impair immune function, reducing the body's capacity to mount effective responses to viral infections, including COVID-19 (Lee et al., 2020; L. Wang et al., 2020).

In addition to biological vulnerability, cancer patients often require frequent interactions with healthcare systems for diagnostics, treatments, and follow-up care. During the pandemic, these interactions may have increased the risk of viral exposure. Simultaneously, public health restrictions and healthcare system strain led to the postponement of routine cancer screenings and delayed diagnoses (Maringe et al., 2020). In the United States, a sharp decline in cancer diagnoses was observed during the early months of the pandemic, which is projected to result in increased late-stage diagnoses and cancer-specific mortality in the coming years (Sharpless, 2020). Interruptions in essential cancer treatment have also contributed to worsened prognoses and excess mortality (Keim-Malpass et al., 2023; Sud et al., 2020).

As noted in earlier sections, several chronic health conditions have been identified as risk factors for severe COVID-19 outcomes. Cancer is among the

most consistently reported of these. Multiple studies have shown that cancer patients are at significantly higher risk for ICU admission, mechanical ventilation, and death following COVID-19 infection compared to individuals without cancer (Dai et al., 2020; Liang et al., 2020; Tian et al., 2020). Among cancer patients, the risk of severe COVID-19 outcomes is modified by a range of factors. In addition to older age and comorbidities, which are known risk factors in the general population, cancer-specific characteristics—such as cancer type, disease stage, and treatment modality—also play a critical role (L. Wang et al., 2020). Patients with hematologic malignancies, lung cancer, or metastatic disease appear to be at highest risk for adverse outcomes; Stage IV cancer patients are more likely to experience severe complications, and those undergoing immunotherapy may also be at elevated risk (Dai et al., 2020; Liang et al., 2020; L. Zhang et al., 2020).

In addition to acute outcomes, the long-term consequences of COVID-19 among cancer patients have garnered increasing attention (Aboueshia et al., 2021; Schneider et al., 2023). The immunosuppression associated with cancer and its treatments may predispose individuals to long COVID (Corey et al., 2021; Su et al., 2022). Although the available evidence is limited, some studies suggest that cancer patients may experience persistent symptoms more frequently than the general population. Reported prevalence rates of long COVID in cancer populations range widely—from over 50% in some cohorts (Dagher et al., 2023; Debie et al., 2024; Monroy-Iglesias et al., 2022) to no

significant difference when compared to non-cancer patients in others (Chai et al., 2021; Fankuchen et al., 2023). Most existing studies have been conducted in single centers or used non-representative samples, highlighting the need for more rigorous population-based research to clarify the magnitude of long COVID risk in this group.

Another area of concern is the multimorbidity among cancer patients. Cancer frequently coexists with other chronic conditions, including cardiovascular disease, diabetes, and arthritis. This overlap can be attributed to shared risk factors such as aging, smoking, and obesity, as well as potential bidirectional pathophysiologic mechanisms. For example, cardiovascular disease and its treatments may contribute to carcinogenesis, while chronic inflammation and immune suppression associated with cancer can accelerate cardiovascular deterioration (Boudoulas et al., 2022). Similarly, diabetes may promote tumorigenesis through hyperglycemia and systemic inflammation, and certain chemotherapies are known to increase the risk of diabetes (I. Ahmad et al., 2023; Hwangbo et al., 2018); Immunosuppressive therapies used in rheumatic diseases have been linked to increased cancer risk (Cho et al., 2024), while cancer treatments such as immune checkpoint inhibitors may induce inflammatory arthritis (Huss et al., 2023). Studies estimate that 40–69% of cancer patients have at least one comorbid condition, and 12–32% have two or more (T. A. Ahmad et al., 2023) . Given that both cancer and many comorbidities are independent risk factors for severe COVID-19 and long COVID,

multimorbidity may not only complicate cancer care but also compound the overall health burden following SARS-CoV-2 infection.

4. Multimorbidity and Its Interaction with COVID-19 Outcomes

Chronic health conditions (CHCs), also referred to as chronic diseases, are broadly defined as conditions lasting one year or more that require ongoing medical attention or limit daily activities. These include a wide range of diseases such as heart disease, cancer, and diabetes (CDC, 2024a). In addition to being the leading causes of death and disability in the United States, CHCs impose a substantial burden on the healthcare system, contributing to an estimated \$4.5 trillion in annual healthcare costs (CDC, 2024a, 2024d). Multimorbidity—the co-occurrence of two or more chronic conditions within an individual—is an increasingly urgent public health challenge. As life expectancy increases and the interconnected nature of many CHCs becomes more evident, a substantial proportion of individuals are now living with multiple coexisting chronic diseases rather than a single condition (Álvarez-Gálvez et al., 2023; Kitsis et al., 2018; Pundole & Suarez-Almazor, 2020; Ritchie & Abel, 2020; Surve et al., 2024). In the United States, approximately six in ten adults have at least one chronic disease, and four in ten have two or more (CDC, 2024a). Multimorbidity is associated with decreased quality of life, increased healthcare utilization, polypharmacy, and a heightened risk of mortality (Huang et al., 2023; Mossadeghi et al., 2023).

As discussed in earlier sections, many CHCs—including cancer—have been associated with greater risk of severe COVID-19 outcomes and long COVID. However, most existing research focuses on single conditions in isolation (Russell et al., 2023). Given the widespread prevalence of multimorbidity, it is plausible that some observed associations between individual diseases and COVID-19 severity may be partially driven by underlying interactions among multiple coexisting conditions. These may include disease–disease, disease–drug, and drug–drug interactions that collectively modify patient outcomes (Carmona-Pirez et al., 2022). Emerging evidence supports the link between multimorbidity and increased risk of severe COVID-19. For example, a study in South Korea demonstrated that the Charlson Comorbidity Index Score (CCIS)—which incorporates the number and severity of comorbid conditions—was predictive of adverse clinical outcomes in hospitalized COVID-19 patients (Kim et al., 2021). Similar findings have been reported in Italy, where CCIS was a strong predictor of COVID-19-related mortality (Iaccarino et al., 2020). In Scotland, the presence and severity of multimorbidity were independently associated with an increased risk of death among hospitalized COVID-19 patients (Agrawal et al., 2022). Likewise, a UK-based observational study found that individuals with multimorbidity consistently faced higher risks of severe SARS-CoV-2 infection than those without multimorbidity (Chudasama et al., 2021). These findings underscore the potentially cumulative burden of chronic conditions on severe COVID-19

outcomes.

On the other hand, due to potential interactions among chronic diseases, the occurrence of multiple conditions in an individual is not random but tends to follow specific disease patterns (Carmona-Pirez et al., 2022) . For instance, cardiometabolic pattern (Kirchberger et al., 2012; Schafer et al., 2010)—characterized by coexisting cardiovascular and metabolic disorders such as hypertension and diabetes—is frequently observed and reflects a strong interconnection between these conditions (Balakumar et al., 2016; Cole & Florez, 2020; Glovaci et al., 2019). Studies have also reported a cardiorespiratory pattern, characterized by the coexistence of cardiovascular and respiratory diseases (Carter et al., 2019; Morgan et al., 2018). Some disease patterns appear to carry a higher risk for severe COVID-19 than others. A Spanish study found that individuals with cardiometabolic patterns had the highest risk of severe COVID-19, and that women with a mental health pattern were also more likely to experience severe outcomes (Carmona-Pirez et al., 2022). Similarly, an Italian study concluded that cardiometabolic multimorbidity was more strongly associated with poor COVID-19 prognosis than individual cardiometabolic risk factors alone, possibly due to endothelial dysfunction (Maddaloni et al., 2020).

The relationship between multimorbidity and long COVID remains less well understood. Some studies have shown that, in non-hospitalized populations, multimorbidity is associated with a higher likelihood of experiencing persistent

symptoms at 12 weeks post-infection (Russell et al., 2023). Another study has found no direct association between multimorbidity and long COVID risk but has reported a correlation between multimorbidity and the number of long COVID symptoms (Wilk et al., 2023). Overall, more high-quality research is needed to clarify how specific multimorbidity patterns influence susceptibility to long-term post-COVID sequelae.

5. COVID-19 Vaccination

Vaccination remains the cornerstone of public health strategies aimed at mitigating the impact of the COVID-19 pandemic. Effective COVID-19 vaccination is the most critical intervention to induce a protective immune response against SARS-CoV-2. Since the initial vaccine rollout in late 2020, widespread vaccination efforts have substantially reduced the severity of COVID-19 illness globally (Zhang et al., 2023). Evidence from both clinical trials and real-world studies consistently demonstrates that vaccinated individuals are less likely to experience severe disease, hospitalization, or death (Fix et al., 2024; Moline et al., 2021; Senevirathne et al., 2024; Xu et al., 2023). Moreover, COVID-19 vaccination has also been associated with a decreased risk of developing long COVID (Ayoubkhani et al., 2022; Watanabe et al., 2023).

Despite these benefits, vaccine efficacy and immunogenicity may vary across populations—particularly among immunocompromised individuals (Di Fusco et al., 2022). Cancer patients represent one such vulnerable group.

Studies have shown that individuals with cancer exhibit significantly lower seroconversion rates following COVID-19 vaccination compared to healthy controls (Sun et al., 2022). This reduced immunogenicity is likely attributable to both disease-related immune dysfunction and treatment-associated immunosuppression (Seneviratne et al., 2022). Additionally, both cancer type and treatment modality appear to influence vaccine response (Sun et al., 2022). Patients with hematologic malignancies, in particular, demonstrate lower antibody responses than those with solid tumors (Tran et al., 2021). Specific treatments such as anti-CD20, BTK inhibitors, and CAR-T therapy have been associated with significantly diminished vaccine-induced immune responses (Sun et al., 2022). Importantly, booster doses have been shown to improve vaccine responsiveness among cancer patients. Research indicates that although response rates remain lower than those observed in the general population, a second vaccine dose significantly improves immunogenicity in cancer patients (Sun et al., 2022; Tran et al., 2021).

Evidence regarding vaccine response among individuals with multimorbidity remains limited and somewhat inconsistent. Some studies have reported that multimorbidity negatively affects antibody production following COVID-19 vaccination (Das et al., 2023), and others have found that the serological response to vaccine is more inadequate among multimorbidity population (Violan et al., 2023). However, one study found that vaccine effectiveness remains consistently good among individuals with a high

multimorbidity burden (Lai et al., 2024). Another European study of adults aged 50 and older found that COVID-19 vaccination was significantly associated with a reduced risk of long COVID among individuals with chronic multimorbidity, though such associations were not observed in other subgroups (Gao et al., 2024). These findings underscore the complexity of vaccine response in multimorbid populations and highlight the need for further investigation.

Importantly, despite concerns about immunogenicity, the benefits of vaccination in high-risk populations are still substantial. Even partial protection can meaningfully reduce the risk of hospitalization and death, and may help mitigate the severity or duration of long COVID symptoms. Guidelines from oncologic and infectious disease societies strongly recommend COVID-19 vaccination for severely immunocompromised people, emphasizing timely scheduling and tailored dosing strategies (CDC, 2025b).

Chapter 3: Manuscript 1: Changes in Cancer-related Mortality During the COVID-19 Pandemic (2020-2021) in Nevada

Abstract

Background: Studies have shown COVID-19 pandemic led to excess mortality globally. However, reports on specific leading causes of death are limited. This study used statewide data to evaluate excess cancer-related death by comparing the expected and observed cancer-related deaths during the first two years of pandemic.

Methods: 2015-2021 Nevada statewide death certificates and Nevada State Demographer's population data were analyzed. We evaluated three outcomes of cancer mortality: cancer as the underlying cause of death, cancer as a contributing cause of death, and a combination of both. Causes of death were determined and provided by the NCHS (ICD-10, 2019 version). Negative binomial regressions were used to model cancer deaths to compare the baseline prior to COVID-19 (2015-2019) with the COVID-19 pandemic period (2020-2021). Observed to expected (O/E) ratios and corresponding confidence intervals were calculated.

Results: During 2020-2021, overall cancer-related deaths, combining underlying and contributing causes of death, were 208 cases lower than expected (O/E=0.98; 95% CI: 0.96-1.00; p=0.053), with a notably reduced mortality for respiratory system cancers (O/E=0.86; 95% CI: 0.83-0.90;

adjusted $p < 0.001$). For cancer as the underlying cause of death, deaths were 550 cases lower than expected ($O/E = 0.95$; 95% CI: 0.93-0.97; $p < 0.001$). In contrast, for cancer as a contributing cause of death, deaths were 189 cases higher than expected ($O/E = 1.23$; 95% CI: 1.20-1.27; $p < 0.001$).

Conclusion: Cancer-related mortality, combining underlying and contributing cause of death, showed a modest decline during the COVID-19 pandemic (2020-2021), primarily driven by fewer deaths related to respiratory system cancers. The causes for the cancer-related mortality reduction could result from the mortality shifting from cancer to COVID-19, lack of diagnosis, and omissions or misclassification in death certification during the pandemic. Future research incorporating data from subsequent years is needed to better monitor and understand changes in cancer mortality during the pandemic.

Keywords:

COVID-19, Cancer, Mortality, Excess Death, Nevada

1. Introduction

The COVID-19 pandemic has brought about one of the most significant public health challenges of this century, profoundly affecting mortality patterns and healthcare systems globally, with the United States being one of the hardest-hit countries (Weinberger et al., 2020; Woolf et al., 2020). The impact of the pandemic extends beyond the direct fatalities due to the virus,

manifesting in various indirect consequences that have reshaped healthcare priorities and patient outcomes. The disruption of routine health services, the heightened burden on healthcare infrastructure, and the psychosocial stress induced by prolonged periods of social isolation and economic uncertainty are among the myriad ways the pandemic has altered the health landscape (Alexander et al., 2022; Schneider et al., 2023).

Cancer, as a prevalent and often life-threatening chronic disease, has been severely affected by these pandemic-related changes (Al-Quteimat & Amer, 2020; Moraliyage et al., 2021). Cancer patients, already burdened by their condition, have faced compounded risks due to COVID-19 (Schneider et al., 2023). They are not only at increased risk of severe outcomes from COVID-19 due to compromised immune functions but also vulnerable to the repercussions of disrupted cancer care (Keim-Malpass et al., 2023). Delayed screenings, postponed treatments, and altered follow-up schedules have emerged as critical concerns, potentially leading to advanced disease stages at diagnosis and suboptimal management of existing cases (Keim-Malpass et al., 2023; London et al., 2020; Moraliyage et al., 2021).

Recognizing these challenges and the potential shift in cancer mortality trends during the pandemic is crucial. Despite the fact that it is known that the COVID-19 is an immediate threat to cancer patients, however, studies on its impacts on real world cancer mortality are lacking. The overlapping causes of death during the pandemic, particularly between COVID-19 and pre-existing

conditions such as cancer, complicate the interpretation of mortality trends and underscore the need for nuanced analyses. In this study, we aim to investigate the impact of the COVID-19 pandemic on cancer-related mortality in Nevada. By analyzing death certificate records from 2015-2021, we seek to unravel how the pandemic has not only influenced the overall number of cancer deaths but also affected specific cancer subtypes. We evaluated cancer mortality through three complementary perspectives: cancer as the underlying cause of death, cancer as a contributing cause of death, and a combined analysis of both. This approach enables us to capture the broader burden of cancer-related mortality, distinguishing between direct effects of cancer and its role as a secondary factor in pandemic-related deaths. This research addresses a critical gap in our understanding of the COVID-19 pandemic's broader impact on chronic diseases, with a particular focus on cancer mortality. It offers an in-depth analysis of cancer mortality trends during a time of unprecedented health challenges, offering insights for healthcare planning and policy formulation to better navigate similar challenges in the future.

2. Methods

Data Source

We analyzed Nevada death certificate records from 2015-2021 obtained from the National Center for Health Statistics (NCHS) for our analysis. These records encompassed decedents who were residents of Nevada at the time of

death. We stratified yearly death counts by age group, sex, and race/ethnicity. The underlying and contributing causes of death were determined by the NCHS using the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) codes. These records were de-identified and exempt from Human Subjects Review by the Institutional Review Board. Nevada population data for 2015-2021 was provided by the Nevada State Demographer's Office, stratified by year, age, sex, and race/ethnicity. The population estimates included individuals in group quarters.

Outcomes and Covariates

We evaluated three outcomes for all cancers and specific cancer subtypes: Cancer as the underlying cause of death, Cancer as contributing causes of death, Cancer as either the underlying cause of death or contributing causes of death (any deaths related to cancer).

The analysis of cancer as the underlying cause of death addressed the research question: During the COVID-19 pandemic, has the mortality rate of cancer as the underlying cause of death changed compared to the pre-pandemic period? Specifically, we aimed to evaluate changes in mortality directly attributable to cancer during the pandemic.

The analysis of cancer as a contributing cause of death addressed the research question: During the COVID-19 pandemic, has the mortality rate of cancer as a contributing cause of death changed compared to the pre-

pandemic period? In this analysis, we aimed to explore changes in the role of cancer as a secondary cause of death during the pandemic, as well as the proportion of cases where COVID-19 was recorded as the underlying cause of death.

The analysis of all cancer-related deaths, including cases where cancer was recorded as either the underlying or a contributing cause of death, addressed the research question: During the COVID-19 pandemic, has the overall cancer-related mortality rate changed compared to the pre-pandemic period? This analysis aimed to assess changes in the overall burden of cancer-related deaths during the pandemic.

Cancers and their subtypes were classified according to the ICD-10 Version:2019 as follows:

- C00-C97: All cancers
- C00-C14: Cancers of the lip, oral cavity, and pharynx
- C15-C26: Cancers of the digestive organs
- C30-C39: Cancers of the respiratory and intrathoracic organs
- C40-C41: Cancers of bone and articular cartilage
- C43-C44: Melanoma and other skin cancers
- C45-C49: Cancers of mesothelial and soft tissue
- C50-C50: Breast cancer
- C51-C58: Cancers of female genital organs
- C60-C63: Cancers of male genital organs

- C64-C68: Cancers of the urinary tract
- C69-C72: Cancers of the eye, brain, and other parts of the central nervous system
- C73-C75: Cancers of the thyroid and other endocrine glands
- C76-C80: Cancers of ill-defined, secondary, and unspecified sites
- C81-C96: Cancers of lymphoid, haematopoietic, and related tissue
- C97: Cancers of independent (primary) multiple sites

The basic model contains three demographic covariates: age group, sex, and race/ethnicity. The age distribution of the decedents was segmented into the following categories: <45 years, 45-64 years, 65-79 years, and 80 years and older, in line with the significant age distribution observed in COVID-19 mortality. Sex was categorized into male and female. Race/ethnicity was categorized into Hispanic and non-Hispanic groups, including American Indian or Alaska Native, Asian or Pacific Islander, Black, and White, based on bridged-race categories. In a year-adjusted model, in addition to these three demographic covariates, year of death was included as a continuous variable.

Statistical Analysis

Demographic characteristics were described using counts and percentages. To estimate the expected number of deaths during 2020-2021, we employed negative binomial regression models, chosen due to the presence of overdispersion in the data. Our models were constructed using data from

2015-2019 as a baseline to represent the pre-pandemic period. The basic models incorporated age group, sex, and race/ethnicity as covariates, and were further adjusted for year to explore temporal trends. An offset was incorporated in our models to account for population counts.

For each category of cancer mortality (overall cancer deaths, specific cancer subtypes), we compared the observed number of deaths in 2020 and 2021 with those predicted by models. To quantify the deviations, we calculated the observed/expected (O/E) ratios, with ratios greater than 1 indicating excess deaths. We constructed 95% confidence intervals (CI) and performed hypothesis tests for these ratios using Byar's approximation method (Breslow & Day, 1987). To control the false discovery rate associated with multiple testing in the analysis of cancer subtypes, we applied the Benjamini-Hochberg correction to calculate adjusted p-values (Benjamini & Hochberg, 1995). The significance level was set at 0.05.

All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc.).

3. Results

Overall Cancer Mortality

Demographic characteristics of all-cause deaths and deaths from cancers in Nevada during the pandemic years of 2020 and 2021 were presented in Table 1. Nevada's all-cause mortality was 21% higher than expected (O/E =1.21;

95%CI: 1.20-1.22; $p < 0.001$). About 75% of excess deaths were associated with COVID-19. The changes for 2020 (O/E=1.19; 95%CI: 1.18-1.20; $p < 0.001$) and 2021 (O/E ratio = 1.24; 95%CI: 1.22-1.25; $p < 0.001$) were similarly elevated. In contrast, cancer mortality, when assessed as the underlying cause of death, showed a marked decline. Observed cancer deaths totaled 10,312 compared to an expected 10,862, yielding an O/E ratio of 0.95 (95%CI: 0.93-0.97; $p < 0.001$). However, when analyzing the years 2020 and 2021 separately, only the change in 2021 was statistically significant (O/E=0.92; 95%CI: 0.89-0.94; $p < 0.001$), with no statistically significant change observed in 2020 (O/E=0.98; 95%CI: 0.96-1.01; $p = 0.178$) (Figure 1). When considering any death related to cancer (either as the underlying or contributing cause), a similar downward trend was observed for 2021 (O/E=0.95; 95%CI: 0.93-0.98; $p < 0.001$) (Figure 2).

Specific Cancer Subtype Mortality

The decline in overall cancer mortality was mainly due to the decline in deaths related to cancers of the respiratory and intrathoracic organs. As one of the leading causes of cancer death, deaths from cancers of the respiratory and intrathoracic organs showed a substantial decrease with an O/E ratio of 0.85 (95%CI: 0.81-0.88; adjusted $p < 0.001$) for the combined two years, with statistically significant reductions observed in both 2020 (O/E=0.92; 95%CI: 0.87-0.97; adjusted $p = 0.043$) and 2021 (O/E=0.77; 95%CI: 0.73-0.82; adjusted

$p < 0.001$) (Figure 1). A consistent downward trend was also observed when considering cancers of the respiratory and intrathoracic organs as either the underlying or contributing cause of death (Figure 2). Conversely, mortality related to cancers of the lip, oral cavity, and pharynx ($O/E = 1.30$; 95%CI: 1.15-1.46; adjusted $p < 0.001$), and male genital organs were higher than expected ($O/E = 1.16$; 95%CI: 1.08-1.24; adjusted $p < 0.001$) (Figure 1 and 2).

Time-adjusted Cancer Mortality

Considering that certain cancer subtypes might naturally fluctuate in mortality over time independent of the COVID-19 pandemic, we incorporated the year of death in our models to further adjust for this natural temporal influence. After testing all cancer subtypes using data from 2015-2019, we found that only the mortality related to cancers of the respiratory and intrathoracic organs showed a statistically significant and sustained decrease over time (adjusted $p = 0.001$). After time-adjustment, the combined two-year O/E ratio for respiratory system cancers was 0.97 (95%CI: 0.94-1.01; $p = 0.189$), with an O/E ratio of 1.05 (95%CI: 0.99-1.10; $p = 0.100$) for 2020 and 0.90 (95%CI: 0.85-0.95; $p < 0.001$) for 2021.

Cancer as Contributing Cause of Death

When examining cancer as a contributing cause of death, there was a general increase across most cancer types. The O/E ratio for overall cancer as

a contributing cause was 1.23 (95%CI: 1.20-1.27; $p < 0.001$), aligning more closely with the excess mortality seen in all-cause deaths. Regarding specific cancer subtypes, statistically significant increases above expected mortality were observed not only in several major cancer types, including cancers of digestive organs (adjusted $p = 0.001$), respiratory and intrathoracic organs (adjusted $p = 0.036$), breast cancer (adjusted $p < 0.001$), and male genital organs (adjusted $p < 0.001$), but also in cancers of the lip, oral cavity, and pharynx (adjusted $p = 0.010$), melanoma and skin (adjusted $p = 0.036$), thyroid and other endocrine glands (adjusted $p < 0.001$), and lymphoid, hematopoietic, and related tissue (adjusted $p < 0.001$). Importantly, many of these increases were related to COVID-19 as the underlying cause of death. For the cases where cancer was listed as a contributing cause of death, a substantial portion had COVID-19 as the underlying cause. In 2020, for example, among the excess cases with digestive organs cancer as a contributing cause, 9 out of 23 excess cases (39.1%) listed COVID-19 as the underlying cause. Similarly, for cancers of respiratory and intrathoracic organs, 19 out of 27 excess cases (70.4%) were due to COVID-19 as the primary cause of death; for breast cancer, 11 out of 33 cases (33.3%); for male genital organ cancers, 10 out of 44 cases (22.7%); and for lymphoid, hematopoietic, and related tissue cancers, 18 out of 33 cases (54.5%) were attributed to COVID-19 as the underlying cause (Figure 3).

4. Discussion

During the COVID-19 pandemic, cancer patients were considered a particularly vulnerable group due to their weakened immune systems from the disease itself and treatments such as chemotherapy or radiotherapy (Kamboj & Sepkowitz, 2009; Liu et al., 2020). Furthermore, cancer patients often require prolonged hospital stays, increasing their risk of exposure to COVID-19 (Aboueshia et al., 2021). Compounding this, compared to non-cancer patients, individuals with cancer not only have a higher risk of contracting COVID-19 but also face a greater likelihood of severe clinical events, including death (H. J. Han et al., 2021; Liang et al., 2020). These factors suggested an expected rise in cancer mortality during the pandemic. However, our real-world study in the state of Nevada, USA, revealed an unexpected finding: from 2020 to 2021, the number of cancers as the underlying cause of death were lower than anticipated ($p < 0.001$). The first explanation that can be thought of is that the excess deaths caused by COVID-19 lead to the shift in the underlying cause of death from cancer to COVID-19. In our analysis of cancer as a contributing cause, we have already found that the number of deaths where many cancer subtypes were listed as contributing causes was higher than expected. A large part of this excess can be attributed to COVID-19 being the underlying cause. This finding aligns with our existing knowledge that cancer patients have a higher risk of death when infected with COVID-19, directly reflecting the life-threatening impact of the virus on this patient group.

However, the increase in deaths with cancer as a contributing cause

cannot fully explain the observed decrease in cancer-related deaths. We propose three possible explanations for this phenomenon: 1. Natural decline in the incidence and mortality of certain major types of cancer, even without the impact of the pandemic; 2. Delays or reductions in cancer diagnosis during the pandemic; 3. Potential omissions or misclassification in death certification during the pandemic.

Natural decline in the incidence and mortality rates of lung cancer

Our analysis revealed that the overall decrease in cancer mortality was primarily driven by cancers of the respiratory and intrathoracic organs, which are among the leading causes of cancer death. The majority of this cancer subtype are cases of lung cancer. Our time-adjusted model confirmed that lung cancer mortality in Nevada had been decreasing over time (adjusted $p=0.001$), even before the COVID-19 pandemic. National cancer statistics in the United States have shown a steady decline in lung cancer incidence since 2006 (Siegel et al., 2024). Nevada has observed a similar trend, with a more rapid decrease in both incidence and mortality rates of lung cancer (Foote et al., 2021). On one hand, this may be attributed to the implementation of lung cancer screening and advances in lung cancer treatment. Lung cancer screening has been proven to reduce mortality rates in high-risk groups by 16%-24% by detecting asymptomatic malignancies amenable to curative treatment (de Koning et al., 2020; Pinsky et al., 2013), but the actual uptake remains low,

especially during the pandemic (Fedewa et al., 2022). On the other hand, public health policies such as smoking restrictions and bans, including the Nevada Clean Indoor Air Act (NCIAA) of 2006 (and subsequent modification in 2011), may also have played a significant role (Jacobs et al., 2013). The NCIAA aims to protect children and adults from cigarette smoke and second-hand smoke in most public places and workplaces. Studies have shown that the incidence and mortality rates of lung cancer in Nevada have rapidly declined in the years following the implementation of the NCIAA and other health policies (Foote et al., 2021).

Delays or reductions in cancer diagnosis during the pandemic

After adjusting for the natural decline over time, we still observed a statistically significant decrease in mortality for cancers of the respiratory and intrathoracic organs in 2021 ($p < 0.001$). This additional decrease prompts consideration of several pandemic-related factors that may have contributed to this trend. In March 2020, stay-at-home orders implemented in many countries to combat the COVID-19 pandemic had substantial clinical impacts on healthcare services. A recent study, encompassing about half of the U.S. population, revealed a decline in the incidence of all cancer types beginning in March 2020, coinciding with the implementation of various state and municipal stay-at-home orders and guidelines. This decline reached its nadir in April 2020 and persisted at lower levels, including for lung and prostate cancers. Despite

a significant drop in cancer incidence from March to May 2020, there was no compensatory surge in incidence by the end of 2020, failing to return to pre-pandemic levels (Howlader et al., 2023). There is ample evidence suggesting that the pandemic led to reductions in cancer screening, diagnosis, treatment, and patient visits (R. C. Chen et al., 2021; Chtourou et al., 2023; Kaufman et al., 2020; Patt et al., 2020). Changes in healthcare access and delivery during the pandemic could have led to underdiagnosis. Concerns about COVID-19 infection might have caused some patients to defer medical appointments and screenings, potentially leading to delayed cancer diagnoses. Furthermore, the prioritization of COVID-19 care in hospitals may have contributed to reduced cancer screenings and diagnoses.

Omissions or misclassification in death certification during the pandemic period

In addition to the delays in cancer diagnosis or registration, death certificates during the pandemic may have had omissions or misclassification. A study in Michigan revealed that a substantial proportion (about 50%) of reviewed COVID-19 death certificates did not list comorbidities (contributing causes of death) that increase the risk of severe COVID-19 infection or death. Guidelines from the CDC and WHO clearly state that comorbidities should be included on COVID-19 death certificates. Such errors could lead to inappropriate conclusions about the morbidity and mortality associated with

COVID-19 (Prahlow et al., 2023).

Comparison with other studies

A study based on the underlying cause of death in Mexico found that cancer mortality in 2020-2021 was 5.3% lower than expected based on data from 2015-2019, despite a significant excess in all-cause mortality observed during this period (Palacio-Mejia et al., 2022). Our study on the underlying cause of death in Nevada showed a very similar result of 5% lower than expected. However, a recent study on national cancer mortality rates in the United States indicated that relying solely on conventional mortality statistics based on the underlying cause may underestimate the impact of the pandemic on cancer patients (Fedeli et al., 2024). The authors of this study found an increase in cancer-related deaths (including both underlying and contributing causes) during the first two years of the pandemic (2020-2021), with a decreasing proportion of deaths attributed to cancer as the underlying cause. Our results largely align with their findings: of 15 cancer subtypes analyzed as the underlying cause of death, only five exceeded expectations, with just one showing a significant increase. When analyzing cancer-related deaths, 10 out of 15 subtypes exceeded expectations, with three showing statistically significant increases. However, it is noteworthy that our data showed an overall modest decrease in cancer-related deaths for 2020-2021, mainly due to a decline in 2021, which contrasts with the national upward trend. In Fedeli et

al.'s study, the nationwide decline in respiratory system cancer-related deaths in the United States narrowed in 2021; in contrast, our study observed an expanded decrease in respiratory system cancer-related deaths in Nevada for the same year. This phenomenon may reflect some systemic differences in Nevada compared to other states. In addition to the positive effects of anti-smoking measures previously mentioned, it could also be related to Nevada's lower lung cancer screening rate. The American Lung Association reported that the screening rate among high-risk population for lung cancer in Nevada is lower than the national level, and there is study pointing out the scarcity of lung cancer screening centers in Nevada (Eberth et al., 2014). In addition, we adjusted for demographic information in the models to obtain more accurate estimates.

Strengths

This study has several notable strengths. First, we utilized Nevada state-level mortality data from the NCHS, which offers high reliability and provides a comprehensive representation of cancer mortality trends during the early phase of the COVID-19 pandemic in Nevada. Second, we analyzed cancer mortality from three distinct perspectives: as an underlying cause, a contributing cause, and a combination of both. This approach offers a multifaceted understanding of the role of cancer in mortality under different classifications. Third, we accounted for potential confounders by adjusting for age, gender, race,

population size, and year of death, ensuring robust and reliable results. Lastly, to control the false discovery rate and reduce the risk of false-positive findings, we applied the Benjamini-Hochberg correction in the analysis of cancer subtypes.

Limitations

Despite its strengths, this study has several limitations. First, this study relies solely on death certificate records, which are influenced by the certifying physician's subjective judgment. As mentioned in the discussion, contributing causes of death were often overlooked during the pandemic, and we lack detailed clinical data to determine whether COVID-19 directly worsened cancer or whether cancer-related deaths involved prior SARS-CoV-2 infection. Second, collider bias may have influenced the observed relationships due to the inherent nature of mortality data, which only captures cases of death and excludes those who survived. The exposure variable (the COVID-19 pandemic) and the outcome variable (cancer-related mortality) are both linked through the collider—mortality. During the pandemic, the recording of COVID-19 as the underlying cause of death while overlooking contributing causes may have led to an underestimation of the cancer-related mortality burden. This selective reporting in death records could potentially distort the observed changes in cancer-related mortality. Third, this study only covers data from 2015 to 2021, focusing on the early phase of the COVID-19 pandemic. Future studies

incorporating data from subsequent years are needed to validate the findings presented here and provide insights into post-pandemic trends. Fourth, the data used in this study are derived from death certificates, which only capture information at the time of death. Therefore, the findings should be interpreted as associations between the pandemic and cancer-related mortality rather than causal inferences.

5. Conclusions

In conclusion, our analysis of death records in Nevada reveals the changes in cancer-related deaths during the first two years of the COVID-19 pandemic (2020-2021). Overall, cancer-related deaths were slightly lower than expected, but the trends varied among different cancer subtypes. Most subtypes cancers either saw higher-than-expected death or no statistically significant changes during COVID-19 pandemics. The substantial decrease in lung cancer-related deaths drove the overall reduction in cancer-related mortality. This is partly due to the continuous decline in lung cancer incidence in Nevada in recent years. On the other hand, it might be due to delayed cancer diagnoses or omissions of cancer as contributing causes on death certificates during the pandemic. Moreover, these indirect effects of the pandemic likely led to a systemic underestimation of the overall cancer-related death burden, not just for lung cancer. The contrasting trends of decreased cancer deaths as the underlying cause and increased cancer deaths as the contributing cause highlight a

potential shift in the role of cancer in mortality during the pandemic. Continued monitoring of cancer-related deaths is necessary to further assess the impact of the COVID-19 pandemic on cancer patients. At the same time, actions should be taken to increase participation rates in recommended cancer screenings among high-risk populations.

Table 1. Demographic Characteristics of All-cause Deaths and Deaths from Cancers: Nevada, 2020-2021

	All-cause deaths (N=60 871)		Deaths from Cancers (n=10 312)	
	No.	%	No.	%
Age				
<45 years	4693	7.7	325	3.2
45-64 years	12 801	21.0	2278	22.1
65-79 years	22 331	36.7	4797	46.5
80+ years	21 046	34.6	2912	28.2
Sex				
Female	26 628	43.7	4820	46.7
Male	34 243	56.3	5492	53.3
Race & Ethnicity				
White [^]	42 322	69.5	7611	73.8
Hispanic	7327	12.0	967	9.4
Black [^]	6223	10.2	893	8.7
Asian or Pacific Islander [^]	4412	7.3	774	7.5
American Indian or Alaskan Native [^]	587	1.0	67	0.7

[^]Non-Hispanic

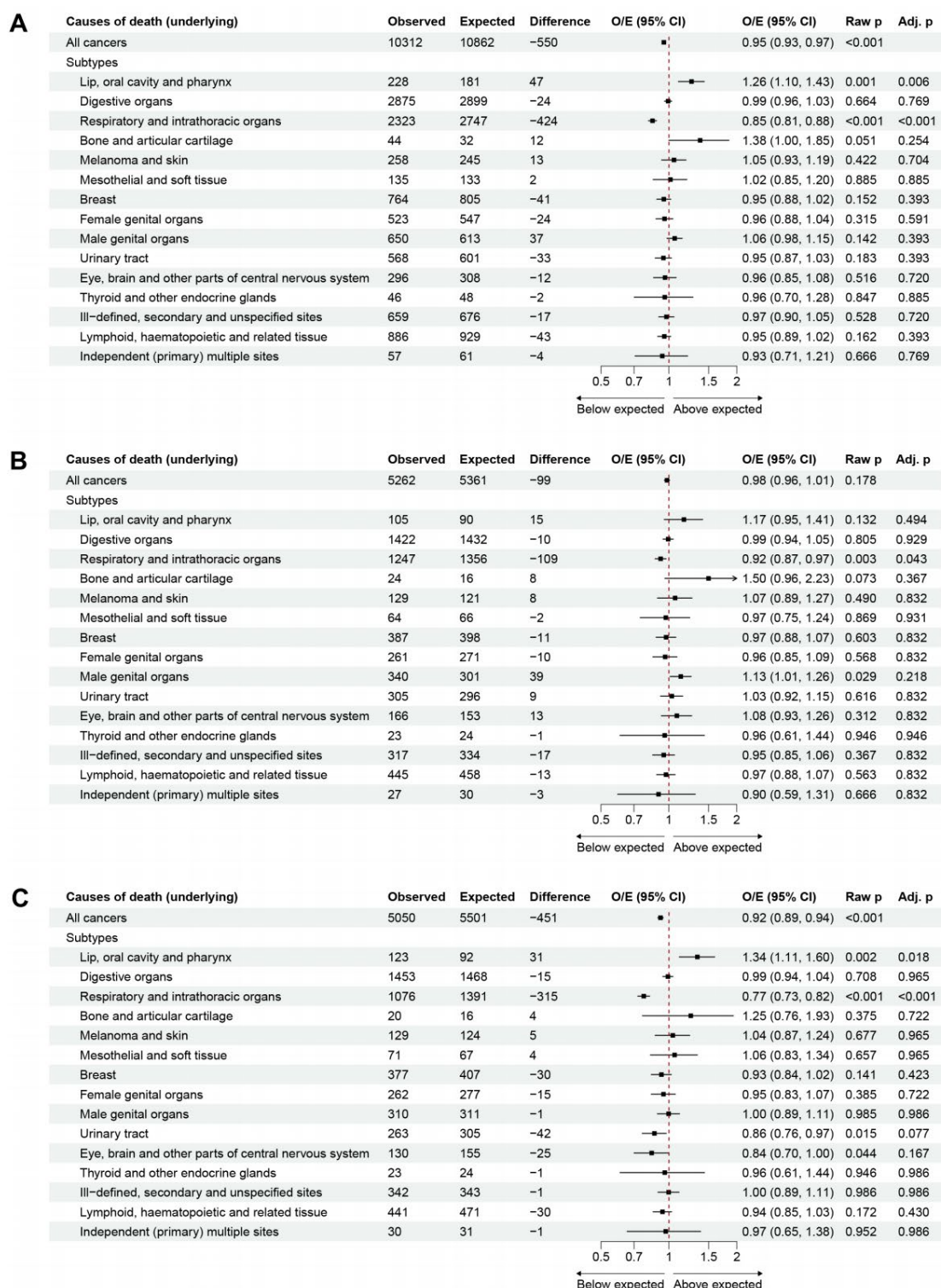


Figure 1. Cancer as the underlying cause of death. (A) 2020-2021, population size = 6,303,726. (B) 2020, population size = 3,145,186. (C) 2021, population size = 3,158,540. "Adj. p" refers to Benjamini-Hochberg adjusted p-values.

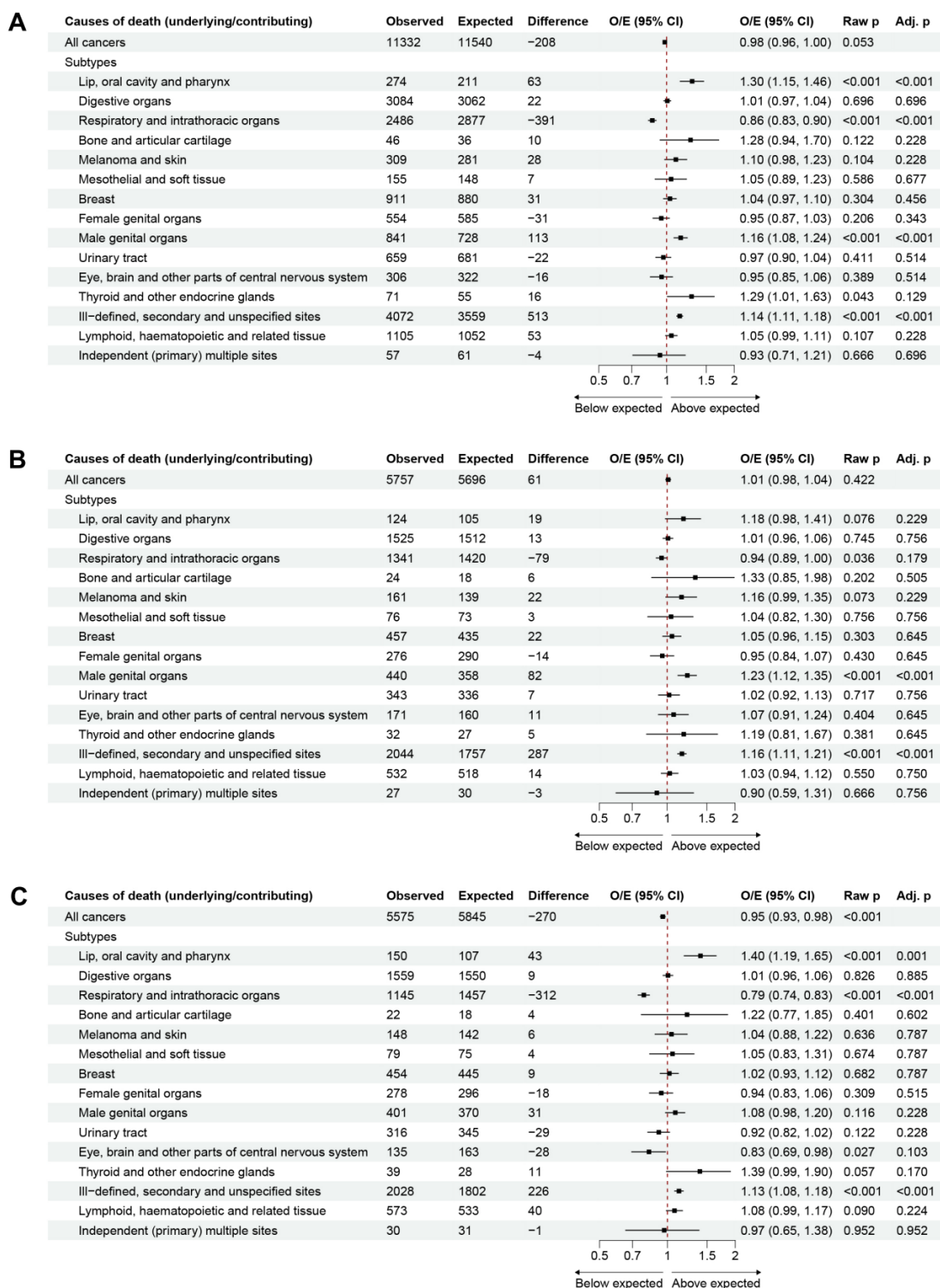


Figure 2. Cancer as either the underlying cause of death or contributing causes of death (any deaths related to cancer). (A) 2020-2021, population size = 6,303,726. (B) 2020, population size = 3,145,186. (C) 2021, population size = 3,158,540. “Adj. p” refers to Benjamini-Hochberg adjusted p-values.

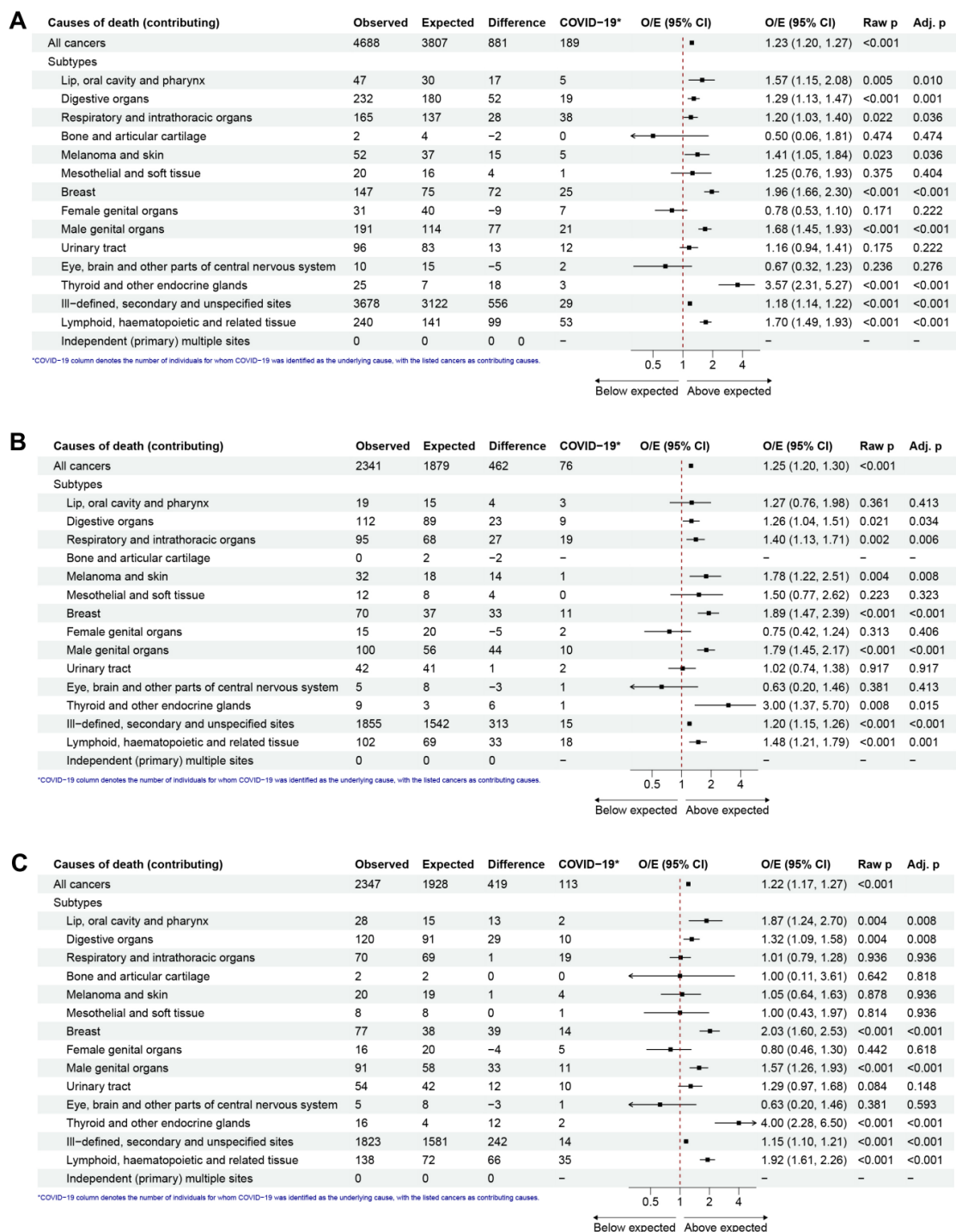


Figure 3. Cancer as the contributing causes of death. (A) 2020-2021, population size = 6,303,726. (B) 2020, population size = 3,145,186. (C) 2021, population size = 3,158,540. “Adj. p” refers to Benjamini-Hochberg adjusted p-values.

Chapter 4: Manuscript 2: Higher Prevalence of Long COVID Observed in Cancer Survivors: Insights from a US Nationwide Survey

This chapter is based on the following peer-reviewed publication:

Wang, L., & Yang, W. (2025). Higher prevalence of long COVID observed in cancer survivors: Insights from a US nationwide survey. *Annals of Epidemiology*, 103, 30–39. doi: 10.1016/j.annepidem.2025.02.004.

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Abstract

Background: Cancer and cancer treatments can weaken the body's immune system, making cancer patients particularly vulnerable to COVID-19. While evidence suggests that cancer patients may be at increased risk for severe outcomes after COVID-19 infection, there is a lack of population-based studies comparing long COVID prevalence between cancer survivors and non-cancer individuals.

Methods: We utilized data from the 2022 Behavioral Risk Factor Surveillance System (BRFSS), analyzing a sample of 120,658 U.S. adults who had tested positive for COVID-19. Long COVID was defined as the presence of COVID-19 symptoms lasting three months or longer. The weighted prevalence of long COVID was compared between cancer survivors and non-cancer individuals.

Crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Multiple imputation was employed to address missing data on COVID-19 vaccination.

Results: Among 17,362 cancer survivors who tested positive for COVID-19, 4,009 reported having long COVID (weighted prevalence = 24.0%), compared to a weighted prevalence of 21.6% in non-cancer individuals ($p < 0.001$). After controlling for covariates and accounting for the complex sampling design, the adjusted OR was 1.17 (95% CI = 1.06–1.30, $p = 0.002$). In participants under 45 years old, cancer survivors had a notably higher prevalence of long COVID compared to non-cancer individuals (32.1% vs. 21.3%, $p < 0.001$), with an adjusted OR of 1.33 (95% CI = 1.07–1.66, $p = 0.012$). In participants aged 45 and above, the prevalence difference was not significant (22.7% vs. 21.9%, $p = 0.324$), with an adjusted OR of 1.14 (95% CI = 1.02–1.27, $p = 0.024$). Regarding the association of COVID-19 vaccination with long COVID, four or more doses were linked to a significant reduced odds of long COVID among cancer survivors (adjusted OR=0.55, 95%CI = 0.34-0.88, $p = 0.013$).

Conclusions: Cancer survivors are observed to have higher odds of developing long COVID, particularly younger survivors. The association of COVID-19 vaccination with long COVID varies between cancer survivors and non-cancer individuals, with cancer survivors requiring more doses to achieve significant reduction in the odds of long COVID.

Keywords:

COVID-19; Long COVID; Cancer survivors; COVID-19 vaccination; BRFSS

1. Introduction

The COVID-19 pandemic has had a profound global impact, leading to significant morbidity and mortality worldwide (Weinberger et al., 2020; Woolf et al., 2020). While the acute phase of COVID-19 has been extensively studied, growing evidence suggests that a substantial proportion of individuals continue to experience a range of persistent symptoms long after the resolution of the initial infection (Fang et al., 2024; Koc et al., 2022). This condition, commonly referred to as "long COVID" or post-acute sequelae of SARS-CoV-2 infection (PASC), includes symptoms such as fatigue, shortness of breath, cognitive dysfunction that can persist for weeks to months (Dagher et al., 2023; Soriano et al., 2022).

During the COVID-19 pandemic, cancer patients were considered a highly vulnerable group due to their weakened immune systems resulting from the disease itself and treatments such as chemotherapy or radiotherapy (Kamboj & Sepkowitz, 2009; Liu et al., 2020). Several studies have documented that cancer patients are more likely to experience severe COVID-19 related outcomes, including higher rates of hospitalization, intensive care unit (ICU) admission, and mortality (H. J. Han et al., 2021; Liang et al., 2020). On the other hand, the long-term impact of COVID-19 in cancer patients is also concerning

given their already complex healthcare needs (Aboueshia et al., 2021; Schneider et al., 2023). The immunosuppression associated with cancer, along with ongoing treatments, may predispose these patients to a higher risk of developing long COVID (Corey et al., 2021; Su et al., 2022). Additionally, the presence of comorbidities often seen in cancer patients may exacerbate the long COVID symptoms, potentially leading to a further deterioration in quality of life (Song & Giuriato, 2023). While some studies have explored cancer patients' susceptibility to long COVID, the findings have been inconsistent. Certain studies report a high prevalence of long COVID among cancer patients, exceeding 50% (Dagher et al., 2023; Debie et al., 2024; Monroy-Iglesias et al., 2022), while others find relatively lower prevalence with no significant difference compared to non-cancer patients (Chai et al., 2021; Fankuchen et al., 2023). The existing evidence largely comes from single-center studies or non-representative samples, highlighting the need for more robust, population-based research.

Understanding the relationship between cancer and long COVID is critical for developing post-pandemic healthcare strategies and ensuring that cancer survivors receive appropriate long-term care and support. This study aims to explore the association between a history of cancer and the development of long COVID using national data from the Behavioral Risk Factor Surveillance System (BRFSS). Our hypothesis is that cancer survivors are associated with higher odds of developing long COVID compared to non-cancer individuals.

The findings of this study could have significant implications for the management and treatment of cancer patients in the context of COVID-19 and may guide future research and public health interventions aimed at mitigating the impact of long COVID in this vulnerable population.

2. Methods

2.1. Data Source and population

This study utilized national data from the 2022 BRFSS, a nationwide cross-sectional telephone survey, including both landline and cellular phones, conducted annually across the United States (CDC, 2024c; Pierannunzi et al., 2013). The BRFSS collects both national- and state-level data on health-related risk behaviors, chronic health conditions, and the use of preventive services among U.S. non-institutionalized adults aged 18 years and older. The data collection is executed by the health departments of all 50 states, the District of Columbia, and three U.S. territories on behalf of the Centers for Disease Control and Prevention (CDC). Participants are randomly selected through a process known as random digit dialing, and trained interviewers administer a standardized set of health-related questions. In 2022, the overall response rate was 45.0%, and 445,132 participants were surveyed.

For the purposes of this study, the sample was restricted to participants who reported a history of COVID-19 infection, as determined by their response to the question, "Has a doctor, nurse, or other health professional ever told you

that you tested positive for COVID-19?" (Erinoso et al., 2024) Participants who answered "Yes" or "Tested positive using a home test without health professional" were included. Only those with complete data on the exposure variable "history of cancer" and the outcome variable "history of long COVID" were included in the statistical analysis. All the original BRFSS variables used in this study are listed in Table S1.

This study was deemed exempt from Institutional Review Board (IRB) review as it utilized de-identified data from secondary, publicly available datasets.

2.2. Exposure: History of Cancer

The primary exposure variable in this study was a history of cancer, defined as the presence of any type of cancer (NCI, 2021). In the BRFSS 2022 Chronic Health Conditions section, this information was captured through two questions: "(Ever told) (you had) skin cancer that is not melanoma?" and "(Ever told) (you had) melanoma or any other types of cancer?". For each question, a response of "Yes" indicated the presence of the respective type of cancer, while a response of "No" indicated its absence. Responses other than "Yes" or "No" were considered as missing data for that question.

Participants who answered "Yes" to either of these two questions were classified as having a history of cancer (exposed), whereas those who answered "No" to both questions were classified as having no history of cancer

(unexposed). If a participant answered "No" to one question but had missing data for the other, they were categorized as having missing data for the exposure variable. Similarly, participants with missing responses to both questions were also categorized as having missing data for the exposure variable.

2.3. Outcome: History of Long COVID

The primary outcome variable in this study was the history of long COVID, defined as the presence of COVID-19 symptoms lasting three months or longer (Hung et al., 2024; WHO, 2022). This variable was based on the question: "Did you have any symptoms lasting 3 months or longer that you did not have prior to having coronavirus or COVID-19?" A response of "Yes" was considered indicative of long COVID, while a response of "No" was considered as the absence of long COVID. Responses other than "Yes" or "No" were treated as missing data for this variable.

For participants who reported a history of long COVID, we further analyzed the frequency and weighted percentage of the primary symptoms they experienced. This analysis was based on the question: "Which of the following was the primary symptom that you experienced?" This was a single-choice question, meaning each participant could select only one primary symptom from the 11 different long COVID symptoms listed:

- Tiredness or fatigue

- Difficulty thinking or concentrating or forgetfulness/memory problems (“brain fog”)
- Difficulty breathing or shortness of breath
- Joint or muscle pain
- Fast-beating or pounding heart (also known as heart palpitations) or chest pain
- Dizziness on standing
- Depression, anxiety, or mood changes
- Symptoms that get worse after physical or mental activities
- You did not have any long-term symptoms that limited your activities.
- Loss of taste or smell
- Some other symptom

2.4. Covariates

This study adjusted for a range of covariates, including age, sex, race/ethnicity, education, marital status, income level, health insurance, body mass index (BMI), smoking history, certain chronic health conditions, and the number of COVID-19 vaccinations received.

Among these covariates, age, sex, race/ethnicity, education, marital status, income level, BMI, and smoking history were considered as confounders because they are associated with both cancer and long COVID, based on prior research (Coughlin, 2019; Erinoso et al., 2024; La Vecchia et al., 1992; Larsen

et al., 2020; M. Li et al., 2020; Schwartz, 2024; Trudel-Fitzgerald et al., 2019) or our data. On the other hand, there was no evidence to suggest that health insurance and the number of COVID-19 vaccinations were causally associated with cancer. Therefore, these two variables were included in the model as risk factors for long COVID.

We included five chronic health conditions that have been associated with long COVID in previous research: chronic obstructive pulmonary disease (COPD), diabetes, asthma, heart disease, and stroke (Erinoso et al., 2024; Hejazian et al., 2024; Hung et al., 2024; Steenblock et al., 2022; Tsampasian et al., 2024). Due to the cross-sectional design of the BRFSS, the temporal relationship between cancer and these chronic health conditions is unclear. These conditions may have a bidirectional relationship with cancer or interact with each other (Florido et al., 2022; Gergen, 2021; Lega & Lipscombe, 2020; Qi et al., 2022; Rayner et al., 2019; Uemura et al., 2021; Wyler von Ballmoos & Almassi, 2022; Zuber, 2023). Consequently, these conditions could act as confounders or mediators in the association between cancer history and long COVID. If they function as mediators, adjusting for them may pull the observed association towards null, which reflects the mediation effect rather than bias. Therefore, we further adjusted for these chronic health conditions in a separate model to account for their potential effects.

All covariates were treated as categorical variables, with categories defined as follows:

- Age: 18–24 / 25–34 / 35–44 / 45–54 / 55–64 / 65+ years
- Sex: Male / Female
- Race: Non-Hispanic White / Non-White or Hispanic
- Education: High School or Less / Attended College or Technical School / Graduated from College or Technical
- Marital Status: Married or Member of an Unmarried Couple / Divorced, Widowed, or Separated / Never Married
- Income Level: Less than \$15,000 / \$25,000 to < \$50,000 / \$50,000 or more
- Health Insurance: Have some form of insurance / Do not have some form of health insurance
- BMI: Healthy Weight or Underweight (less than 25) / Overweight (25 to less than 30) / Obese (30 or greater)(CDC, 2024b)
- Smoking History: Never Smoked / Current or Former Smoker
- COPD (Chronic Obstructive Pulmonary Disease): Yes / No
- Diabetes: Yes / No
- Asthma: Current / Never or Former
- Heart disease: Yes / No
- Stroke: Yes / No
- Number of COVID-19 Vaccinations Received: None / One / Two / Three / Four or More

The variable for the number of COVID-19 vaccinations received was derived from two questions: "Have you received at least one dose of a COVID-19 vaccination?" and the follow-up question, "How many COVID-19 vaccinations have you received?" Participants who had missing data for the first question, as well as those who answered "Yes" to the first question but did not provide a valid response to the second question, were categorized as having missing data for this covariate.

2.5. Statistical Methods: Primary Analyses

Data were weighted using standard BRFSS analysis practices (CDC, 2023) to control for nonresponse bias and to enhance the generalizability of the results. Categorical variables are presented as frequencies and weighted percentages. The Taylor series linearization method was used to estimate the 95% confidence intervals (CIs) for weighted percentages. Comparisons between the exposed (history of cancer) and unexposed groups regarding outcomes and covariates were conducted using Rao-Scott chi-square tests. Among participants who reported long COVID, the distribution of primary symptoms was also compared. If an overall significant difference was observed, post hoc tests were performed for each symptom category. The p-values from post hoc tests were adjusted using the Bonferroni correction to account for multiple comparisons.

Both crude and adjusted odds ratios (ORs) are reported with corresponding

95% CIs for the exposure variable and covariates. Model 1 adjusted for potential confounders including age, sex, race/ethnicity, education, marital status, income level, health insurance, BMI, and smoking history. The ORs from Model 1 were considered the primary estimates for the association between cancer history and long COVID in this study. Model S1 further adjusted for additional chronic health conditions: COPD, asthma, diabetes, heart disease, and stroke. We provided results that simultaneously adjusted for these five conditions as well as results that separately adjusted for each condition. As mentioned in section 2.4, due to the unclear temporal relationship between cancer and these chronic health conditions, the results from Model S1 should be interpreted with caution and are provided mainly for reference.

Because not all states collected information on the number of COVID-19 vaccinations received, the proportion of missing data for this variable is quite high (61.0%). Therefore, vaccination status was not included in Models 1 and S1. Instead, Model 2 specifically builds on Model 1 by further adjusting for the number of COVID-19 vaccinations received.

2.6. Statistical Methods: Stratified Analyses and Sensitivity Analyses

Since age is a risk factor for severe COVID-19 outcomes (Mahase, 2020), stratified analyses were also conducted for Models 1 and S1 based on age groups (<45 years and ≥45 years) to explore the differential impact of age.

For Model 2, in addition to conducting a complete case analysis (CCA),

multiple imputation (MI) was employed as a sensitivity analysis to explore potential changes in CCA results related to missing vaccination status data (P. Li et al., 2015). MI was performed using fully conditional specification (FCS), with 50 imputations and 40 iterations. The imputation model included variables such as history of cancer, history of long COVID, age, sex, race/ethnicity, education, marital status, income level, health insurance, BMI, smoking history, and design weight. The MI was restricted to participants with no missing data on these variables to ensure consistency with the sample analyzed in Model 1. Additionally, stratified analyses based on cancer history were conducted to explore the association of COVID-19 vaccination with long COVID within both the exposed and unexposed populations.

All statistical analyses were performed using SAS 9.4 (Cary, NC). The significance level was set at 0.05.

3. Results

3.1. Sample Characteristics of the Two Groups

A total of 120,658 participants were included in this study, with 17,362 in the cancer group (10.1%, 95% CI = 9.8%–10.5%) and 103,296 in the non-cancer group (89.9%, 95% CI = 89.5%–90.2%). Figure 1 shows sample sizes for each analysis stage. Table 1 presents the sample characteristics of the two groups. Significant differences were observed between the groups across various characteristics. Specifically, compared to the non-cancer group, the

cancer group had a higher proportion of older participants ($p < 0.001$), a greater proportion of females ($p < 0.001$), more Non-Hispanic Whites ($p < 0.001$), a higher level of education ($p < 0.001$), and a lower rate of those who have never married ($p < 0.001$). Additionally, the cancer group had a higher proportion of participants with health insurance ($p < 0.001$), a greater proportion of BMI above the normal range ($p < 0.001$) and a greater prevalence of smoking history ($p < 0.001$). Regarding chronic health conditions, the cancer group exhibited higher prevalences of COPD ($p < 0.001$), diabetes ($p < 0.001$), current asthma ($p < 0.001$), heart disease ($p < 0.001$), and stroke history ($p < 0.001$) compared to the non-cancer group. Notably, a higher proportion of individuals in the cancer group had received three or more doses of the COVID-19 vaccine compared to those in the non-cancer group ($p < 0.001$).

3.2. Prevalence of Long COVID in the Two Groups

As shown in Table 2, the prevalence of long COVID was significantly higher among cancer survivors compared to the non-cancer group (24.0% vs. 21.6%, $p < 0.001$). The crude OR was 1.15 (95% CI = 1.06–1.24, $p < 0.001$).

After adjusting for demographic factors, BMI, and smoking history in Model 1 (Table 3), the adjusted OR was 1.17 (95% CI = 1.06–1.30, $p = 0.002$). Further adjustment for 5 chronic health conditions in Model S1 yielded an adjusted OR of 1.10 (95% CI = 0.99–1.22, $p = 0.067$) (Table S2).

In the stratified analysis of participants under 45 years of age, a more

pronounced difference was observed between the two groups (32.1% vs. 21.3%, $p < 0.001$). The crude OR in this age group was 1.75 (95% CI = 1.40–2.18, $p < 0.001$) (Table 2). In Model 1, the adjusted OR for cancer history was 1.33 (95% CI = 1.07–1.66, $p = 0.012$) (Table 3), while in Model S1, the adjusted OR was 1.25 (95% CI = 1.00–1.56, $p = 0.050$) (Table S3).

However, among participants aged 45 and above, the difference between the two groups was not significant (22.7% vs. 21.9%, $p = 0.324$). The crude OR was 1.05 (95% CI = 0.96–1.14, $p = 0.321$) (Table 2). In Model 1, the adjusted OR for cancer history was 1.14 (95% CI = 1.02–1.27, $p = 0.024$) (Table 3), and in Model S1, the adjusted OR was 1.06 (95% CI = 0.95–1.19, $p = 0.273$) (Table S4).

3.3. Association of COVID-19 Vaccination with Long COVID: CCA and MI Analyses

In the complete case analysis (CCA), we extended Model 1 by further adjusting for the number of COVID-19 vaccinations received (Model 2). It is important to note that due to the significant amount of missing data for the vaccination variable, the sample size in Model 2's CCA analysis ($n = 36,887$) was considerably smaller than in Model 1 ($n = 92,862$). In Model 2, the adjusted OR for cancer history was 1.24 (95% CI = 1.08–1.42, $p = 0.003$). Among the overall population, receiving three or more doses of the COVID-19 vaccine was associated with reduced odds of long COVID (three doses OR = 0.77, 95% CI

= 0.67-0.89, $p < 0.001$; four or more doses OR = 0.75, 95% CI = 0.61-0.91, $p = 0.004$) (Table 4). A similar association was observed among non-cancer participants. However, within the cancer survivors, only those who received four or more doses of the COVID-19 vaccine showed a significant reduction in the odds of long COVID (OR = 0.55, 95% CI = 0.34–0.88, $p = 0.013$). Although the cancer survivors who received three doses also showed a reduction in the odds of long COVID, this reduction did not reach statistical significance (OR = 0.77, 95% CI = 0.50–1.17, $p = 0.221$).

We conducted a multiple imputation (MI) analysis as a sensitivity analysis. Using the MI dataset allowed us to match the sample size of Model 2 with that of Model 1. In the MI Model 2, the OR for cancer history was 1.18 (95% CI = 1.07–1.31, $p = 0.001$). Among the overall population and within the non-cancer participants, receiving two or more doses of the COVID-19 vaccine was significantly associated with reduced odds of long COVID (overall population: two does OR = 0.86, 95% CI = 0.77-0.97, $p = 0.014$; three doses OR = 0.74, 95% CI = 0.65-0.84, $p < 0.001$; four or more doses OR = 0.68, 95% CI = 0.57-0.81, $p < 0.001$; non-cancer participants: two does OR = 0.86, 95% CI = 0.76-0.97, $p = 0.018$; three doses OR = 0.74, 95% CI = 0.64-0.84, $p < 0.001$; four or more doses OR = 0.70, 95% CI = 0.58-0.85, $p < 0.001$) (Table S5). However, similar to the CCA findings, within the cancer survivors, only receiving four or more doses of the vaccine was associated with significantly reduced odds of long COVID (OR = 0.61, 95% CI = 0.40–0.93, $p = 0.022$). The association of

receiving three doses with long COVID did not reach statistical significance (OR = 0.75, 95% CI = 0.53–1.07, $p = 0.109$).

3.4. Primary Symptoms of Long COVID

As shown in Table 5, the top three primary symptoms of long COVID reported by participants in the cancer group were tiredness or fatigue (28.9%), difficulty breathing or shortness of breath (20.8%), and loss of taste or smell (14.7%). This pattern was also observed in the non-cancer group. However, the proportion of the cancer group reporting tiredness or fatigue and difficulty breathing or shortness of breath as their primary long COVID symptoms was slightly higher compared to the non-cancer group (28.9% vs 25.8%).

4. Discussion

In this study, we utilized 2022 BRFSS national data to explore the weighted prevalence of long COVID among U.S. adults who had previously tested positive for COVID-19, comparing cancer survivors with non-cancer individuals. Our findings revealed that the prevalence of long COVID among cancer survivors was significantly higher than that of in the non-cancer group (24.0% vs 21.6%, $p < 0.001$). After adjusting for demographic factors, BMI, and smoking history, the adjusted OR was 1.17 (95% CI = 1.06–1.30), indicating that cancer survivors had a 17.0% higher odds of developing long COVID compared to non-cancer individuals.

There is currently limited research specifically focusing on the prevalence of long COVID among cancer patients. We have compiled findings from some studies on this topic and explored potential reasons for discrepancies in the results:

Dagher et al. analyzed data from 312 cancer patients infected with COVID-19 in the early pandemic and found that 60% experienced COVID-19-related symptoms lasting more than 30 days (Dagher et al., 2023); Debie et al. found that among 49 cancer patients, 79.6% developed new symptoms during or after SARS-CoV-2 infection that persisted longer than four weeks (Debie et al., 2024); Monroy-Iglesias et al. reported that 51.3% of 80 cancer patients presented symptoms that occurred or got worse over 4 weeks after COVID-19 diagnosis (Monroy-Iglesias et al., 2022). These three studies all reported a prevalence of long COVID exceeding 50% among cancer patients. This is substantially higher than the findings of our study and other research. One possible explanation is that these studies defined long COVID using a shorter symptom duration window of over 30 days or four weeks, whereas the current WHO definition specifies symptoms must either continue or new symptoms develop three months after the initial SARS-CoV-2 infection (WHO, 2022), which was adopted by our study and some other research. As such, their definitions may have been more sensitive, capturing cases with shorter symptom durations and leading to higher prevalence estimates. Additionally, discrepancies among these studies may arise from their single-center designs, differences in sample size and

sample characteristics.

Fankuchen et al. employed the current WHO definition of long COVID. They compared the long COVID prevalence between 52 cancer patients and 200 non-cancer controls, finding no statistically significant difference between the groups (29% vs 34%) (Fankuchen et al., 2023). Our observed prevalence among cancer patients is similar to their findings. However, their prevalence in the non-cancer group is higher than ours, likely because their control group was matched to the cancer group, whereas our control group was not.

Cortellini et al. also used the WHO definition of long COVID. They followed 186 cancer patients and found that 16.6% reported at least one sequelae (Cortellini et al., 2022). This prevalence is lower than our findings. One potential explanation is that their study excluded patients with advanced or metastatic malignancies, whose health status tends to be poorer.

Chai et al. followed 114 cancer survivors and 432 non-cancer survivors for one year after COVID-19 infection and reported a prevalence of at least one persistent symptom at 23% in cancer survivors compared to 30% in the non-cancer group, also without a statistically significant difference (Chai et al., 2021). The authors did not specify whether their definition of long COVID accounted for symptom duration. Our prevalence estimate for cancer patients aligns closely with theirs. Similar to Fankuchen's study, Chai's study also used matching techniques, which may explain why the non-cancer group's prevalence was higher than ours.

Different Prevalence of Long COVID in Younger and Older Cancer Survivors

In the age-stratified analysis, we observed notable differences in the prevalence of long COVID between cancer survivors and non-cancer individuals among those under 45 years of age (32.1% vs. 21.3%, $p < 0.001$). Interestingly, in participants aged 45 and above, the prevalence of long COVID among cancer survivors was only 22.7%, which is nearly equivalent to the 21.9% observed in the non-cancer group ($p = 0.324$). Although the adjusted OR in Model 1 for this older age group reached statistical significance ($p = 0.024$), it was still weaker than the adjusted OR observed in the younger group. Notably, the cohorts in Fankuchen's and Chai's studies are older populations, and their studies also did not find a statistically significant difference in long COVID prevalence between cancer and non-cancer groups.

Previous studies have established that both cancer and older age are significant risk factors for severe outcomes following COVID-19 infection (S. Han et al., 2022; Liang et al., 2020; Mahase, 2020). Therefore, it was initially expected that the association between cancer history and long COVID would be more pronounced in the older population. One possible explanation for the lack of a significant association in the older age group could be survivorship bias. Older cancer patients are at a higher risk of death following COVID-19 infection, and thus, the health status of surviving older cancer patients is likely

to be better than those who have passed away, although still poorer than that of the general population (Holmes et al., 2014). This may reduce the absolute difference in long COVID prevalence between groups. Furthermore, the BRFSS targets noninstitutionalized adults, which means that cancer survivors included in this study are likely healthier than institutionalized cancer patients, potentially leading to an underestimation of long COVID prevalence in the older cancer survivor group. Another possible explanation for the higher prevalence of long COVID among younger cancer survivors is the potential impact of cancer treatment. Younger patients are often able to tolerate more intensive cancer therapies, such as high-dose chemotherapy, which can weaken the body's immune system (Bleyer, 2007; Tralongo et al., 2021). This immunosuppression may increase the likelihood of developing long COVID after a COVID-19 infection (Su et al., 2022) in this population.

Association of COVID-19 Vaccination with Long COVID in Cancer Survivors

In the CCA analysis of Model 2, which further adjusted for the number of COVID-19 vaccinations received, the OR for cancer history remained statistically significant ($p = 0.003$). When stratifying by cancer history, we found that among cancer survivors, only those who had received four or more doses of the COVID-19 vaccine showed a significant reduction in the odds of developing long COVID ($p = 0.013$). In contrast, among the non-cancer

participants, receiving three or more doses significantly was associated with reduced odds of long COVID (three doses $p = 0.001$, four or more doses $p = 0.047$). A possible explanation for this discrepancy could be the lower COVID-19 vaccination seroconversion rate observed in cancer survivors compared to the non-cancer population. This phenomenon was discussed by Tran et al. in a meta-analysis, which highlighted the reduced seroconversion rates in cancer patients post-vaccination (Tran et al., 2021). Seneviratne et al. also found that immunogenicity of vaccines was lower in patients with cancer compared to healthy individuals, as reported in their narrative review (Seneviratne et al., 2022). They pointed out that disease-associated immune dysfunction and treatment-related immunosuppression are likely to cause poor immunogenicity with COVID-19 vaccination (Seneviratne et al., 2022). Additionally, Sun et al., in their systematic review, indicated that cancer types and types of therapy could also influence the vaccine response in cancer patients (Sun et al., 2022).

Primary symptoms of long COVID in Cancer Survivors

Regarding the primary symptoms of long COVID, the top three symptoms reported by both cancer survivors and the non-cancer group were tiredness or fatigue, difficulty breathing or shortness of breath, and loss of taste or smell. This pattern was consistent across both groups. However, it is important to note that this survey question was not a multiple-choice item; each participant was only allowed to select one symptom as their primary long COVID symptom.

Therefore, the percentages reported here should not be interpreted as the prevalence of these symptoms in the broader population, but rather as an indication of which symptoms were most commonly prioritized by participants as the most impactful.

Clinical implications of our findings

The findings of this study have important clinical and public health implications. Given that cancer survivors, particularly younger individuals, exhibit a higher prevalence of long COVID, healthcare providers should be vigilant in monitoring and managing persistent symptoms in this vulnerable population. Screening for long COVID symptoms should be integrated into routine cancer follow-up care, allowing for early intervention and supportive management. Additionally, given the differential response to COVID-19 vaccination observed in cancer survivors, clinicians should advocate for enhanced vaccination strategies tailored to this population, potentially including additional booster doses. Public health policies should also emphasize targeted outreach efforts to increase vaccine uptake and ensure equitable access to post-COVID care resources for cancer survivors. Future research should explore the underlying mechanisms driving the increased odds of long COVID in cancer survivors, as well as develop evidence-based guidelines for the long-term management of these patients.

Study Strengths and Limitations

A major strength of this study is its use of the BRFSS national dataset. The BRFSS provides a large sample size obtained through a rigorous sampling method, offering a national population representation that is unmatched by other studies. Furthermore, to the best of our knowledge, this is the first US population-based study to estimate the prevalence of long COVID among cancer survivors and compare it to that of non-cancer individuals. Additionally, we assessed the role of COVID-19 vaccination in association with long COVID among cancer survivors and conducted sensitivity analyses using multiple imputation to strengthen our findings.

However, this study also has several limitations:

First, BRFSS is a cross-sectional survey, and data were collected from a single time point, making it challenging to establish causal relationships.

Second, all exposure, outcome, and covariate data were self-reported by participants, which may introduce recall bias and misclassification of diseases.

Third, due to the large amount of missing data on cancer types in the BRFSS and the fact that some participants have multiple cancer histories, we were limited in our ability to conduct analyses specific to cancer type. Furthermore, the BRFSS does not collect lab data reflecting immunosuppression status and detailed information on medication use or cancer treatments, all of which could potentially influence long COVID risk. Additionally, the BRFSS lacks data on COVID-19 vaccine types and brands,

and the timing of COVID-19 infection, further limiting our ability to assess how these factors might influence the association of COVID-19 vaccines with long COVID among cancer survivors.

Fourth, BRFSS does not include institutionalized individuals, such as cancer patients in nursing homes or long-term care facilities, who may have a higher likelihood of long COVID. This exclusion could potentially lead to an underestimation of long COVID prevalence among cancer survivors. Moreover, given that cancer patients are at higher risk for severe outcomes from COVID-19, including death (S. Han et al., 2022; Liang et al., 2020), it is also important to consider that those who died from COVID-19 are not represented in this analysis. Therefore, the association explored in this study is specifically between cancer survivors and long COVID, and should not be generalized to all cancer patients.

Lastly, the timeframe used to define long COVID (three months) in the BRFSS may differ from definitions used in some other studies. This variation could limit the comparability of our findings.

5. Conclusions

This study provides important insights into the prevalence of long COVID among cancer survivors compared to non-cancer individuals, using data from the 2022 BRFSS. Our findings indicate that cancer survivors are observed to have higher odds of developing long COVID, particularly those under 45 years

of age. Moreover, the association of COVID-19 vaccination with long COVID appears to vary between cancer survivors and the non-cancer population, with cancer survivors requiring a higher number of vaccine doses to achieve significant reduction in the odds of long COVID.

Table 1. Sample Characteristics of Cancer Survivors and Non-cancer Participants

Variable	Cancer (n = 17,362)			Non-cancer (n = 103,296)			P-value
	Unweighted n	Weighted n	Weighted % (95% CI)	Unweighted n	Weighted n	Weighted % (95% CI)	
Age							<0.001
18–24 years	112	116,087	1.5 (1.1, 1.9)	9,491	10,632,683	15.4 (14.9, 15.9)	
25–34 years	335	299,084	3.8 (3.1, 4.6)	16,845	15,254,402	22.1 (21.6, 22.6)	
35–44 years	928	637,029	8.2 (7.1, 9.2)	19,444	13,954,353	20.2 (19.7, 20.7)	
45–54 years	2,018	1,166,922	15.0 (13.6, 16.3)	19,012	11,285,945	16.4 (15.9, 16.8)	
55–64 years	3,786	1,810,619	23.2 (21.9, 24.6)	18,201	9,743,201	14.1 (13.7, 14.5)	
65+ years	10,183	3,760,204	48.3 (46.6, 49.9)	20,303	8,102,099	11.7 (11.4, 12.1)	
	Number of missing = 0						
Sex							<0.001
Male	7,594	3,359,362	43.1 (41.5, 44.8)	47,758	32,422,151	47.0 (46.4, 47.6)	
Female	9,768	4,430,583	56.9 (55.2, 58.5)	55,538	36,550,533	53.0 (52.4, 53.6)	
	Number of missing = 0						
Race/ethnicity							<0.001
Non-Hispanic white	15,159	6,266,313	82.3 (80.7, 83.9)	70,802	37,595,154	55.8 (55.2, 56.4)	
Non-White or Hispanic	1,756	1,346,437	17.7 (16.1, 19.3)	29,902	29,756,553	44.2 (43.6, 44.8)	
	Number of missing = 3,039 (2.5%)						
Education							<0.001
High School or less	4,270	2,440,760	31.5 (29.8, 33.2)	29,329	24,691,244	35.9 (35.3, 36.5)	
Attended College or Technical School	4,899	2,598,541	33.5 (31.9, 35.1)	29,278	22,105,422	32.2 (31.6, 32.7)	
Graduated from College or Technical	8,140	2,716,731	35.0 (33.6, 36.4)	44,364	21,955,987	31.9 (31.4, 32.4)	
	Number of missing = 378 (0.3%)						
Marital Status							<0.001
Married or A member of an unmarried couple	11,167	5,214,823	67.3 (65.8, 68.8)	60,905	38,922,062	56.9 (56.3, 57.5)	
Divorced or Widowed or Separated	5,063	1,967,665	25.4 (24.1, 26.7)	19,838	10,258,447	15.0 (14.6, 15.4)	

Never married	1,045	568,214	7.3 (6.4, 8.3)	21,812	19,264,484	28.1 (27.6, 28.7)	
Number of missing = 828 (0.7%)							
Income Level							0.151
Less than \$15,000	1,791	879,320	13.7 (12.3, 15.1)	11,067	7,789,801	13.5 (13.0, 14.0)	
\$25,000 to < \$50,000	3,412	1,420,056	22.1 (20.6, 23.6)	20,358	13,739,722	23.8 (23.3, 24.4)	
\$50,000 or more	9,174	4,118,213	64.2 (62.4, 65.9)	56,315	36,118,529	62.7 (62.0, 63.3)	
Number of missing = 18,541 (15.4%)							
Health Insurance							<0.001
Have some form of insurance	16,722	7,400,373	97.7 (96.9, 98.4)	94,491	61,089,036	92.6 (92.2, 92.9)	
Do not have some form of health insurance	252	177,610	2.3 (1.6, 3.1)	5,422	4,915,818	7.4 (7.1, 7.8)	
Number of missing = 3,771 (3.1%)							
BMI							<0.001
Normal Weight or Underweight	4,598	1,970,327	26.9 (25.5, 28.4)	27,098	19,137,583	29.9 (29.3, 30.5)	
Overweight	6,055	2,636,078	36.0 (34.5, 37.6)	33,106	21,427,616	33.5 (32.9, 34.0)	
Obese	5,782	2,708,652	37.0 (35.4, 38.7)	36,547	23,470,767	36.7 (36.1, 37.2)	
Number of missing = 7,472 (6.2%)							
Smoking history							<0.001
Never smoked	9,693	4,300,456	55.5 (53.9, 57.1)	65,795	46,138,966	67.3 (66.7, 67.9)	
Current or former smoker	7,556	3,446,590	44.5 (42.9, 46.1)	36,855	22,419,219	32.7 (32.1, 33.3)	
Number of missing = 759 (0.6%)							
COPD							<0.001
Yes	2,258	1,104,008	14.2 (13.1, 15.4)	6,419	3,486,122	5.1 (4.8, 5.3)	
No	15,029	6,650,480	85.8 (84.6, 86.9)	96,524	65,232,272	94.9 (94.7, 95.2)	
Number of missing = 428 (0.4%)							
Diabetes							<0.001
Yes	3,525	1,572,817	20.2 (18.9, 21.6)	13,535	7,963,308	11.6 (11.2, 12.0)	
No	13,822	6,208,478	79.8 (78.4, 81.1)	89,613	60,881,455	88.4 (88.0, 88.8)	
Number of missing = 163 (0.1%)							

Asthma								<0.001
Current	2,240	1,051,844	13.6 (12.5, 14.8)	12,139	7,743,376	11.3 (10.9, 11.7)		
Never or former	14,973	6,656,217	86.4 (85.2, 87.5)	90,354	60,612,857	88.7 (88.3, 89.1)		
	Number of missing = 952 (0.8%)							
Heart disease								<0.001
Yes	2,808	1,194,736	15.6 (14.3, 16.8)	6,518	3,114,588	4.6 (4.3, 4.8)		
No	14,324	6,477,302	84.4 (83.2, 85.7)	96,016	65,321,110	95.4 (95.2, 95.7)		
	Number of missing = 992 (0.8%)							
Stroke								<0.001
Yes	1,222	649,356	8.4 (7.2, 9.5)	3,037	1,642,692	2.4 (2.2, 2.6)		
No	16,065	7,115,091	91.6 (90.5, 92.8)	100,047	67,175,777	97.6 (97.4, 97.8)		
	Number of missing = 287 (0.2%)							
Number of COVID-19 vaccinations received								<0.001
None	994	464,682	17.7 (15.4, 19.9)	8,731	5,704,728	24.3 (23.4, 25.1)		
One	271	102,715	3.9 (3.1, 4.7)	2,266	1,397,332	5.9 (5.5, 6.4)		
Two	1,618	660,985	25.1 (22.9, 27.4)	11,741	7,406,158	31.5 (30.6, 32.4)		
Three	2,491	913,231	34.7 (32.4, 37.1)	13,115	7,190,343	30.6 (29.7, 31.5)		
Four or more	1,498	488,335	18.6 (16.3, 20.9)	4,315	1,798,998	7.7 (7.2, 8.1)		
	Number of missing = 73,618 (61.0%)							

95% CI: 95% confidence interval

Table 2. Prevalence of Long COVID among Cancer Survivors and Non-cancer Participants

Population	Group	Unweighted n of group	Weighted n of group	Unweighted n of long COVID	Weighted n of long COVID	Weighted % (95% CI)	p-value	Crude OR (95% CI)
Overall	Cancer	17,362	7,789,945	4,009	1,868,609	24.0 (22.6, 25.4)	<0.001	1.15 (1.06, 1.24)
	Non-cancer	103,296	68,972,684	22,581	14,884,991	21.6 (21.1, 22.1)		
Age < 45	Cancer	1,375	1,052,200	432	338,106	32.1 (27.4, 36.9)	<0.001	1.75 (1.40, 2.18)
	Non-cancer	45,780	39,841,439	9,793	8,493,470	21.3 (20.6, 22.0)		
Age ≥ 45	Cancer	15,987	6,737,745	3,577	1,530,503	22.7 (21.3, 24.1)	0.324	1.05 (0.96, 1.14)
	Non-cancer	57,516	29,131,245	12,788	6,391,520	21.9 (21.2, 22.7)		

95% CI: 95% confidence interval; OR: odds ratio

Table 3. Model 1 Adjusted Odds Ratios for Long COVID in Cancer Survivors Compared to Non-Cancer Participants

Variable	Overall		Age < 45		Age ≥ 45	
	aOR (95% CI)	p-value	aOR (95% CI)	p-value	aOR (95% CI)	p-value
Cancer history						
Yes	1.17 (1.06, 1.30)	0.002	1.33 (1.07, 1.66)	0.012	1.14 (1.02, 1.27)	0.024
No	(Reference)		(Reference)		(Reference)	
Age						
18–24 years	(Reference)		(Reference)			
25–34 years	1.09 (0.96, 1.25)	0.192	1.12 (0.98, 1.29)	0.102		
35–44 years	1.11 (0.97, 1.29)	0.141	1.14 (0.98, 1.33)	0.083		
45–54 years	1.14 (0.99, 1.33)	0.073			(Reference)	
55–64 years	1.01 (0.87, 1.17)	0.873			0.88 (0.80, 0.98)	0.019
65+ years	0.78 (0.67, 0.91)	0.001			0.67 (0.60, 0.75)	<0.001
Sex						

Male	(Reference)		(Reference)		(Reference)	
Female	1.73 (1.62, 1.84)	<0.001	1.73 (1.57, 1.90)	<0.001	1.75 (1.60, 1.90)	<0.001
Race/ethnicity						
Non-Hispanic white	(Reference)		(Reference)		(Reference)	
Non-White or Hispanic	0.92 (0.86, 0.99)	0.035	0.94 (0.85, 1.04)	0.245	0.89 (0.80, 1.00)	0.040
Education						
High School or less	(Reference)		(Reference)		(Reference)	
Attended College or Technical School	1.14 (1.05, 1.24)	0.001	1.17 (1.04, 1.32)	0.010	1.12 (1.01, 1.25)	0.040
Graduated from College or Technical	0.86 (0.79, 0.93)	<0.001	0.79 (0.70, 0.89)	<0.001	0.94 (0.84, 1.06)	0.302
Marital Status						
Married or A member of an unmarried couple	(Reference)		(Reference)		(Reference)	
Divorced or Widowed or Separated	1.18 (1.08, 1.29)	<0.001	1.28 (1.10, 1.49)	0.001	1.09 (0.98, 1.21)	0.099
Never married	0.99 (0.90, 1.08)	0.781	1.03 (0.92, 1.15)	0.599	0.89 (0.73, 1.09)	0.256
Income Level						
Less than \$15,000	(Reference)					
\$25,000 to < \$50,000	0.86 (0.77, 0.96)	0.006	0.90 (0.77, 1.06)	0.195	0.82 (0.70, 0.95)	0.007
\$50,000 or more	0.77 (0.69, 0.86)	<0.001	0.87 (0.74, 1.02)	0.085	0.66 (0.57, 0.77)	<0.001
Health Insurance						
Have some form of insurance	0.82 (0.72, 0.95)	0.006	0.81 (0.69, 0.96)	0.015	0.85 (0.67, 1.08)	0.177
Do not have some form of health insurance	(Reference)					
BMI						
Normal Weight or Underweight	(Reference)		(Reference)		(Reference)	
Overweight	1.20 (1.10, 1.31)	<0.001	1.18 (1.05, 1.33)	0.007	1.24 (1.10, 1.40)	0.001
Obese	1.54 (1.42, 1.67)	<0.001	1.50 (1.34, 1.67)	<0.001	1.61 (1.42, 1.81)	<0.001
Smoking history						
Never smoked	(Reference)		(Reference)		(Reference)	
Current or former smoker	1.24 (1.16, 1.33)	<0.001	1.17 (1.06, 1.30)	0.003	1.31 (1.20, 1.42)	<0.001

95% CI: 95% confidence interval; aOR: adjusted odds ratio

Table 4. Model 2 Adjusted Odds Ratios for Long COVID in Cancer Survivors Compared to Non-Cancer Participants: CCA analysis

Variable	Overall		Cancer		Non-cancer	
	aOR (95% CI)	p-value	aOR (95% CI)	p-value	aOR (95% CI)	p-value
Cancer history						
Yes	1.24 (1.08, 1.42)	0.003				
No	(Reference)					
Number of COVID-19 vaccinations received						
None	(Reference)		(Reference)		(Reference)	
One	1.02 (0.83, 1.26)	0.860	2.18 (1.29, 3.68)	0.004	0.96 (0.77, 1.20)	0.748
Two	0.89 (0.78, 1.02)	0.092	0.81 (0.52, 1.24)	0.324	0.90 (0.78, 1.04)	0.142
Three	0.77 (0.67, 0.89)	<0.001	0.77 (0.50, 1.17)	0.221	0.77 (0.67, 0.89)	0.001
Four or more	0.75 (0.61, 0.91)	0.004	0.55 (0.34, 0.88)	0.013	0.80 (0.64, 1.00)	0.047
Age						
18–24 years	(Reference)		(Reference)		(Reference)	
25–34 years	1.12 (0.88, 1.41)	0.362	2.61 (0.70, 9.80)	0.155	1.10 (0.87, 1.40)	0.435
35–44 years	1.15 (0.90, 1.47)	0.249	1.67 (0.49, 5.72)	0.416	1.16 (0.90, 1.48)	0.258
45–54 years	1.25 (0.98, 1.61)	0.075	1.60 (0.49, 5.26)	0.441	1.28 (0.99, 1.65)	0.062
55–64 years	1.02 (0.79, 1.31)	0.898	1.56 (0.48, 5.08)	0.459	1.02 (0.78, 1.32)	0.908
65+ years	0.89 (0.69, 1.14)	0.356	1.45 (0.44, 4.74)	0.542	0.87 (0.67, 1.13)	0.296
Sex						
Male	(Reference)		(Reference)		(Reference)	
Female	1.74 (1.57, 1.93)	<0.001	1.76 (1.34, 2.31)	<0.001	1.74 (1.56, 1.95)	<0.001
Race/ethnicity						
Non-Hispanic white	(Reference)		(Reference)		(Reference)	
Non-White or Hispanic	0.91 (0.82, 1.02)	0.112	0.98 (0.68, 1.41)	0.901	0.91 (0.81, 1.02)	0.115
Education						
High School or less	(Reference)		(Reference)		(Reference)	
Attended College or Technical School	1.14 (1.01, 1.30)	0.035	1.09 (0.80, 1.48)	0.600	1.16 (1.01, 1.32)	0.035
Graduated from College or Technical	0.94 (0.82, 1.07)	0.336	0.91 (0.66, 1.25)	0.552	0.94 (0.82, 1.09)	0.411

Marital Status

Married or A member of an unmarried couple	(Reference)		(Reference)		(Reference)	
Divorced or Widowed or Separated	1.08 (0.94, 1.23)	0.271	1.03 (0.74, 1.42)	0.881	1.08 (0.94, 1.25)	0.283
Never married	1.06 (0.91, 1.23)	0.483	0.95 (0.52, 1.73)	0.859	1.06 (0.91, 1.24)	0.438

Income Level

Less than \$15,000	(Reference)		(Reference)		(Reference)	
\$25,000 to < \$50,000	0.96 (0.82, 1.13)	0.629	1.07 (0.69, 1.64)	0.766	0.96 (0.80, 1.14)	0.605
\$50,000 or more	0.84 (0.71, 0.98)	0.028	0.72 (0.45, 1.15)	0.166	0.86 (0.72, 1.02)	0.073

Health Insurance

Have some form of insurance	0.76 (0.61, 0.94)	0.013	0.45 (0.22, 0.92)	0.029	0.77 (0.61, 0.96)	0.022
Do not have some form of health insurance	(Reference)		(Reference)		(Reference)	

BMI

Normal Weight or Underweight	(Reference)		(Reference)		(Reference)	
Overweight	1.23 (1.07, 1.41)	0.004	1.36 (0.95, 1.93)	0.091	1.21 (1.05, 1.41)	0.010
Obese	1.55 (1.36, 1.77)	<0.001	1.81 (1.27, 2.59)	0.001	1.52 (1.32, 1.75)	<0.001

Smoking history

Never smoked	(Reference)		(Reference)		(Reference)	
Current or former smoker	1.22 (1.10, 1.35)	<0.001	1.43 (1.13, 1.81)	0.003	1.19 (1.06, 1.33)	0.003

CCA: complete case analysis; 95% CI: 95% confidence interval; aOR: adjusted odds ratio

Table 5. Long COVID Primary Symptoms of Cancer Survivors and Non-cancer Participants

Symptom	Cancer (n = 3,846)			Non-cancer (n = 21,557)			Overall test	Post hoc test	
	Unweighted	Weighted	Weighted %	Unweighted	Weighted	Weighted %	p-value	p-value	Adjusted p-value
	n	n	(95% CI)	n	n	(95% CI)			
Tiredness or fatigue	1,205	519,450	28.9 (26.0, 31.9)	5,813	3,669,707	25.8 (24.7, 26.9)		0.043	0.469
Difficulty thinking or concentrating or forgetfulness/memory problems (sometimes referred to as 'brain fog')	350	174,914	9.7 (7.5, 12.0)	2,200	1,398,836	9.8 (9.0, 10.6)		0.944	1.000
Difficulty breathing or shortness of breath	742	373,323	20.8 (17.7, 23.9)	4,003	2,648,646	18.6 (17.6, 19.6)		0.169	1.000
Joint or muscle pain	184	98,290	5.5 (4.2, 6.7)	1,183	902,072	6.3 (5.6, 7.0)	0.021	0.260	1.000
Fast-beating or pounding heart (also known as heart palpitations) or chest pain	83	36,090	2.0 (1.4, 2.6)	636	431,192	3.0 (2.6, 3.5)		0.012	0.133
Dizziness on standing	75	31,550	1.8 (1.1, 2.4)	330	222,363	1.6 (1.2, 2.0)		0.603	1.000
Depression, anxiety, or mood changes	26	11,306	0.6 (0.3, 1.0)	294	216,627	1.5 (1.2, 1.9)		0.003	0.037
Symptoms that get worse after physical or mental activities	31	12,493	0.7 (0.3, 1.1)	207	133,134	0.9 (0.7, 1.1)		0.304	1.000

You did not have any long-term symptoms that limited your activities.	201	90,283	5.0 (3.9, 6.2)	1,147	745,935	5.2 (4.7, 5.8)	0.742	1.000
Loss of taste or smell	547	262,960	14.7 (12.2, 17.1)	3,661	2,465,452	17.3 (16.3, 18.3)	0.060	0.664
Some other symptoms	402	184,287	10.3 (8.4, 12.1)	2,083	1,394,055	9.8 (8.9, 10.7)	0.650	1.000

Number of missing = 1,187 (4.5%); 95% CI: 95% confidence interval

Chapter 5: Manuscript 3: Multimorbidity and Long COVID: Evidence from a Nationally Representative U.S. Survey

Abstract

Background: Long COVID presents ongoing challenges to public health, particularly among individuals with pre-existing chronic health conditions (CHCs). This study investigates the association between ten CHCs and long COVID using nationally representative U.S. survey data, examining associations at the individual, cumulative, and pattern-based levels.

Methods: We analyzed 2023 Behavioral Risk Factor Surveillance System (BRFSS) national data, focusing on ten CHCs: heart attack, coronary heart disease (CHD), stroke, current asthma, cancer, chronic obstructive pulmonary disease (COPD), depressive disorder, kidney disease, arthritis, and diabetes. Weighted logistic regression models were used to estimate adjusted odds ratios (aORs) for long COVID associated with each CHC. CHC burden was categorized into four groups (0, 1, 2, ≥ 3) to assess dose-response relationships. Additionally, Latent Class Analysis (LCA) was used to identify distinct multimorbidity patterns. We also examined whether COVID-19 vaccination was associated with reduced long COVID risk across different multimorbidity groups.

Results: Among 197,943 eligible participants, the prevalence of long COVID in the United States in 2023 is 13.8% (95% CI = 13.4-14.1). All ten CHCs were significantly associated with increased odds of long COVID, with the strongest

associations observed for COPD (aOR = 2.37, 95% CI = 2.11-2.66), asthma (aOR = 1.95, 95% CI = 1.79-2.13), and CHD (aOR = 1.78, 95% CI = 1.55-2.05). A clear dose-response relationship was observed, with aORs increasing from 1.47 (95% CI = 1.35-1.61) for one CHC to 3.30 (95% CI = 2.95-3.69) for three or more. LCA identified four distinct multimorbidity clusters, all significantly associated with long COVID—particularly the Severe Multimorbidity Cluster (aOR = 3.46, 95% CI = 2.91-4.10) and the Mental-Respiratory Cluster (aOR = 2.65, 95% CI = 2.38-2.95). In most multimorbidity groups, COVID-19 vaccination was not significantly associated with reduced odds of long COVID.

Conclusions: This study not only demonstrates that each of the ten CHCs is associated with increased odds of long COVID, but also highlights that individuals with multimorbidity face an even greater health burden. Notably, individuals with severe multimorbidity and those with respiratory and mental health conditions may face the highest burden. Targeted prevention and management strategies are critical for mitigating long COVID's impact among high-risk groups.

Keywords:

Chronic Health Conditions; Long COVID; Multimorbidity; Latent Class Analysis; BRFSS; COVID-19 vaccination.

1. Introduction

The COVID-19 pandemic has had a lasting impact on global public health (Weinberger et al., 2020; Woolf et al., 2020). While most individuals recover from the acute phase of SARS-CoV-2 infection, a significant subset continues to experience persistent symptoms, commonly known as long COVID (Taquet et al., 2021). Long COVID is defined as a chronic condition that occurs after SARS-CoV-2 infection and is present for at least 3 months (WHO, 2022). It affects a substantial number of COVID-19 survivors, placing considerable strain on healthcare systems, communities, and individuals (C. Chen et al., 2022; Soriano et al., 2022; Subramanian et al., 2022). As long COVID continues to affect millions worldwide, understanding its risk factors has become a critical priority for public health and clinical management (Greenhalgh et al., 2024; Koc et al., 2022).

Previous studies have identified several potential risk factors for long COVID, including older age, female sex, and severe acute COVID-19 infection (Greenhalgh et al., 2024; Yong, 2021). Emerging evidence suggests that individuals with pre-existing chronic health conditions (CHCs) may also be at heightened risk (Greenhalgh et al., 2024). CHCs, also known as chronic diseases, are defined broadly as conditions lasting one year or more that require ongoing medical care or limit daily activities, encompass a wide range of diseases, such as heart disease, cancer, and diabetes (CDC, 2024a). In addition to being the leading causes of death and disability in the United States, CHCs impose a substantial burden on the healthcare system, contributing to

an estimated \$4.5 trillion in annual health care costs (CDC, 2024a, 2024d).

With increasing life expectancy and the bidirectional relationships among many CHCs, a substantial proportion of individuals experience multiple coexisting conditions rather than a single disease (Álvarez-Gálvez et al., 2023; Kitsis et al., 2018; Pundole & Suarez-Almazor, 2020; Ritchie & Abel, 2020; Surve et al., 2024). In the United States, six in ten adults have at least one chronic disease, and four in ten have two or more (CDC, 2024a). The presence of multiple CHCs not only elevates the risk of adverse health outcomes but also reduces quality of life and imposes a greater burden on healthcare resources (Huang et al., 2023). For individuals recovering from COVID-19, the potential post-infection consequences of multimorbidity are particularly concerning. While existing studies have examined the associations between individual chronic diseases—such as COPD, cancer, and diabetes—and long COVID (Erinoso et al., 2024; Steenblock et al., 2022; L. Wang & Yang, 2025), little is known about whether having multiple CHCs further increases susceptibility to long COVID or how distinct multimorbidity patterns influence long COVID risk.

To address these gaps, we utilized nationally representative data from the 2023 Behavioral Risk Factor Surveillance System (BRFSS) to comprehensively examine the association between CHCs and long COVID from three perspectives: (1) individual CHCs, (2) cumulative CHC burden, and (3) multimorbidity patterns identified via Latent Class Analysis (LCA). Additionally, we examined whether COVID-19 vaccination was associated with reduced long

COVID risk across different multimorbidity groups.

By elucidating the relationship between CHCs and long COVID, this study provides important insights into the additional health risks faced by individuals with pre-existing chronic conditions following COVID-19 infection. Furthermore, our findings help identify potentially vulnerable populations, inform targeted prevention strategies, and enhance the broader understanding of long COVID susceptibility in individuals with multimorbidity.

2. Methods

2.1. Data Source and population

This study utilized data from the 2023 BRFSS, a nationally representative, cross-sectional telephone survey conducted annually across the United States. The BRFSS collects national- and state-level data on health-related risk behaviors, chronic health conditions, and the utilization of preventive services among non-institutionalized adults aged 18 years and older.

The survey is coordinated by the Centers for Disease Control and Prevention (CDC) and implemented by health departments in all 50 states, the District of Columbia, and three U.S. territories. Participants are selected through a random digit dialing method, ensuring a random and representative sampling of the U.S. adult population. Trained interviewers administer a standardized questionnaire that encompasses a broad range of health-related topics.

For this analysis, the study population was restricted to individuals who

reported a history of COVID-19 infection. Participants were identified based on their response to the question: "Have you ever tested positive for COVID-19 (using a rapid point-of-care test, self-test, or laboratory test) or been told by a doctor or other health care provider that you have or had COVID-19?" Those who answered "Yes" were included in the study sample. Additionally, only participants with complete data on the primary outcome variable, long COVID, and with at least one non-missing value among the 10 CHCs variables were retained for statistical analysis.

This study was exempt from Institutional Review Board (IRB) review as it relied exclusively on publicly available, de-identified secondary data.

2.2. Exposure: Chronic Health Conditions

From the Chronic Health Conditions section of the 2023 BRFSS, we identified ten CHCs for analysis: heart attack, coronary heart disease (CHD), stroke, current asthma, cancer, chronic obstructive pulmonary disease (COPD), depressive disorder, kidney disease, arthritis, and diabetes. Each CHC was assessed as a binary variable (Yes/No).

To evaluate the association between CHCs and long COVID, we employed three different analytical approaches:

1. Individual CHCs: Each of the ten CHCs was analyzed separately to estimate its association with long COVID.

2. **Cumulative CHC Score:** A composite score was generated by summing the total number of CHCs reported by each participant. Based on this score, participants were categorized into four groups: no CHC (0), one CHC (1), two CHCs (2), and three or more CHCs (≥ 3). This classification allowed for an assessment of the dose-response relationship between multimorbidity and long COVID risk.
3. **Latent classes of CHCs:** We applied LCA to identify distinct patterns of CHC co-occurrence and assess their association with long COVID.

2.3. Outcome: Long COVID

The primary outcome variable in this study was current long COVID, defined based on participants' responses to the question: "Do you currently have symptoms lasting 3 months or longer that you did not have prior to having coronavirus or COVID-19?" Participants who responded "Yes" were classified as having long COVID, while those who responded "No" were classified as not having long COVID. Any responses other than "Yes" or "No" were treated as missing data and excluded from the analysis.

2.4. Covariates

This study adjusted for a range of covariates, including age, sex, race/ethnicity, education, marital status, income level, health insurance, body mass index (BMI), smoking history. All covariates were treated as categorical

variables, with categories defined as follows:

- Age: 18–24 / 25–34 / 35–44 / 45–54 / 55–64 / 65+ years
- Sex: Male / Female
- Race: Non-Hispanic White / Non-White or Hispanic
- Education: High School or Less / Attended College or Technical School / Graduated from College or Technical
- Marital Status: Married or Member of an Unmarried Couple / Divorced, Widowed, or Separated / Never Married
- Income Level: Less than \$15,000 / \$25,000 to < \$50,000 / \$50,000 or more
- Health Insurance: Have some form of insurance / Do not have some form of health insurance
- BMI: Healthy Weight or Underweight (less than 25) / Overweight (25 to less than 30) / Obese (30 or greater)
- Smoking History: Never Smoked / Current or Former Smoker

Because not all states collected information on the number of COVID-19 vaccinations received, the proportion of missing data for this variable is quite high (67.4%). Moreover, there is currently no solid evidence that COVID-19 vaccinations can cause chronic diseases, so this variable was not considered as a confounding factor. Therefore, we didn't adjust for COVID-19 vaccinations regarding the associations between CHCs and long COVID. Instead, we

examined whether COVID-19 vaccination was associated with reduced long COVID risk across different multimorbidity groups.

The variable for the number of COVID-19 vaccinations received was derived from two questions: "Have you received at least one dose of a COVID-19 vaccination?" and the follow-up question, "How many COVID-19 vaccinations have you received?" Participants who had missing data for the first question, as well as those who answered "Yes" to the first question but did not provide a valid response to the second question, were categorized as having missing data for this covariate. The categories for the number of COVID-19 vaccinations received are as follows: None / One / Two / Three / Four / Five or More.

2.5. Statistical Methods

Data were weighted following standard BRFSS analytical procedures to account for nonresponse bias and ensure the generalizability of the results. Categorical variables were summarized using weighted frequencies and percentages. The pairwise correlations among the ten CHCs were assessed using weighted phi correlation coefficients. Comparisons between exposed and unexposed groups regarding outcome and covariate distributions were conducted using Rao-Scott chi-square tests. To estimate the association between CHCs and long COVID, both crude and adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were reported. We also examined whether

COVID-19 vaccination was associated with reduced long COVID risk across different multimorbidity groups.

To identify distinct CHC co-occurrence patterns, we applied LCA, assigning participants to mutually exclusive latent classes based on the ten CHCs. The mixture model structure was specified as complex to account for the BRFSS complex survey design. We fitted a series of LCA models, starting with a two-class model and sequentially increasing the number of classes up to ten. The optimal number of latent classes was determined using the Vuong-Lo-Mendell-Rubin (VLMR) likelihood ratio test and the Lo-Mendell-Rubin (LMR) adjusted likelihood ratio test. A non-significant p-value ($p > 0.05$) in these tests indicated that adding an additional class did not significantly improve model fit, favoring the previous ($n-1$) class model. Additional model selection criteria included the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), sample size-adjusted BIC (aBIC), and entropy, which provided complementary insights into model fit.

LCA models were estimated using Mplus 8.3, while all other statistical analyses were performed using SAS 9.4. A significance level of 0.05 was applied for all statistical tests.

3. Results

3.1. Latent Class Analysis of CHCs

A total of 197,943 participants were included in this study. Table 1 presents

the model fit statistics for LCA models ranging from two to ten latent classes. The VLMR likelihood ratio test and the LMR adjusted likelihood ratio test indicated that the five-class model provided a significantly better fit than the four-class model ($p = 0.033$ and $p = 0.035$, respectively). However, the addition of a sixth class did not result in a significant improvement in model fit ($p = 0.609$ and $p = 0.611$). Therefore, the five-class solution was selected as the optimal model. Figure 1 illustrates the trends in AIC, BIC, and aBIC as the number of classes increased. The distribution of each latent class, along with other sample characteristics, is presented in Table 2. Figure 2 shows the pairwise weighted phi correlation coefficients among the ten CHCs. Figure 3 illustrates the response probabilities for each of the five latent classes across the ten CHCs:

- **Class 1: Severe Multimorbidity Cluster**

This class is characterized by high probabilities of exposure to all ten CHCs, indicating a severe chronic disease burden. Individuals in this class are likely to experience multiple coexisting chronic conditions.

- **Class 2: Mental-Respiratory Cluster**

This class exhibits elevated probabilities of depressive disorder (57.1%) and current asthma (59.4%). It also has a higher probability of COPD (25.8%) compared to other classes, except for the Severe Multimorbidity Cluster. This group primarily represents individuals with mental health conditions and respiratory diseases.

- **Class 3: Cardio-Metabolic Cluster**

This class is characterized by relatively high probabilities of cardiovascular diseases, including heart attack (70.8%), CHD (51.0%), and stroke (15.6%). Additionally, this class has a notable probability of diabetes (37.4%), second only to the Severe Multimorbidity Cluster. These findings suggest that this group is primarily composed of individuals with cardiovascular and metabolic disorders.

- **Class 4: Cancer-Arthritis Cluster**

This class exhibits a relatively high probability of cancer (27.5%) and arthritis (60.3%), second only to the Severe Multimorbidity Cluster. This class likely represents individuals who experience immune dysfunction and chronic inflammation.

- **Class 5: Low CHC Burden Cluster**

This class is characterized by consistently low probabilities of exposure to all CHCs, indicating minimal chronic health burden. Individuals in this group represent the healthiest segment of the study population.

3.2. Sample Characteristics Across Latent Classes

Table 3 presents the distribution of sample characteristics across the five latent CHC classes. Regarding the number of CHCs, The Low CHC Burden Cluster exhibited the lowest burden of chronic health conditions, with 58.5% of individuals reporting no CHCs, 38.9% having only one CHC, and 2.6% having two CHCs. Notably, none of the individuals in this class had three or more CHCs.

In contrast, the Severe Multimorbidity Cluster demonstrated the highest disease burden, with all individuals (100%) reporting at least three coexisting CHCs. The remaining three clusters fell between these two extremes, with the majority of individuals having at least two chronic conditions. Specifically, in the Mental-Respiratory Cluster, 48.8% had two CHCs, while 50.8% had three or more; In the Cardio-Metabolic Cluster, 28.5% had two CHCs, whereas 70.6% had three or more; In the Cancer-Arthritis Cluster 62.2% had two CHCs, while 31.3% had three or more.

Age distributions varied across the latent classes. The Severe Multimorbidity Cluster, Cardio-Metabolic Cluster, and Cancer-Arthritis Cluster had a higher proportion of older adults, compared to the Low CHC Burden Cluster. The Mental-Respiratory Cluster exhibited a slightly higher proportion of middle-aged and older individuals than the Low CHC Burden Cluster, but their overall age distributions remained similar.

Sex distribution also differed across the classes. The Severe Multimorbidity Cluster, Mental-Respiratory Cluster, and Cancer-Arthritis Cluster had a higher proportion of females. In contrast, the Cardio-Metabolic Cluster had a higher proportion of males.

Although variations existed in the remaining sample characteristics among the four Multimorbidity clusters, they exhibited consistent trends when compared to the Low CHC Burden Cluster: Individuals in these four clusters were more likely to be non-Hispanic White, had lower levels of education,

reported lower income levels, and had a higher proportion of being divorced, widowed, or separated. In addition, they had higher proportion of health insurance coverage, exhibited a higher prevalence of overweight and obesity, as well as higher proportion of smoking history.

3.3. Prevalence of Long COVID Across Groups

The overall prevalence of long COVID in the United States in 2023 is 13.8% (95% CI = 13.4-14.1). Table 4 shows that individuals with each of the ten CHCs have a significantly higher prevalence of long COVID than those without the respective condition. These differences were statistically significant for all CHCs (Table 4). Specifically, the prevalence of long COVID ranged from 15.2% (95% CI: 14.0–16.3) among individuals with cancer to 29.0% (95% CI: 27.3–30.8) among those with COPD.

For cumulative CHC score, there is a clear dose-response relationship between the number of CHCs and long COVID prevalence. Participants with no CHC exposure had the lowest prevalence of long COVID at 9.3% (95% CI: 8.9–9.8). As the number of CHCs increased, the prevalence rose progressively: 13.8% (95% CI: 13.1–14.4) among those with one CHC, 18.0% (95% CI: 17.0–19.1) among those with two CHCs, and 26.0% (95% CI: 24.8–27.1) among those with three or more CHCs. These differences were statistically significant ($p < 0.001$).

When analyzing latent CHC classes, the Severe Multimorbidity Cluster had

the highest prevalence of long COVID at 32.8% (95% CI: 29.7–35.8), followed closely by the Mental-Respiratory Cluster at 28.2% (95% CI: 26.6–29.8). The Cancer-Arthritis Cluster exhibited a moderate prevalence of 18.3% (95% CI: 17.3–19.4), while the Cardio-Metabolic Cluster had a slightly lower prevalence at 16.3% (95% CI: 14.3–18.2). The Low CHC Burden Cluster had the lowest long COVID prevalence at 11.2% (95% CI: 10.8–11.6). These differences were also statistically significant ($p < 0.001$).

3.4. Association Between CHCs and Long COVID

Table 5 presents the unadjusted and adjusted ORs with corresponding 95% CIs for the association between CHCs and long COVID. The results indicate that individual CHCs, cumulative CHC score, and latent CHC classes are all significantly associated with increased odds of long COVID, even after adjusting for all covariates.

Participants exposed to each of the individual CHCs had higher odds of long COVID compared to their unexposed counterparts, with all associations remaining statistically significant (Table 5). COPD exhibited the strongest association with long COVID (aOR = 2.37, 95% CI: 2.11–2.66, $p < 0.001$), followed by current asthma (aOR = 1.95, 95% CI: 1.79–2.13, $p < 0.001$) and CHD (aOR = 1.78, 95% CI: 1.55–2.05, $p < 0.001$), both of which also demonstrated strong positive associations with long COVID.

A dose-response relationship was observed between cumulative CHC

burden and long COVID. Compared to participants with no CHC exposure, participants with one CHC had an aOR of 1.47 (95% CI: 1.35–1.61, $p < 0.001$), while those with two CHCs had an aOR of 2.13 (95% CI: 1.89–2.39, $p < 0.001$). Participants with three or more CHCs had the highest risk, with an aOR of 3.30 (95% CI: 2.95–3.69, $p < 0.001$).

The results from the LCA further support these findings. Compared to participants in the Low CHC Burden Cluster, the Severe Multimorbidity Cluster had the highest odds of long COVID (aOR = 3.46, 95% CI: 2.91–4.10, $p < 0.001$). The Mental-Respiratory Cluster had the second-highest odds (aOR = 2.65, 95% CI: 2.38–2.95, $p < 0.001$). Participants in the Cancer-Arthritis Cluster (aOR = 1.82, 95% CI: 1.62–2.05, $p < 0.001$) and the Cardio-Metabolic Cluster (aOR = 1.61, 95% CI: 1.34–1.94, $p < 0.001$) also had significantly elevated odds of long COVID.

3.5. The associations between COVID-19 vaccine and long COVID

Table 6 presents the aORs for the association between the number of COVID-19 vaccine doses and the odds of long COVID, stratified by cumulative CHC burden and latent CHC classes.

For cumulative CHC burden, significant associations between vaccination and reduced odds of long COVID were observed in several subgroups. Among individuals with no chronic conditions, receiving three doses (aOR = 0.71, 95% CI: 0.55–0.93, $p = 0.013$) or four doses (aOR = 0.68, 95% CI: 0.48–0.97, $p =$

0.034) was significantly associated with lower odds of long COVID. In individuals with one CHC, both four doses (aOR = 0.68, 95% CI: 0.49–0.94, $p = 0.019$) and five doses (aOR = 0.63, 95% CI: 0.42–0.95, $p = 0.026$) were similarly associated with reduced odds. Among those with three or more CHCs, only receiving five doses was significantly associated with reduced long COVID odds (aOR = 0.60, 95% CI: 0.37–0.96, $p = 0.034$). In the subgroup with exactly two CHCs, no statistically significant association between vaccine dose and long COVID risk was observed.

For latent CHC classes, significant associations were found only in the Low CHC Burden Cluster, where receiving four doses (aOR = 0.68, 95% CI: 0.53–0.87, $p = 0.002$) or five doses (aOR = 0.69, 95% CI: 0.51–0.92, $p = 0.012$) was linked to lower odds of long COVID. No significant associations were identified between vaccination and long COVID in the other multimorbidity clusters.

4. Discussion

This study provides comprehensive evidence on the relationship between CHCs and long COVID using nationally representative data from the 2023 BRFSS. Our findings demonstrate that CHCs are significantly associated with increased odds of long COVID, and this relationship is evident at multiple levels—individual CHCs, cumulative CHC burden, and multimorbidity patterns identified via LCA. Notably, the impact of some CHCs on long COVID risk varied by age, with younger adults experiencing stronger associations compared to

older adults.

Key Findings

At the individual CHC level, all ten chronic conditions examined were associated with significantly higher odds of long COVID, a finding that aligns with prior research suggesting potential links between these diseases and long COVID risk (Erinoso et al., 2024; Greenhalgh et al., 2024; Hejazian et al., 2024; Hung et al., 2024; Song & Giuriato, 2023; Steenblock et al., 2022; Tsampasian et al., 2024; L. Wang & Yang, 2025; Yong, 2021). Unlike previous studies that often focused on single chronic conditions, our study simultaneously assessed all ten CHCs within the same population, allowing for a direct comparison of their relative associations with long COVID. Among these conditions, COPD (aOR = 2.37, 95% CI = 2.11-2.66) and asthma (aOR = 1.95, 95% CI = 1.79-2.13) exhibited the strongest associations after adjusting for covariates. There is evidence that the lungs are among the most affected organs in COVID-19 infection (Torres-Castro et al., 2021). Patients with COVID-19 often experience pulmonary dysfunction, and the infection may exacerbate pre-existing respiratory conditions such as COPD and asthma, leading to more severe and prolonged post-infection complications (Chiner-Vives et al., 2022; Torres-Castro et al., 2021). Our findings reinforce this notion, suggesting that individuals with pre-existing lower respiratory diseases may bear a substantially greater health burden following COVID-19 infection

A clear dose-response relationship was observed between the number of CHCs and the odds of long COVID, indicating that individuals with a greater number of chronic conditions face a progressively higher risk. Specifically, compared to individuals with no CHCs, those with three or more conditions had more than threefold higher odds of long COVID (aOR = 3.30, 95% CI = 2.95-3.69). This magnitude of association exceeds that observed for any individual CHC, highlighting the cumulative burden imposed by multimorbidity. Previous studies have shown that both the type and number of coexisting chronic conditions can exacerbate the negative consequences of multimorbidity, including a reduction in health-related quality of life (Pefoyo et al., 2015). In addition, there is evidence that patients with multiple pre-existing conditions are at the highest risk for severe COVID-19 outcomes (Pietzner et al., 2024). Our findings build upon this literature by demonstrating that multimorbidity not only worsens acute outcomes but also contributes to the long-term health burden faced by COVID-19 survivors.

LCA identified one Low CHC Burden Cluster and four distinct multimorbidity clusters: the Severe Multimorbidity Cluster, Mental-Respiratory Cluster, Cardio-Metabolic Cluster, and Cancer-Arthritis Cluster. The Severe Multimorbidity Cluster was characterized by high probabilities across all ten CHCs, with every individual in this group having at least three chronic conditions. The Mental-Respiratory Cluster exhibited elevated probabilities of depressive disorder, along with the two respiratory conditions asthma and COPD. This pattern is

consistent with previous research documenting a bidirectional relationship between depression and chronic lower respiratory diseases (Rubin, 1993; Yohannes & Alexopoulos, 2014). The Cardio-Metabolic Cluster was defined by high probabilities of cardiovascular diseases and diabetes, a combination supported by extensive literature highlighting the strong interconnection between these conditions (Balakumar et al., 2016; Cole & Florez, 2020; Glovaci et al., 2019). Notably, this cluster also showed elevated probabilities of cancer and kidney disease, which is consistent with prior studies suggesting cross-linkages among these four conditions (I. Ahmad et al., 2023; Boudoulas et al., 2022; Koye et al., 2018; Laffin & Bakris, 2021; Malyszko et al., 2020). The Cancer-Arthritis Cluster was marked by relatively high probabilities of cancer and arthritis. The co-occurrence of these conditions may stem not only from shared risk factors (Cho et al., 2024), but also from treatment-related complications. For instance, immunosuppressive therapies used to manage rheumatoid arthritis may increase cancer risk (Cho et al., 2024), while immune checkpoint inhibitors for cancer treatment have been linked to inflammatory arthritis (Huss et al., 2023).

All four multimorbidity clusters were significantly associated with increased odds of long COVID. The Severe Multimorbidity Cluster exhibited the highest risk (aOR = 3.46, 95% CI = 2.91-4.10), closely mirroring the findings from the cumulative CHC analysis, where individuals with three or more CHCs had an aOR of 3.30 (95% CI = 2.95-3.69). This consistency suggests that individuals

with extensive multimorbidity represent the most vulnerable subgroup in terms of long COVID susceptibility. The Mental-Respiratory Cluster had the second-highest risk of long COVID (aOR = 2.65, 95% CI = 2.38-2.95), aligning with the individual CHC analysis in which COPD (aOR = 2.37, 95% CI = 2.11-2.66) and asthma (aOR = 1.95, 95% CI = 1.79-2.13) were among the conditions most strongly associated with long COVID. These findings further emphasize the substantial post-COVID burden faced by individuals with chronic lower respiratory diseases. Interestingly, while 50.8% of individuals in the Mental-Respiratory Cluster had three or more CHCs, this proportion was even higher in the Cardio-Metabolic Cluster (70.6%). However, the Cardio-Metabolic Cluster exhibited a lower adjusted odds ratio (aOR = 1.61, 95% CI = 1.34-1.94) than the Mental-Respiratory Cluster, suggesting that the specific type of chronic conditions—not merely the number—plays a critical role in long COVID risk. In particular, the presence of chronic respiratory conditions, which directly affect the organ system most impacted by SARS-CoV-2, may confer disproportionately high risk, even when cumulative CHC burden is similar or lower.

Finally, we examined the association between the number of COVID-19 vaccine doses and the odds of long COVID across different levels of cumulative CHC burden and latent CHC classes. Among individuals with no chronic conditions, receiving three or four vaccine doses was significantly associated with reduced odds of long COVID. In those with one CHC and in the Low CHC

Burden Cluster, receiving four or more doses was similarly associated with lower odds. Among individuals with three or more CHCs, a significant reduction in long COVID risk was observed only among those who received five doses. No significant associations were found in other cumulative CHC categories or latent classes. These findings may be partly explained by diminished vaccine-induced immune responses in individuals with certain chronic conditions. For example, patients with chronic kidney disease often exhibit immune system dysfunction, which can impair the effectiveness of vaccine-induced immunity (Rossi et al., 2023). Polivka et al. reported that individuals with COPD showed reduced vaccine effectiveness against SARS-CoV-2 infection and hospitalization (Polivka et al., 2023). Ford et al. suggested that depression may contribute to reduced COVID-19 vaccine immunogenicity (Ford & Savitz, 2022). Similarly, Seneviratne et al. found that vaccine-induced immunogenicity was significantly lower in patients with cancer compared to healthy individuals, attributing this to disease-related immune dysfunction and treatment-induced immunosuppression (Seneviratne et al., 2022). On the other hand, for most CHC categories and latent classes, we observed a downward trend in the point estimates (aORs) with increasing vaccine doses, even when not statistically significant. This pattern suggests that receiving additional COVID-19 vaccine doses may be associated with a reduced risk of long COVID, although further research is needed to confirm this relationship.

Clinical implications of our findings

The findings of this study have important clinical implications for the management of patients with chronic health conditions in the context of long COVID. Given the observed strong association between cumulative CHC burden and long COVID, healthcare providers should actively assess and monitor individuals with multimorbidity for persistent post-COVID symptoms. Special attention should be directed toward patients in high-risk multimorbidity clusters, such as the Severe Multimorbidity Cluster and the Mental-Respiratory Cluster, who demonstrated the highest odds of long COVID. The clinical burden of long COVID in individuals with pre-existing CHCs may further accelerate disease progression and negatively impact quality of life. We recommend that routine follow-up care for patients with chronic conditions include screening for long COVID symptoms, allowing for early detection and timely referral to appropriate supportive care.

In addition, our findings raise concerns about the attenuated association between COVID-19 vaccination and reduced long COVID risk among individuals with multimorbidity burden. Nevertheless, clinicians should continue to encourage booster vaccination, as it remains a key strategy in preventing SARS-CoV-2 infection.

Study Strengths and Limitations

This study has several notable strengths. First, it utilizes a large, nationally

representative dataset, which enhances the generalizability of the findings to the U.S. adult population. In addition, the study simultaneously evaluates individual CHCs, cumulative disease burden, and multimorbidity patterns, providing a comprehensive understanding of the relationship between chronic conditions and long COVID.

However, several limitations should be acknowledged. First, the cross-sectional design of the BRFSS precludes causal inference. Although the 2023 BRFSS collects data on current long COVID status, which partially mitigates concerns about temporality, the exact timing of CHC onset and SARS-CoV-2 infection remains unknown. Second, all variables were self-reported, which may introduce recall bias and misclassification. Additionally, the BRFSS lacks detailed clinical information, such as acute infection severity, medication use, and vaccine type, which could influence long COVID risk. Finally, because the BRFSS only samples the non-institutionalized adult population, it excludes individuals residing in long-term care facilities—a group likely to have higher multimorbidity risk.

5. Conclusions

Using nationally representative data, this study demonstrates that chronic health conditions—especially when multiple conditions co-occur—are strongly associated with increased odds of long COVID. The risk is not only cumulative but also influenced by the specific configuration of chronic conditions, with

certain multimorbidity clusters showing disproportionately elevated risks. In most multimorbidity groups, no association was observed between COVID-19 vaccination and reduced odds of long COVID, highlighting the need for further research. These results have important implications for long COVID prevention and chronic disease management in the post-pandemic era. Tailored public health strategies and clinical follow-up are warranted for individuals with pre-existing health conditions, especially those with complex multimorbidity patterns.

Table 1. Model fit statistics for LCA models ranging from two to ten latent classes

# of Class	AIC	BIC	aBIC	Entropy	VLMR p-value	LMR p-value
2	1113638.852	1113852.962	1113786.223	0.709	<0.001	<0.001
3	1106846.502	1107172.766	1107071.069	0.699	<0.001	<0.001
4	1102923.295	1103361.712	1103225.056	0.625	<0.001	<0.001
5	1100957.017	1101507.587	1101335.972	0.676	0.033	0.035
6	1100237.888	1100900.611	1100694.038	0.612	0.609	0.611
7	1099448.299	1100223.175	1099981.644	0.552	0.129	0.130
8	1099162.506	1100049.535	1099773.045	0.598	0.820	0.821
9	1098896.252	1099895.434	1099583.986	0.628	0.665	0.665
10	1098753.753	1099865.088	1099518.682	0.613	0.221	0.221

Table 2. Descriptive statistics of study sample from BRFSS Data 2023

Variable	Unweighted n	Weighted n	Weighted % (95% CI)
Latent Classes of CHCs			
Severe Multimorbidity Cluster	4,296	1,982,327	1.7 (1.6, 1.8)
Mental-Respiratory Cluster	13,554	7,712,879	6.5 (6.3, 6.7)
Cardio-Metabolic Cluster	6,950	3,091,361	2.6 (2.5, 2.8)
Cancer-Arthritis Cluster	35,550	16,225,881	13.7 (13.4, 14.0)
Low CHC Burden Cluster	137,593	89,352,004	75.5 (75.1, 75.9)
Number of missing = 0			
Cumulative CHCs score			
0 CHC	74,917	52,247,033	44.1 (43.7, 44.6)
1 CHC	60,323	35,890,386	30.3 (29.9, 30.8)
2 CHCs	33,835	17,060,212	14.4 (14.1, 14.7)
≥3 CHCs	28,868	13,166,821	11.1 (10.9, 11.4)
Number of missing = 0			
Heart Attack			

Yes	9,112	4,237,631	3.6 (3.4, 3.8)
No	188,106	113,626,125	96.4 (96.2, 96.6)
Number of missing = 725 (0.4%)			
CHD			
Yes	9,665	4,328,475	3.7 (3.5, 3.8)
No	186,890	113,308,597	96.3 (96.2, 96.5)
Number of missing = 1388 (0.7%)			
Stroke			
Yes	6,788	3,278,504	2.8 (2.6, 2.9)
No	190,714	114,841,887	97.2 (97.1, 97.4)
Number of missing = 441 (0.2%)			
Asthma			
Current	22,366	13,084,408	11.1 (10.8, 11.4)
Never or former	174,044	104,360,447	88.9 (88.6, 89.2)
Number of missing = 1533 (0.8%)			
Cancer			
Yes	31,873	12,897,247	10.9 (10.7, 11.2)
No	164,924	104,891,597	89.1 (88.8, 89.3)
Number of missing = 1146 (0.6%)			
COPD			
Yes	13,181	6,386,164	5.4 (5.2, 5.6)
No	184,082	111,500,680	94.6 (94.4, 94.8)
Number of missing = 680 (0.3%)			
Depressive Disorder			
Yes	44,761	26,965,456	22.9 (22.5, 23.3)
No	152,286	90,776,690	77.1 (76.7, 77.5)
Number of missing = 896 (0.5%)			
Kidney Disease			
Yes	8,501	4,102,446	3.5 (3.3, 3.6)

No		188,833	113,894,709	96.5 (96.4, 96.7)
	Number of missing = 609 (0.3%)			
Arthritis				
Yes		62,433	29,094,253	24.7 (24.3, 25.1)
No		134,583	88,715,474	75.3 (74.9, 75.7)
	Number of missing = 927 (0.5%)			
Diabetes				
Yes		26,975	14,555,509	12.3 (12.0, 12.7)
No		170,697	103,587,991	87.7 (87.3, 88.0)
	Number of missing = 271 (0.1%)			
Age				
18–24 years		13,193	15,310,966	12.9 (12.6, 13.3)
25–34 years		25,038	21,672,909	18.3 (17.9, 18.7)
35–44 years		30,486	21,475,290	18.1 (17.8, 18.5)
45–54 years		31,905	19,349,857	16.3 (16.0, 16.7)
55–64 years		36,649	18,819,473	15.9 (15.5, 16.3)
65+ years		60,672	21,735,957	18.4 (18.0, 18.7)
	Number of missing = 0			
Sex				
Male		90,190	54,878,969	46.4 (45.9, 46.9)
Female		107,753	63,485,482	53.6 (53.1, 54.1)
	Number of missing = 0			
Race/ethnicity				
Non-Hispanic white		145,990	69,533,108	60.0 (59.5, 60.5)
Non-White or Hispanic		47,640	46,278,999	40.0 (39.5, 40.5)
	Number of missing = 4313 (2.2%)			
Education				
High School or less		50,710	38,661,813	32.8 (32.3, 33.3)
Attended College or Technical School		52,002	36,736,604	31.2 (30.7, 31.6)

Graduated from College or Technical	94,621	42,501,081	36.0 (35.6, 36.5)
Number of missing = 610 (0.3%)			
Marital Status			
Married or A member of an unmarried couple	121,763	70,225,745	59.8 (59.3, 60.3)
Divorced or Widowed or Separated	40,564	18,601,772	15.8 (15.5, 16.2)
Never married	34,319	28,660,468	24.4 (24.0, 24.8)
Number of missing = 1297 (0.7%)			
Income Level			
Less than \$15,000	17,553	11,222,547	11.4 (11.0, 11.7)
\$25,000 to < \$50,000	35,666	21,278,186	21.6 (21.1, 22.0)
\$50,000 or more	114,142	66,160,809	67.1 (66.6, 67.6)
Number of missing = 30582 (15.4%)			
Health Insurance			
Have some form of insurance	183,373	106,209,849	94.0 (93.7, 94.2)
Do not have some form of health insurance	8,049	6,829,710	6.0 (5.8, 6.3)
Number of missing = 6521 (3.3%)			
BMI			
Normal Weight or Underweight	55,382	34,557,149	31.1 (30.6, 31.6)
Overweight	65,893	38,470,627	34.6 (34.1, 35.1)
Obese	65,224	38,119,312	34.3 (33.8, 34.8)
Number of missing = 11444 (5.8%)			
Smoking history			
Never smoked	125,519	79,087,021	67.2 (66.8, 67.7)
Current or former smoker	71,231	38,595,550	32.8 (32.3, 33.2)
Number of missing = 1193 (0.6%)			
Number of COVID-19 vaccinations received			
None	9,484	5,812,246	18.0 (17.3, 18.6)
One	3,297	1,908,000	5.9 (5.5, 6.3)
Two	14,544	8,342,303	25.8 (25.1, 26.4)

Three	19,058	9,392,970	29.0 (28.3, 29.7)
Four	11,747	4,765,659	14.7 (14.2, 15.2)
Five or more	6,436	2,152,078	6.6 (6.3, 7.0)

Number of missing = 133377 (67.4%)

Table 3. Sample characteristics across the five latent CHC classes

Variable	Severe Multimorbidity Cluster	Mental-Respiratory Cluster	Cardio-Metabolic Cluster	Cancer-Arthritis Cluster	Low CHC Burden Cluster
	Weighted % (95% CI)	Weighted % (95% CI)	Weighted % (95% CI)	Weighted % (95% CI)	Weighted % (95% CI)
Cumulative CHCs score					
0 CHC	0	0	0	0	58.5 (57.9, 59.0)
1 CHC	0	0.4 (0.1, 0.6)	0.8 (0.5, 1.2)	6.5 (5.9, 7.1)	38.9 (38.4, 39.5)
2 CHCs	0	48.8 (47.1, 50.6)	28.5 (25.9, 31.2)	62.2 (61.1, 63.3)	2.6 (2.4, 2.8)
≥3 CHCs	100.0 (100.0, 100.0)	50.8 (49.1, 52.6)	70.6 (68.0, 73.3)	31.3 (30.3, 32.4)	0
Age					
18–24 years	0.7 (0.0, 1.6)	13.3 (11.9, 14.7)	1.0 (0.1, 2.0)	2.4 (1.6, 3.2)	15.5 (15.0, 15.9)
25–34 years	2.9 (0.6, 5.2)	18.4 (17.0, 19.9)	1.5 (0.8, 2.1)	5.5 (4.8, 6.1)	21.6 (21.1, 22.0)
35–44 years	5.7 (4.1, 7.4)	16.9 (15.7, 18.1)	3.9 (2.9, 4.9)	9.2 (8.5, 9.9)	20.6 (20.2, 21.1)
45–54 years	15.5 (13.2, 17.9)	17.3 (16.1, 18.6)	11.4 (9.4, 13.3)	14.9 (14.1, 15.7)	16.7 (16.3, 17.2)
55–64 years	28.3 (25.3, 31.2)	18.0 (16.7, 19.3)	26.6 (23.6, 29.6)	23.7 (22.7, 24.8)	13.7 (13.2, 14.1)
65+ years	46.9 (43.5, 50.3)	16.0 (14.9, 17.1)	55.6 (52.6, 58.6)	44.3 (43.2, 45.5)	11.9 (11.6, 12.3)
Sex					
Male	37.7 (34.3, 41.2)	28.2 (26.6, 29.9)	66.4 (63.5, 69.2)	41.5 (40.3, 42.7)	48.3 (47.7, 48.9)
Female	62.3 (58.8, 65.7)	71.8 (70.1, 73.4)	33.6 (30.8, 36.5)	58.5 (57.3, 59.7)	51.7 (51.1, 52.3)
Race/ethnicity					

Non-Hispanic white	65.0 (61.4, 68.6)	62.8 (60.9, 64.7)	67.1 (63.9, 70.3)	70.0 (68.7, 71.4)	57.6 (57.0, 58.2)
Non-White or Hispanic	35.0 (31.4, 38.6)	37.2 (35.3, 39.1)	32.9 (29.7, 36.1)	30.0 (28.6, 31.3)	42.4 (41.8, 43.0)
Education					
High School or less	48.4 (45.1, 51.8)	37.3 (35.5, 39.0)	43.6 (40.7, 46.5)	35.4 (34.2, 36.6)	31.2 (30.6, 31.8)
Attended College or Technical School	36.1 (32.9, 39.4)	34.8 (33.1, 36.5)	31.6 (28.8, 34.5)	33.7 (32.6, 34.8)	30.3 (29.7, 30.8)
Graduated from College or Technical	15.5 (13.7, 17.2)	27.9 (26.4, 29.4)	24.7 (22.4, 27.1)	30.9 (29.9, 31.9)	38.5 (38.0, 39.1)
Marital Status					
Married or A member of an unmarried couple	50.9 (47.5, 54.4)	52.2 (50.4, 53.9)	65.2 (62.6, 67.8)	62.4 (61.2, 63.6)	60.0 (59.4, 60.5)
Divorced or Widowed or Separated	41.1 (37.9, 44.4)	22.0 (20.7, 23.3)	28.3 (25.9, 30.6)	26.3 (25.4, 27.3)	12.4 (12.0, 12.8)
Never married	7.9 (5.5, 10.3)	25.8 (24.3, 27.4)	6.6 (5.3, 7.9)	11.2 (10.2, 12.3)	27.7 (27.1, 28.2)
Income Level					
Less than \$15,000	36.3 (32.7, 39.8)	20.5 (19.0, 22.0)	18.3 (16.1, 20.5)	15.5 (14.5, 16.5)	9.1 (8.7, 9.5)
\$25,000 to < \$50,000	31.4 (28.2, 34.7)	26.2 (24.6, 27.7)	31.0 (27.9, 34.1)	25.2 (24.0, 26.3)	20.0 (19.5, 20.5)
\$50,000 or more	32.3 (28.9, 35.7)	53.4 (51.5, 55.2)	50.7 (47.5, 54.0)	59.3 (58.0, 60.6)	70.9 (70.4, 71.5)
Health Insurance					
Have some form of insurance	98.1 (97.5, 98.7)	94.7 (93.8, 95.6)	96.6 (95.5, 97.7)	96.9 (96.3, 97.4)	93.2 (92.8, 93.5)
Do not have some form of health insurance	1.9 (1.3, 2.5)	5.3 (4.4, 6.2)	3.4 (2.3, 4.5)	3.1 (2.6, 3.7)	6.8 (6.5, 7.2)
BMI					
Normal Weight or	16.5 (13.7, 19.3)	22.4 (20.9, 23.8)	19.8 (17.6, 22.1)	23.7 (22.5, 24.8)	33.9 (33.3, 34.5)

Underweight					
Overweight	26.3 (23.2, 29.4)	28.3 (26.6, 30.0)	37.8 (34.9, 40.7)	33.9 (32.7, 35.0)	35.4 (34.8, 35.9)
Obese	57.2 (53.7, 60.7)	49.3 (47.5, 51.1)	42.4 (39.4, 45.4)	42.5 (41.3, 43.7)	30.7 (30.2, 31.3)
Smoking history					
Never smoked	40.8 (37.3, 44.3)	56.2 (54.4, 57.9)	47.5 (44.6, 50.4)	56.0 (54.9, 57.2)	71.5 (70.9, 72.0)
Current or former smoker	59.2 (55.7, 62.7)	43.8 (42.1, 45.6)	52.5 (49.6, 55.4)	44.0 (42.8, 45.1)	28.5 (28.0, 29.1)
Number of COVID-19 vaccinations received					
None	17.8 (13.3, 22.3)	16.9 (14.5, 19.3)	13.9 (9.7, 18.0)	13.3 (12.0, 14.5)	19.1 (18.4, 19.9)
One	7.3 (4.7, 9.9)	6.0 (4.7, 7.3)	5.6 (3.6, 7.7)	4.6 (3.8, 5.5)	6.1 (5.7, 6.5)
Two	24.3 (18.7, 29.9)	25.0 (22.4, 27.6)	18.7 (15.7, 21.7)	21.5 (20.0, 23.1)	27.0 (26.2, 27.8)
Three	24.0 (19.9, 28.0)	28.9 (26.4, 31.5)	31.9 (27.3, 36.4)	29.2 (27.4, 31.0)	29.0 (28.2, 29.8)
Four	18.3 (13.8, 22.7)	15.8 (13.9, 17.8)	17.9 (14.8, 21.0)	19.8 (18.4, 21.3)	13.4 (12.9, 14.0)
Five or more	8.4 (5.4, 11.3)	7.4 (6.1, 8.6)	12.1 (9.0, 15.1)	11.5 (10.4, 12.6)	5.4 (5.0, 5.8)

Table 4. Prevalence of long COVID across groups

Variable	Weighted % (95% CI)	p-value
Heart Attack		<0.001
Yes	21.0 (19.1, 23.0)	
No	13.5 (13.1, 13.8)	
CHD		<0.001
Yes	21.3 (19.4, 23.1)	
No	13.4 (13.1, 13.8)	
Stroke		<0.001
Yes	21.3 (19.2, 23.5)	
No	13.5 (13.2, 13.9)	

Asthma		<0.001
Yes	24.1 (22.9, 25.2)	
No	12.4 (12.1, 12.8)	
Cancer		0.007
Yes	15.2 (14.0, 16.3)	
No	13.6 (13.2, 13.9)	
COPD		<0.001
Yes	29.0 (27.3, 30.8)	
No	12.9 (12.5, 13.2)	
Depressive Disorder		<0.001
Yes	20.9 (20.1, 21.7)	
No	11.6 (11.3, 12.0)	
Kidney Disease		<0.001
Yes	20.2 (18.2, 22.1)	
No	13.5 (13.2, 13.8)	
Arthritis		<0.001
Yes	19.7 (19.0, 20.4)	
No	11.8 (11.4, 12.2)	
Diabetes		<0.001
Yes	17.5 (16.3, 18.7)	
No	13.2 (12.9, 13.6)	
Cumulative CHCs score		<0.001
0 CHC	9.3 (8.9, 9.8)	
1 CHC	13.8 (13.1, 14.4)	
2 CHCs	18.0 (17.0, 19.1)	
≥3 CHCs	26.0 (24.8, 27.1)	
Latent Classes of CHCs		<0.001
Severe Multimorbidity Cluster	32.8 (29.7, 35.8)	
Mental-Respiratory Cluster	28.2 (26.6, 29.8)	

Cardio-Metabolic Cluster	16.3 (14.3, 18.2)
Cancer-Arthritis Cluster	18.3 (17.3, 19.4)
Low CHC Burden Cluster	11.2 (10.8, 11.6)

Table 5. Unadjusted and adjusted ORs for the association between CHCs and long COVID

	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Individual CHCs				
Heart attack	1.71 (1.52, 1.93)	<0.001	1.48 (1.28, 1.71)	<0.001
CHD	1.74 (1.55, 1.95)	<0.001	1.78 (1.55, 2.05)	<0.001
Stroke	1.73 (1.52, 1.97)	<0.001	1.47 (1.28, 1.70)	<0.001
Current asthma	2.23 (2.07, 2.40)	<0.001	1.95 (1.79, 2.13)	<0.001
Cancer	1.14 (1.04, 1.25)	0.007	1.19 (1.04, 1.37)	0.012
COPD	2.77 (2.53, 3.03)	<0.001	2.37 (2.11, 2.66)	<0.001
Depressive disorder	2.00 (1.88, 2.13)	<0.001	1.72 (1.60, 1.85)	<0.001
Kidney disease	1.62 (1.43, 1.84)	<0.001	1.44 (1.24, 1.68)	<0.001
Arthritis	1.83 (1.73, 1.94)	<0.001	1.77 (1.65, 1.91)	<0.001
Diabetes	1.39 (1.28, 1.52)	<0.001	1.18 (1.05, 1.33)	0.008
Cumulative CHCs score				
0 CHC	Reference		Reference	
1 CHC	1.56 (1.44, 1.68)	<0.001	1.47 (1.35, 1.61)	<0.001
2 CHCs	2.15 (1.97, 2.34)	<0.001	2.13 (1.89, 2.39)	<0.001
≥3 CHCs	3.42 (3.15, 3.70)	<0.001	3.30 (2.95, 3.69)	<0.001
Latent Classes of CHCs				
Severe Multimorbidity Cluster	3.86 (3.35, 4.45)	<0.001	3.46 (2.91, 4.10)	<0.001
Mental-Respiratory Cluster	3.11 (2.85, 3.39)	<0.001	2.65 (2.38, 2.95)	<0.001

Cardio-Metabolic Cluster	1.54 (1.33, 1.78)	<0.001	1.61 (1.34, 1.94)	<0.001
Cancer-Arthritis Cluster	1.78 (1.64, 1.92)	<0.001	1.82 (1.62, 2.05)	<0.001
Low CHC Burden Cluster	Reference		Reference	

Adjusted OR = odds ratio adjusted for age, sex, race/ethnicity, education, marital status, income level, health insurance, BMI, and smoking history

Table 6. Adjusted ORs for the association between the number of COVID-19 vaccine doses and long COVID

Population	Number of COVID-19 vaccinations received	Adjusted OR (95% CI)	p-value
0 CHC group			
	0 dose	Reference	
	1 dose	1.15 (0.76, 1.75)	0.503
	2 doses	0.81 (0.62, 1.07)	0.141
	3 doses	0.71 (0.55, 0.93)	0.013
	4 doses	0.68 (0.48, 0.97)	0.034
	≥5 doses	0.66 (0.43, 1.03)	0.064
1 CHC group			
	0 dose		
	1 dose	1.19 (0.76, 1.88)	0.441
	2 doses	1.17 (0.88, 1.55)	0.291
	3 doses	1.09 (0.82, 1.47)	0.547
	4 doses	0.68 (0.49, 0.94)	0.019
	≥5 doses	0.63 (0.42, 0.95)	0.026
2 CHCs group			
	0 dose		
	1 dose	0.97 (0.60, 1.58)	0.902
	2 doses	1.22 (0.86, 1.72)	0.261
	3 doses	0.84 (0.60, 1.18)	0.325

	4 doses	0.93 (0.62, 1.39)	0.717
	≥5 doses	1.26 (0.76, 2.07)	0.372
≥3 CHCs group	0 dose		
	1 dose	1.52 (0.91, 2.51)	0.107
	2 doses	1.16 (0.81, 1.67)	0.415
	3 doses	1.01 (0.71, 1.45)	0.944
	4 doses	0.70 (0.49, 1.02)	0.061
	≥5 doses	0.60 (0.37, 0.96)	0.034
Low CHC Burden Cluster	0 dose		
	1 dose	1.17 (0.86, 1.58)	0.320
	2 doses	0.95 (0.78, 1.15)	0.600
	3 doses	0.88 (0.72, 1.07)	0.187
	4 doses	0.68 (0.53, 0.87)	0.002
	≥5 doses	0.69 (0.51, 0.92)	0.012
Severe Multimorbidity Cluster	0 dose		
	1 dose	1.46 (0.61, 3.48)	0.396
	2 doses	1.03 (0.47, 2.26)	0.935
	3 doses	0.99 (0.50, 1.97)	0.974
	4 doses	0.90 (0.42, 1.92)	0.775
	≥5 doses	0.78 (0.29, 2.13)	0.627
Mental-Respiratory Cluster	0 dose		
	1 dose	2.04 (1.10, 3.80)	0.024
	2 doses	1.35 (0.87, 2.11)	0.184
	3 doses	1.23 (0.79, 1.92)	0.360

	4 doses	0.90 (0.56, 1.46)	0.679
	≥5 doses	0.88 (0.50, 1.56)	0.665
Cardio-Metabolic Cluster			
	0 dose		
	1 dose	1.10 (0.35, 3.43)	0.876
	2 doses	1.33 (0.59, 2.96)	0.490
	3 doses	0.99 (0.45, 2.19)	0.975
	4 doses	1.24 (0.49, 3.14)	0.655
	≥5 doses	0.56 (0.20, 1.57)	0.269
Cancer-Arthritis Cluster			
	0 dose		
	1 dose	0.83 (0.46, 1.49)	0.531
	2 doses	1.19 (0.84, 1.68)	0.333
	3 doses	0.82 (0.58, 1.17)	0.268
	4 doses	0.73 (0.50, 1.06)	0.095
	≥5 doses	0.88 (0.53, 1.44)	0.604

Adjusted OR = odds ratio adjusted for age, sex, race/ethnicity, education, marital status, income level, health insurance, BMI, and smoking history

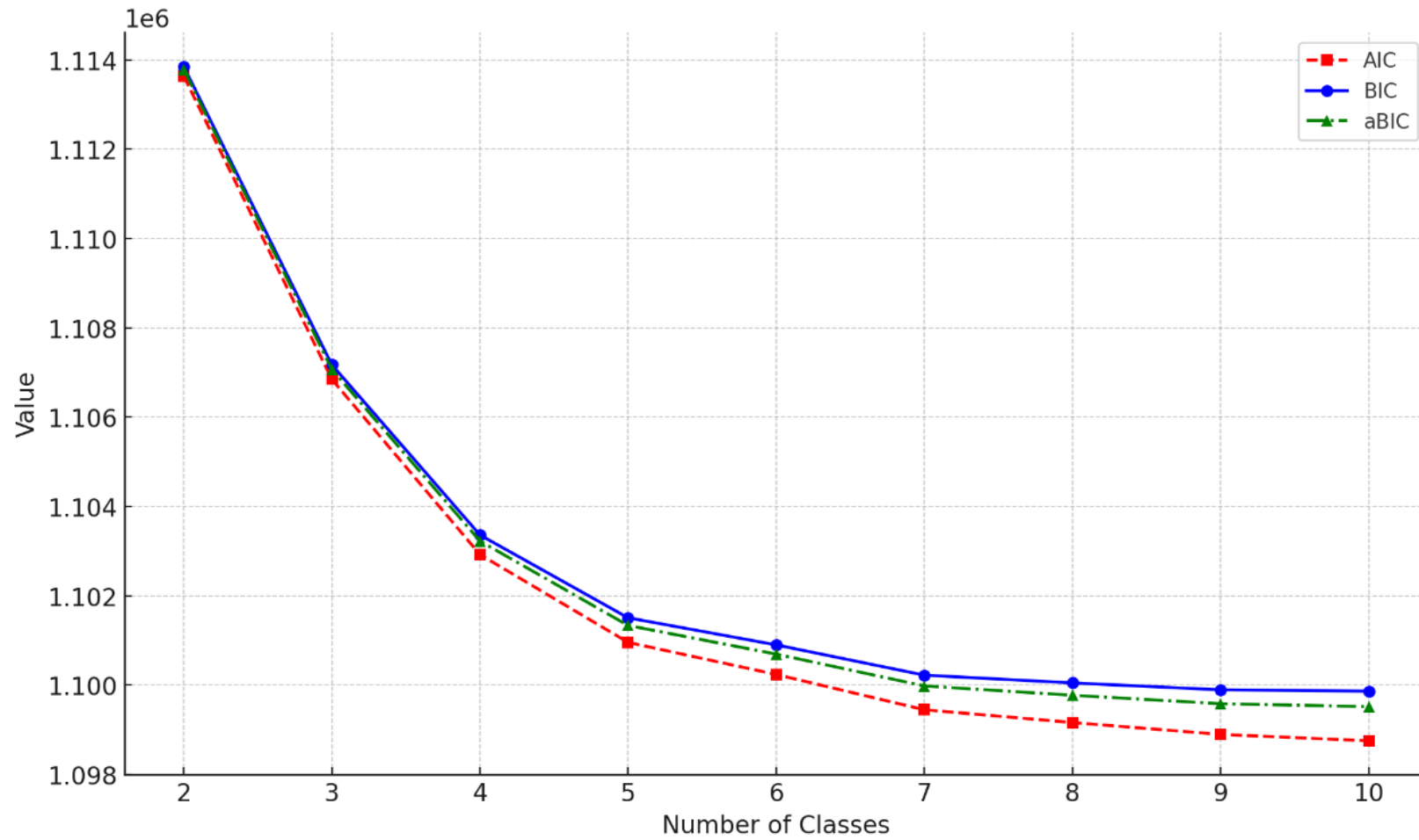


Figure 1. Trends in AIC, BIC, and aBIC as the number of classes increased

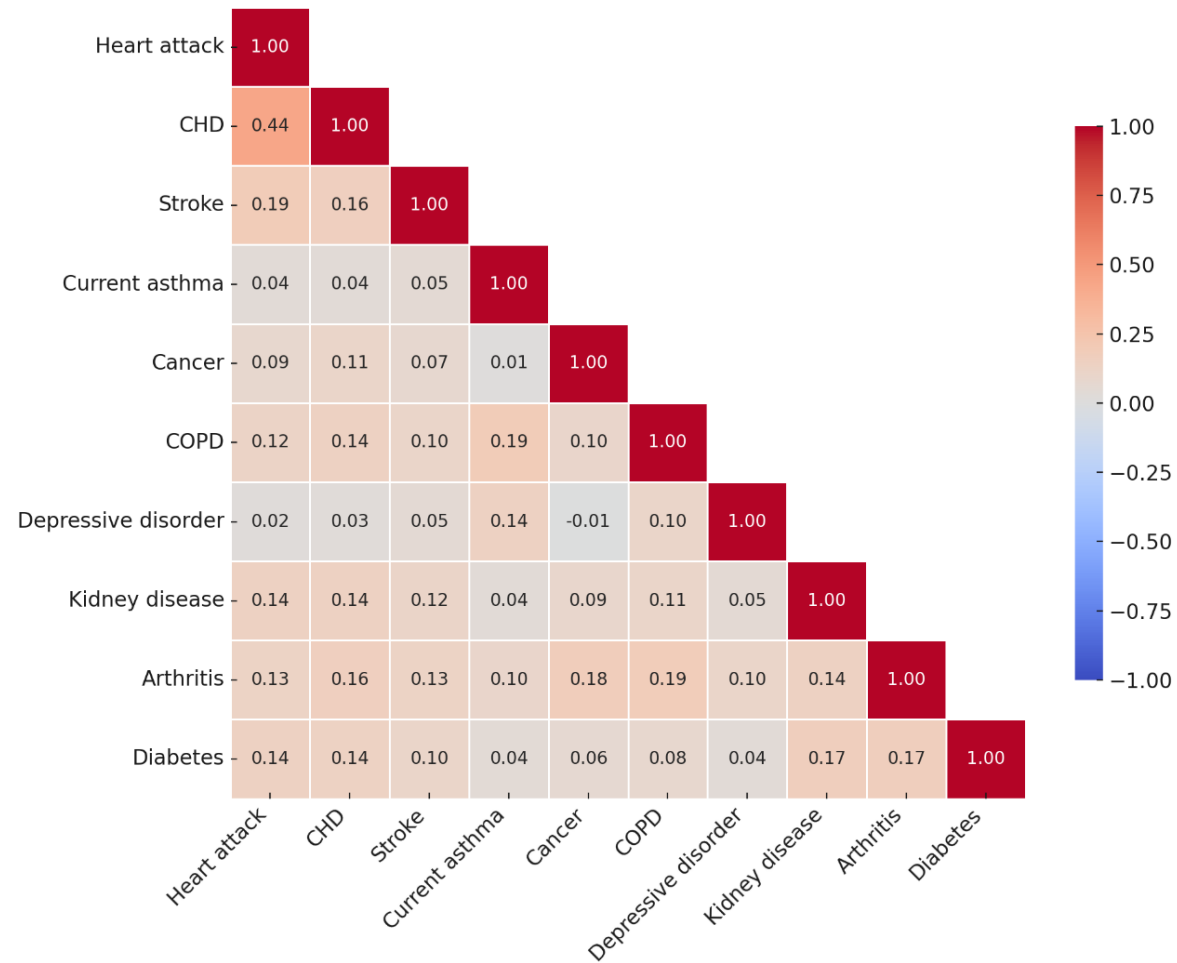


Figure 2. Pairwise weighted phi correlation coefficients among the ten CHCs

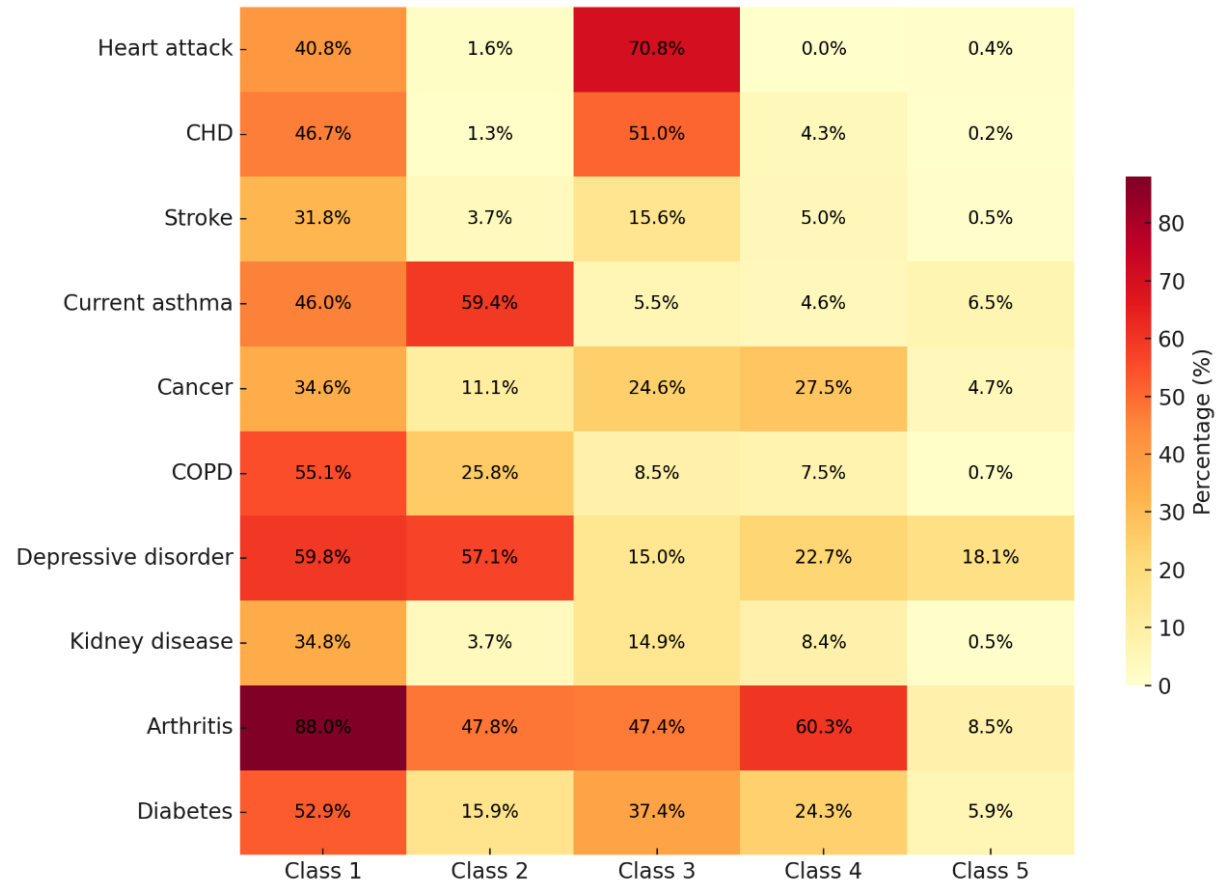


Figure 3. Response probabilities for each of the five latent classes across the ten CHCs. Class 1 = Severe Multimorbidity Cluster; Class 2 = Mental-Respiratory Cluster; Class 3 = Cardio-Metabolic Cluster; Class 4 = Cancer-Arthritis Cluster; Class 5 = Low CHC Burden Cluster.

Chapter 6: Closing Discussion

This dissertation set out to investigate the multifaceted impact of the COVID-19 pandemic on individuals with cancer, a population characterized by heightened clinical vulnerability. Through three distinct but interrelated studies, it aimed to explore short- and long-term outcomes among cancer patients, with a particular focus on mortality patterns and long COVID. We observed notable shifts in cancer-related mortality patterns during the pandemic and identified that cancer survivors may face an elevated risk of developing long COVID following acute infection. This risk further increases with the number of chronic health conditions (CHCs) or when individuals exhibit specific multimorbidity patterns. Alarming, in cancer survivors and those with multimorbidity, COVID-19 vaccination did not show the same protective association against long COVID as observed in the general population. These findings underscore the importance of ongoing surveillance and targeted preventive strategies for cancer patients in the post-pandemic era.

The first manuscript used death certificate data from Nevada to analyze changes in cancer-related mortality from three perspectives: cancer as the underlying cause of death, as a contributing cause, and cancer as either the underlying cause of death or contributing causes of death. Existing evidence indicates that individuals with cancer not only have a higher risk of contracting COVID-19 but also face increased likelihood of severe outcomes, including

death (H. J. Han et al., 2021; Liang et al., 2020). These factors would suggest a rise in cancer mortality during the pandemic. However, our real-world study revealed an unexpected finding: from 2020 to 2021, overall cancer-related mortality mildly declined, and deaths where cancer was listed as the underlying cause were significantly lower than expected.

A plausible explanation is that excess deaths caused by COVID-19 may have shifted the underlying cause from cancer to COVID-19. Our analysis showed that the number of deaths where many cancer subtypes were listed as contributing causes was higher than anticipated. A large part of this excess can be attributed to COVID-19 being the underlying cause. This supports existing knowledge that cancer patients face a higher risk of death when infected with COVID-19. On the other hand, the overall reduction in cancer-related mortality was driven by the substantial decrease in lung cancer-related deaths. This is partly due to the continuous decline in lung cancer incidence in Nevada in recent years. Additionally, delays or reductions in cancer diagnosis during the pandemic may have led to underestimates of cancer-related mortality and could result in more late-stage diagnoses and cancer-specific deaths in the coming years (Sharpless, 2020). While not directly related to the biological interaction between COVID-19 and cancer, these disruptions reflect the broader systemic challenges during the pandemic—including interruptions in cancer screening, treatment, and follow-up—that have likely contributed to suboptimal management and worse outcomes for patients (Keim-Malpass et al., 2023;

London et al., 2020; Moraliyage et al., 2021). Furthermore, underreporting of cancer as a contributing cause of death during the pandemic, due to overwhelmed health systems and incomplete documentation, may have further contributed to underestimations of total cancer-related mortality (Prahlow et al., 2023).

The second and third manuscripts investigated long-term sequelae of COVID-19. Manuscript 2 used nationally representative BRFSS 2022 data to examine the lifetime prevalence of long COVID among cancer survivors. Our findings revealed that cancer survivors had a significantly higher prevalence than non-cancer individuals (24.0% vs. 21.6%, $p < 0.001$), with an adjusted OR of 1.17 (95% CI = 1.06–1.30), indicating a 17% higher odds. Prior studies show inconsistent results—some reporting high prevalence of long COVID among cancer patients exceeding 50% (Dagher et al., 2023; Debie et al., 2024; Monroy-Iglesias et al., 2022), while others find relatively lower prevalence with no significant difference compared to non-cancer patients (Chai et al., 2021; Fankuchen et al., 2023). Many of these studies rely on small, single-center samples. In contrast, BRFSS provides a nationally representative dataset, offering a national population representation that is unmatched by other studies. We also discussed variation in long COVID prevalence across studies. One key factor is the definition of long COVID: studies reporting $>50\%$ prevalence all used a threshold of symptoms persisting for 1 month or 4 weeks which is more sensitive (Dagher et al., 2023; Debie et al., 2024; Monroy-Iglesias et al., 2022),

while BRFSS and many others use a 3-month threshold.

Another finding is the age-stratified difference in long COVID prevalence. Among those under 45, cancer survivors had significantly higher prevalence than non-cancer individuals, while no such difference was observed in the older group. This is surprising, as older age and cancer are both known risk factors for severe COVID-19 outcomes (S. Han et al., 2022; Liang et al., 2020; Mahase, 2020). We expected to observe greater prevalence differences in the older age group. One explanation may be survivorship bias: older cancer patients may have had higher COVID-related mortality, or institutionalized individuals may have been underrepresented in the BRFSS sample, potentially leading to an underestimation of long COVID prevalence in the older cancer survivor group. Another possible explanation is that younger patients, more likely to undergo intensive treatments such as high-dose chemotherapy, which can weaken the body's immune system (Bleyer, 2007; Tralongo et al., 2021). This immunosuppression may increase the likelihood of developing long COVID after a COVID-19 infection in this population (Su et al., 2022).

Manuscript 3 used nationally representative data from BRFSS 2023. Unlike the 2022 dataset, BRFSS 2023 measured the prevalence of long COVID within that specific year, rather than capturing lifetime prevalence. As a result, we observed a substantially lower long COVID prevalence among cancer survivors in 2023 compared to 2022, which reflects a more current picture of the long COVID burden.

In this third study, we explored the association between long COVID and 10 types of chronic health conditions (CHCs), including cancer. We found that all 10 CHCs were significantly associated with higher odds of developing long COVID. This supports prior evidence that existing chronic conditions are important risk factors for long COVID and also validates our second study's findings that cancer survivors are at increased risk. Furthermore, we observed a clear dose-response relationship between the number of CHCs and the odds of long COVID, indicating that individuals with a greater number of chronic conditions face progressively higher risk. While earlier research has shown the cumulative effect of CHC count on severe COVID-19 outcomes, our findings offer new evidence linking CHC burden to persistent long COVID symptoms.

In addition, we conducted latent class analysis (LCA) and identified four multimorbidity clusters and one low-CHC burden group among COVID-19 survivors. All four multimorbidity clusters were significantly associated with increased odds of long COVID. Notably, the Severe Multimorbidity Cluster and the Mental-Respiratory Cluster were associated with the highest long COVID risk. Importantly, the probabilities of cancer were high in three clusters: Severe Multimorbidity, Cardio-Metabolic, and Cancer-Arthritis. This suggests that cancer may play an important role within multimorbidity patterns and supports previous findings that cancer frequently coexists with other chronic diseases. It also indicates that cancer survivors' long COVID risk may be further exacerbated by the presence of multimorbidity.

In addition to establishing heightened long COVID risk in cancer survivors and multimorbid individuals, Studies 2 and 3 found that a higher dose of the COVID-19 vaccine may be needed in these high-risk groups than in the control group to be associated with a reduced odds of long COVID. This finding is consistent with existing literature showing that cancer patients exhibit lower seroconversion rates following COVID-19 vaccination compared to healthy controls (Sun et al., 2022) and that multimorbidity negatively affects antibody production (Das et al., 2023). While our data cannot establish causality, these results suggest that cancer survivors and individuals with multimorbidity may face a greater post-infection health burden and should be encouraged to receive booster vaccinations.

Together, these three studies offer a layered understanding of how the pandemic has affected individuals with cancer. Manuscript 1 addressed the acute endpoint of mortality; Manuscripts 2 and 3 extended the scope to post-acute sequelae and explored the role of cancer and complex multimorbidity. This progression—from immediate outcomes to long-term effects, and from single conditions to complex disease clusters—offers an epidemiologically coherent narrative of risk and resilience in the cancer population. A central insight emerging from these studies is that vulnerability to COVID-19 among cancer patients cannot be fully understood in isolation. The risks they face stem not only from acute infection but also from prolonged consequences. In addition, these risks are amplified not only by cancer itself but by coexisting chronic

conditions, treatment-related immunosuppression, and systemic disruptions in care caused by the pandemic as well.

These findings have several important implications for public health and clinical practice:

First, ongoing surveillance of cancer incidence and mortality is warranted, along with preparation for a potential rise in late-stage diagnoses and cancer-specific deaths. It is also essential to develop contingency plans for chronic disease management during future public health emergencies, particularly under healthcare system strain. At the same time, actions should be taken to increase participation rates in recommended cancer screenings among high-risk populations.

Second, the elevated risk of long COVID among cancer survivors highlights the importance of implementing post-infection monitoring protocols tailored to this population, including early symptom detection and appropriate referrals to supportive care services. Screening for long COVID symptoms should be integrated into routine cancer follow-up care, allowing for early intervention and symptom management.

Third, the identification of multimorbidity patterns emphasizes the need for more nuanced strategies in risk stratification and resource allocation. Rather than addressing chronic conditions in isolation, public health systems should consider the interaction and cumulative burden of coexisting diseases. Given the observed strong association between cumulative CHC burden and long

COVID, healthcare providers should actively assess and monitor individuals with multimorbidity for persistent post-COVID symptoms. Particular attention should be paid to patients in high-risk multimorbidity groups. For patients with pre-existing CHCs, the clinical burden of long COVID may further accelerate disease progression and negatively impact quality of life.

Finally, vaccination strategies must be optimized for individuals with cancer and multimorbidity. While immune response may be lower in these populations, vaccination remains an essential tool for reducing severe outcomes. Clinicians should advocate for enhanced vaccination strategies tailored to these high-risk populations. Public health policies should also emphasize targeted outreach efforts to increase vaccine uptake and ensure equitable access to post-COVID care resources for these patients. Booster scheduling should be personalized and incorporated into immunocompromised patient care guidelines. Further high-quality evidence is also needed to evaluate the effectiveness of vaccines in preventing long COVID in these vulnerable groups.

The COVID-19 pandemic has not only posed an acute infectious threat but has also exposed potential vulnerabilities in chronic disease management. Cancer patients—already burdened with complex care demands—have faced disproportionate risks across the care continuum, from mortality to long-term recovery. By examining cancer mortality trends, long COVID prevalence, and multimorbidity patterns, this dissertation offers new real-world insights into shifting cancer mortality, elevated long COVID risk among cancer survivors,

and the additive impact of multimorbidity. It calls for continued vigilance regarding the health burden faced by cancer survivors in the post-pandemic era and supports the creation of more equitable and adaptive models of care.

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Appendix I. Chapter 4 Table S1. Original BRFSS variables

Relevant variables in the analysis	BRFSS questions	BRFSS value	BRFSS value label
Study population selection	Has a doctor, nurse, or other health professional ever told you that you tested positive for COVID 19?	1	Yes
		2	No
		3	Tested positive using home test without health professional
		7	Don't know/Not Sure
		9	Refused
		BLANK	Not asked or Missing
History of Cancer	(Ever told) (you had) melanoma or any other types of cancer?	1	Yes
		2	No
		7	Don't know / Not sure
		9	Refused
		BLANK	Not asked or Missing
History of Cancer	(Ever told) (you had) skin cancer that is not melanoma?	1	Yes
		2	No
		7	Don't know / Not sure
		9	Refused
		BLANK	Not asked or Missing
History of Long COVID	Did you have any symptoms lasting 3 months or longer that you did not have prior to having coronavirus or COVID-19?	1	Yes
		2	No
		7	Don't know/Not Sure
		9	Refused
		BLANK	Not asked or Missing

Long COVID primary symptom	Which of the following was the primary symptom that you experienced? Was it....	<p>1 Tiredness or fatigue Difficulty thinking or concentrating or forgetfulness/memory</p> <p>2 problems (sometimes referred to as 'brain fog')</p> <p>3 Difficulty breathing or shortness of breath</p> <p>4 Joint or muscle pain</p> <p>5 Fast-beating or pounding heart (also known as heart palpitations) or chest pain</p> <p>6 Dizziness on standing</p> <p>7 Depression, anxiety, or mood changes</p> <p>8 Symptoms that get worse after physical or mental activities</p> <p>9 You did not have any long-term symptoms that limited your activities.</p> <p>10 Loss of taste or smell</p> <p>11 Some other symptom</p> <p>77 Don't know/Not Sure</p> <p>99 Refused</p> <p>BLANK Not asked or Missing</p>
Age	Six-level imputed age category	<p>1 Age 18 to 24</p> <p>2 Age 25 to 34</p> <p>3 Age 35 to 44</p> <p>4 Age 45 to 54</p> <p>5 Age 55 to 64</p> <p>6 Age 65 or older</p>

Sex	Calculated sex variable	1	Male
		2	Female
Race/ethnicity	White non-Hispanic race group	1	Non-Hispanic White
		2	Non-White or Hispanic
		9	Don't know/Not sure/Refused
		BLANK	Missing
Education	Level of education completed	1	Did not graduate High School
		2	Graduated High School
		3	Attended College or Technical School
		4	Graduated from College or Technical School
		9	Don't know/Not sure/Missing
Marital status	Are you: (marital status)	1	Married
		2	Divorced
		3	Widowed
		4	Separated
		5	Never married
		6	A member of an unmarried couple
		9	Refused
BLANK	Not asked or Missing		
Income level	Income categories	1	Less than \$15,000
		2	\$15,000 to < \$25,000
		3	\$25,000 to < \$35,000
		4	\$35,000 to < \$50,000
		5	\$50,000 to < \$100,000

		6	\$100,000 to < \$200,000
		7	\$200,000 or more
		9	Don't know/Not sure/Missing
Health insurance	Adults who had some form of health insurance	1	Have some form of insurance
		2	Do not have some form of health insurance
		9	Don't know, refused or missing insurance response
BMI	Four-categories of Body Mass Index (BMI)	1	Underweight
		2	Normal Weight
		3	Overweight
		4	Obese
		BLANK	Don't know/Refused/Missing
Smoking history	Four-level smoker status: Everyday smoker, Someday smoker, Former smoker, Non-smoker	1	Current smoker - now smokes every day
		2	Current smoker - now smokes some days
		3	Former smoker
		4	Never smoked
		9	Don't know/Refused/Missing
COPD	(Ever told) (you had) C.O.P.D. (chronic obstructive pulmonary disease), emphysema or chronic bronchitis?	1	Yes
		2	No
		7	Don't know / Not sure
		9	Refused
		BLANK	Not asked or Missing
Diabetes	(Ever told) (you had) diabetes?	1	Yes

		2	Yes, but female told only during pregnancy
		3	No
		4	No, pre-diabetes or borderline diabetes
		7	Don't know/Not Sure
		9	Refused
		BLANK	Not asked or Missing
Asthma	Computed asthma status	1	Current
		2	Former
		3	Never
		9	Don't know/Not Sure Or Refused/Missing
Heart disease	Respondents that have ever reported having coronary heart disease (CHD) or myocardial infarction (MI)	1	Reported having MI or CHD
		2	Did not report having MI or CHD
		BLANK	Not asked or Missing
Stroke	(Ever told) (you had) a stroke.	1	Yes
		2	No
		7	Don't know/Not sure
		9	Refused
		BLANK	Not asked or Missing
Number of COVID-19 vaccinations	Have you received at least one dose of a COVID-19 vaccination?	1	Yes
		2	No
		7	Don't know/Not sure
		9	Refused
		BLANK	Not asked or Missing

Number of COVID-19 vaccinations	How many COVID-19 vaccinations have you received?	1	One
		2	Two
		3	Three
		4	Four or more
		7	Don't know/Not sure
		9	Refused
		BLANK	Not asked or Missing

Appendix II. Chapter 4 Table S2. Model S1 Adjusted Odds Ratios for Long COVID in Cancer Survivors Compared to Non-Cancer Participants: Overall Population

Variable	Adjusted for 5 CHCs		Adjusted for COPD		Adjusted for Diabetes		Adjusted for Asthma		Adjusted for Heart disease		Adjusted for Stroke	
	aOR (95% CI)	p-value	aOR (95% CI)	p-value	aOR (95% CI)	p-value	aOR (95% CI)	p-value	aOR (95% CI)	p-value	aOR (95% CI)	p-value
Cancer history												
Yes	1.10 (0.99, 1.22)	0.067	1.14 (1.03, 1.26)	0.014	1.17 (1.06, 1.30)	0.002	1.14 (1.03, 1.26)	0.009	1.16 (1.04, 1.28)	0.006	1.16 (1.05, 1.29)	0.004
No	(Reference)		(Reference)		(Reference)		(Reference)		(Reference)		(Reference)	
Age												
18–24 years	(Reference)		(Reference)		(Reference)		(Reference)		(Reference)		(Reference)	
25–34 years	1.08 (0.94, 1.24)	0.284	1.09 (0.95, 1.24)	0.226	1.09 (0.96, 1.25)	0.194	1.08 (0.94, 1.24)	0.268	1.10 (0.96, 1.26)	0.178	1.09 (0.95, 1.25)	0.203
35–44 years	1.08 (0.94, 1.25)	0.286	1.10 (0.95, 1.27)	0.194	1.11 (0.96, 1.28)	0.171	1.10 (0.95, 1.27)	0.216	1.12 (0.97, 1.29)	0.132	1.11 (0.96, 1.28)	0.164
45–54 years	1.09 (0.94, 1.27)	0.246	1.12 (0.97, 1.30)	0.122	1.12 (0.97, 1.30)	0.122	1.14 (0.98, 1.32)	0.092	1.13 (0.97, 1.31)	0.109	1.13 (0.98, 1.31)	0.095
55–64 years	0.93 (0.80, 1.09)	0.378	0.97 (0.84, 1.13)	0.709	0.99 (0.85, 1.15)	0.864	1.00 (0.86, 1.16)	0.952	0.99 (0.85, 1.14)	0.841	1.00 (0.86, 1.16)	0.982
65+ years	0.68 (0.58, 0.80)	<0.001	0.72 (0.62, 0.84)	<0.001	0.75 (0.64, 0.88)	<0.001	0.78 (0.67, 0.91)	0.002	0.73 (0.63, 0.86)	<0.001	0.76 (0.65, 0.89)	0.001
Sex												
Male	(Reference)		(Reference)		(Reference)		(Reference)		(Reference)		(Reference)	
Female	1.70 (1.59, 1.82)	<0.001	1.72 (1.61, 1.83)	<0.001	1.73 (1.62, 1.84)	<0.001	1.67 (1.57, 1.79)	<0.001	1.77 (1.66, 1.89)	<0.001	1.73 (1.62, 1.84)	<0.001
Race/ethnicity												
Non-Hispanic white	(Reference)		(Reference)		(Reference)		(Reference)		(Reference)		(Reference)	
Non-White or Hispanic	0.93 (0.86, 1.00)	0.047	0.93 (0.87, 1.01)	0.067	0.92 (0.85, 0.99)	0.023	0.92 (0.86, 0.99)	0.033	0.93 (0.86, 1.00)	0.043	0.93 (0.86, 1.00)	0.043
Education												
High School or less	(Reference)		(Reference)		(Reference)		(Reference)		(Reference)		(Reference)	
Attended College or Technical School	1.14 (1.05, 1.23)	0.003	1.15 (1.06, 1.24)	0.001	1.15 (1.06, 1.24)	0.001	1.13 (1.04, 1.23)	0.003	1.14 (1.05, 1.24)	0.001	1.14 (1.05, 1.24)	0.001
Graduated from College or Technical	0.87 (0.79, 0.94)	0.001	0.87 (0.80, 0.94)	0.001	0.86 (0.79, 0.94)	<0.001	0.86 (0.79, 0.93)	<0.001	0.86 (0.79, 0.93)	<0.001	0.86 (0.79, 0.94)	<0.001

Marital Status												
Married or A member of an unmarried couple	(Reference)		(Reference)		(Reference)		(Reference)		(Reference)		(Reference)	
Divorced or Widowed or Separated	1.14 (1.04, 1.25)	0.004	1.16 (1.06, 1.26)	0.001	1.18 (1.08, 1.29)	<0.001	1.17 (1.07, 1.28)	0.001	1.17 (1.07, 1.27)	0.001	1.17 (1.07, 1.28)	<0.001
Never married	0.97 (0.88, 1.07)	0.582	0.98 (0.89, 1.08)	0.650	0.99 (0.90, 1.09)	0.858	0.97 (0.89, 1.07)	0.581	0.99 (0.90, 1.09)	0.784	0.99 (0.90, 1.09)	0.788
Income Level												
Less than \$15,000	(Reference)		(Reference)		(Reference)		(Reference)		(Reference)		(Reference)	
\$25,000 to < \$50,000	0.92 (0.82, 1.03)	0.144	0.89 (0.80, 1.00)	0.040	0.86 (0.77, 0.96)	0.008	0.88 (0.79, 0.98)	0.025	0.87 (0.78, 0.97)	0.014	0.87 (0.78, 0.97)	0.010
\$50,000 or more	0.85 (0.76, 0.96)	0.006	0.82 (0.73, 0.91)	<0.001	0.78 (0.70, 0.87)	<0.001	0.80 (0.71, 0.89)	<0.001	0.79 (0.71, 0.88)	<0.001	0.78 (0.70, 0.87)	<0.001
Health Insurance												
Have some form of insurance	0.78 (0.68, 0.90)	0.001	0.81 (0.71, 0.93)	0.003	0.82 (0.72, 0.95)	0.006	0.80 (0.70, 0.92)	0.002	0.82 (0.71, 0.94)	0.004	0.82 (0.71, 0.94)	0.005
Do not have some form of health insurance	(Reference)		(Reference)		(Reference)		(Reference)		(Reference)		(Reference)	
BMI												
Normal Weight or Underweight	(Reference)		(Reference)		(Reference)		(Reference)		(Reference)		(Reference)	
Overweight	1.21 (1.11, 1.32)	<0.001	1.21 (1.11, 1.32)	<0.001	1.20 (1.10, 1.31)	<0.001	1.20 (1.10, 1.30)	<0.001	1.21 (1.11, 1.32)	<0.001	1.20 (1.10, 1.31)	<0.001
Obese	1.50 (1.38, 1.63)	<0.001	1.53 (1.40, 1.66)	<0.001	1.52 (1.40, 1.65)	<0.001	1.51 (1.39, 1.64)	<0.001	1.55 (1.42, 1.68)	<0.001	1.55 (1.42, 1.68)	<0.001
Smoking history												
Never smoked	(Reference)		(Reference)		(Reference)		(Reference)		(Reference)		(Reference)	
Current or former smoker	1.18 (1.10, 1.26)	<0.001	1.19 (1.11, 1.28)	<0.001	1.24 (1.16, 1.33)	<0.001	1.23 (1.15, 1.32)	<0.001	1.22 (1.14, 1.31)	<0.001	1.24 (1.16, 1.32)	<0.001
COPD												
Yes	1.61 (1.42, 1.83)	<0.001	1.87 (1.67, 2.11)	<0.001								
No	(Reference)		(Reference)									
Diabetes												
Yes	1.11 (1.01, 1.22)	0.038			1.16 (1.06, 1.28)	0.002						
No	(Reference)				(Reference)							
Asthma												
Current	1.54 (1.40, 1.69)	<0.001					1.66 (1.52, 1.82)	<0.001				
Never or former	(Reference)						(Reference)					
Heart disease												
Yes	1.24 (1.10, 1.40)	0.001							1.43 (1.27, 1.60)	<0.001		
No	(Reference)								(Reference)			
Stroke												
Yes	1.16 (0.98, 1.37)	0.087									1.35 (1.16, 1.58)	<0.001
No	(Reference)										(Reference)	

CHCs: chronic health conditions; 95% CI: 95% confidence interval; aOR: adjusted odds ratio

Appendix III. Chapter 4 Table S3. Model S1 Adjusted Odds Ratios for Long COVID in Cancer Survivors Compared to Non-Cancer Participants: Age < 45

Attended College or Technical School	1.10 (0.99, 1.23)	0.082	1.13 (1.01, 1.26)	0.030	1.12 (1.01, 1.25)	0.038	1.10 (0.99, 1.23)	0.080	1.11 (1.00, 1.24)	0.060	1.12 (1.00, 1.25)	0.042
Graduated from College or Technical	0.95 (0.85, 1.07)	0.379	0.96 (0.85, 1.07)	0.442	0.95 (0.85, 1.06)	0.362	0.94 (0.84, 1.06)	0.304	0.93 (0.83, 1.04)	0.226	0.95 (0.85, 1.06)	0.329
Marital Status												
Married or A member of an unmarried couple	(Reference)		(Reference)		(Reference)		(Reference)		(Reference)		(Reference)	
Divorced or Widowed or Separated	1.08 (0.97, 1.20)	0.186	1.08 (0.97, 1.20)	0.154	1.10 (0.99, 1.22)	0.092	1.09 (0.98, 1.21)	0.118	1.08 (0.97, 1.20)	0.146	1.09 (0.98, 1.21)	0.124
Never married	0.89 (0.73, 1.09)	0.271	0.89 (0.73, 1.09)	0.268	0.90 (0.74, 1.09)	0.275	0.88 (0.72, 1.08)	0.218	0.90 (0.73, 1.09)	0.281	0.89 (0.73, 1.09)	0.263
Income Level												
Less than \$15,000	(Reference)		(Reference)		(Reference)		(Reference)		(Reference)		(Reference)	
\$25,000 to < \$50,000	0.91 (0.77, 1.07)	0.235	0.86 (0.74, 1.00)	0.053	0.83 (0.71, 0.96)	0.013	0.85 (0.73, 0.99)	0.033	0.84 (0.72, 0.98)	0.025	0.83 (0.71, 0.97)	0.017
\$50,000 or more	0.78 (0.67, 0.92)	0.003	0.73 (0.63, 0.85)	<0.001	0.68 (0.58, 0.79)	<0.001	0.70 (0.60, 0.81)	<0.001	0.69 (0.60, 0.81)	<0.001	0.68 (0.58, 0.79)	<0.001
Health Insurance												
Have some form of insurance	0.78 (0.61, 1.00)	0.053	0.81 (0.64, 1.03)	0.085	0.85 (0.66, 1.08)	0.174	0.82 (0.64, 1.04)	0.100	0.84 (0.66, 1.07)	0.152	0.84 (0.66, 1.07)	0.158
Do not have some form of health insurance	(Reference)		(Reference)		(Reference)		(Reference)		(Reference)		(Reference)	
BMI												
Normal Weight or Underweight	(Reference)		(Reference)		(Reference)		(Reference)		(Reference)		(Reference)	
Overweight	1.26 (1.11, 1.42)	<0.001	1.26 (1.11, 1.42)	<0.001	1.23 (1.09, 1.39)	0.001	1.24 (1.10, 1.40)	0.001	1.25 (1.10, 1.42)	0.001	1.24 (1.09, 1.40)	0.001
Obese	1.54 (1.36, 1.74)	<0.001	1.59 (1.40, 1.79)	<0.001	1.56 (1.38, 1.77)	<0.001	1.56 (1.38, 1.76)	<0.001	1.60 (1.42, 1.81)	<0.001	1.61 (1.43, 1.82)	<0.001
Smoking history												
Never smoked	(Reference)		(Reference)		(Reference)		(Reference)		(Reference)		(Reference)	
Current or former smoker	1.21 (1.11, 1.33)	<0.001	1.22 (1.12, 1.34)	<0.001	1.30 (1.20, 1.42)	<0.001	1.30 (1.19, 1.42)	<0.001	1.28 (1.17, 1.40)	<0.001	1.31 (1.20, 1.42)	<0.001
COPD												
Yes	1.68 (1.45, 1.95)	<0.001	1.96 (1.71, 2.25)	<0.001								
No	(Reference)		(Reference)									
Diabetes												
Yes	1.13 (1.00, 1.27)	0.043			1.18 (1.05, 1.32)	0.005						
No	(Reference)				(Reference)							
Asthma												
Current	1.61 (1.41, 1.84)	<0.001					1.81 (1.60, 2.05)	<0.001				
Never or former	(Reference)						(Reference)					
Heart disease												
Yes	1.20 (1.06, 1.37)	0.005							1.39 (1.22, 1.57)	<0.001		
No	(Reference)								(Reference)			
Stroke												
Yes	1.08 (0.89, 1.29)	0.443									1.26 (1.06, 1.50)	0.008
No	(Reference)										(Reference)	

CHCs: chronic health conditions; 95% CI: 95% confidence interval; aOR: adjusted odds ratio

Appendix V. Chapter 4 Table S5. Model 2 Adjusted Odds Ratios for Long COVID in Cancer Survivors Compared to Non-Cancer Participants: MI analysis

Variable	Overall		Cancer		Non-cancer	
	aOR (95% CI)	p-value	aOR (95% CI)	p-value	aOR (95% CI)	p-value
Cancer history						
Yes	1.18 (1.07, 1.31)	0.001				
No	(Reference)					
Number of COVID-19 vaccinations received						
None	(Reference)		(Reference)		(Reference)	
One	0.94 (0.78, 1.14)	0.524	1.24 (0.69, 2.21)	0.466	0.92 (0.75, 1.12)	0.405
Two	0.86 (0.77, 0.97)	0.014	0.86 (0.60, 1.22)	0.396	0.86 (0.76, 0.97)	0.018
Three	0.74 (0.65, 0.84)	<0.001	0.75 (0.53, 1.07)	0.109	0.74 (0.64, 0.84)	<0.001
Four or more	0.68 (0.57, 0.81)	<0.001	0.61 (0.40, 0.93)	0.022	0.70 (0.58, 0.85)	<0.001
Age						
18–24 years	(Reference)		(Reference)		(Reference)	
25–34 years	1.08 (0.94, 1.23)	0.278	1.38 (0.57, 3.29)	0.475	1.07 (0.94, 1.23)	0.306
35–44 years	1.11 (0.96, 1.28)	0.144	1.43 (0.62, 3.32)	0.403	1.11 (0.96, 1.28)	0.176
45–54 years	1.17 (1.01, 1.35)	0.040	1.18 (0.52, 2.68)	0.691	1.18 (1.02, 1.38)	0.030
55–64 years	1.06 (0.91, 1.23)	0.460	1.29 (0.57, 2.92)	0.538	1.05 (0.90, 1.23)	0.534
65+ years	0.85 (0.73, 1.00)	0.051	1.07 (0.48, 2.40)	0.872	0.84 (0.71, 0.99)	0.042
Sex						
Male	(Reference)		(Reference)		(Reference)	
Female	1.75 (1.64, 1.87)	<0.001	1.69 (1.42, 2.02)	<0.001	1.76 (1.64, 1.88)	<0.001
Race/ethnicity						
Non-Hispanic white	(Reference)		(Reference)		(Reference)	
Non-White or Hispanic	0.96 (0.89, 1.03)	0.250	1.22 (0.90, 1.65)	0.198	0.94 (0.87, 1.01)	0.112
Education						
High School or less	(Reference)		(Reference)		(Reference)	
Attended College or Technical School	1.17 (1.08, 1.27)	<0.001	1.18 (0.95, 1.47)	0.143	1.17 (1.07, 1.27)	<0.001
Graduated from College or Technical	0.92 (0.84, 1.00)	0.064	0.94 (0.75, 1.19)	0.630	0.92 (0.84, 1.01)	0.071
Marital Status						

Married or A member of an unmarried couple	(Reference)		(Reference)		(Reference)	
Divorced or Widowed or Separated	1.17 (1.08, 1.28)	<0.001	1.05 (0.86, 1.28)	0.616	1.19 (1.08, 1.31)	<0.001
Never married	0.99 (0.90, 1.09)	0.836	0.99 (0.70, 1.40)	0.953	0.99 (0.90, 1.10)	0.901
Income Level						
Less than \$15,000	(Reference)		(Reference)		(Reference)	
\$25,000 to < \$50,000	0.86 (0.77, 0.95)	0.005	0.85 (0.66, 1.11)	0.245	0.86 (0.76, 0.97)	0.011
\$50,000 or more	0.78 (0.70, 0.87)	<0.001	0.71 (0.54, 0.95)	0.020	0.78 (0.70, 0.88)	<0.001
Health Insurance						
Have some form of insurance	0.85 (0.74, 0.98)	0.020	0.63 (0.36, 1.09)	0.097	0.86 (0.74, 0.99)	0.032
Do not have some form of health insurance	(Reference)		(Reference)		(Reference)	
BMI						
Normal Weight or Underweight	(Reference)		(Reference)		(Reference)	
Overweight	1.20 (1.10, 1.31)	<0.001	1.15 (0.91, 1.45)	0.254	1.21 (1.10, 1.33)	<0.001
Obese	1.54 (1.42, 1.67)	<0.001	1.43 (1.13, 1.80)	0.003	1.55 (1.42, 1.69)	<0.001
Smoking history						
Never smoked	(Reference)		(Reference)		(Reference)	
Current or former smoker	1.23 (1.15, 1.32)	<0.001	1.32 (1.11, 1.56)	0.002	1.22 (1.13, 1.31)	<0.001

MI: multiple imputation; 95% CI: 95% confidence interval; aOR: adjusted odds ratio