

Long Covid after Breakthrough COVID-19: the post-acute sequelae of breakthrough COVID-19

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Abstract

The post-acute sequelae of COVID-19 have been described¹, but whether breakthrough COVID-19 (that is the disease that ensues following vaccine breakthrough SARS-CoV-2 infection) results in post-acute sequelae is not yet clear. Here we use the national healthcare databases of the US Department of Veterans Affairs to characterize 6-month risks of incident post-acute sequelae in people with breakthrough COVID-19 who survived for at least 30 days after diagnosis. We show that compared to people with no evidence of COVID-19, beyond the first 30 days of illness, people with breakthrough COVID-19 exhibit a higher risk of death and broad array of incident post-acute sequelae in the pulmonary system, as well as extrapulmonary sequelae that include cardiovascular disorders, coagulation disorders, gastrointestinal disorders, general disorders (e.g., fatigue), kidney disorders, mental health disorders, metabolic disorders, musculoskeletal disorders, and neurologic disorders. Our analyses by care setting of the acute phase of the disease show that people who were not hospitalized during the first 30 days after diagnosis with breakthrough COVID-19 exhibit a small but not insignificant increase in risk of death and post-acute sequelae; the risks are further increased in people who were hospitalized during the acute phase of the disease. Our comparative approach shows that people with breakthrough COVID-19 exhibit lower risks of death and post-acute sequelae than people with COVID-19 who were not previously vaccinated for it; and in analyses among individuals who were hospitalized during the acute phase of the disease, people with breakthrough COVID-19 exhibit higher risks of death and post-acute sequelae than people with seasonal influenza. Altogether, our findings show increased risks of death and post-acute sequelae in people with breakthrough COVID-19; the risks are evident among those who were not hospitalized during the acute phase of the disease. Our comparative approach provides context for understanding the risks in relation to COVID-19 without prior vaccination and seasonal influenza. The findings will inform the ongoing effort to optimize strategies for prevention of breakthrough SARS-CoV-2 infections and will guide development and optimization of post-acute care pathways for people with breakthrough COVID-19.

Main

The post-acute sequelae in people with COVID-19 have been characterized¹. Increasingly, vaccinated individuals are being diagnosed with COVID-19 as a result of breakthrough SARS-CoV-2 infection – we will refer to it here as breakthrough COVID-19²⁻⁴. Whether people with breakthrough COVID-19 experience post-acute sequelae is not clear. Addressing this knowledge gap is important to guide public health policy and post-acute COVID-19 care strategies.

Here we leverage the breadth and depth of the electronic health care databases of the US Department of Veterans Affairs to address the question of whether people with breakthrough COVID-19 develop post-acute sequelae. We characterize the risks and 6-month burdens of a panel of pre-specified outcomes in a cohort of people who experienced breakthrough SARS-CoV-2 infection after completion of vaccination vs a control group and by care setting of the acute phase of breakthrough COVID-19 (that is whether people were not hospitalized or hospitalized during the first 30 days after diagnosis). We then undertake a

comparative evaluation of the magnitude of risk in people with breakthrough COVID-19 vs those with COVID-19 and no prior vaccination and separately hospitalized people with breakthrough COVID-19 vs those hospitalized with seasonal influenza.

Post-acute sequelae in people with breakthrough COVID-19 vs control

There were 16,035, and 3,569,525 participants in the breakthrough COVID-19 group and a control group of users of the Veterans Health Administration with no record of a positive COVID-19 test, respectively. The demographic and health characteristics of the breakthrough COVID-19 and the control groups before and after weighting are presented in Extended Data Table 1 and Supplementary Table 1, respectively. Overall rate of breakthrough was 7.26 (95% CI 7.25, 7.26) per 1000 persons at 6-months; rates of breakthrough by vaccine type are presented in Extended Data Table 1.

For all analyses, we provide two measures of risk: (1) we estimated the adjusted hazard ratios of a set of incident pre-specified outcomes in people with breakthrough COVID-19 vs the control group; (2) we estimated the adjusted excess burden of each outcome due to breakthrough COVID-19 per 1,000 persons 6-months after a positive COVID-19 test on the basis of the difference between the estimated incidence rate in individuals with breakthrough COVID-19 and the control group. Assessment of standardized mean differences of participant characteristics (from data domains including diagnoses, medications, and laboratory test results) after application of weighting showed they are well balanced in each analysis of incident outcomes (Supplementary Fig. 1 and Supplementary Fig. 2).

Compared to the control group, people who survived the first 30 days of breakthrough COVID-19 exhibited an increased risk of death (Hazard Ratio (HR) 1.53; 95% confidence interval (CI): 1.36, 1.72) and excess burden of death estimated at 11.45 (95% CI: 7.77, 15.58) per 1000 persons with breakthrough COVID-19 at 6 months; all burden estimates represent excess burden and are given per 1,000 persons with breakthrough COVID-19 at 6 months. People with breakthrough COVID-19 also had an increased risk of having at least one post-acute sequela (HR 1.59 (1.53, 1.65); burden of 98.64 (89.01, 108.51)) (Supplementary Table 2).

Compared to the control group, 30-day survivors of breakthrough COVID-19 exhibited increased risk of post-acute sequelae in the pulmonary (HR 2.33 (2.16, 2.50); burden 49.53 (43.53, 55.94)), and several extrapulmonary organ systems including cardiovascular disorders (HR 2.01 (1.85, 2.20); burden 31.37 (26.26, 36.91)), coagulation disorders (HR 2.93 (2.52, 3.42); burden 13.40 (10.53, 16.73)), fatigue (HR 2.16 (1.92, 2.43); burden 19.75 (15.69, 24.30)), gastrointestinal disorders (HR 1.48 (1.34, 1.64); burden 17.15 (12.12, 22.67)), kidney disorders (HR 1.92 (1.69, 2.18); burden 19.34 (14.53, 24.75)), mental health disorders (HR 1.42 (1.32, 1.53); burden 24.94 (19.07, 31.21)), metabolic disorders (HR 1.46 (1.29, 1.66); burden 15.34 (9.61, 21.80)), musculoskeletal disorders (HR 1.75 (1.57, 1.95); burden 20.44 (15.54, 25.87)), and neurologic disorders (HR 1.79 (1.55, 2.06); burden 11.00 (7.65, 31.14)). Risk and excess burden of each individual sequela and by organ system are provided in Figure 1 (Supplementary Table 3) and Figure 2 (Supplementary Table 2), respectively.

Post-acute sequelae in people with breakthrough COVID-19 vs the control group by care setting of the acute phase of the disease

The demographic and health characteristics of people with breakthrough COVID-19 by mutually exclusive groups of those who were not hospitalized, and those who were hospitalized, during the acute phase of the disease before and after weighting are provided in Extended Data Table 2 and Supplementary Tables 4-5. Evaluation of standardized mean differences of baseline participant characteristics after the application of the weighting suggested good balance Supplementary Fig. 3-4.

Compared to the control group, people who were not hospitalized during the first 30 days of breakthrough COVID-19 exhibited an increased risk of death (HR 1.20 (1.02-1.40); burden 3.77 (0.36, 7.76)); the risk was further increased in those who were hospitalized (HR 2.12 (1.77, 2.53); burden 44.59 (31.12, 60.41)). The risk of having at least one post-acute sequela was evident in non-hospitalized people (HR 1.30 (1.24, 1.36); burden 51.35 (41.29, 61.77)) and further increased in those who were hospitalized (HR 2.91 (2.72, 3.13); burden 311.06 (285.90, 336.57)) (Fig. 3 and Supplementary Tables 6-7).

People who were not hospitalized exhibited small but significant increased risk of post-acute sequelae in all the examined organ systems including cardiovascular, coagulation, gastrointestinal, kidney, mental health, metabolic, musculoskeletal, neurologic, and the pulmonary system, as well as increased risk of fatigue (Fig 3. and Supplementary Table 6). The risks were further increased in people who were hospitalized (Fig. 3 and Supplementary Table 7).

Comparative evaluation of post-acute sequelae in breakthrough COVID-19 vs COVID-19 without prior vaccination

To place the magnitude of risk of post-acute sequelae in of people with breakthrough COVID-19 in the larger context of post-acute COVID-19 manifestations, we developed a comparative approach to evaluate the risk of organ system involvement in people with breakthrough COVID-19 vs people with COVID-19 and no prior history of vaccination (Extended Data Table 3). Assessment of standardized mean differences of baseline characteristics in the weighted cohorts suggested good balance (Supplemental Fig. 5, and Supplementary Table 8).

People with breakthrough COVID-19 exhibited lower risk of death (HR 0.65 (0.55, 0.76); burden -12.97 (-16.58, -8.74); negative values denote reduced burden in breakthrough COVID-19 relative to COVID-19) and lower risk of post-acute sequelae (HR 0.87 (0.83, 0.92); burden -30.60 (-42.25, -18.49)) compared to those with COVID-19 and no prior history of vaccination (Figure 4 and Supplementary Table 9).

Comparatively, the risk of post-acute sequelae in the cardiovascular, coagulation, metabolic, and pulmonary organ systems, as well as risk of fatigue, was lower in people with breakthrough COVID-19 vs those with COVID-19 without prior vaccination. Lower risk was not statistically significant in kidney, gastrointestinal, mental health, and neurologic organ systems. None of the outcomes exhibited a higher

risk among people with breakthrough COVID-19 compared to those with COVID-19 without prior vaccination.

Comparative evaluation of post-acute sequelae in hospitalized people with breakthrough COVID-19 vs people hospitalized with seasonal influenza

We developed a comparative analysis to better understand how people hospitalized with breakthrough COVID-19 fare relative to those who are hospitalized with seasonal influenza. Demographic and health characteristics before and after weighting are provided in Extended Data Table 4 and Supplementary Table 10. Examination of standardized mean differences of baseline characteristics after application of overlap weighting demonstrated good balance Supplementary Fig. 6.

Compared to people who were hospitalized with seasonal influenza, people who were hospitalized during the acute phase of breakthrough COVID-19 and survived the first 30 days exhibited an increased risk of death (HR 1.47 (1.28, 1.69); burden 28.70 (24.45, 32.97)), and increased risk of having at least one post-acute sequela (HR 1.15 (1.09, 1.22); burden 50.03 (40.98, 59.24)) (Fig. 5 and Supplementary Table 11). People with breakthrough COVID-19 exhibited increased risk of sequelae in all the examined organ systems compared to those with seasonal influenza.

Positive and negative outcome controls:

To assess whether our approach reproduces established knowledge, we tested the association between COVID-19 and the pre-specified outcomes where, based on prior evidence, we would expect a positive association with each outcome. The results showed that compared to the control group, people with COVID-19 and without prior vaccination exhibited increased risk of all the outcomes (Extended Data Fig. 1 and Supplementary Table 12).

To assess the putative presence of spurious associations, we tested the association between breakthrough COVID-19 and two negative outcome controls where there was no biologic plausibility or epidemiologic evidence that an association is expected. We used the same data source, cohort building process, covariate selection approach (including predefined demographic and health characteristics and algorithmically selected high dimensional covariates), analytic methods, and interpretation of results to test the association between breakthrough COVID-19 and risk of accidental injury or poisoning and – separately – risk of atopic dermatitis. The results suggested no significant association between breakthrough COVID-19 and risk of either negative outcome controls (Extended Data Table 5).

Discussion

In this study of 16,035, people with breakthrough COVID-19 and 3,569,525 controls, we show that people who survive the first 30 days of breakthrough COVID-19 exhibit increased risk of death and post-acute sequelae in the pulmonary and several extrapulmonary organ systems. The risks of death and post-acute sequelae were small but evident (and not trivial) among people whose disease did not necessitate

hospitalization during the acute phase of breakthrough COVID-19 (this group represents most people with breakthrough COVID-19). Our results show clear and consistent risk gradient in that the risks and burdens of all outcomes examined (death and post-acute sequelae) increased in a graded fashion according to the care setting of the acute infection and were consistently higher in those who were hospitalized during the acute phase of the disease. Our comparative approach shows that in people with breakthrough COVID-19, the risks of death and post-acute sequelae are lower than COVID-19 without prior vaccination; in comparative analyses among people who were hospitalized during the acute phase of the disease, those with breakthrough COVID-19 exhibited higher risks of death and post-acute sequelae than those with seasonal influenza. The constellation of findings show that the burden of death and disease experienced by people with breakthrough disease is not trivial. Our comparative analyses provide a framework to better evaluate and understand risks of the post viral condition in people with breakthrough COVID-19. The findings emphasize the need for continued optimization of prevention strategies of breakthrough SARS-CoV-2 infections and will inform care approaches for people with breakthrough COVID-19.

Our findings show that long covid with its myriad sequelae also manifests in vaccinated individuals who experience a breakthrough SARS-CoV-2 infection; the risk of post-acute sequelae was higher in people with breakthrough COVID-19 vs those with no COVID-19, and lower in people with breakthrough COVID-19 vs those with COVID-19 who had not been previously vaccinated for it. This suggests risk reduction conferred by vaccination for COVID-19. It also emphasizes that in order to lessen the risk and burden of post-acute sequelae (death and disease), prevention of breakthrough SARS-CoV-2 should be a goal of public health policy. Strategies aimed at reducing risk of breakthrough SARS-CoV-2 infection by maintaining vaccine effectiveness through optimization of vaccine schedules and boosters which may be augmented (or otherwise complemented) by employment of non-pharmaceutical interventions (e.g., masking) may yield less breakthrough infections and subsequently less risk of post-acute sequelae.

Here we provide evidence of increased risk of death and post-acute sequelae following breakthrough COVID-19. Although the absolute rates are smaller than those post-COVID-19 without prior vaccination, given the scale of the pandemic and the potential for breakthrough cases to continue to accumulate, the overall burden of death and disease following breakthrough COVID-19 will likely be substantial, will further add to the toll of this pandemic and will represent an additional strain on already overwhelmed health systems. In planning and development of health resources, governments and health systems should take into account the care needs of people with post-acute sequelae after breakthrough COVID-19⁵.

The mechanism or mechanisms underlying the reduced risk of post-acute sequelae in people with breakthrough COVID-19 vs those with COVID-19 without prior vaccination is not clear. It is possible that some sequelae are mediated by mechanistic pathways in the immune system that are influenced by vaccination.

We also show that the risk of post-acute sequelae is higher in people with breakthrough COVID-19 than in people with seasonal influenza – a well characterized respiratory viral illness. This extends prior evidence showing that the risk of post-acute sequelae in people with COVID-19 was higher than those with seasonal influenza and again emphasizes the importance of prevention of both COVID-19 and breakthrough COVID-19¹.

This study has several strengths. To our knowledge, this is the first large study to characterize the risks of post-acute sequelae of breakthrough COVID-19 at 6 months. We leveraged the vast national healthcare databases of the US Department of Veterans Affairs (the largest nationally integrated healthcare delivery system in the US) to characterize the risk and 6-month burden of a comprehensive set of pre-specified incident health outcomes in patients who survived the first 30 days of breakthrough COVID-19. In addition to evaluating risk of breakthrough COVID-19 vs those with no evidence of COVID-19 in the overall cohort and by care setting of the acute phase of the disease (non-hospitalized and hospitalized), we also undertook a comparative evaluation of breakthrough COVID-19 vs COVID-19 in people who had not been previously vaccinated and separately vs seasonal influenza. We employed advanced statistical methodologies and adjusted through weighting for a battery of predefined covariates selected based on prior knowledge and algorithmically selected covariates from high dimensional data domains including diagnoses, prescription records, and laboratory test results. We evaluated the rigor of our approach by testing positive and negative outcome controls to determine whether our approach would produce results consistent with pre-test expectations.

The study has several limitations. The breakthrough COVID-19 and COVID-19 groups only included those that had a positive test for COVID-19 and did not include those who may have had an infection with SARS-CoV-2 but were not tested; however, if present, this will bias the estimates toward the null. Although we balanced our cohorts by vintage to account for temporal variation in characteristics of the SARS-CoV-2 infection (e.g., variants), our analyses did not directly include data on the different variants of SARS-CoV-2. Although the VA population is comprised of mostly males, it includes 8-10% females which across the groups in our study included 347,589 female participants. Although we adjusted through overlap weighting approach for a large battery of predefined and algorithmically selected covariates, and while our approach demonstrated good balance for more than 734 covariates (including all those which were available in the data but not included in the weighting process) from several data domains including diagnoses, prescription medications, and laboratory test results, and resulted in successful testing of positive outcome controls and negative outcome controls, we cannot completely rule out residual confounding. Finally, the COVID-19 global pandemic is highly dynamic, as vaccine uptake continues to increase, as vaccine schedules continue to be optimized, as treatment strategies of the acute phase of COVID-19 continue to improve, and as new variants of the virus emerge, it is likely that the epidemiology of breakthrough COVID-19 and its downstream sequelae may also change over time.

In sum the findings provide evidence of increased risk of death and post-acute sequelae in people with breakthrough COVID-19 at 6 months. The risks are manifest even among people whose acute disease did not necessitate hospitalization. Our comparative approach establishes that the risks of death and post-

acute sequelae in people with breakthrough COVID-19 are lower than those with COVID-19 without prior vaccination, but higher than those with seasonal influenza. The constellation of findings emphasizes the need for continued optimization of strategies to prevent breakthrough SARS-CoV-2 infections in the first place and will guide care approaches of people with breakthrough COVID-19.

Methods

All participants that were eligible for this study were enrolled; no a-priori sample size analyses were conducted to guide enrollment. All analyses were observational, and investigators were aware of participant exposure and outcome status.

Setting

Cohort participants were identified from the United States Veterans Health Administration (VHA) electronic health databases. The VHA provides healthcare to discharged veterans of the US armed forces in a nationally integrated network of healthcare systems that includes more than 1,415 healthcare facilities. Veterans enrolled in the VHA have access to a comprehensive medical benefits package which includes outpatient services, preventive, primary and specialty care, mental health care, geriatric care, inpatient hospital care, extended long term care, prescriptions, home healthcare, medical equipment, and prosthetics. The VHA healthcare databases are updated daily.

Cohorts

We first identified users of the VHA who were alive on February 1, 2021 (N=3,879,376). Use of the VHA was defined as having record of at least one encounter with the VHA health care system in the year prior; an encounter was defined as use of any outpatient or inpatient service, receipt of medication, or use of laboratory service (Extended Data Figure 2). Among these, there were 74,730 participants with a record of a first positive COVID-19 test from February 1, 2021 to August 31, 2021, and 3,622,737 with no record of any positive COVID-19 test. Participants were followed until October 26, 2021.

To construct a group of people with breakthrough COVID-19, we selected, from those with a positive COVID-19 test (N=74,730), those with a record of completion of an Ad26.COVS, mRNA-1273, or BNT162b2 vaccination before the date of their first positive COVID-19 test (N=16,678). Completion of vaccination was defined following CDC guidelines at the 14th day after the second shot of the mRNA-1273 or BNT162b2 vaccination series, or the 14th day after the first shot of the Ad26.COVS vaccination. Setting the date of first positive COVID-19 test as time zero (T_0), we then selected those alive 30 days after T_0 , resulting in a cohort of 16,035 participants in the breakthrough COVID-19 group.

To build the control group of people with no evidence of COVID-19, we then utilized the 3,622,737 users of the VHA who had no record of a COVID-19 test. Among these participants we randomly assigned a T_0 to each participant in the group on the basis of the distribution of the T_0 dates in those with breakthrough COVID-19. We finally selected those who were alive 30 days after their T_0 (n=3,569,525).

To build the group of people with COVID-19 and without prior vaccination, we identified from the 74,730 people with a first positive COVID-19 test from February 1, 2021 to August 31, 2021, 50,975 who had no record of any COVID-19 vaccination up through 30 days after T_0 , where the date of a participant's first positive COVID-19 test was set as T_0 . We then selected the 48,536 who were alive 30 days after T_0 to comprise the group of people with COVID-19 and no prior vaccination.

To compare post-acute sequelae of those hospitalized with breakthrough COVID-19 during the acute phase of the illness to those hospitalized with seasonal influenza, we separately identified 15,160 VHA users hospitalized with positive seasonal influenza test 5 days before or 30 days after the test between October 1, 2016 and February 29, 2020. We set the date of the positive seasonal influenza test as T_0 . To ensure no overlap with the breakthrough COVID-19 group, participants who had no record of a positive COVID-19 test were then selected ($n=14,841$). From these, we selected 14,154 who were alive 30 days after their T_0 to constitute the seasonal influenza group.

Data sources

Data used in this study was obtained from the VHA Corporate Data Warehouse (CDW). Within CDW, the patient data domain provided information on demographic characteristics; the outpatient encounters domain and inpatient encounters domain provided information on health characteristics including data on timing and location of interactions with the healthcare system, diagnoses, and procedures; the pharmacy and bar code medication administration domains provided medication records; the laboratory results domain provided laboratory test information in both in outpatient and inpatient settings^{6,7}. The COVID-19 Shared Data Resource (CSDR) provided information on COVID-19 test results and COVID-19 vaccination status. The 2019 Area Deprivation Index (ADI) at each cohort participant residential address was used as a contextual measure of socioeconomic disadvantage⁸.

Post-acute Sequelae

We pre-specified a set of outcomes based on prior evidence on the post-acute sequelae of COVID-19^{6,7,9-13}. Outcomes were defined using validated definitions leveraging information from several data domains including diagnoses, prescription medications, and laboratory test results^{6,7,14-20}. Incident post-acute sequelae were examined in a cohort with no record of the health condition in the year prior to T_0 . The pre-specified outcomes included incident acute coronary disease, acute kidney injury, anxiety, atrial fibrillation, atrial flutter, chronic kidney disease, constipation or diarrhea, cough, deep vein thrombosis, type 2 diabetes mellitus, prescription of diabetes medications, estimated glomerular filtration rate decline of $\geq 50\%$, fatigue, gastroesophageal reflux disease, heart failure, hypoxemia, memory loss, mood disorder, muscle or joint pain, myocardial infarction, myocarditis, pulmonary embolism, shortness of breath, sleep disorders, smell disorders, stroke, substance abuse, superficial venous thrombosis, tachycardia, coagulation disorders, and ventricular arrhythmias. We additionally examined outcomes of death and having at least one of post-acute sequelae that was defined at the time of the first incident pre-specified post-acute sequelae in each participant.

Additionally, we defined a set of outcomes where we aggregated the pre-specified post-acute sequelae, were applicable, by organ system. These included cardiovascular disorders, coagulation, fatigue, gastrointestinal disorders, kidney disorders, mental health disorders, metabolic disorders, musculoskeletal disorders, neurologic disorders, and pulmonary disorders. All outcomes were assessed starting from 30 days after T_0 .

Covariates

We included a set of predefined covariates based on prior knowledge and algorithmically selected covariates.

Predefined covariates included demographic information (age, race, and sex), contextual information (ADI), measures of the intensity of healthcare interaction in the year prior to T_0 including the number of outpatient visits, the number of inpatient visits, the number of unique medications the participant received a prescription for, the number of routine blood panels that were performed, as well as a prior history of receiving an influenza vaccination. We also included smoking status as a covariate. Health characteristics included a prior history of anxiety, cancer, cardiovascular disease, cerebrovascular disease, chronic kidney disease, dementia, depression, type 2 diabetes mellitus, chronic obstructive pulmonary disease, and peripheral artery disease, as well as systolic blood pressure and body mass index (BMI). In consideration of the dynamicity of the pandemic, in comparison of those with breakthrough COVID-19 with those who had COVID-19 with no prior history of a vaccination, we also included the calendar week of testing positive, average hospital bed occupancy in the participants hospital system the during the week of T_0 , and the total number of hospital beds available in the participants hospital system, and complexity of the hospital system. All continuous covariates were treated as natural cubic splines unless heavily skewed towards zero.

In addition to the predefined covariates, we leveraged the high dimensionality of VA data where we developed and deployed a high dimensional variable selection algorithm to identify covariates that may potentially confound the examined associations²¹. Using the Clinical Classifications Software Refined (CCSR) version 2021.1 available from the Healthcare Cost and Utilization Project sponsored by the Agency for Healthcare Research and Quality, more than 70,000 ICD-10 diagnoses codes in the year prior to T_0 for each participant were classified into 540 diagnostic categories²²⁻²⁴. Using the VA drug classification system, 3,425 different medications we classified into 543 medication classes^{25,26}. Finally, laboratory results from 38 different laboratory measurements were classified into 62 laboratory test abnormalities, defined by being above or below the corresponding reference ranges, on the basis of the recorded Logical Observation Identifiers Names and Codes. A two-step approach was applied to ensure balance between groups across high-dimensional variables. Of the high dimensional variables that occurred at least 100 times in participants in each group (up to 707), we examined their balance in models only weighting for the predefined variables; those with standardized mean differences greater than 0.1 were then included in final weighting models.

Statistics

Median (interquartile range), mean (standard deviation), and frequency (percentage) of select characteristics are reported in the breakthrough COVID-19 group, COVID-19 group without prior vaccination, the control group with no record of a positive COVID-19 test, and the seasonal influenza group, where appropriate. Characteristics of those with breakthrough COVID-19 by hospitalization status are additionally presented. Vaccination characteristics for those with breakthrough COVID-19 are reported, as well as breakthrough COVID-19 rates per 1000 persons at 6 months for those vaccinated from January 1 to August 31, 2021.

We estimated the risk of each pre-specified post-acute sequelae associated with breakthrough COVID-19 compared to the control group in separate models in cohorts with no prior history of the outcome being examined. In consideration of the potential competing risk of death, we conducted logistic regression with predefined and algorithmically selected covariates to predict the probability of death and constructed stabilized inverse probability of censoring due to death weights²⁷. These weights were then subsequently used in a model that estimated a propensity score of the probability of group assignment^{28,29}. A summary weight of the inverse probability of death and overlap weighting for group assignment were then applied to Cox survival models. The estimated hazard ratios for each outcome and the estimated incidence rate difference (referred to as excess burden) between groups per 1,000 participants at 6 months after the start of follow-up in each group are presented. Standard errors were estimated by applying the robust sandwich variance estimator method. Covariate balance among all predefined and high dimensional variables were assessed for each model through the standardized mean difference. We present the distribution of the standardized mean difference for all models, where a difference <0.1 was taken as evidence of balance. We additionally present characteristics of the breakthrough COVID-19 and control group after application of weighting in a cohort where no participants were excluded.

We then examined the risk and excess burden associated with breakthrough COVID-19 by care setting of the acute phase (first 30 days) of the disease. Using a similar analytic approach, we estimated risk of organ system involvement, the outcome of at least one post-acute sequela, and death between those with a breakthrough COVID-19 that were hospitalized during the acute phase of the disease and the control group. Analyses additionally conducted in the comparison of those with breakthrough COVID-19 not hospitalized during the acute phase of the disease and the control group.

We additionally compared the risks and excess burden of post-acute sequelae by organ system, of at least one post-acute sequela, and death between breakthrough COVID-19 and those with COVID-19. In consideration of the emergence of delta during our enrollment period, and potential differences in duration of follow-up, we included as a covariate the vintage of the disease (represented by a spline of the week of testing positive for COVID-19). Finally, we compared the risks and excess burden of post-acute outcomes by organ system, of any post-acute sequela, and death between those hospitalized with breakthrough COVID-19 and those hospitalized with seasonal influenza.

Positive and negative controls

We examined, as positive outcome controls, the risks of the pre-specified post-acute sequelae in those with COVID-19 compared to the control group as a means of testing whether our approach would reproduce established knowledge⁹⁻¹³.

The application of negative outcome control may help detect both suspected and unsuspected sources of spurious biases. We, therefore, tested accidental injury or poisoning and atopic dermatitis as negative outcome controls – where no prior knowledge suggests an association is expected. The successful testing of negative outcome controls may lessen concerns about biases in outcome ascertainment, unmeasured confounding, and other latent biases^{30,31}.

All analyses were conducted in SAS Enterprise Guide 8.2, and all figures were generated in R 4.0.3. This study was approved the VA St. Louis Health Care System Institutional Review Board.

Declarations

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Disclaimer: The contents do not represent the views of the US Department of Veterans Affairs or the US government.

Data availability: The data that support the findings of this study are available from the US Department of Veterans Affairs. VA data are made freely available to researchers behind the VA firewall with an approved VA study protocol. For more information, please visit <https://www.virec.research.va.gov> or contact the VA Information Resource Center (VIReC) at VIReC@va.gov

Code Availability: SAS programing codes will be made available on upon request.

Ethical approval: This research project was reviewed and approved by the Institutional Review Board of the Department of Veterans Affairs Saint Louis Health Care System.

Competing interests: The authors declare no conflict of interest.

Author Contributions: ZAA, BB, and YX contributed to the development of the study concept and design. ZAA, BB, and YX contributed to data analysis and interpretation. ZAA drafted the manuscript. Critical revision of the manuscript was contributed to by ZAA, BB, and YX. ZAA provided administrative, technical, and material support. ZAA provided supervision and mentorship. ZAA is the guarantor of the work. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of

any portion of the work are appropriately investigated and resolved. All authors approved the final version of the report. The corresponding author attests that all the listed authors meet the authorship criteria and that no others meeting the criteria have been omitted.

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Extended Data Figure Legends

Extended Data Figure 1: Risk of post-acute sequelae in people with COVID-19 compared to the control group. Incident outcomes were assessed from 30 days after the positive COVID-19 test to end of follow-up. All results are in comparison to the control group that consisted of those with no record of a positive COVID-19 test. Adjusted hazard ratios (dots) and 95% confidence intervals (error bars) are presented. AKI, acute kidney injury; CKD, chronic kidney disease; GERD, gastroesophageal reflux disease.

Extended Data Figure 2: Cohort flowchart.

Figures

Figure 1

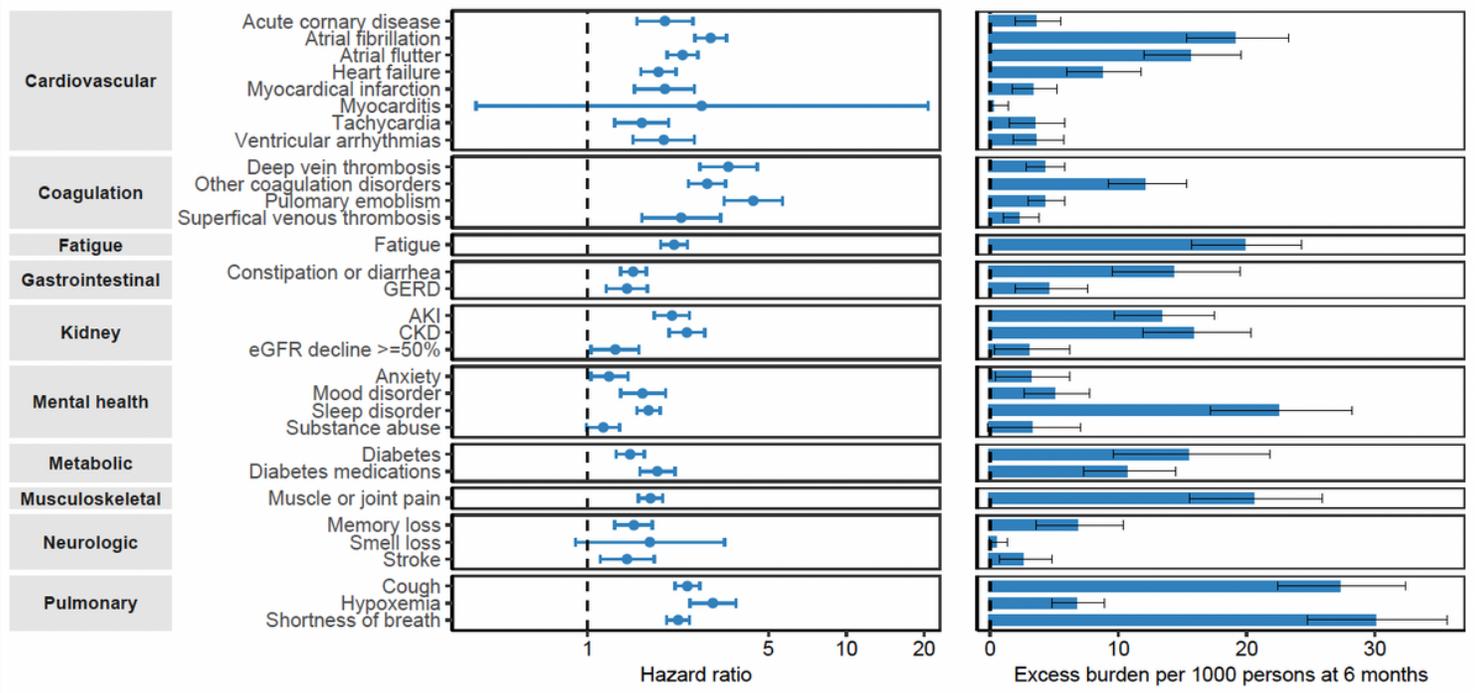


Figure 1

Risk and 6-month excess burden of post-acute sequelae in people with breakthrough COVID-19 compared to the control group. Incident outcomes were assessed from 30 days after the positive COVID-19 test to end of follow-up. All results are in comparison to the control group that consisted of those with no record of a positive COVID-19 test. Adjusted hazard ratios (dots) and 95% confidence intervals (error bars) are presented, as are estimated excess burden (bars) and 95% confidence intervals (error bars). Burdens are presented per 1000 persons at 6 months of follow-up. AKI, acute kidney injury; CKD, chronic kidney disease; GERD, gastroesophageal reflux disease.

Figure 2

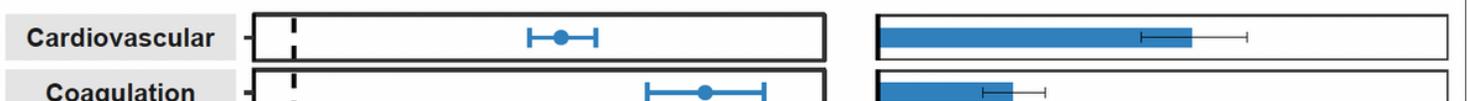


Figure 2

Risk and 6-month excess burden of post-acute sequelae by organ system in people with breakthrough COVID-19 compared to the control group. Incident outcomes were assessed from 30 days after the positive COVID-19 test to end of follow-up. All results are in comparison to the control group that consisted of those with no record of a positive COVID-19 test. Adjusted hazard ratios (dots) and 95% confidence intervals (error bars) are presented, as are estimated excess burden (bars) and 95% confidence intervals (error bars). Burdens are presented per 1000 persons at 6 months of follow-up.

Figure 3

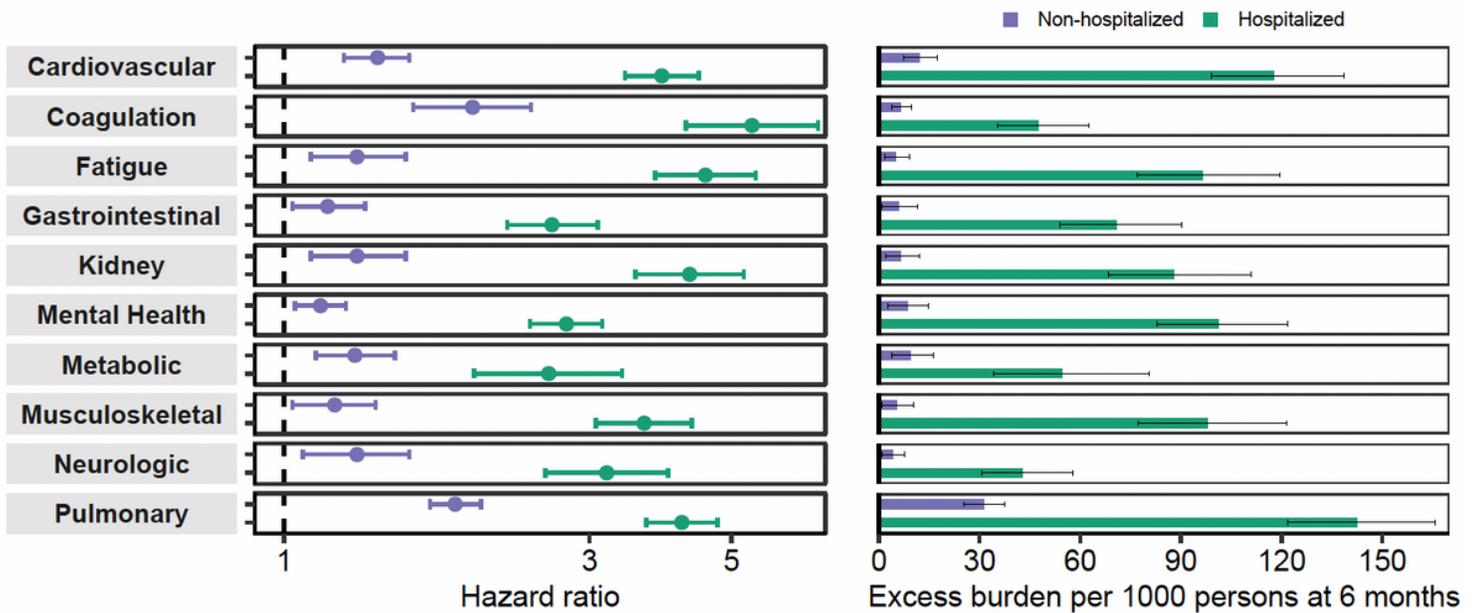


Figure 3

Risk and 6-month excess burden of post-acute sequelae by organ system in those with breakthrough COVID-19 by care setting of the acute phase of the disease. Risk and excess burden were estimated in mutually exclusive groups defined by care setting of breakthrough COVID-19 (not hospitalized and hospitalized) during the acute phase of the disease. Incident outcomes were assessed from 30 days after the positive COVID-19 test to end of follow-up. All results are in comparison to the control group of those with no record of a positive COVID-19 test. Adjusted hazard ratios (dots) and 95% confidence intervals (error bars) are presented, as are estimated excess burden (bars) and 95% confidence intervals (error bars). Burdens are presented per 1000 persons at 6 months of follow-up.

Figure 4

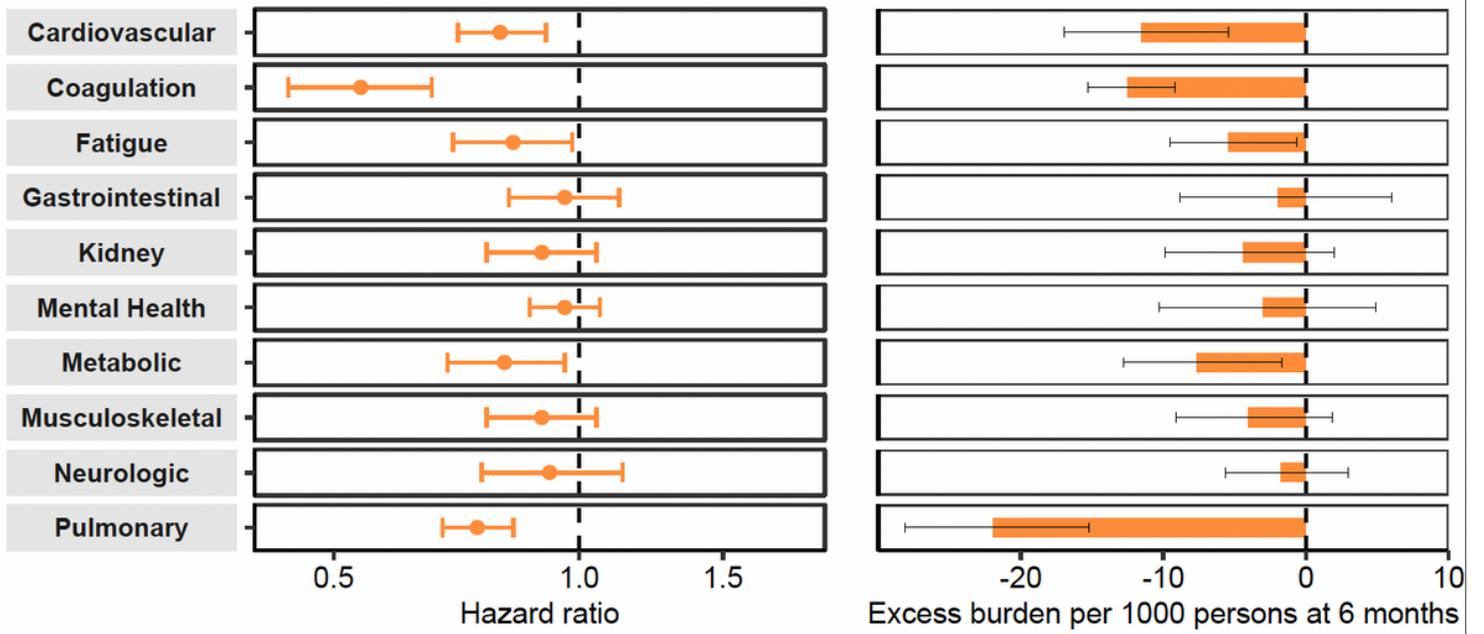


Figure 4

Risk and 6-month excess burden of post-acute sequelae by organ system in people with breakthrough COVID-19 compared to those with COVID-19 without prior vaccination. Incident outcomes were assessed from 30 days after the positive COVID-19 test to end of follow-up. All results are in comparison to those with COVID-19 without prior vaccination. Adjusted hazard ratios (dots) and 95% confidence intervals (error bars) are presented, as are estimated excess burden (bars) and 95% confidence intervals (error bars). Burdens are presented per 1000 persons at 6 months of follow-up.

Figure 5

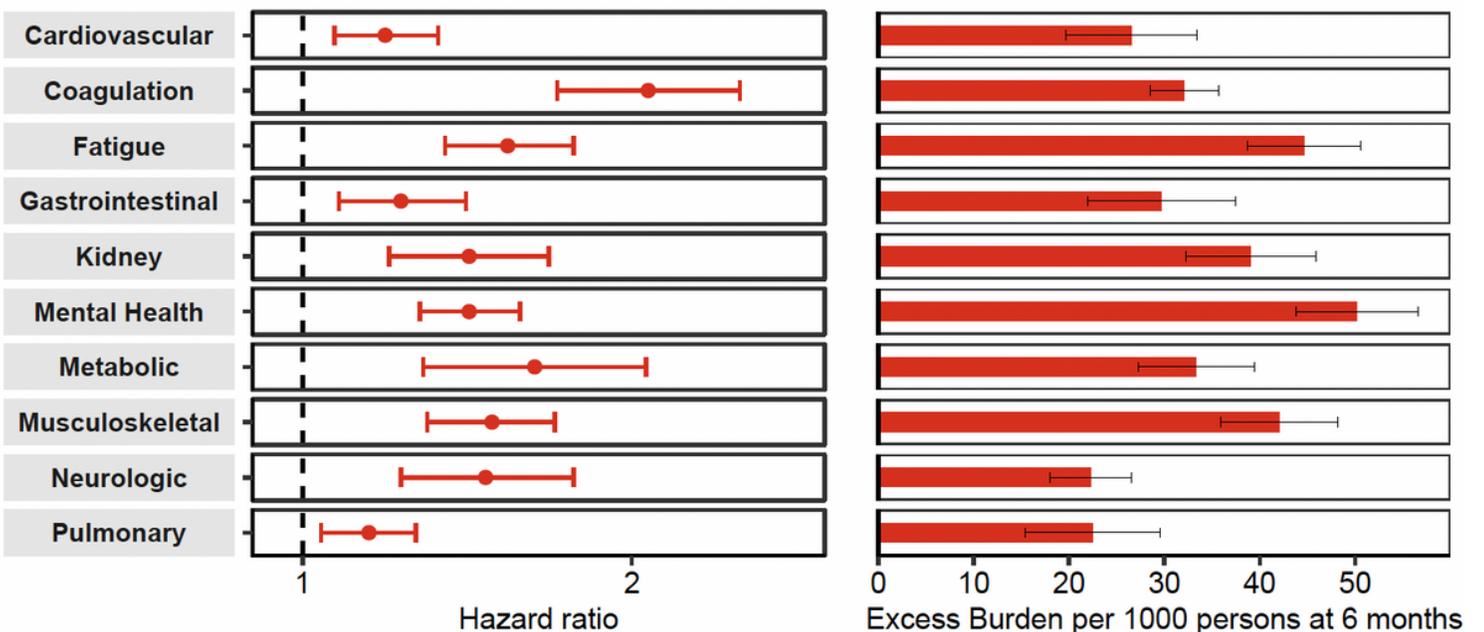


Figure 5

Risk and 6-month excess burden of post-acute sequelae by organ system in people who were hospitalized during the acute phase of breakthrough COVID-19 compared to those hospitalized with seasonal influenza. Incident outcomes were assessed from 30 days after the positive COVID-19 test to end of follow-up. All results are in comparison to those who were hospitalized with seasonal influenza. Adjusted hazard ratios (dots) and 95% confidence intervals (error bars) are presented, as are estimated excess burden (bars) and 95% confidence intervals (error bars). Burdens are presented per 1000 persons at 6 months of follow-up.

Supplementary Files

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