MILLIMAN WHITE PAPER

Post-acute COVID-19 mortality and morbidity effects

Brian Ivanovic, DO, MS

Milliman

Executive Summary

The World Health Organization recently declared COVID-19 EG.5 (Eris) to be a new coronavirus variant of interest at a time when infections and hospitalizations are again on the increase in the United States. Another highly mutated strain, BA.2.86, has now emerged in multiple countries. These are reminders that the pandemic is not yet behind us. What has been particularly notable about this pandemic, in contrast to recent influenza pandemics, is the development of persistent adverse health effects in a portion of infected individuals ranging from disparate symptoms such as cough and fatigue to new onset disease and premature mortality.

Much of the literature exploring persistent health effects after COVID-19 infection has focused on persistent symptoms, where those symptoms have occasionally lasted months or years after infection. Based on US government survey data, as many as 18 million individuals may currently be experiencing some level of persistent symptoms, of whom five million may experience symptoms that significantly limit their activity. These individuals have been classified as having long COVID. There has been more limited investigation of the findings that some individuals—even months after their infection—have developed new-onset disease or died prematurely.

This white paper focuses on published literature investigating the emergence of excess mortality and new-onset disease of insurance underwriting significance occurring beyond 30 days from the time of infection. Papers considering what might contribute to the emergence of these adverse morbidity and mortality effects are also reviewed, to provide an understanding of the mechanisms that might lead to organ damage and contribute to premature death.

In the reviewed papers, severity of original infection has been identified as a factor increasing the risk of adverse morbidity and mortality in the post-acute period. Since multiple organ systems are vulnerable to the COVID-19 virus, the range of adverse morbidity effects is quite varied, including findings of elevated cardiovascular risk (ischemic heart disease, heart failure, myocarditis, and coagulation disorders), neuropsychiatric risk (stroke, dementia, Parkinson's, depression), and renal and endocrine risk (diabetes).

Elevated risk of disability has also been noted in European studies compared to non-infected comparison groups. In papers investigating mortality outcomes, the pattern of observed mortality indicates a significant decline in risk as time from index COVID-19 infection increases. A key limitation of these papers is that the length of follow-up is one year or less, leaving the question of how long it takes for risks to return to a baseline state unanswered. Additionally, for individuals experiencing less-severe infections, the magnitude of relative risk is reduced after considering differences in average ages between those hospitalized for their infections and those not requiring hospitalization.

COVID-19's overall mortality effects persist in vital statistics data. The pandemic is not over, so it is impossible to predict how long these effects will last. However, longer-term follow-up studies may confirm the continued tapering of morbidity and mortality risks associated with COVID-19 infections. Finally, the risk of disease emergence in the post-acute period reaffirms the value of objective and rapidly accessible prescription, billing, and summarized electronic health record information to underwriters seeking to confirm the health status of applicants applying for insurance.

Introduction:

Multiple reports and studies in general population[1,2] and insured groups[3] have identified significant acute mortality impacts associated with SARS-CoV-2, subsequently referred to in this paper as COVID-19. Beyond the significant acute effects of COVID-19 on mortality, researchers have identified increases in both morbidity and mortality in the post-acute period, defined by some researchers as the time beyond 30 days from initial infection.[4] Individuals experiencing persistent symptoms in the post-acute period meet the definition for having long COVID or post-COVID conditions. Given the serious nature of some of the later-onset health problems these individuals face, it's important for insurers assuming life and health risk on such individuals to better understand post-acute COVID-19 morbidity and mortality.

As the COVID-19 pandemic has progressed, general population studies have now been published, providing initial insight into health effects experienced by individuals with post-acute COVID-19 during the first year after infection. This paper's purpose is to identify and summarize that literature, to understand what has been learned and what the implications of those findings might be over the longer-term post-pandemic period. Understanding the level of excess morbidity and mortality risk associated with post-acute COVID conditions, and whether that risk impacts COVID-19 survivors differentially, could provide information to assist insurers in pricing if these longer-term effects are material.

This paper is divided into four major sections. Section I provides the framework, scope, and definitions for this review. Section II summarizes published literature on post-acute COVID mortality effects. Section III considers the literature that has identified increased incident morbidity associated with post-acute COVID—a finding that has potential implications on longer term morbidity and mortality trends. In the concluding section we consider what has been reviewed and its implications for underwriting.

I. Background

CORONAVIRUS HISTORY IN HUMANS, PANDEMIC DECLARATION, AND RECOGNITION OF POST-ACUTE COVID-19 SEQUELAE

COVID-19 is the seventh coronavirus to infect humans.[5] Four of the seven types (229E, NL63, OC43 and HKU1), have been identified since the 1960s. Those coronaviruses typically cause mild to moderate upper-respiratory infections including some common colds. A more dangerous pathogen, SARS-CoV, was responsible for several outbreaks of severe acute respiratory syndrome in the early 2000s; fortunately, no cases have been identified since 2004. The more notable coronavirus strains that have gained widespread attention over the past decade are Middle East Respiratory Syndrome (MERS) and COVID-19.

MERS was first reported in Saudi Arabia in 2012. It was associated with higher acute morbidity and mortality compared to what has been observed with COVID-19 thus far. Persistent alterations in lung function, mental health issues, cardiovascular and neurologic disease, and reduced exercise capacity have been observed in MERS survivors. [6,7,8,9]

Unlike MERS, COVID-19 rapidly spread across the globe. The World Health Organization declared it a public health emergency of international concern at the end of January 2020, and a pandemic in March.[10] By the late spring of 2020, it became apparent that some individuals infected with COVID-19 were also experiencing persistent health effects. Most of these effects were symptoms of varying severity, but as will be reviewed in this paper, researchers also identified new-onset disease and, in some cases, observed deaths at higher-than-expected rates in previously infected individuals. In October of 2021, more than 18 months after the declaration of the pandemic, a new ICD-10 medical billing code U09.9, "Post COVID-19 condition," was released, allowing clinicians and researchers to more easily identify individuals with persistent health issues believed to be related to COVID-19.

[1] Sabo S., Johnson S., "Pandemic Disrupted Historical Mortality Patterns, Caused Largest Jump in Deaths in 100 Years" *Census.gov,* Mar 24, 2022 U.S. Deaths Spiked as COVID-19 Continued (census.gov) Accessed 8 July 2023

[2] SeyedAlinaghi S., Mirzapour P., Dadras O., et al., Characterization of SARS-CoV-2 different variants and related morbidity and mortality: a systematic review. *Eur J Med Res,* 26, 51 (2021). https://doi.org/10.1186/s40001-021-00524-8

[3] Individual Life COVID-19 Project Work Group, U.S. Individual Life COVID-19 Reported Claims Analysis – 4Q 2022 Update, June 2023 *SOA* U.S. Individual Life COVID-19 Reported Claims Analysis – Q4 (soa.org) Accessed 8, July 2023

[4] National Center for Immunization and Respiratory Diseases (NCIRD), Division of Viral Diseases, "Long COVID or Post-COVID Conditions" *CDC.gov,* Dec 16, 2022 Long COVID or Post-COVID Conditions | CDC Accessed 8, July 2023

[5] National Center for Immunization and Respiratory Diseases (NCIRD), Division of Viral Diseases, "Human Coronavrius Types" *CDC.gov,* Feb 15, 2020 Human Coronavirus Types | CDC Accessed 8, July 2023

[6] Ahmed H., Patel K., C. Greenwood D., et al., Long-term clinical outcomes in survivors of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome coronavirus (MERS) outbreaks after hospitalization or ICU admission: A systematic review and meta-analysis. *J Rehab Med*, 52(5), 1–11 (2020) https://doi.org/10.2340/16501977-2694

[7] Batawi S., Tarazan N., Al-Raddadi R., et al., Quality of life reported by survivors after hospitalization for Middle East respiratory syndrome (MERS). *Hlth Qual Life Outcomes*, 17:101 (2019) https://doi.org/10.1186/s12955-019-1165-2

[8] O'Sullivan O. Long-term sequelae following previous coronavirus epidemics. *Clin Med* (Lond). Jan;21(1): e68-e70. (2021) doi.org/10.7861/clinmed.2020-0204

[9] Roychoudhury S, Das A, Sengupta P, et al., Viral Pandemics of the Last Four Decades: Pathophysiology, Health Impacts and Perspectives. *Int J Env Res Pub Hlth.* 2020; 17(24):9411. https://doi.org/10.3390/ijerph17249411

[10] "Coronavirus disease (COVID-19) pandemic" *WHO.int* Coronavirus disease (COVID-19) pandemic (who.int) Accessed 8 July 2023

VARYING TERMINOLOGY

The delay in having an indicator for individuals experiencing persistent health effects from COVID-19 contributed to an environment where varying terminology emerged to identify affected individuals. Many alternative terms can be found, complicating literature searches for individuals with this condition. One can find post-acute COVID-19 effects described as long COVID, long-haul COVID, chronic COVID, post-acute sequelae of SARS-CoV2 infection (PASC), along with the post COVID-19 condition term. Additionally, the variation in persistent symptoms experienced by individuals meant that none of these labels defined a specific symptom but rather a potential constellation of symptoms or newly emerged disease. As a result, identification of the specific outcome and the time frame of its emergence, not the label applied, is required when reviewing this body of literature.

THEORIZED PATHWAYS TO POST-ACUTE ADVERSE OUTCOMES

Researchers' understanding of why individuals experience persistent post-acute COVID effects is still evolving. Several theorized pathways are identified in the literature that may explain at least some of the observed effects that will be discussed in this paper. The following list summarizes some of the more common theorized pathways to post-acute adverse outcomes.

- Cytokines causing damage to host cells
- Low-grade inflammation
- Upregulation of pro-coagulant factors increasing tissue damage
- Vascular endothelial damage leading to hyper-coagulability
- Persistent viral reservoirs in multiple organs

Alterations that may occur in some individuals in their immune system response to a COVID-19 infection are thought to be central to a number of pathways that can lead to tissue damage and persistent effects. A cytokine storm is an aberrant response of the immune system to infection which can lead to tissue damage due to the release of pro-inflammatory molecules that can have both immediate and possibly long-term effects on organs.[11] Levels of inflammatory markers such as C-reactive protein, D-dimer, neutrophil and lymphocyte counts have been observed to be elevated in individuals experiencing certain post-acute COVID sequelae.[12] When functioning normally, the lining of our blood vessels (vascular endothelium) expresses molecules that help prevent blood clotting. This function can be disrupted during viral and bacterial infections, leading to both micro-vascular tissue damage and blood clots[13] Unlike the influenza virus, which binds to hemagglutinin receptors exclusively in the respiratory tract, COVID-19 binds to angiotensin-converting enzyme 2 (ACE2) receptors present in many organs throughout the body. This provides an opportunity for persistent viral reservoirs to exist and, possibly, lead to prolonged infection or reinfections in some individuals.[14] Within infected organs recent research has identified that mitochondrial function may become impaired, leading to organ failure.[15] Therefore, multiple mechanisms may contribute to post-acute COVID-19 sequelae.

PERSISTENT SYMPTOMS IN THE POST-ACUTE PERIOD VS. NEW ONSET DISEASE AND MORTALITY

When considering the nature of the post-acute COVID-19 literature, there is a greater emphasis on symptoms being experienced by individuals after the acute phase of the infection vs. new onset disease or premature death. While it is clear that individuals experiencing symptoms lasting months suffer a decline in their quality of life, this paper will focus on the literature that followed individuals who developed new-onset disease or died outside of the acute period of infection as these endpoints can more directly be associated with pricing ramifications for life and health products.

[11] Mangalmurti N, Hunter CA., Cytokine Storms: Understanding COVID-19. *Immunity.* 2020;53(1):19-25. https://doi.org/10.1016/j.immuni.2020.06.017

[12] Maamar M, Artime A, Pariente E, et al., Post-COVID-19 syndrome, low-grade inflammation and inflammatory markers: a cross-sectional study. *Curr Med Res Opin*. 2022;38(6):901-909. https://doi.org/10.1080/03007995.2022.204299

[13] Conway, E.M., Mackman, N., Warren, R.Q. et al., Understanding COVID-19-associated coagulopathy. *Nat Rev Immunol* 22, 639–649 (2022). https://doi.org/10.1038/s41577-022-00762-9

[14] Buonsenso D, Piazza M, Boner AL, et al., Long COVID: A proposed hypothesis-driven model of viral persistence for the pathophysiology of the syndrome. *Allergy Asthma Proc.* 2022;43(3):187-193. https://doi.org/10.2500/aap.2022.43.220018

[15] Guarnieri J, Dybas J, Fazelinia H, et al., Core mitochondrial genes are down-regulated during SArS-COV-2 infection of rodent and human hosts. *Sci Translational Med* 2023;15(708) https://DOI:10.1126/scitranslmed.abq1533 Accessed 13 Aug 2023

II. Mortality considerations

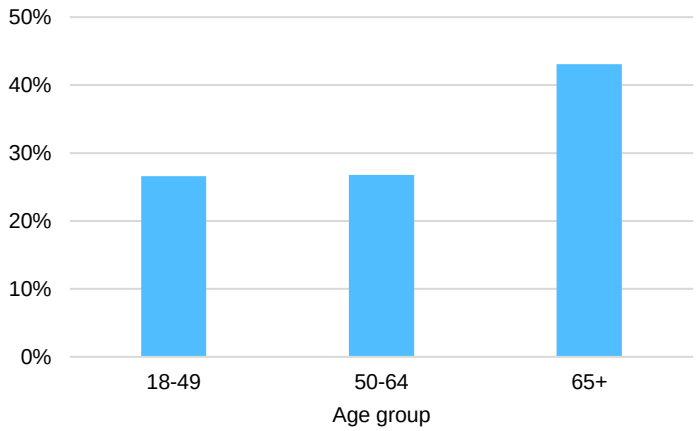
Of the 1.1 million+ U.S. COVID-19 deaths reported by the CDC (Centers for Disease Control)[16] through - late September 2023 and nearly seven million deaths worldwide[17], acute COVID-19 mortality remains the dominant infectious disease risk for life insurers' in-force blocks. Different COVID-19 variants have been associated with varying levels of virulence. The most-current circulating strains exhibit some of the lowest levels of mortality observed to date. However, COVID-19 continues to evolve, with new strains infecting individuals even if they have been previously infected and/or immunized.

While post-acute COVID-19 mortality is fortunately less common than during the acute infection[18], the window to observe the cumulative mortality impact of COVID-19 in those that did not die acutely remains short as of the writing of this paper (≈3½ years). In this paper, post-acute mortality will be defined as deaths occurring more than 30 days from the original date of infection. Published papers on post-acute COVID-19 mortality, as will be reviewed in this white paper, suggest residual excess risks may extend through the first year after infection. Longer follow-up studies have not yet been published.

In considering this research, note that studies presenting information on deaths occurring in the post-acute period come from many different countries. Various methods were used to identify comparison cohorts matching study participants. The study participants included tend to be concentrated in groups exposed to the original COVID-19 virus or other early variants. The findings of earlier studies might not reflect post-acute risks in individuals infected with more recent variants. It is important to note that eligibility for inclusion in a portion of the studies was based on being hospitalized for a COVID-19 infection. Hospitalization indicates that those infections were considered more severe; most individuals infected with COVID-19, even with earlier variants, were not hospitalized. Cohort selection was not contingent on the presence of a post COVID-19 condition billing code as that code had not yet been released, nor was selection based on persistent symptoms. All that was required was a history of COVID infection.

The risk of hospitalization for an acute infection is not uniform across age as noted in the following figure.[19]

ESTIMATED PREVALENCE OF HOSPITALIZATION FOR COVID-19: CDC FEBRUARY 2020-SEPTEMBER 2021



Individuals 65 and older were at a significantly elevated risk for hospitalization for COVID-19 infection between February 2020 and September 2021. Older individuals generally have a higher burden of health issues compared to younger individuals. Certain comorbid conditions more prevalent as age increases contribute to the risk of more severe COVID-19 infections. As a result, the average age of hospitalized cohorts is higher than non-hospitalized groups. Material differences in the expected death rates by age group will mean that the magnitude of absolute or relative excess deaths between study cohorts can vary, making risk comparisons between cohorts of different age difficult.

The length of the observation period, type, and pattern of excess mortality are also important when considering outcomes measured in these studies. Studies of chronic disease providing relative mortality risk estimates typically create statistics based on five or more years of observation. We have not had five years to assess the long-term impact of COVID-19 on mortality. Current risk estimates will likely change as longer follow-up studies are published.

[16] "COVID Data Tracker" *CDC.gov,* Jun 22, 2023 CDC COVID Data Tracker: Home Accessed 8 July 2023

[17] "WHO Coronavirus (COVID-19) Dashboard" *WHO.int* WHO Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data Accessed 8 July 2023

[18] Faes C, Abrams S, Van Beckhoven D, et al. Time between Symptom Onset, Hospitalisation and Recovery or Death: Statistical Analysis of Belgian COVID-19 Patients. Int J Environ Res Public Health, 2020 October 17

[19] "Estimated COVID-19 Burden" *CDC.gov,* Aug 12. 2022 Estimated COVID-19 Burden | CDC Accessed 8 July 2023

Some studies only provided an overall risk for the full period of observation while others provided data on sub-annual intervals, allowing for derivation of relative risk estimates for different sub-annual intervals. The pattern of excess mortality over time within an interval is important to consider. A general theme emerging out of the available studies is that post-acute excess deaths are not uniformly distributed over the study period. Rather, they are concentrated earlier in the post-acute period. We see an analogous situation with certain underwriting impairments such as individuals recovering from cancer or coronary artery bypass surgery, where a substantial portion of the excess mortality is concentrated near the precipitating event. This pattern has ramifications when assessing the future magnitude of excess mortality in individuals who have survived beyond this higher excess-mortality risk period. With this background let's consider the findings of studies looking at post-acute mortality in hospitalized cohorts.

POST-ACUTE MORTALITY IN HOSPITALIZED COHORTS

The following table summarizes a subset of studies of post-acute COVID-19 mortality in hospitalized cohorts.

PARTICIPANTS FOLLOWED POST HOSPITAL DISCHARGE						INTERVAL AVAILABLE FOR ANALYSIS			
STUDY	**COUNTRY**	**COHORT SIZE**	**AGE[1]**	**% FEMALE**	**COHORT ACCRUAL-PERIOD**	**>30D-3M**	**>3M-6M**	**>6M**	**COMPARISON POPULATION PROVIDED**
Bhaskaran et al.	UK	24,673	66 (53-78)	44%	Feb-Dec 2020	X			Yes
Gunster et al.	Germany	8,679	69 (57-82)	46%	Feb-April 2020	X	X		--[2]
Butler et. al.	US	16,431	63 (26)	48%	Mar 20-Jan 21	X	X	X	--[2]
Meza-Torres et al.	UK	1,307	55 (14)	54%	Mar 20-Apr 21		30d to 6m		--[2]
Manious et al.	US	178	--[3]	58%	Jan-Jun2020	X	X	X	Yes
Ortega-Paz et al.[4]	Spain/Italy	4,583	63 (17)	43%	Feb-Jul 2020	X	X	X	Yes
Tisler et al.	Estonia	3,949	65 (17)	54%	Feb 20-Feb 21	X	X	X	Yes

[1] Age is either mean or median. Interquartile age range or standard deviation provided in parenthesis.
[2] Expected mortality calculated from time-frame matched country specific life table
[3] Average age not provided, 46% were less than age 65.
[4] Study did not separate hospitalized vs. not hospitalized, 92% were hospitalized.

In many of these papers it was possible to derive sub-interval relative mortality, either based on specific statistics provided in the paper or based on calculating subinterval relative mortality estimates using standard techniques developed for analysis of survival and mortality curves.[20,21] These studies were predominantly from western countries and included individuals in their mid to late 60s. The patient accrual periods were during the first 6 to 16 months of the pandemic. The studies ranged widely in cohort size and approximately half followed study participants to a maximum of one year. Study cohorts were formed from linked primary care – hospital registries (Bhaskaran et al.,[22] Butler et al.,[23] Manious et al.,[24] Meza-Torres et al.[25]), and hospital registries, (Gunster et al.,[26] Ortega-Paz et al.,[27] Tisler et al. [28]).

[20] "Basic Mortality Methodology Course" *American Academy of Insurance Medicine* The American Academy of Insurance Medicine (aaimedicine.org)

[21] Pokorski RJ, Mortality methodology and analysis seminar, *J Ins Med* 1988;20(4);20-45

[22] Bhaskaran K, Rentsch CT, Hickman G, et al. Overall and cause-specific hospitalisation and death after COVID-19 hospitalisation in England: A cohort study using linked primary care, secondary care, and death registration data in the OpenSAFELY platform. *PLoS Med*. 2022;19(1):e1003871. https://doi.org/10.1371/journal.pmed.1003871

[23] Butler M, Best J, Mohan S, et al., Mechanical ventilation for COVID-19: Outcomes following discharge from inpatient treatment. *PLoS ONE* 2023;18(1): e0277498. https://doi.org/10.1371/journal.pone.0277498

[24] Mainous A, Rooks B, Wu V, et al., Post-acute Sequelae Among Adults: 12 Month Mortality Risk. *Frontiers in Med* 2021; 8 https://doi.org/10.3389/fmed.2021.778434

[25] Meza-Torres B, Delanerolle G, Okusi C, et al. Differences in Clinical Presentation With Long COVID After Community and Hospital Infection and Associations With All-Cause Mortality: English Sentinel Network Database Study. *JMIR Public Health Surveill*. 2022;8(8):e37668. https://doi.org/10.2196/37668

[26] Gunster C. Busse R, Spoden M, et al., 6-month mortality and readmissions of hospitalized COVID-19 patients: A nationwide cohort study of 8,679 patients in Germany *PLoS ONE* 2021 16(8): e0255427. https://doi.org/10.1371/journal. pone.0255427

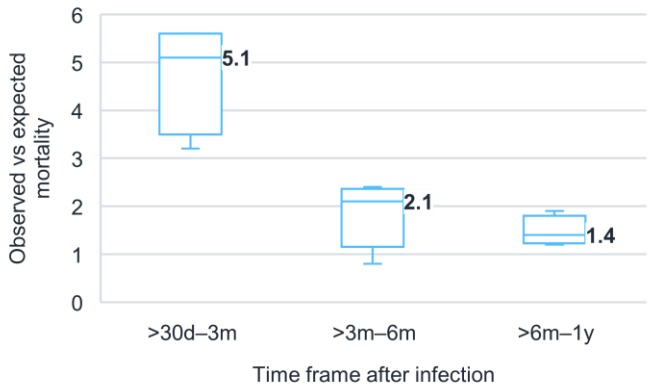
[27] Ortega-Paz L, Arevalos V, Fernandez-Rodrıguez D, et al. One-year cardiovascular outcomes after coronavirus disease 2019: The cardiovascular COVID-19 registry. *PLoS ONE* 2022 17(12): e0279333. https://doi.org/10.1371/journal.pone.0279333

[28] Tisler A, Stirrup O, Pisarev H, et al., Post-acute sequelae of COVID-19 among hospitalized patients in Estonia: Nationwide matched cohort study. *PLoS ONE* 2022 17(11): e0278057. https://doi.org/10.1371/journal.pone.0278057

Across the whole period of observation, Bhaskaran found a statistically significant 4.8-fold increase in the multivariate hazard of all-cause mortality from 30 days to three months after hospital discharge. The studies by Gunster, Butler and Meza-Torres did not include a matched non-COVID comparison population, only providing cumulative all-cause mortality results at different intervals after hospitalization. Gunster's study group experienced 5.4 times higher mortality between 30 days and six months as compared to expected mortality matched by average age and length of exposure from a 2022 German total population life table.[29] Based on a UK population life table, Meza-Torres' COVID-19 cohort had a 6.2-fold increase in mortality between 30 days and six months after the index infection.[30] Butler's hospitalized COVID cohort that was not mechanically ventilated experienced a 2.1-fold increase in mortality between 30 days and one year after discharge based on a New York state life table.[31] Multivariate adjusted all-cause mortality hazard ratio results over a period of observation between 30 days post hospitalization to one year for Manious, Ortega-Paz, and Tiser was 2.5, 2.8, and 2.6 times expected morality, respectively, all representing statistically significant increases in mortality in their COVID-infected groups of individuals who had survived for 30 days post hospital discharge.

The findings from this group of studies suggested that longer duration follow-up after the post-acute period was associated with lower relative mortality risk, a result that implies that whatever issues were causing post-acute COVID mortality might be moderating over time. To assess this further, estimates of the ratio of observed to expected all-cause mortality were calculated for three sub-interval periods; 30 days to three months, three months to six months, and six months to one year for the studies that had information available for at least one of the periods. The following graph aggregates these ratios within boxplots for the six studies where the appropriate sub-annual interval data was available.

RISK OF EXCESS MORTALITY IN THE POST-ACUTE COVID PERIOD: HOSPITALIZED COHORTS



A higher risk of death in the immediate post-acute period is seen in the graph with evidence of reduced risk in latter periods. While most studies demonstrated a persistence of elevated observed to expected all-cause mortality risk within each subinterval, calculations of subinterval mortality in the Ortega-Paz study suggested risk was not elevated in the three to six-month time frame in their hospitalized cohort but was elevated before and after that sub-interval. The next section presents equivalent information on post-acute mortality in non-hospitalized groups of individuals whose COVID-19 infection was presumably less severe.

POST-ACUTE MORTALITY IN NON-HOSPITALIZED COHORTS

Most individuals infected with COVID-19 are not hospitalized. For that reason, it is important to consider whether elevations in mortality in the post-acute period after COVID infection not requiring hospitalization are also observed. In all but one study, the average age of non-hospitalized cohorts (≈45-55) was significantly lower than for hospitalized cohorts. They had similar patient accrual periods to the hospitalized cohort studies, meaning that we are again observing the effect of earlier COVID-19 infections in these cohorts and not any effects that might be observed from more recent infections. Most followed study participants to a maximum of one year. Two of the studies did not provide separate results for their non-hospitalized study populations, which could impact the magnitude of excess risk compared to studies with cohorts that were 100% non-hospitalized. The following table summarizes a subset of studies of post-acute COVID mortality in predominantly non-hospitalized cohorts.

[29] 2020 German Total Population Life Table, Last modified Jun 3, 2022, *Mortality.org* Human Mortality Database Accessed 8 July 2023

[30] 2020 United Kingdom Population Life Table, Last modified May 27, 2022, *Mortality.org* Human Mortality Database Accessed 8 July 2023

[31] 2020 New York State Life Table, *National Vital Statistics Reports* 2022: 71:2 National Vital Statistics Reports Volume 71, Number 2 August 23, 2022 (cdc.gov) Accessed 8 July 2023

PREDOMINANTLY NON-HOSPITALIZED GROUPS						INTERVAL AVAILABLE FOR ANALYSIS			
STUDY	COUNTRY	COHORT SIZE	AGE[1]	% FEMALE	COHORT ACCRUAL-PERIOD	>30D-3M	>3M-6M	>6M	COMPARISON POPULATION PROVIDED
Manious et al.	US	246	--[3]	65%	Jan 20-Jun 20		30d to 12m		Yes
Maestre-Muniz et al.	Spain	321	56 (18)	45%	Mar 20-Jun 20	X	X	X	--[2]
Uuskula et al.	Estonia	61,063	44 (21)	54%	Feb 20-Feb 21	X	X	X	Yes
Raisi-Estabragh et al.[4]	UK	17,871	65 (58-73)	53%	Mar 20-Feb 21	X			Yes
Meza-Torres et al.	UK	6,316	45 (15)	67%	Mar 20-Apr 21		30d to 6m		--[2]
DeVries et al.[4]	US	13,435	50 (15)	59%	Apr 20-Jul 21	X	X	X	Yes

[1] Age is either mean or median. Interquartile age range or standard deviation provided in parenthesis.
[2] Expected mortality calculated from time-frame matched country specific life table.
[3] Average age not provided, 80% were less than age 65.
[4] Percent non-hospitalized in Raisi-Estabragh and DeVries studies: 80% and 73% respectively.

The proportion of non-hospitalized individuals in the DeVries et al.[32] study was 73%. In the Raisi-Estabragh et al.[33] study the non-hospitalized proportion was 80%. Neither the previously cited studies by Manious et al. and Meza-Torres et al. nor the new studies by Maestre-Muniz et al.[34], and Usuküla et al.[35] included hospitalized individuals in the specific cohorts reviewed here.

Individuals in these studies were obtained from commercial health plans (DeVries), emergency rooms (Maestre-Muniz), or linked primary care-hospital-vital status registries (Raisi-Estabragh, Usuküla, Manious et al., Meza-Torres). The all-cause mortality risk estimates in these predominantly non-hospitalized groups are more varied than the hospitalized cohorts, and there are fewer studies available upon which to draw conclusions. Younger average ages in most of the studies may have contributed to more elevated ratios of observed to expected mortality.

Across a brief period of observation in the post-acute period (30d to ≈4.7 months) Raisi-Estabragh noted a 9.7-fold statistically significant increase in the hazard of mortality in their post-acute COVID group compared to a matched uninfected cohort. Over a follow-up period beginning 30 days post infection and ending six months post infection, Meza-Torres did not find elevated mortality in their UK non-hospitalized group based on expected mortality from a gender- and time-frame-matched UK population life table.

During a one-year period of observation for those who survived at least 30 days after COVID-19 diagnosis, DeVries noted a 2.3-fold increase in all-cause mortality in their post-acute COVID group compared to a matched non-COVID infected cohort. Other investigators found widely divergent increases in all-cause mortality when following study populations out to one year. Maestre-Muniz found a 5.2-fold increase compared to expected mortality matched by average age and length of exposure from a 2022 total population life table from Spain.[36] Manious found a non-statistically significant 1.3-fold increase in all-cause mortality risk over their 11-month follow-up beyond the acute period of infection. No increase in mortality was observed in Usuküla's non-severe COVID Estonian study cohort compared to a matched population referent.

There are fewer available studies of predominantly non-hospitalized cohorts, so it is not possible to produce summary boxplots for all three subinterval periods within the first annual interval. For the 30-day to 3-month time frame, observed to expected mortality was elevated 7.8-fold and 5.3-fold in the Maestre Muniz and DeVries studies, respectively. Between three months and six months, risk was elevated 10.4-fold and 2.2-fold respectively by the same investigators. For the six-month to one-year period, the respective elevations were 3.9-fold and 1.1-fold. Similar to the results from the hospitalized COVID-19 cohorts, the findings from this group of studies suggest that longer duration follow-up after the post-acute period was associated with lower relative mortality risk or possibly no increased risk in at least some groups.

[32] DeVries A, Shambhu S, Sloop S, et al., One-Year Adverse Outcomes Among US Adults With Post–COVID-19 Condition vs Those Without COVID-19 in a Large Commercial Insurance Database. *JAMA Health Forum. 2023*;4(3): e230010. https://doi.org/10.1001/jamahealthforum.2023.0010

[33] Raisi-Estabragh Z, Cooper J, Salih A, et al. Cardiovascular disease and mortality sequelae of COVID-19 in the UK Biobank. *Heart.* 2022;109(2):119-126. https://doi.org/10.1136/heartjnl-2022-321492

[34] Maestre-Muñiz MM, Arias Á, Mata-Vázquez E, et al., Long-Term Outcomes of Patients with Coronavirus Disease 2019 at One Year after Hospital Discharge. *J of Clin Med.* 2021; 10(13):2945. https://doi.org/10.3390/jcm10132945

[35] Uusküla A, Jürgenson T, Pisarev H, et al., Long-term mortality following SARS-CoV-2 infection: A national cohort study from Estonia, *Lancet Regional Health - Europe*, 2022; 18:100394 https://doi.org/10.1016/j.lanepe.2022.100394

[36] 2020 Spain Population Life Table, Last modified Feb 23, 2022, *Mortality.org* Human Mortality Database Accessed 8 July 2023

From an underwriting perspective these studies suggest that time from index COVID infection is an important consideration in assessing the magnitude of any post-acute excess risk. This seems particularly true in individuals who experienced more severe infections, where at least some studies have found evidence of persistent risk extending out at least one year from the index COVID infection. In this next section we will review risk factors for post-acute COVID mortality as identified in the reviewed papers.

RISK FACTORS FOR POST-ACUTE MORTALITY

Several risk factors have been noted to increase post-acute COVID all-cause mortality risk. Many are the same factors that contribute to more severe acute COVID infections and symptoms associated with long COVID, but some researchers specifically investigating risks for post-acute COVID mortality have noted differences. As an example of where differences in risk factors have been observed, female gender has been considered a risk factor for the persistent symptoms associated with long COVID, however, Gunster found male gender to be a risk factor for post-acute COVID mortality. Gunster's finding is consistent with male gender also being a risk factor for acute COVID mortality.[37] Increasing age, a higher burden of pre-existing disease, proximity to the time of index infection, and more severe infection have also been reported to increase post-acute COVID mortality risk within the papers reviewed.

Reinfection with COVID-19 also increases risk of death. Data from New York State and the UK suggests that approximately 5% to 10% of individuals have been reinfected with COVID.[38,39] With the ongoing evolution of new variants and limited time of effectiveness of current vaccines, reinfection of a larger number of individuals seems likely. Two studies conducted on U.S. Veterans have evaluated the risk associated with COVID reinfection. In the study by Al-Aly et al.[40] non-hospitalized individuals were noted to have a 1.3-fold increased hazard of all-cause mortality beyond the first 30 days of illness through a six-month follow-up. Bowie et al., identified that this increased risk of death after reinfection declined over a six-month time frame.[41]

The relation between vaccinations and post-acute COVID mortality seems less clear than what has been observed specific to vaccine effects during the acute infection phase. More recent vaccinations lower the risk of infection severity, hospitalization, and mortality.[42] However, the effectiveness of vaccination is reduced over time and as new strains emerge, vaccines designed against legacy strains lose effectiveness.[43] Finally, current vaccine booster uptake rates in the U.S. are low; only 17% of residents have obtained the updated bivalent booster dose.[44] Al-Aly et al. found a 33% reduction in the risk of death in vaccinated U.S. Veterans who became reinfected with COVID-19, suggesting partial protection against reinfection-related mortality over a six-month time frame. In contrast, Bowe et al.'s study failed to find any reduction in the risk of death in a vaccinated reinfected group as compared with a reinfected cohort who had not been vaccinated. Furthermore, this lack of effect persisted when the vaccinated reinfected group was further analyzed by number of vaccinations received. In a much-younger study population compared with the Veterans' study, Meza-Torres et al. identified a profound reduction in all-cause mortality with vaccination (odds ratio 0.10) in individuals having a diagnosis of, or referral for, long COVID. However, given the time frame of study accrual, less than 3.5% of their study cohort had been vaccinated. Similarly, the patient accrual period for other studies reviewed in this paper generally predated widespread vaccine availability, so we are left without a substantial body of literature from which to draw a definitive conclusion on the impact of vaccinations on mortality in the post-acute period.

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

[38] "COVID-19 Reinfection Data" *Coronavirus.health.ny.gov* COVID-19 Reinfection Data | Department of Health (ny.gov) Accessed 8 July 2023

[39] "Cases in United Kingdom" Last updated July 6, 2023, *Coronavirus.data.gov.uk* Cases in the UK | Coronavirus in the UK (data.gov.uk) Accessed 8 July 2023

[40] Al-Aly, Z., Bowe, B. & Xie, Y. Long COVID after breakthrough SARS-CoV-2 infection. *Nat Med* 2022 28, 1461–1467 https://doi.org/10.1038/s41591-022-01840-0

[41] Bowe, B., Xie, Y. & Al-Aly, Z. Acute and postacute sequelae associated with SARS-CoV-2 reinfection. Nat Med 2022 28, 2398–2405 https://doi.org/10.1038/s41591-022-02051-3

[42] "Impact of vaccination on risk of COVID-19 related mortality" *CDC.gov* Nov 16, 2022 Impact of Vaccination on Risk of COVID-19–Related Mortality (cdc.gov) Accessed 8 July 2023

[43] Wu N, Joyal-Desmarais K, Ribeiro P, et al., Long-term effectiveness of COVID-19 vaccines against infections, hospitalizations, and mortality in adults: findings from a rapid living systematic evidence synthesis and meta-analysis up to December, 2022 *Lancet: Resp Med* 2023 11(5):439-52 https://doi.org/10.1016/S2213-2600(23)00015-2

[44] "COVID-19 Vaccinations in the United States" May 11, 2023 *CDC.gov* CDC COVID Data Tracker: Vaccinations in the US Accessed 8 July 2023

III. Morbidity considerations

While the current evidence identifies a declining pattern of excess mortality risk in the post-acute COVID period, studies in western populations have also identified elevated risk of certain diseases of underwriting significance developing in individuals infected with COVID-19. Recall that the COVID virus binds to ACE2 receptors throughout the body, potentially infecting and damaging many different organs. Many of these conditions are chronic and may increase subsequent mortality risk in affected individuals.

If COVID infections increase the incidence of future disease, a higher morbidity burden could impact future mortality rates, mortality trends, and the protective value of underwriting screens designed to identify those morbidity endpoints in applicants. In this next section, we will review the current evidence detailing the types of chronic disease risk that have been investigated and review some evidence that suggests that risks associated with certain conditions emerging in the post-acute period may only be transiently elevated.

Many of the studies that will be reviewed identify higher morbidity risk in individuals with severe COVID-19 infections requiring hospitalization. Because most COVID infections do not require hospitalization, the focus in this section will be on risks observed in individuals with COVID infections that were less severe. These study populations were either predominantly or completely made up of non-hospitalized individuals. Similar to the magnitude of risk observed with post-acute COVID mortality, a few articles looking at the pattern of risk over time find a decline in incident disease emergence as the time frame between COVID-19 infection and onset of disease emergence increases. Because long-term outcomes secondary to emergence of incident disease should be a key interest of companies holding long-term risk on policyholders, we will focus on risk estimates reflective of the longest available follow-ups. For those interested in risk estimates on hospitalized cohorts and over shorter durations of follow-up, the reader is referred to the referenced papers in this section.

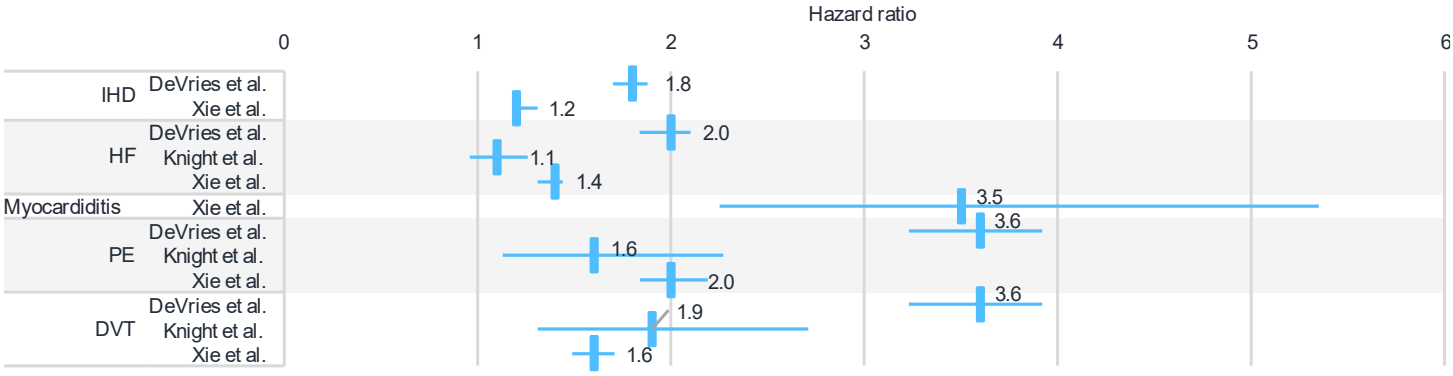
CARDIOVASCULAR OUTCOMES IN THE POST-ACUTE PERIOD

Five different cardiovascular disease endpoints were investigated in this group of papers, including: ischemic heart disease (IHD), heart failure (HF), myocarditis, pulmonary embolus (PE), and deep vein thrombosis (DVT). To reinforce the underwriting significance of these cardiovascular conditions, estimates of elevated risk based as noted in published literature are provided.

With respect to cardiovascular disease, publications assessing the mortality risk of IHD identify a 2.7-fold increase in all-cause mortality risk.[45]The equivalent increases in mortality risk for HF, myocarditis, PE and DVT were in the 2- to 3-fold range.[46,47,48,49]

CARDIOVASCULAR INCIDENT OUTCOMES, PREDOMINANTLY NON-HOSPITALIZED COHORTS

Outcomes measured at 12 months



[45] Reynolds, H, Shaw L, Min J, et. al., Outcomes in the ISCHEMIA Trial Based on Coronary Artery Disease and Ischemia Severity, Circulation 2021 144 (13):1024-1038 https://doi.org/10.1161/CIRCULATIONAHA.120.049755

[46] Wilkin J, Hileman G, Genuardi J, et.al., Analysis of Long-Term Care Insurance Experience for Insured by Diagnosis at Issue, https://www.soa.org/globalassets/assets/library/journals/actuarial-practice-forum/2007/october/apf-2007-10-hileman-genuardi.pdf Accessed Sept. 9th, 2023

[47] Lampejo T, Durkin SM, Bhatt N, et. al., Acute myocarditis: aetiology, diagnosis and management. Clin Med (Lond). 2021;21(5):e505-e510. doi:10.7861/clinmed.2021-0121

[48] Gómez, C.A., Sun, CK., Tsai, IT. et al. Mortality and risk factors associated with pulmonary embolism in coronavirus disease 2019 patients: a systematic review and meta-analysis. Sci Rep 11, 16025 (2021). https://doi.org/10.1038/s41598-021-95512-7

[49] Sogaard K, Schmidt M, Pedersen L, et al., 30-Year Mortality After Venous Thromboembolism: A Population based Cohort Study, Circulation. 2014;130:829–836 https://doi.org/10.1161/CIRCULATIONAHA.114.009107

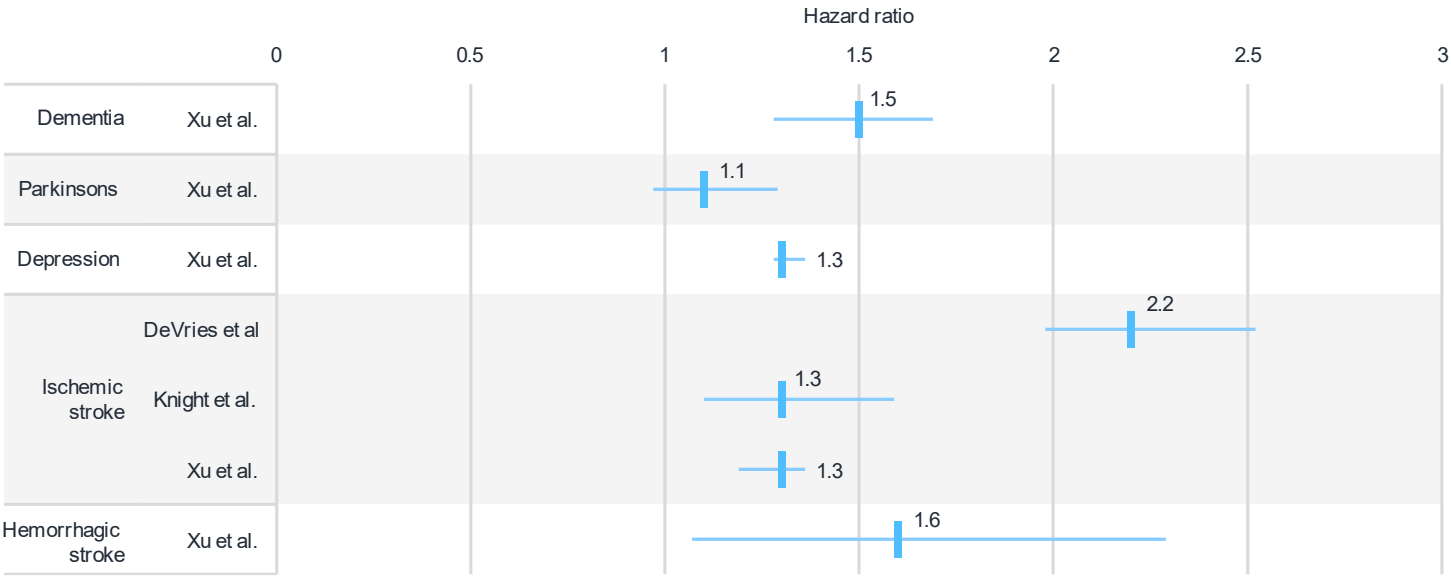
Studies investigating the risk of cardiovascular disease emerging in the post-acute COVID period are summarized in the above graph. The DeVries study of individuals (average age 50, 73% non-hospitalized) from a commercial U.S. insurance database assessed four of the five listed cardiovascular outcomes over a 12-month period. Compared to matched controls, risk for the measured cardiovascular outcomes was elevated between 1.8 times (IHD) and 3.6 times (PE and DVT) compared to an uninfected control group. In a U.S. Veterans population (average age 60, 100% non-hospitalized) Xie et al. found elevated risks against a matched control population for all five outcomes, ranging from a 1.2-fold elevation for IHD to more than a three-fold elevation for myocarditis[50]. Knight et al. identified a persistent elevation of cardiovascular risk in weeks 27 to 49 of follow-up after COVID-19 diagnosis (average age 47, 100% non-hospitalized) fold increase) and DVT (1.9-fold increase). [51] Heart failure risk was also elevated in the Knight study, but the result did not achieve statistical significance compared to elevations in risks that were statistically significant in other studies.

With a decline in risk estimates over longer duration, not all studies looking at cardiovascular outcomes in non-hospitalized individuals with COVID-19 in the post-acute period found statistically significant elevations in cardiovascular disease risk. Included in this group are studies by Rezel-Potts et al.[52] on a UK cohort and Mizrahi et al.[53] on an Israeli cohort. In both cases the average age of their study participants was low (35 and 25, respectively).

NEUROPSYCHIATRIC OUTCOMES

NEUROPSYCHIATRIC INCIDENT OUTCOMES, PREDOMINANTLY NON-HOSPITALIZED COHORTS

Outcomes measured at 12 months



[50] Xie, Y., Xu, E., Bowe, B. et al. Long-term cardiovascular outcomes of COVID-19. *Nat Med* 2022 28, 583–590 https://doi.org/10.1038/s41591-022-01689-3

[51] Knight R, Walker V, Ip S, et al., Association of COVID-19 With Major Arterial and Venous Thrombotic Diseases: A Population-Wide Cohort Study of 48 Million Adults in England and Wales *Circulation* 2022 146(12):892-906 https://doi.org/10.1161/CIRCULATIONAHA.122.060785

[52] Rexel-Potts E, Douiri A, Sun X, et al., Cardiometabolic outcomes up to 12 months after COVID-19 infection. A matched cohort study in the UK. *PLoS Med* 2022 19(7): e1004052 https://doi.org/10.1371/journal.pmed.1004052

[53] Mizrahi B, Sudry T, Flaks-Manov N, et al., Long covid outcomes at one year after mild SARS-CoV-2 infection: nationwide cohort study *BMJ* 2023; 380: e072529 https://doi.org/10.1136/bmj-2022-072529

Studies investigating the emergence of neuropsychiatric conditions in the post-acute period have also been published. These conditions include neurologic conditions such as dementia, Parkinson's disease, and stroke and psychiatric conditions such as depression. As found with the various cardiovascular disease endpoints previously discussed, mortality risk is also elevated in those developing neuropsychiatric conditions. Survival after a diagnosis of certain forms of dementia can be less than seven years.[54,55] Relative increases in mortality for Parkinson's and depression can be elevated more than 2-fold.[56,57] For stroke, a 2- to 4-fold increase in mortality risk has been observed.[58,59]

The studies by DeVries et al. and Knight et al. reviewed in the cardiovascular section also included risk estimates for ischemic stroke, with both investigators finding statistically significant elevations in ischemic stroke (1.3x and 2.2x increase, respectively) compared to their respective matched control populations. In another study of U.S. Veterans by Xu et al.,[60] (average age 60, 100% non-hospitalized) a wide variety of neurologic and psychiatric outcomes were assessed. In addition to finding an increased risk of ischemic stroke compared to a matched uninfected control group, Xu noted statistically significant elevations in hemorrhagic stroke (1.6x), depression (1.3x) and dementia (1.5x increase). The risk for Parkinson's disease was also elevated in the Xu study but was not statistically significant. The Rezel-Potts and Mizrahi studies of much younger non-hospitalized COVID-infected populations also investigated neuropsychiatric outcomes, without finding statistically significant elevations in risk.

RENAL AND ENDOCRINE OUTCOMES

Downstream mortality risk is also elevated with renal disease and diabetes. Even with timely dialysis, individuals developing end-stage renal disease have a 20% to 50% risk of death over 24 months.[61,62] All-cause mortality risk in diabetes can range from a 1.5- to 5-fold elevation depending on age, severity and complications.[63,64] In a shorter period of follow up (5½ months) the previously discussed study by Bowe et al. (average age 62, 100% non-hospitalized) found a 1.8-fold increase in end-stage renal disease risk. Kidney injury during the acute phase of a COVID infection may predispose individuals to later-onset chronic kidney disease[65].

The risk for type II diabetes at one year post infection was increased in the previously discussed Mizrahi (≈1.3x) and Xie (1.25x) studies. In a Canadian study with a follow-up of 8.5 months, Naveed et al. noted a 1.2-fold increased risk of incident insulin- or noninsulin-dependent diabetes in a COVID-positive cohort compared to matched controls.[66] Naveed estimated that their study findings translated to a 3% to 5% excess burden of diabetes at the population level. Cromer et al. noted that newly diagnosed diabetes at COVD-19 presentation was associated with lower serum glucose levels but higher inflammatory markers.[67] Their study found about half of these individuals had a regression in diabetes, suggesting residual stress hyperglycemia as the putative pathophysiologic mechanism.

[54] Price A, Farooq R, Yuan JM, et al., Mortality in dementia with Lewy bodies compared with Alzheimer's dementia: a retrospective naturalistic cohort study. *BMJ Open.* 2017;7(11):e017504. Published 2017 Nov 3. doi:10.1136/bmjopen-2017-017504

[55] Duckett L, Alzheimer's Dementia: Morbidity and Mortality, *J of Insurance Medicine*, 2001; 33:227-234

[56] Bäckström D, Granåsen G, Domellöf M, et al., Early predictors of mortality in parkinsonism and Parkinson disease, A population-based study *Neurology* Nov 2018, 91 (22) e2045-e2056; DOI: 10.1212/WNL.0000000000006576

[57] Oude Voshaar, R., Aprahamian, I., Borges, M., et al.,Excess mortality in depressive and anxiety disorders: The Lifelines Cohort Study. *European Psychiatry*, 64(1), E54. doi:10.1192/j.eurpsy.2021.2229

[58] Lund R, Lacunar Infarction, Mortality over time and mortality relative to other ischemic strokes, *J of Insurance Medicine,* 2014; 44:32-37

[59] Rutten-Jacobs LC, Rutten-Jacobs LC, Arntz RM, et al. Long-term mortality after stroke among adults aged 18 to 50 years. *JAMA*. 2013 Mar;309(11):1136-1144. DOI: 10.1001/jama.2013.842. PMID: 23512060.

[60] Xu, E., Xie, Y. & Al-Aly, Z. Long-term neurologic outcomes of COVID-19. Nat Med 2022 28, 2406–2415. https://doi.org/10.1038/s41591-022-02001-z

[61] Hashmi MF, Benjamin O, Lappin SL. End-Stage Renal Disease. [Updated 2023 Feb 19]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK499861/ Accessed Sept 27, 2023

[62] Neild G, Life expectancy with chronic kidney disease: an educational review, *Pediatr Nephrol* (2017) 32:243–248 DOI 10.1007/s00467-016-3383-8

[63] Freitas S, MacKenzie R, Wylde D, All-cause mortality for diabetics or individuals with hyperglucemia applying for life insurance J of Insurance Medicine 2016;46:2–12 https://doi.org/10.17849/0743-6661-46.1.2

[64] Baena-Diez J, Penafiel J, Subirana I, Risk of Cause-Specific Death in Individuals With Diabetes: A Competing Risks Analysis, Diabetes Care 2016;39:1987–1995 | DOI: 10.2337/dc16-0614

[65] Yende S, Parikh C, Long COVID and kidney disease, Nature Reviews Nephrology, December 2021: 792-793

[66] Naveed Z, Velásquez García HA, Wong S, et al. Association of COVID-19 Infection With Incident Diabetes [published correction appears in JAMA Netw Open. 2023 May 1;6(5): e2316822]. *JAMA Netw Open.* 2023;6(4): e238866. https://doi.org/10.1001/jamanetworkopen.2023.8866

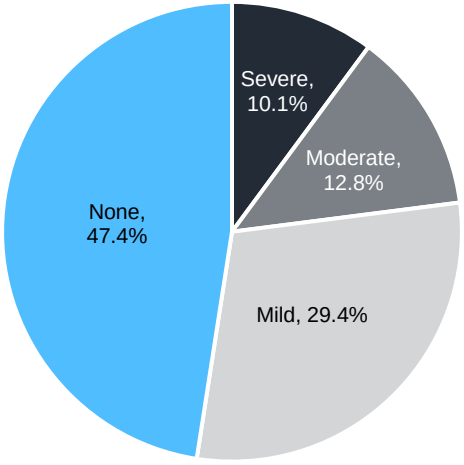
[67] Cromer S, Colling C, Schatoff D, et al., Newly diagnosed diabetes vs. pre-existing diabetes upon admission for COVID-19: Associated factors, short-term outcomes, and long-term glycemic phenotypes, Journal of Diabetes and its Complications. *J Diabetes Comp* 2022 36(4)108145 https://doi.org/10.1016/j.jdiacomp.2022.108145

OTHER ADVERSE OUTCOMES

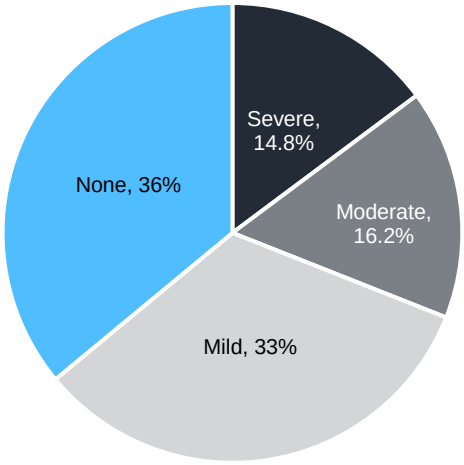
Disability

Significant disability is also an adverse prognostic indicator. Individuals with disability have a more than 2-fold increase in all-cause mortality risk depending on the underlying nature of the disability.[68,69]

WHODAS: CONTROL GROUP



WHODAS: > 12 WEEKS AFTER POSITIVE COVID-19 PCR



In a study of 52,000 Swedish public employes (average age mid-40s) self-assessed disability status was obtained using the World Health Organization Disability Assessment Schedule on groups testing positive and negative for COVID-19. This assessment inquires on the areas of cognition, mobility, self-care, getting along, and life activities & participation, with responses recorded on a five-point Likert scale. Over an average follow-up period of six to seven months after testing, Kröönström et al. found higher rates of moderate and severe disability in those with COVID-19 as illustrated in the pie-chart figures above.[70]

Morbidity after breakthrough COVID infection

Similar to the finding that recurrent COVID-19 infection increased mortality risk in the post-acute period, the previously referenced U.S. Veterans study by Al-Aly et al. identified increased cardiac, vascular, neurologic, and selected other morbidity risks in those who were vaccinated but became reinfected in follow-up through six months.

INCIDENT OUTCOMES IN REINFECTED NON-HOSPITALIZED COHORT AT SIX MONTHS		HAZARD RATIO OF OUTCOME AFTER BTI*
CARDIAC		
	Acute coronary disease	1.54 (1.37-1.72)
	Heart failure	1.55 (1.38-1.74)
VASCULAR		
	Pulmonary embolism	2.82 (2.32-3.44)
	Venous thromboembolism (DVT)	1.94 (1.58 -2.38)
NEUROLOGIC		
	Neurocognitive decline	1.45 (1.26 - 1.66)
	Stroke	1.57 (1.19-2.07)
OTHER SELECTED		
	Pulmonary disease	1.95 (1.54-2.48)
	Chronic kidney disease	1.15 (1.04-1.27)
	Liver disease	1.37 (1.20-1.56)

*BTI = Breakthrough infection

Al-Aly et al. Nature Review Nephrology 19. 1-2, 2023

Al-Aly found an approximately 1.5-fold increase in the risk of acute coronary disease, heart failure, neurocognitive decline, and stroke, with higher risks observed for pulmonary embolism, pulmonary disease, and DVT. Lower, but still statistically significant, increases in risk were also observed for chronic kidney disease and liver disease.

[68] Majer I, Nusselder W, Mackenbach J, et al., Risk Associated With Disability: A PopulationBased Record Linkage Study, *Am J Public Health*. 2011; 101:e9–e15. https://doi:10.2105/AJPH.2011.300361

[69] Forman-Hoffman VL, Ault KL, Anderson WL, et al. Disability status, mortality, and leading causes of death in the United States community population. *Med Care*. 2015;53(4):346-354. https://doi:10.1097/MLR.0000000000000321

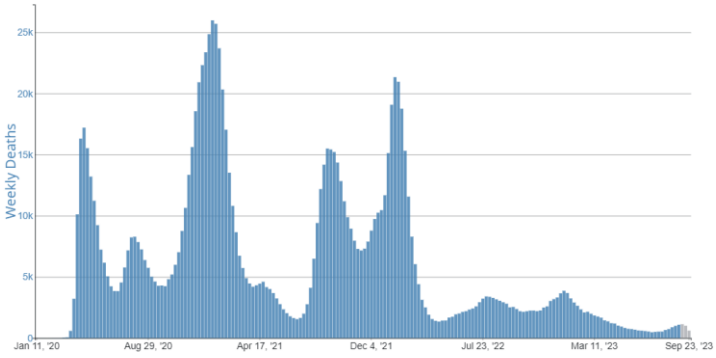
[70] Kröönström, L.A., Krause, J., Larsson, S.B. et al. Long-term self-reported health and disability after COVID-19 in public employees. *BMC Public Health* 2022 22(2400) https://doi.org/10.1186/s12889-022-14820-3

IV. Discussion

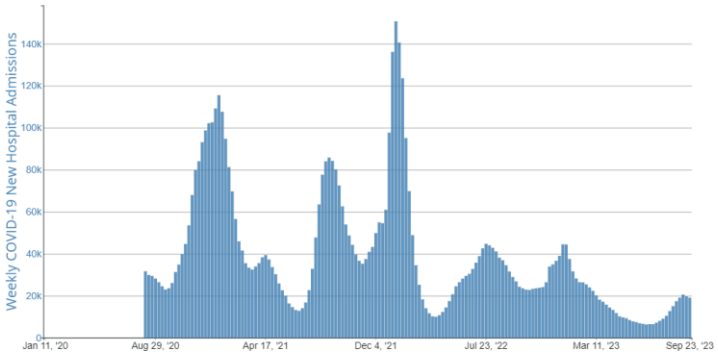
The COVID-19 pandemic has had a profound effect on short-term mortality trends globally. This literature review summarizes information from papers published predominantly in the US and Europe on mortality and certain disease risks of underwriting significance that we are now learning about in the post-acute period. For studies finding elevated risks, this literature suggests that the magnitude of those risks declines over time. While the current length of follow-up available in the studies reviewed in this white paper is not sufficient to determine whether the mortality and disease risks continue to decline or resolve beyond the first year in most populations, Bowe et al., recently reported on two-year outcomes in their VA study cohort. They found persistent elevations of mortality and morbidity in the post-acute period out to two years in those originally hospitalized for their COVID infection and even noted some persistent elevations of certain morbidity risks at two years in those who had been infected but had not been hospitalized.[71] We await additional studies to see if these persistent risks associated with the original COVID-19 infections are observed in other study populations.

Based on the period of accrual for study participants in this series of papers we do not yet have insight into whether these effects are also associated with later COVID-19 variants. There has been significant variability in the virulence of this virus based on fluctuations in COVID-related deaths and hospitalizations over time, as noted in the following CDC graphics.[72]

PROVISIONAL COVID-19 DEATHS, BY WEEK, IN THE UNITED STATES, REPORTED TO CDC



COVID-19 NEW HOSPITAL ADMISSIONS, BY WEEK, IN THE UNITED STATES, REPORTED TO CDC



Centers for Disease Control and Prevention, COVID Data Tracker. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2023, September 19. https://covid.cdc.gov/covid-data-tracker

Recent death and hospitalization trends observed over the past year look very favorable. However, it is important to note that mutations of viruses which allow for easier transmissibility or (though less common) increased virulence can have a more adverse impact in a population[73] At a scientific briefing for the White House earlier this year, the probability of a more virulent COVID strain emerging over the next two years was estimated to be between 20% and 40%.[74]

The past year has seen a moderation in deaths and hospitalizations due to recent COVID infections. However, that trend is not necessarily mirrored in the broader constellation of less-specific symptoms and conditions that result in post-COVID morbidity and mortality.

[71] Bowe, B., Xie, Y. & Al-Aly, Z. Postacute sequelae of COVID-19 at 2 years. Nat Med (2023). (Accessed August 28, 2023) https://doi.org/10.1038/s41591-023-02521-2

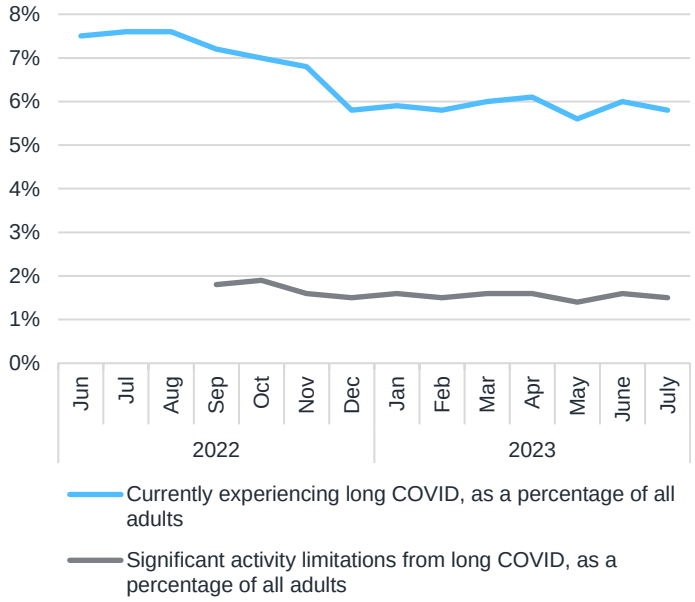
[72] "COVID Data Tracker" CDC.gov CDC COVID Data Tracker: Trends by Geographic Area Accessed 8 July 2023

[73] National Science Foundation. "How viruses evolve, and in some cases, become deadly." ScienceDaily, 27 January 2012. www.sciencedaily.com/releases/2012/01/120126224526.htm Accessed 8 July 2023

[74] Diamond D, Disease experts warn White House of potential for omicron-like wave of illness. May 5, 2023 *Washington Post* Disease experts warn White House of potential for omicron-like wave of illness (msn.com) Accessed 8 July 2023

Data from the U.S. Census Bureau Household Pulse Survey reports on the current prevalence of individuals experiencing long COVID.[75]

INDIVIDUALS CURRENTLY EXPERIENCING LONG COVID AS A PERCENTAGE OF THE US POPULATION



To get a sense of impact at the population level, the graph displays survey results as a percentage of the total U.S. population. Questions on long COVID were added to the survey beginning in June 2022, well into a phase of the pandemic characterized by a lower number of weekly deaths and hospitalizations. The definition was specific to symptoms lasting three months or longer from the time of infection. In September of 2022, a second question was added about significant activity limitations due to long COVID.

Over the period in which survey results are available, there has been less fluctuation in the prevalence of those currently experiencing long COVID (or those experiencing significant activity limitations due to it) compared to time-trends in COVID-19 mortality. As of the last survey date, approximately 5.5% or roughly 18 million people in the U.S. are currently experiencing long COVID. About 1.4%, roughly five million people, report having significant activity limitations due to it. Thus, while acute COVID-19 deaths and hospitalizations have been on a consistent downward trajectory since early 2023, survey data does not find a significant downward prevalence in those currently experiencing long COVID. If anything, decreases are even less evident among those with significant activity limitations due to long COVID. A recently published report based on data from another US health interview survey found a lower prevalence of individuals experiencing long COVID in 2022, suggesting that the underlying population sample being surveyed may influence long COVID estimates.[76]

One reason for the lack of correlation between the mortality data and long COVID data is the average length of time it takes for certain long COVID symptoms to resolve. In an Israeli study, Mizrahi et. al. found that even after mild infections, some symptoms persisted for up to a year. If the risk of long COVID is linked to the underlying virulence of the virus, that should become apparent in future data. For now, it may be premature to assume that recent COVID-19 infections will result in less serious manifestations of disease or mortality due to long COVID. However, there should be no dispute that if fewer individuals are infected, fewer will be at risk of developing long COVID or other post-acute COVID sequelae.

OVERALL RECENT U.S. POPULATION MORTALITY TRENDS AND COVID-19

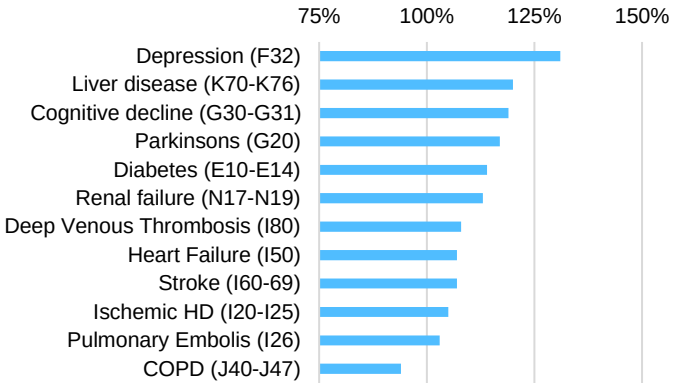
Beyond the studies referenced in this report there is limited data on the downstream mortality impact associated with COVID-19. What data is available cannot be split by the time frame of disease onset relative to the time of COVID-19 infection. Despite that, there are indications of adverse cause-specific death-rate trends in many of the conditions linked to post-acute COVID sequelae in this report. It is important to note that one cannot apportion these deaths between pre-existing conditions and conditions that developed during the pandemic. Nor is it possible to determine whether additional deaths occurred because of delays in care during the pandemic.

[75] "Household Pulse Survey, 2022–2023". *National Center for Health Statistics. U.S. Census Bureau*, Long COVID. Generated interactively: from https://www.cdc.gov/nchs/covid19/pulse/long-covid.htm Accessed 8 July 2023

[76] Adjaye-Gbewonyo D, Vahratian A, Perrine CG, et al., Long COVID in adults: United States, 2022. NCHS Data Brief, no 480. Hyattsville, MD: National Center for Health Statistics. 2023. DOI: https://dx.doi.org/10.15620/cdc:132417. Accessed Sept 26th, 2023

The following figure summarizes the percentage change in cause-specific death rates for diseases that have been found in the post-acute COVID period in the U.S. population based on the CDC's Wide-ranging ONline Data for Epidemiologic Research (WONDER) database.[77]

PERCENT CHANGE IN US CAUSE-SPECIFIC DEATH RATES, AGES 15-84, SELECTED DISEASES POTENTIALLY ASSOCIATED WITH COVID-19: 2022 VS. 2019



[1] Preliminary vital statistic data.

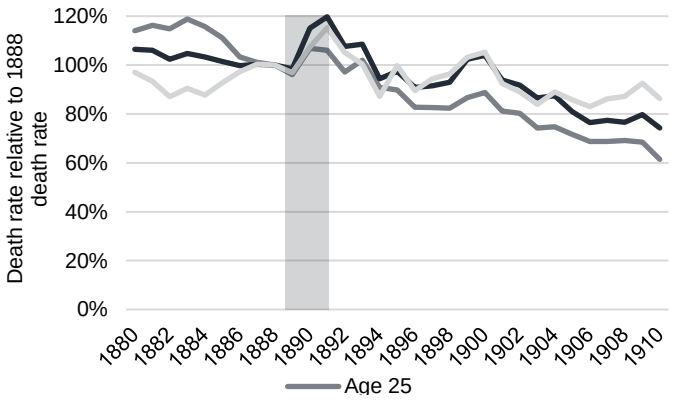
CDC WONDER has provisional cause-specific death rate data that can be analyzed by ICD-10 codes for 2022. Deaths due to the above causes represented about one third of all causes of death in recent years and for 2022 represent approximately 34% of the all-cause death rate for this age range. Instead of looking at all ages, the data was intentionally restricted to ages 15-84 because it was felt that age range would capture most individuals purchasing voluntary insurance products.

Based on provisional vital statistics data, the age-adjusted all-cause death rate in 2022 for ages 15-84 was 108% of the pre-pandemic 2019 all-cause death rate for the same age band. Specific to this age group, there has been a significant decline in COVID-19 deaths in 2022 compared to 2021 (≈133,000 deaths vs 336,000). However, death rates for heart failure (HF), stroke, and renal failure all increased from 2019 through 2022. Post-acute COVID effects may have contributed to these adverse trends. The magnitude and persistence of adverse trends in these underlying causes of death since 2019 may be easier to assess in subsequent years once we have provisional full-year 2023 data.

Can the experience of prior severe coronavirus outbreaks shed any light on how long COVID-19 will have a negative impact on morbidity and mortality? Researchers studying individuals who contracted MERS noted persistent health effects up to 18 months after infection. However, most of those individuals were hospitalized, indicating more severe infections may have an increased risk of prolonged symptoms.

From a historic standpoint, the 1889-1891 pandemic appears to have shared a number of characteristics with the current COVID-19 pandemic, suggesting that a coronavirus was the causative agent in that earlier pandemic. There were reports at that time of COVID-19-like symptoms occurring in multiple organs, prolonged recoveries, and clotting disorders.[78,79] As with COVID-19, the middle-aged and elderly experienced more adverse impacts, and some experienced symptoms for months (unlike what was observed after the 1918 influenza pandemic). Recognizing limitations in the quality of 19th century vital statistics data, based on UK reported death rates for the total population at attained ages 25, 45 and 65, it took five to six years for those death rates to consistently move below a pre-1889 baseline.[80]

UK AGE-SPECIFIC DEATH RATE TRENDS; 1880-1910 STATED AS A PERCENTAGE OF THE 1888 DEATH RATE. (GRAY SHADED AREA REPRESENTS 1889-1891 PANDEMIC)



It will take more time to assess whether elevation in death rates related to the COVID-19 pandemic through 2022 will recover to pre-pandemic levels at a faster or slower rate.

[77] "Wide-ranging Online Data for Epidemiologic Research (CDC WONDER)" May 18, 2023 CDC WONDER Accessed 8 July 2023

[78] Brüssow H, Brüssow L. Clinical evidence that the pandemic from 1889 to 1891 commonly called the Russian flu might have been an earlier coronavirus pandemic. *Microb Biotechnol* 2021;14(5):1860-1870. https://doi.org/10.1111/1751-7915.13889

[79] Brüssow H, What we can learn from the dynamics of the 1889 'Russian flu' pandemic for the future trajectory of COVID-19. *Microbial Biotech* 2021 14(6), 2244–2253 https://doi.org/10.1111/1751-7915.13916

[80] 1880-1910 United Kingdom Population Life Table, Last modified May 27, 2022, *Mortality.org* Human Mortality Database Accessed 8 July 2023

UNDERWRITING IMPLICATIONS

Claims experience has shown that COVID-19 is a morbidity and mortality risk factor in insured groups.[81,82,83] The literature in this review also indicates that adverse impacts may emerge beyond the acute phase, possibly contributing to adverse pricing results over several years. In applicants, this review suggests that new disease emergence of varying nature and duration in the post-acute period is a possibility. The pandemic also had a material impact on chronic disease management and adherence to treatments. This impact might have been partially offset by an accelerated adoption of telemedicine and other e-health aids.[84] It will take more time to assess the net impact of the pandemic on the future trajectory of established chronic diseases known to be adversely impacted by infection with COVID-19 as well as new incident disease subsequent to COVID infection. Those topics are outside the scope of this report.

If anything, the COVID-19 pandemic makes it even more essential for underwriters to have objective medical information to assist in fair and accurate risk assessment. With its late-onset effects, COVID adds another reason to ensure that information on applicants is up to date and comprehensive. Understanding both the short- and longer-term health experience an individual had after contracting COVID-19 is critical to assessing its underwriting significance. The industry has increasing access to information on applicants to aid in the detection of new problems of underwriting significance. Milliman IntelliScript's Irix®[85]suite of products, drawing upon both prescription histories and medical billing data, provides concise insight into almost any applicant's health history. Additional detail will soon be available with the use of the Irix EHR electronic health record product.

For applicants with a more recent history of COVID-19, and in particular those whose infection required hospitalization, underwriters are well-advised to use prescription histories, medical billing codes, and electronic health records to monitor changes in the severity of pre-existing chronic disease and the clinical course of new-onset disease. Underwriters should also be aware that for certain conditions such as post-acute incident diabetes, they may find evidence of regression or resolution over time in some individuals and thus should be willing to review ratings if additional evidence obtained later suggests that such conditions have improved or resolved with a longer passage of time.

Milliman

Milliman is among the world's largest providers of actuarial, risk management, and technology solutions. Our consulting and advanced analytics capabilities encompass healthcare, property & casualty insurance, life insurance and financial services, and employee benefits. Founded in 1947, Milliman is an independent firm with offices in major cities around the globe.

milliman.com

CONTACT

Brian Ivanovic, DO, MS
brian.ivanovic@milliman.com

[81] Britt T, Correia P, Hurley P, et al., Group Life COVID-19 Mortality Survey Report. Nov 2022 *SOA* Group Life COVID-19 Mortality Survey (soa.org) Accessed 8 July 2023

[82] Bergerson M, Dalton A, Easton R, et al., COVID-19 Impact on Long-Term Care Insurance 2020 Survey. March 2021 COVID-19 Impact on Long-Term Care Insurance (soa.org) Accessed 8 July 2023

[83] Natsis A, Quantifying Long Term Effects of COVID-19 on Health Care Costs. April 2023 *SOA* Quantifying Long Term Effects of COVID-19 on Health Care Costs (soa.org) Accessed 8 July 2023

[84] Olmastroni E, Galimberti F, Tragni E, et al., Impact of COVID-19 Pandemic on Adherence to Chronic Therapies: A Systematic Review. *Int J Env Research Public Hlth* 2023; 20(5):3825. https://doi.org/10.3390/ijerph20053825

[85] "Irix®: Transforming Data Into Actionable Knowledge for Underwriters" *Rxhistories.com* Accessed 8 July 2023 Accessed 8 July 2023