Pharmacotherapy and pulmonary fibrosis risk after SARS-CoV-2 infection: a prospective nationwide cohort study in the United States

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Summary

Background Pulmonary fibrosis is characterized by lung parenchymal destruction and can increase morbidity and mortality. Pulmonary fibrosis commonly occurs following hospitalization for SARS-CoV-2 infection. As there are medications that modify pulmonary fibrosis risk, we investigated whether distinct pharmacotherapies (amiodarone, cancer chemotherapy, corticosteroids, and rituximab) are associated with differences in post-COVID-19 pulmonary fibrosis incidence.

Methods We used the National COVID-19 Cohort Collaboration (N3C) Data Enclave, which aggregates and harmonizes COVID-19 data across the United States, to assess pulmonary fibrosis incidence documented at least 60 days after COVID-19 diagnosis among adults hospitalized between January 1st, 2020 and July 6th, 2022 without pre-existing pulmonary fibrosis. We used propensity scores to match pre-COVID-19 drug-exposed and unexposed cohorts (1:1) based on covariates with known influence on pulmonary fibrosis incidence, and estimated the association of drug exposure with risk for post-COVID-19 pulmonary fibrosis. Sensitivity analyses considered pulmonary fibrosis incidence documented at least 30- or 90-days post-hospitalization and pulmonary fibrosis incidence in the COVID-19-negative N3C population.

Findings Among 5,923,394 patients with COVID-19, we analyzed 452,951 hospitalized adults, among whom pulmonary fibrosis incidence was 1.1 per 100-person-years. 277,984 hospitalized adults with COVID-19 were included in our primary analysis, among whom all drug exposed cohorts were well-matched to unexposed cohorts (standardized mean differences <0.1). The post-COVID-19 pulmonary fibrosis incidence rate ratio (IRR) was 2.5 (95% CI 1.2–5.1, P = 0.01) for rituximab, 1.6 (95% CI 1.3–2.0, P < 0.0001) for chemotherapy, and 1.2 (95% CI 1.0–1.3, P = 0.02) for corticosteroids. Amiodarone exposure had no significant association with post-COVID-19 pulmonary fibrosis (IRR = 0.8, 95% CI 0.6–1.1, P = 0.24). In sensitivity analyses, pre-COVID-19 corticosteroid use was not consistently associated with post-COVID-19 pulmonary fibrosis. In the COVID-19 negative hospitalized population (n = 1,240,461), pulmonary fibrosis incidence was lower overall (0.6 per 100-person-years) and for patients exposed to all four drugs.

Interpretation Recent rituximab or cancer chemotherapy before COVID-19 infection in hospitalized patients is associated with increased risk for post-COVID-19 pulmonary fibrosis.

Abbreviations: CI, Confidence interval; DLCO, Diffusion capacity of the lung for carbon monoxide; FVC, Forced vital capacity; HR, Hazard ratio; HRCT, High-resolution computed tomography; ILD, Interstitial lung disease; IPF, Idiopathic pulmonary fibrosis; IRB, Institutional review board; PF, Pulmonary fibrosis; PFT, Pulmonary function testing; SD, Standard deviation

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Keywords: Pulmonary fibrosis; Post-COVID; Pharmacotherapy; SARS-CoV-2; Rituximab

Research in context

Evidence before this study

We searched PubMed, Medline, and European PMC for studies published before January 1, 2023, with the search terms "amiodarone", "cancer chemotherapy", "corticosteroids", "rituximab", "COVID", "pulmonary fibrosis", and "interstitial lung disease". We found no studies reporting associations between these pharmacotherapeutic agents and risk of post-COVID-19 pulmonary fibrosis.

Added value of this study

We found that treatment with rituximab or cancer chemotherapies prior to hospitalization was associated with an increased risk of post-hospitalization pulmonary fibrosis among patients who were hospitalized in the United States with SARS-CoV-2 infection.

Implications of all the available evidence

Hospitalized patients with SARS-CoV-2 infection who received rituximab or cancer chemotherapies prior to hospitalization may be at an increased risk of post-COVID-19 pulmonary fibrosis. Strategies for risk mitigation should be considered.

Introduction

Pulmonary fibrosis is characterized by the destruction of normal lung parenchymal structure, often leading to irreversible architectural distortion, gas exchange impairment, reduced quality of life, and higher mortality. Current literature suggests substantially impaired lung function is present in COVID-19 survivors after hospitalization.[1–3] Pulmonary fibrosis following SARS-CoV-2 respiratory viral infection occurs as a sequela of severe lung damage in which a significant fraction of patients hospitalized with acute respiratory distress syndrome develop progressive pulmonary fibrosis.[4] Radiological evidence of post-COVID-19 pulmonary fibrosis is common on chest CT scans of patients with severe COVID-19.[5–8] These persistent abnormalities vary in prevalence from a tenth to three-quarters of patients requiring hospitalization or recurring outpatient care at 60 days after first COVID-19 diagnosis.[9,10] With over 640 million people diagnosed with COVID-19, and worldwide mortality exceeding six million deaths, there is a pressing need to identify factors that may complicate the post-infection course and increase the risk of post-COVID-19 pulmonary fibrosis.[11]

There are several potential risk factors for the development of pulmonary fibrosis in COVID-19 patients, including older age, male sex, preexisting lung conditions, and requirement for ventilation support.[9–12] However, it is also possible that certain medications could contribute to the development or worsening of pulmonary fibrosis in patients with COVID-19, whereas other medications might ameliorate pulmonary fibrosis risk. Some medications have been shown to have toxic effects on the lungs or to increase inflammation, which may potentiate the development of pulmonary fibrosis. For example, prolonged administration of amiodarone or cancer chemotherapies such as bleomycin has long been known to induce pulmonary fibrosis.[13,14] In contrast, immunomodulatory therapies such as corticosteroids and rituximab or other biological agents directed against immune subcellular components are often administered to ameliorate inflammatory processes that may lead to pulmonary fibrosis.[15,16] Whether medications administered for comorbid diseases that predated acute COVID-19 influence the development of post-COVID-19 pulmonary fibrosis is unknown.

The objective of this study was to investigate whether distinct classes of pharmacotherapy (amiodarone, cancer chemotherapies, corticosteroids, and rituximab) are associated with the risk of post-COVID-19 pulmonary fibrosis. We hypothesized that the use of amiodarone or cancer chemotherapies prior to SARS-CoV-2 infection would be associated with an increased risk of post-

COVID-19 pulmonary fibrosis, while the use of corticosteroids or rituximab would be associated with a decreased risk of post-COVID-19 pulmonary fibrosis in hospitalized patients with SARS-CoV-2 infection. We used a national electronic health record data repository to determine the relative risk of post-COVID-19 pulmonary fibrosis based on the data available for hospitalized adults (aged 18 years and older) at 60 days post-hospitalization for SARS-CoV-2 infection by pre-infection drug exposure.

Methods

Study setting

Our analysis was conducted with electronic health record (EHR) data using tools accessed through the National COVID-19 Cohort Collaboration (N3C) Data Enclave (see Supplementary Material page 5).[17] The N3C repository is hosted and supported by the National Institutes of Health (NIH) National Center for Advancing Translational Sciences (NCATS). N3C aggregates and harmonizes EHR data for patients with laboratory-confirmed or suspected COVID-19 during encounters after January 1, 2020 from sites across the United States.[17] Based on demographic characteristics, COVID-19 positive cases are matched to COVID-19 negative controls at a ratio of 1:2.[18] For each patient, N3C data contributors were asked to provide all available historical details from their EHRs within 2 years before the patient's first recorded COVID-19 test date (or diagnosis date if no prior test was recorded) and all details after that date, including drug exposure information, with detailed inpatient and outpatient records. The study followed the Strengthening the Reporting of Observational studies in Epidemiology guidelines (see Supplementary Material page 3).[19]

Study population

We identified adult (age ≥18 years) patients in the N3C enclave who had laboratory-confirmed SARS-CoV-2 infection (at least one positive SARS-CoV-2 PCR or antigen test result) or suspected[18] COVID-19 from January 1, 2020 to June 31, 2022 (see Fig. 1). COVID-19 index date was defined as the first positive SARS-CoV-2 PCR or antigen test or first COVID-19 diagnosis. Subsequent COVID-19 diagnoses were not factored into the analyses. Patients were included if they were hospitalized with COVID-19, defined as the first hospitalization encounter between one day before and 14 days after their first COVID-19 diagnosis. Our analyses were limited to inpatients with complete hospitalization episodes, as documented in the EHR by either discharge or death. Patients who did not have a follow-up visit at least 60 days after their index date or who died within the first 60 days after their first COVID-19 diagnosis were excluded from analysis because their outcome status could not be assessed. Patients who were diagnosed with pulmonary fibrosis before day 60 that was not also recorded after day 60 were not labeled as having pulmonary fibrosis to reduce the risk of capturing acute COVID-19 lung damage that does not progress to chronic pulmonary fibrosis.[20–22] We excluded patients who had a pre-existing diagnosis of pulmonary fibrosis, as identified by whether that diagnosis, defined by the "pulmonary fibrosis ITM" concept set (See Supplementary Table S1), was assigned at any time prior to or on the same day as their first COVID-19 positive test.[23] Lung CT imaging and pulmonary function test results were not meaningfully available in the N3C data enclave (FVC and/or DLCO results were available for approximately 1% of the full cohort); therefore pulmonary fibrosis was limited to diagnoses captured in the EHR. We excluded patients with missing data on age, sex, hospitalization status, and those with implausible data points, such as COVID-19 diagnosis in 2017 or individuals for whom the date of death predated their date of admission. Our analyses included 54 clinical sites that met N3C standards of data quality for analysis.

Pre-COVID-19 infection drug exposure definition

Included patients were categorized based on exposure prior to COVID-19 diagnosis to four drugs of interest: rituximab, cancer chemotherapeutic agents, systemic corticosteroids, and amiodarone. Patients were considered exposed if the drug's effects could have reasonably been anticipated to persist at the time of COVID-19 infection. Therefore, we designated the exposure window for rituximab[24] as six months prior to the COVID-19 index date, systemic corticosteroids[25] as two weeks prior, chemotherapy[26–28] as two years prior, and amiodarone[29] as four months prior. Because evidence emerged several months into the COVID-19 pandemic that demonstrated corticosteroid use (e.g., dexamethasone) could reduce mortality,[30] the timeframe for corticosteroids excludes the period beginning 24 h prior to the first COVID-19 diagnosis date up to time of death or discharge. This avoids capturing corticosteroid use to treat COVID-19 rather than comorbid disease. Exposure group membership was determined independently by drug and was not mutually exclusive across groups.

Statistical analysis

We constructed propensity scores using a logistic regression model including covariates selected a priori to predict the probability of exposure to each drug before COVID-19 diagnosis. Covariates included in all models were age at COVID-19 diagnosis, sex, race, ethnicity, modified Charlson Comorbidity Index (mCCI) score, history of chronic lung diseases, and contributing data site. Several sites contributed too few patients to estimate statistical associations between data partner membership and drug exposure or our outcome in multivariable models. Therefore, for each drug exposure

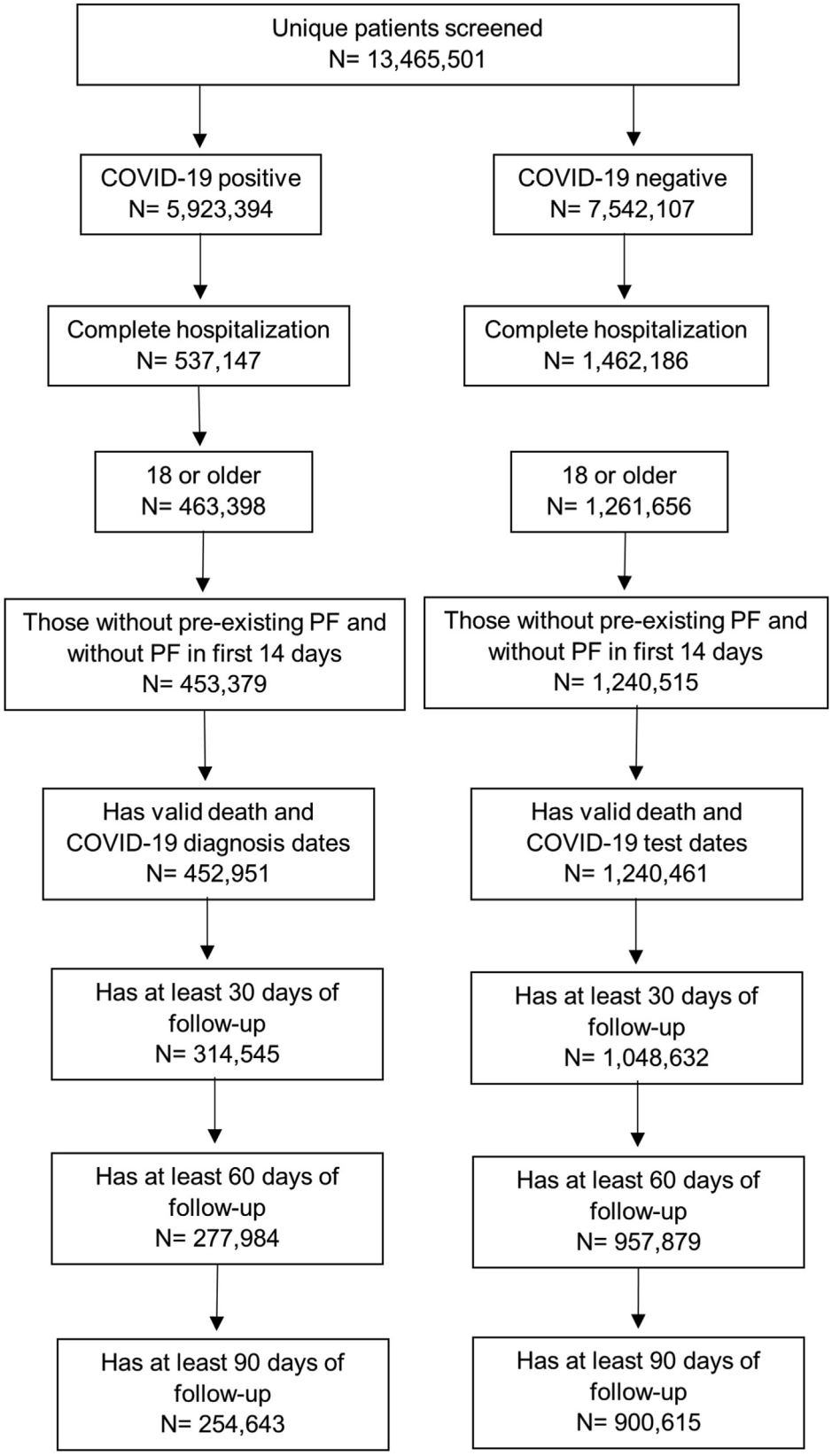

Fig. 1: STROBE diagram depicting flow chart of adult hospitalized patients in the COVID-19 positive and COVID-19 negative population.

cohort we created a categorical variable with levels for each data partner whose patient counts exceeded five percent of the exposed cohort, and the remaining patients aggregated into an "Other Data Partners" category. We masked the N3C data partner identifiers with an arbitrary identifier for this manuscript. The mCCI was calculated as described by Quan et al.[31] For each examined drug, additional covariates include comorbidities associated with the drug type: (i) connective tissue disease for rituximab and steroids; (ii) cancer for chemotherapy; and (iii) arrhythmia for amiodarone.

We used R's MatchIt package,[32] with a 1:1 nearest neighbor matching algorithm without replacement, and a caliper of 0.2 pooled standard deviations[32] (SDs) of the estimated propensity score to generate comparison groups. We assessed covariate balance independently of sample size by evaluating the absolute value of the standardized mean difference (SMD), interpreting an SMD greater than 0.1 as significant. Continuous variables are presented as means with SDs and categorical variables as frequency with percentages. All statistical tests were two-sided and a p-value of less than 0.05 was considered statistically significant.

The primary outcome was new diagnosis of pulmonary fibrosis documented at least 60 days after first COVID-19 diagnosis to remove candidates who only had acute COVID-19 lung damage.[21,33–37] Patients were followed from their COVID-19 index date to either their diagnosis of pulmonary fibrosis or if never diagnosed with pulmonary fibrosis, their most recent outpatient follow-up visit. If they had a pulmonary fibrosis diagnosis at least once after 60 days, they were counted as having pulmonary fibrosis, and outcome status was not changed based on additional follow up visits.

We calculated the incidence rate as number of cases per 100 person-years for the matched drug exposed and control groups. We then used a Poisson regression model to estimate each drug's post-COVID-19 pulmonary fibrosis incidence rate ratio. Cluster-robust standard errors that accounted for the site-level clustering of the data were used to calculate 95% confidence intervals.[38] We then estimated adjusted outcome models which included indicator variables for COVID-19 vaccination status (patients were considered vaccinated if they had any vaccine dose at least 14 days before their first COVID-19 indication), and receiving COVID-specific therapies (dexamethasone, Remdesivir, and immunomodulatory drugs) during hospitalization.

All analyses were complete case analyses and were performed using Python version 3.6[39] and R version 3.5[40] within the N3C Data Enclave.

Sensitivity analysis

Primary outcome sensitivity analyses

We performed sensitivity analyses that alternatively applied more stringent and lenient cut-offs for new-onset pulmonary fibrosis. We defined new-onset pulmonary fibrosis in these sensitivity analyses as a diagnosis documented at least (1) 30 days; and (2) 90 days after first COVID-19 diagnosis in keeping with current European Respiratory Society recommendations on Long COVID-19 follow-up for evidence of high-resolution computerized tomography (HRCT)-identified pulmonary fibrosis.[20] Patients were excluded if they did not have a follow-up visit observed at least 30 days or 90 days after their index date; or if they died within 30 or 90 days, respectively. Additionally, we conducted a Cox proportional hazard regression treating death as censoring (death rates by cohort available in Supplementary Table S9).

COVID-19 negative analysis

To comparatively assess the risk of new pulmonary fibrosis after drug exposure and absent a COVID-19 diagnosis, we repeated this analysis among COVID-19 negative patients in the N3C Enclave. We identified adult patients with a negative COVID-19 test and no record of a positive COVID-19 test or diagnosis, from January 1, 2020 to July 6, 2022. The index date was defined as the first negative SARS-CoV-2 PCR or antigen test. Patients were included if they were hospitalized within 14 days after their index date and if at least 60 days have passed since their index date. We excluded patients that had an existing pulmonary fibrosis diagnosis, defined as being present on or before their index date. All statistical analytic methods were conducted as described in the primary analysis.

Ethical review

This study was approved by the University of Chicago Institutional Review Board with a waiver of the informed consent requirement (IRB21-0650, approved on 4/30/2022). This study was approved by the N3C data request review committee under DUR-7DB5C39. The N3C data transfer to NCATS is performed under a Johns Hopkins University Reliance Protocol # IRB00249128 or individual site agreements with NIH. The N3C Data Enclave is managed under the authority of the NIH; information can be found at https://ncats.nih.gov/n3c/resources.

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

We analyzed data for 5,923,394 patients with a recorded diagnosis of COVID-19 between January 1st, 2020 and July 6th, 2022, of whom 452,951 were hospitalized adults with no pre-existing pulmonary fibrosis or pulmonary fibrosis within the first 14 days of hospitalization and all of whom had valid death, last follow-up, and COVID-19 diagnosis dates.

Propensity score matching

COVID-19 positive patients who had exposure to the four drugs of interest (rituximab n = 1035, chemotherapeutic agent n = 9011, systemic corticosteroids n = 43,862, and amiodarone n = 5861) were well-matched (Fig. 2; i.e., standardized mean difference (SMD) of <0.1 for each covariate) to patients without exposure to that drug. There were 3021 observations (6%) in the corticosteroid cohort that could not be matched because they fell outside the caliper range and were thus removed. There were three removed observations in the rituximab cohort, one from the chemotherapeutic agent group, and one from the amiodarone cohort (less than 1% in each). Matching results were similar in the 30-day and 90-day cohorts used in sensitivity analyses (see Supplementary Figures S1 and S2).

Population descriptive statistics

All matched cohorts (See Supplementaary Tables S2–S5) were predominantly White (rituximab = 69% [1415/2064], chemotherapy = 65% [11,620/18,022], steroid = 61% [53,085/87,724], amiodarone = 68% [7953/11,722]) and non-Hispanic (rituximab = 82% [1698/2064], chemotherapy = 84% [15,045/18,022], steroid = 80% [70,321/87,724], amiodarone = 86% [10,073/11,722]), and most were predominantly female (rituximab = 53% [1098/2064], chemotherapy = 58% [10,467/18,022], steroid = 56% [48,700/87,724], amiodarone = 37% [4342/11,722]). The mean age ± SD ranged from 57 ± 16 years in the rituximab cohort, 58 ± 16 years in the corticosteroid cohort, 60 ± 17 years in the chemotherapy cohort and 67 ± 13 years in the amiodarone cohort. Because steroids are given for a broad range of conditions, we have included the proportion of underlying conditions in Supplementary Table S6.

In the matched rituximab COVID-19 cohort (n = 2064), mean follow-up was 419 days (SD 232; median follow-up 373 days [IQR 232–599]). In the matched chemotherapeutic agent COVID-19 cohort (n = 18,022), mean follow-up was 336 days (SD 334; median follow-up 285 days [IQR 166–500]). In the matched systemic corticosteroid COVID-19 cohort (n = 87,724), mean

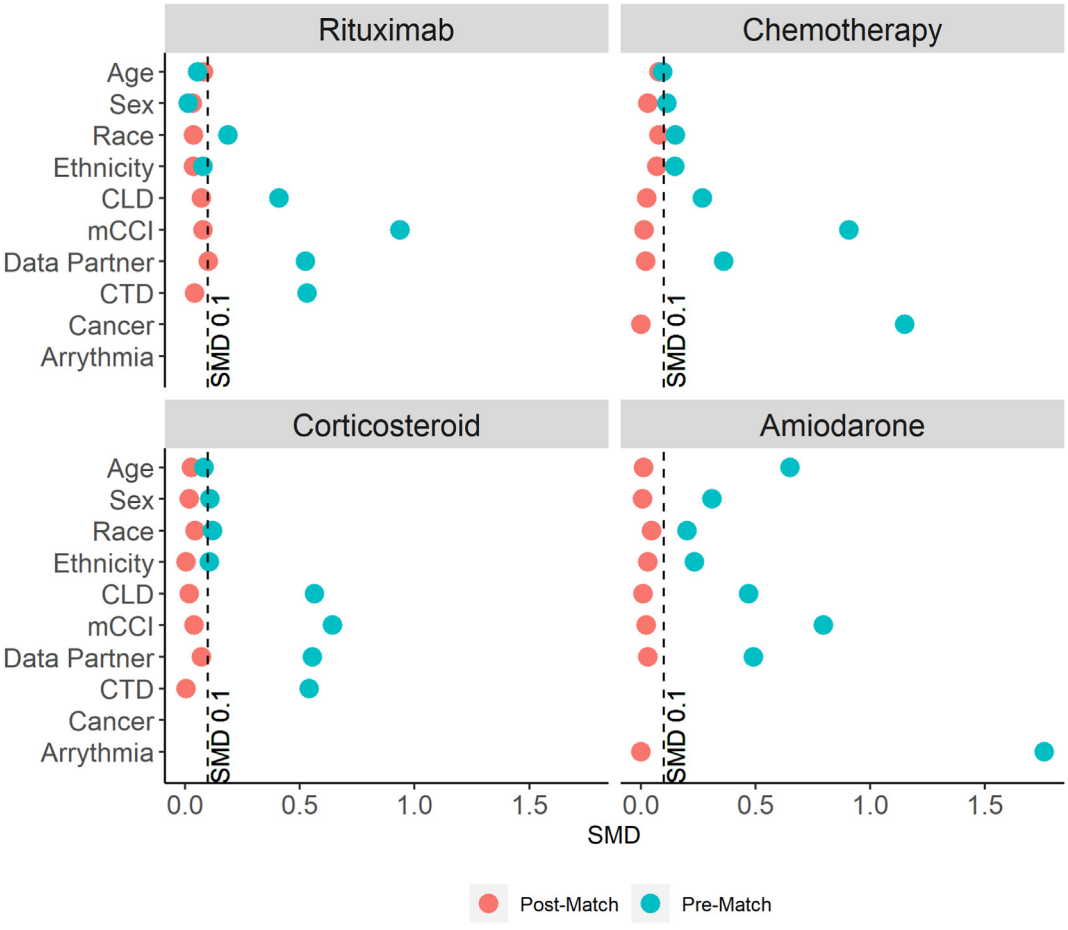

Fig. 2: Covariate balance pre- and post- propensity score matching, 60-day cohort.

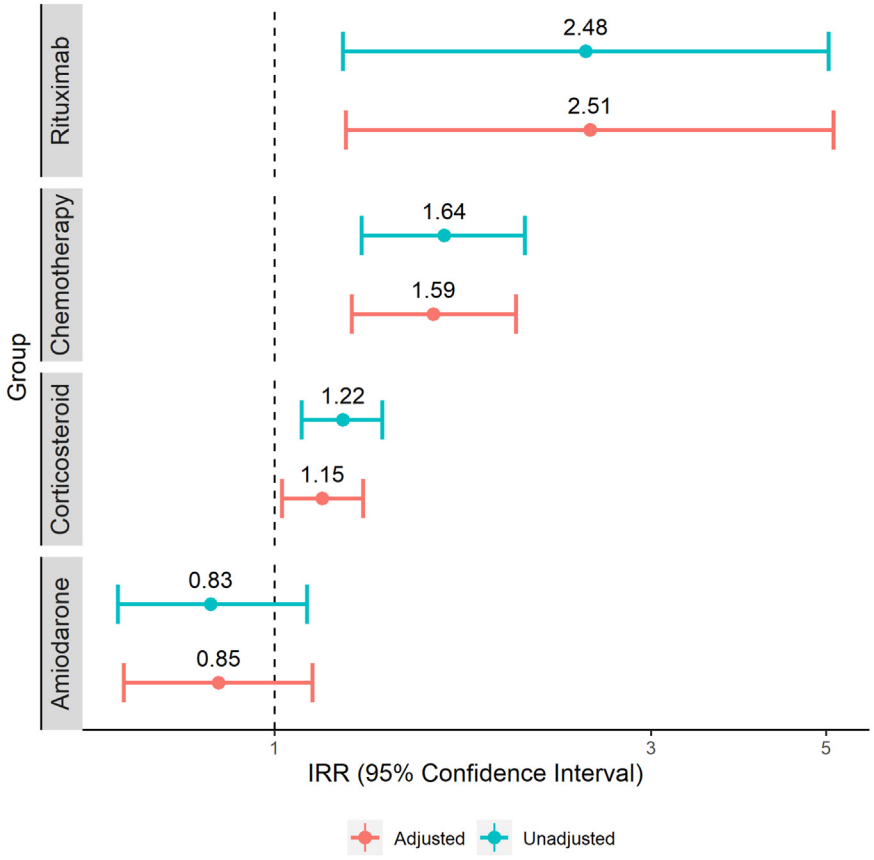

Fig. 3: Incidence Rate Ratios, new PF diagnosis at least 60 days post COVID-19 diagnosis.

follow-up was 343 days (SD 205; median follow-up 298 days [IQR 171–508]). In the matched amiodarone COVID-19 cohort (n = 11,722), mean follow-up was 325 days (SD 203; median follow-up 269 days [IQR 157–489]).

Incidence of new pulmonary fibrosis during follow-up

The overall incidence of new pulmonary fibrosis was 1.1 per 100 person-years among our 452,951 COVID-positive hospitalized patients. The mean follow-up duration after index date was 1.17 years for patients who developed pulmonary fibrosis and 1 year for those who did not.

The incidence of pulmonary fibrosis in patients exposed to rituximab was 2.8 cases per 100 person-years compared with 1.1 cases per 100 person-years in the matched controls (IRR = 2.5, 95% CI 1.2–5.0, P = 0.01) (Fig. 3). Among patients exposed to chemotherapy, the incidence of pulmonary fibrosis was 2.2 per 100 person-years compared to 1.3 per 100 person-years (IRR = 1.6, 95% CI 1.3–2.0, P < 0.0001). The incidence rate ratios (IRR) and confidence intervals for rituximab and chemotherapy exposures were not changed appreciably by adjusting our analyses for vaccination status or COVID-specific therapies received during hospitalization. The incidence of new pulmonary fibrosis among people exposed to corticosteroids was 1.5 per 100 person-years compared to 1.2 per 100 person-years in the unexposed matched cohort (IRR = 1.2, 95% CI 1.0–1.3, P = 0.02). There was no significant association between amiodarone and pulmonary fibrosis (IRR = 0.8, 95% CI 0.6–1.1, P = 0.24) (Fig. 3).

The results of our sensitivity analyses (see Supplementary Figures S3 and S4) using a more lenient (30 days) and more strict (90 days) follow-up show that the IRR for pulmonary fibrosis following exposure to rituximab and chemotherapy increases as the time interval increases (from IRR = 1.9 at 30 days to IRR = 2.6 at 90 days for rituximab and IRR = 1.4 at 30 days to IRR = 1.6 at 90 days for chemotherapy), indicating that when the diagnosis of pulmonary fibrosis is most certain (at 90 days) the association of rituximab exposure and chemotherapy exposure and new pulmonary fibrosis diagnosis is greatest. The IRR for corticosteroids and amiodarone remains similar across all follow-up time periods.

We also analyzed models with age–drug interactions, to test for graduated pulmonary fibrosis IRRs by age. None of the interaction term estimates were statistically significant (Supplementary Table S7). Analyses among the corticosteroid population removing caliper restrictions on the propensity score matching stage found similar results (See Supplementary Table S8).

Our Cox regression models found similar results, with the rituximab HR = 2.5 (95% CI 1.2–5.0), chemotherapy HR = 1.7 (95% CI 1.3–2.2), corticosteroid HR = 1.2 (95% CI 1.1–1.4), and amiodarone HR = 0.8 (95% CI 0.6–1.1) (Supplementary Figure S5).

COVID-19 negative analysis

Among our COVID-19 negative population (n = 1,240,461), the overall rate of new pulmonary fibrosis diagnosis at 60 days was 0.5 per 100 person years, half the rate of the COVID-19 positive population. The IRRs for all four drugs were greater than 1 and statistically significant, indicating that exposure to these drugs is associated with greater rates of pulmonary fibrosis independent of COVID-19 diagnosis (Fig. 4). The IRR of new pulmonary fibrosis among those exposed to rituximab was 1.7 (95% CI 1.0–2.9, P = 0.03), lower than the IRR among the COVID-19 positive population. The IRRs for chemotherapy (IRR = 1.7, 95% CI 1.5–1.9, P < 0.0001) and steroids (IRR = 1.3, 95% CI 1.2–1.4, P < 0.0001) were similar to the COVID-19 positive population IRRs. However, unlike in the COVID-19 positive population, there was a significant association between amiodarone and pulmonary fibrosis (IRR = 1.4, 95% CI 1.2–1.7, P < 0.0001).

Cox regression models among the COVID-19 negative population also found similar results, with the rituximab HR = 1.5 (95% CI 0.9–2.6), chemotherapy HR = 1.6 (95% CI 1.4–1.8), corticosteroid HR = 1.2 (95% CI 1.1–1.3), and amiodarone HR = 1.4 (95% CI 1.1–1.6).

Discussion

In this nationwide cohort study, we examined the association between several commonly-used medications and the risk of post-COVID-19 pulmonary fibrosis. We found that rituximab and cancer chemotherapeutic drugs were associated with an increased risk of post-COVID-19 pulmonary fibrosis in COVID-positive individuals compared to those who did not receive these medications. This increased risk was observed over and above the risk of these medications in those who did not contract COVID.

We summarized risk for pulmonary fibrosis using incidence risk ratios with findings that are informative for public health and of interest to patients and clinicians. While new cases of idiopathic pulmonary fibrosis were reported in the general US population to occur at an annual rate of 93.7 per 100,000 person-years in 2011, overall, the number of pulmonary fibrosis cases has been increasing in incidence.[41,42] As such, the U.S. annual incidence of preclinical cases of pulmonary fibrosis is presently much higher at 1023 per 100,000 person-years (95% CI 511–1831).[43] Our conservative estimates of pulmonary fibrosis incidence in those who did not contract COVID-19 were on the lower end of this spectrum at 600 per 100,000 person-years. However, these estimates appear higher after COVID-19 hospitalization, with an annual incidence of 1100 per 100,000 person-years. In parallel, recent studies suggest that this tremendous increase in lung parenchymal distortion may ultimately impact up to eleven percent of patients after hospitalization with COVID.[9]

A plethora of evidence implicates commonly used pharmacotherapy in the subsequent development of pulmonary fibrosis (www.pneumotox.com). These include the prolonged use of cancer chemotherapeutic drugs (such as bleomycin or gemcitabine), rheumatologic medications (such as rituximab), amiodarone, and antibiotics, which together constitute the most common drug causes of pulmonary fibrosis.[44] Conversely, immunomodulatory medications such as corticosteroids, directed against immune cells or cytokines, may be given for inflammatory lung conditions and are thought to inhibit related pathways that contribute to the pathogenesis of pulmonary fibrosis.[15] However, recent evidence suggests that prolonged corticosteroid administration may be detrimental in idiopathic pulmonary fibrosis.[45,46]

Rituximab is a monoclonal antibody that works by targeting CD20-positive B cells and is used to treat a variety of autoimmune and lymphoproliferative disorders. Treatment with rituximab considerably increases the risk of developing severe post-COVID-19 outcomes (risk ratios 1.7–5.5).[47] Similar to other biologic disease-modifying anti-rheumatic agents such as Tofacitinib,[48] the use of rituximab has been linked to lung toxicity and fibrosis.[44,49,50] However, the mechanism by which rituximab may increase the risk of post-COVID-19 fibrosis is not fully understood. It is possible that the drug's immunosuppressive effects may disrupt the body's ability to effectively clear viral infections, leading to an increased risk of fibrosis. Alternatively, rituximab may directly alter the fibrotic process itself, either through its effects on B cells or through other mechanisms. Rituximab significantly increased pulmonary fibrosis risk when compared to matched controls in the COVID-negative population. However, this risk was substantially amplified among patients within the COVID-positive population that were exposed to rituximab suggesting a synergistic effect with SARS-CoV-2 infection on the fibrotic process. Further research is needed to fully understand the underlying mechanisms by which rituximab may increase the risk of post-COVID-19 fibrosis.

Chemotherapy, in which drugs are administered to kill cancer cells, was also associated with an increased

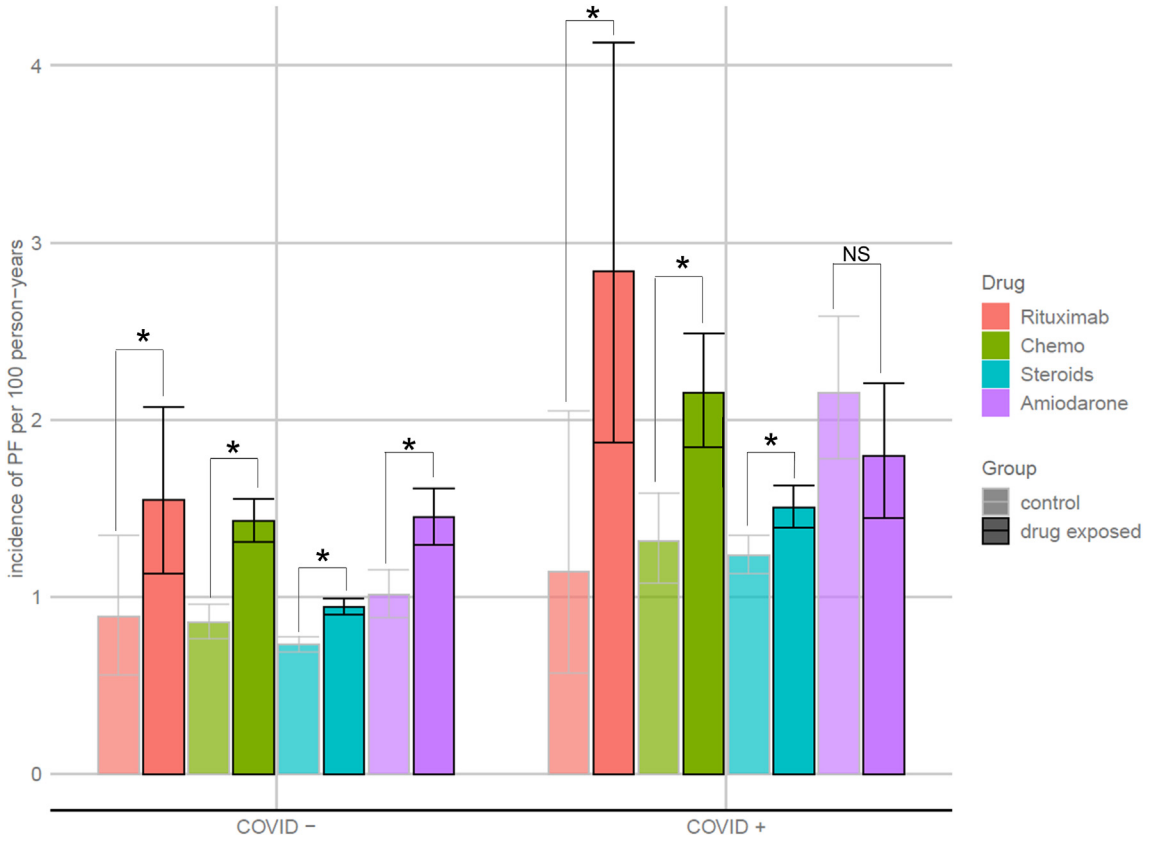

Fig. 4: Pulmonary fibrosis (PF) incidence at least 60 days post COVID-19 testing across all four drug categories in the COVID-19 negative and the COVID-19 positive populations. *Significant P-value for within-group t-test comparisons between propensity-matched drug cohorts for all four drugs in the COVID-19 negative and the COVID-19 positive populations; NS = non-significant.

risk of post-COVID-19 pulmonary fibrosis. Patients with cancer are particularly vulnerable to SARS-CoV-2 pneumonitis, and cancer chemotherapy is known to have a range of side effects, including immunosuppression, which may increase the risk of infections, severe organ complications, and death.[51–56] Therefore, it is possible that similar to sequelae observed among patients infected with other RNA viruses, the immunosuppressive effects of chemotherapy may lead to a reactivation of SARS-CoV-2 in cancer patients who have recovered from prior COVID-19 infection thus prolonging inflammation and heightening risk for post-COVID-19 pulmonary fibrosis.[57] We demonstrated a statistically significant association between the use of chemotherapy and the development of pulmonary fibrosis consistent with previous studies that show a higher incidence of pulmonary fibrosis in patients receiving cancer chemotherapy.[58–60] Additionally, several mechanistic studies have shown that chemotherapeutic agents activate fibroblast proliferation and collagen synthesis, which are key pathogenic processes in the development of pulmonary fibrosis.[61–63] These results provide strong rationale for further investigation into the potential risks of chemotherapy and the need for caution in prescribing these drugs in patients with acute COVID. Further research is also needed to better understand the specific mechanisms by which chemotherapy may increase the risk of post-COVID-19 fibrosis.

The use of corticosteroids, a class of immunomodulatory drugs used to reduce systemic inflammation and frequently administered to patients with morphologic inflammatory features within the lung parenchyma,[15] was associated with a marginally increased risk of post-COVID-19 pulmonary fibrosis when compared with matched controls. Notably, this pulmonary fibrosis risk was greater in COVID-positive individuals receiving corticosteroid therapy compared to those in the COVID-negative cohort who received corticosteroid therapy. As corticosteroids are known to have a range of side effects, including profound immunosuppression and the worsening of outcomes in fibrotic lung disease,[45] this observation again raises the possibility of pulmonary fibrosis propagation following the disruption of innate

immunologic mechanisms responsible for effective viral clearance. It is plausible that the use of corticosteroids may propagate the fibrotic process that occurs in the setting of COVID-19, leading to an increased risk of post-COVID-19 fibrosis. However, further research is needed to confirm this possibility and to understand the specific mechanisms by which corticosteroids may increase the risk of post-COVID-19 fibrosis.

Amiodarone, a drug that is used to treat heart rhythm disorders, and strongly linked to occurrence of pulmonary fibrosis,[13,44] was not associated with an increased risk of post-COVID-19 fibrosis. However, our findings confirm that use of amiodarone amplifies the risk of pulmonary fibrosis in the absence of SARS-CoV-2 positivity.

Importantly, the risk of post-COVID-19 fibrosis associated with the use of these medications appeared to be independent of age. This suggests that the increased risk of post-COVID-19 fibrosis may not be limited to specific age groups, and highlights the importance of considering the potential for these medications to increase the risk of post-COVID-19 fibrosis in all individuals.

Limitations

Our study has several inherent limitations. First, in our analysis of this cohort, the code-based diagnoses and drugs used for cohort identification, covariate annotation, and outcome definitions are subject to user-created concept sets within the N3C data enclave and preexisting or follow-up lung CT imaging, pulmonary function test results, development of symptoms, disease burden, hospital/GP contacts, and new antifibrotic therapy use were not meaningfully available. Despite thorough review, it is possible that our analysis suffers from underidentification or non-specific definitions of conditions and drug exposures. In particular, the chemotherapy concept set contains a wide range of therapeutics with different mechanisms and toxicity profiles. Relatedly, the data harmonization process may have resulted in data being lost due to inconsistent definitions. Second, data is only linked to that within the same N3C data contributor (e.g., health system), and subjects with records at another N3C data contributor or a site not included in N3C would not have their records linked to our analysis. This may be particularly consequential in the case of vaccination status, due to many patients being vaccinated at retail pharmacies. Third, certain patient level datapoints such as lung CT imaging report and pulmonary function test indices were not captured in the N3C enclave thus precluding our ability to determine severity of lung function impairment, diagnostic ascertainment, progressive pulmonary fibrosis, or the potential for improvement in lung injury over time among those with a pulmonary fibrosis diagnosis. Thus, our analyses were limited to diagnoses of pulmonary fibrosis as documented by clinicians at the respective clinical sites. Fourth, while we attempted to account for covariates based on potential influence on the outcome of new pulmonary fibrosis and/or exposure to the selected drug, unmeasured variables may have influenced exposure status, and there may be differential impacts of measured variables (i.e. sex, ethnicity). For example, N3C contained limited data on drug dosing and duration prior to SARS-CoV2 infection and so we were unable to account for potential implications of drug dose or duration variation on the clinical trajectory of patients with post-COVID-19 pulmonary fibrosis. Additionally we were unable to account for preexisting subclinical lung nodules or interstitial lung abnormalities. Lastly, the different variants of SARS-CoV-2 that were dominant during different waves of the COVID-19 pandemic may have had different potentials to induce pulmonary fibrosis. Due to the date shifting in the N3C deidentified dataset, we could not conduct sensitivity analyses accounting for the dominant variant at the time of COVID-19 diagnosis.

It is important to note that the IRRs obtained within the COVID-positive and COVID-negative populations were derived independently. As such, cross-cohort comparisons of the magnitude of this risk should be interpreted within that context. There may have been other pulmonary fibrosis causing exposures in the non-COVID population that were not accounted for, and study participants taking these therapeutics were at higher risk of developing pulmonary fibrosis regardless of COVID.

In conclusion, in this cohort, the use of rituximab or cancer chemotherapeutic drugs was associated with an increased risk of pulmonary fibrosis in patients hospitalized with COVID-19. This information is of public health significance for clinicians and patients navigating treatment decisions together and would be valuable in guiding future research. It is important to note that COVID might not necessarily have been the pulmonary fibrosis causing exposure in the COVID population, as study participants taking these therapeutics may have been at higher risk of developing pulmonary fibrosis regardless of COVID. Although our study provides important insights into the potential role of COVID-19 in the development of pulmonary fibrosis, we also acknowledge that other factors may contribute, and more research is needed to fully understand this complex relationship.

Contributors

Authorship was determined using ICMJE recommendations.

Conceptualisation: AA, AES, JS. Data curation: All authors (AA, RB, TJB, VZ, HZ, RK, BKP, AES, WFP, and JS). Formal analysis: RB, TJB, WFP. Funding acquisition: AA, WFP, JS. Investigation: All authors (AA, RB, TJB, VZ, HZ, RK, BKP, AES, WFP, and JS). Methodology: AA, RB, TJB, WFP, JS. Project administration: AA, TJB, JS. Resources, software: AA, RB, TJB, N3C Consortium. Supervision: AA, TJB, WFP, JS. Validation: AA, RB, TJB, WFP, JS. Visualisation: AA, RB, WFP. Writing – original draft: AA, RB. Writing – review & editing: AA, RB, TJB, VZ, RK, BKP, AES, WFP, JS. RB and TJB have directly accessed and verified the underlying data reported in the manuscript.

Data sharing statement

Patient-level data underlying this article cannot be shared publicly due to data privacy and security requirements of the NCATS N3C Data Enclave.

Conflict of interest disclosures

RB, TJB, VZ, HZ, AES, and RK have nothing to disclose. AA has received speaking and advisory board fees from Genentech and Boehringer Ingelheim and is supported by a career development award from the National Heart, Lung, and Blood Institute (NHLBI K23HL146942), and grant funding from the American College of Chest Physicians and the Pulmonary Fibrosis Foundation. BKP is supported by a career development award from the NHLBI (K23-HL148387) and funding from the Walder Foundation and the Center for Healthcare Delivery Science and Innovation at the University of Chicago. WFP is supported by a career development award from the NHLBI (K08HL150291). JS has research and training funding from NIH, NSF, and the Burroughs Wellcome Fund, and has a potential financial interest in PulmOne Advanced Medical Diagnostics, Ltd, Israel.

Declaration of interests

RB, TJB, VZ, HZ, AES, and RK have nothing to disclose. AA has received speaking and advisory board fees from Genentech and Boehringer Ingelheim and is supported by a career development award from the National Heart, Lung, and Blood Institute (NHLBI K23HL146942), and grant funding from the American College of Chest Physicians and the Pulmonary Fibrosis Foundation. BKP is supported by a career development award from the NHLBI (K23-HL148387) and funding from the Walder Foundation and the Center for Healthcare Delivery Science and Innovation at the University of Chicago. JS has research and training funding from NIH, NSF, and the Burroughs Wellcome Fund, and has a potential financial interest in PulmOne Advanced Medical Diagnostics, Ltd, Israel.

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IN3C data partners with released data

The following institutions whose data is released or pending:

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Appendix B. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2023.100566.

References

1 Sahanic S, Tymoszuk P, Luger A, et al. COVID-19 and its continuing burden after 12 months: a longitudinal observational prospective multicentre trial. *ERJ Open Res*. 2023;9(2):317–2022. https://doi.org/10.1183/23120541.00317-2022.

2 Huang L, Li X, Gu X, et al. Health outcomes in people 2 years after surviving hospitalisation with COVID-19: a longitudinal cohort study. *Lancet Respir Med*. 2022;10(9):863–876. https://doi.org/10.1016/S2213-2600(22)00126-6.

3 Han X, Chen L, Fan Y, et al. Longitudinal assessment of chest CT findings and pulmonary function after COVID-19 infection. *Radiology*. 2023;307(2):e222888. https://doi.org/10.1148/radiol.222888.

4 John AE, Joseph C, Jenkins G, Tatler AL. COVID-19 and pulmonary fibrosis: a potential role for lung epithelial cells and fibroblasts. *Immunol Rev*. 2021;302(1):228–240. https://doi.org/10.1111/imr.12977.

5 Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *Lancet Infect Dis*. 2020;20(4):425–434. https://doi.org/10.1016/S1473-3099(20)30086-4.

6 Chung M, Bernheim A, Mei X, et al. CT imaging features of 2019 novel coronavirus (2019-nCoV). *Radiology*. 2020;295(1):202–207. https://doi.org/10.1148/radiol.2020200230.

7 Zhou S, Wang Y, Zhu T, Xia L. CT features of coronavirus disease 2019 (COVID-19) pneumonia in 62 patients in Wuhan, China. *AJR Am J Roentgenol*. 2020;214(6):1287–1294. https://doi.org/10.2214/AJR.20.22975.

8 Pan Y, Guan H, Zhou S, et al. Initial CT findings and temporal changes in patients with the novel coronavirus pneumonia (2019-nCoV): a study of 63 patients in Wuhan, China. *Eur Radiol*. 2020;30(6):3306–3309. https://doi.org/10.1007/s00330-020-06731-x.

9 Stewart I, Jacob J, George PM, et al. Residual lung abnormalities following COVID-19 hospitalization: interim analysis of the UKILD post-COVID-19 study. *Am J Respir Crit Care Med*. 2022;207(6):693–703. https://doi.org/10.1164/rccm.202203-0564OC.

10 Sonnweber T, Sahanic S, Pizzini A, et al. Cardiopulmonary recovery after COVID-19: an observational prospective multicentre trial. *Eur Respir J*. 2021;57(4):2003481.

11 WHO. *Coronavirus disease (COVID-19) pandemic*. World Health Organization; 2022. https://www.who.int/emergencies/diseases/novel-coronavirus-2019. Accessed February 10, 2023.

12 Li X, Shen C, Wang L, et al. Pulmonary fibrosis and its related factors in discharged patients with new corona virus pneumonia: a cohort study. *Respir Res*. 2021;22(1):203. https://doi.org/10.1186/s12931-021-01798-6.

13 Schwaiblmair M, Berghaus T, Haeckel T, Wagner T, von Scheidt W. Amiodarone-induced pulmonary toxicity: an underrecognized and severe adverse effect? *Clin Res Cardiol*. 2010;99(11):693–700. https://doi.org/10.1007/s00392-010-0181-3.

14 Izbicki G, Segel MJ, Christensen TG, Conner MW, Breuer R. Time course of bleomycin-induced lung fibrosis. *Int J Exp Pathol*. 2002;83(3):111–119. https://doi.org/10.1046/j.1365-2613.2002.00220.x.

15 Johannson KA, Chaudhuri N, Adegunsoye A, Wolters PJ. Treatment of fibrotic interstitial lung disease: current approaches and future directions. *Lancet*. 2021;398(10309):1450–1460. https://doi.org/10.1016/S0140-6736(21)01826-2.

16 Adegunsoye A, Strek ME. Therapeutic approach to adult fibrotic lung diseases. *Chest*. 2016;150(6):1371–1386. https://doi.org/10.1016/j.chest.2016.07.027.

17 Haendel MA, Chute CG, Bennett TD, et al. The national COVID-19 cohort collaborative (N3C): rationale, design, infrastructure, and deployment. *J Am Med Inform Assoc*. 2021;28(3):427–443. https://doi.org/10.1093/jamia/ocaa196.

18 Collaborative NCC. National COVID-19 Cohort Collaborative phenotype and data acquisition. Last updated March 11 https://github.com/National-COVID-Cohort-Collaborative/Phenotype_Data_Acquisition/wiki/Latest-Phenotype; 2022. Accessed February 10, 2023.

19 Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007;370(9596):1453–1457. https://doi.org/10.1016/s0140-6736(07)61602-x.

20 Hama Amin BJ, Kakamad FH, Ahmed GS, et al. Post COVID-19 pulmonary fibrosis; a meta-analysis study. *Ann Med Surg (Lond)*. 2022;77:103590. https://doi.org/10.1016/j.amsu.2022.103590.

21 Myall KJ, Mukherjee B, Castanheira AM, et al. Persistent post-COVID-19 interstitial lung disease. An observational study of corticosteroid treatment. *Ann Am Thorac Soc*. 2021;18(5):799–806. https://doi.org/10.1513/AnnalsATS.202008-1002OC.

22 UNITE NIH.GOV codeset ID: 585490095. https://unite.nih.gov/workspace/hubble/external/search/v2/?objectId=ri.phonograph2-objects.main.object.1776a137-9bee-435d-91ed-84af975f1269&tab=tab_662f99df&profile=general-view. Accessed February 10, 2023.

23 Tran L, Baars JW, Aarden L, Beijnen JH, Huitema AD. Pharmacokinetics of rituximab in patients with CD20 positive B-cell malignancies. *Hum Antibodies*. 2010;19(1):7–13. https://doi.org/10.3233/HAB-2010-0215.

24 Jusko WJ, Ferron GM, Mis SM, Kahan BD, Zimmerman JJ. Pharmacokinetics of prednisolone during administration of sirolimus in patients with renal transplants. *J Clin Pharmacol*. 1996;36(12):1100–1106. https://doi.org/10.1002/j.1552-4604.1996.tb04162.x.

25 Fragoulis GE, Nikiphorou E, Larsen J, Korsten P, Conway R. Methotrexate-associated pneumonitis and rheumatoid arthritis-interstitial lung disease: current concepts for the diagnosis and treatment. *Front Med*. 2019;6:238. https://doi.org/10.3389/fmed.2019.00238.

26 Fleming RA, Eldridge RM, Johnson CE, Stewart CF. Disposition of high-dose methotrexate in an obese cancer patient. *Cancer*. 1991;68(6):1247–1250. https://doi.org/10.1002/1097-0142(19910915)68:6%3C1247::AID-CNCR2820680611%3E3.0.CO;2-O.

27 Evans WE, Yee GC, Crom WR, Pratt CB, Green AA. Clinical pharmacology of bleomycin and cisplatin. *Head Neck Surg*. 1981;4(2):98–110. https://doi.org/10.1002/hed.2890040204.

28 Pollak PT, Bouillon T, Shafer SL. Population pharmacokinetics of long-term oral amiodarone therapy. *Clin Pharmacol Ther*. 2000;67(6):642–652. https://doi.org/10.1067/mcp.2000.107047.

29 Group RC, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with covid-19. *N Engl J Med*. 2021;384(8):693–704. https://doi.org/10.1056/nejmoa2021436.

30 Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. 2011;173(6):676–682. https://doi.org/10.1093/aje/kwq433.

31 Ho D, Imai K, King G, Stuart EA. MatchIt: nonparametric preprocessing for parametric causal inference. *J Stat Software*. 2011;42(8):1–28. https://doi.org/10.18637/jss.v042.i08.

32 Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat*. 2011;10(2):150–161. https://doi.org/10.1002/pst.433.

33 Zou JN, Sun L, Wang BR, et al. The characteristics and evolution of pulmonary fibrosis in COVID-19 patients as assessed by AI-assisted chest HRCT. *PLoS One*. 2021;16(3):e0248957. https://doi.org/10.1371/journal.pone.0248957.

34 Ali RMM, Ghonimy MBI. Post-COVID-19 pneumonia lung fibrosis: a worrisome sequelae in surviving patients. *Egypt J Radiol Nucl Med*. 2021;52(1):101. https://doi.org/10.1186/s43055-021-00484-3.

35 Marvisi M, Ferrozzi F, Balzarini L, Mancini C, Ramponi S, Uccelli M. First report on clinical and radiological features of COVID-19 pneumonitis in a Caucasian population: factors predicting fibrotic evolution. *Int J Infect Dis*. 2020;99:485–488. https://doi.org/10.1016/j.ijid.2020.08.054.

36 Yang ZL, Chen C, Huang L, et al. Fibrotic changes depicted by thin-section CT in patients with COVID-19 at the early recovery stage: preliminary experience. *Front Med*. 2020;7:605088. https://doi.org/10.3389/fmed.2020.605088.

37 Antoniou KM, Vasarmidi E, Russell AM, et al. European Respiratory Society statement on long COVID-19 follow-up. *Eur Respir J*. 2022;60(2):2102174. https://doi.org/10.1183/13993003.02174-2021.

38 Abadie A, Spiess J. Robust post-matching inference. *J Am Stat Assoc*. 2022;117(538):983–995. https://doi.org/10.1080/01621459.2020.1840383.

39 Python Software Foundation. Python language reference, version 2.7. Available at: http://www.python.org. Accessed February 10, 2023.

40 R Core Team. *R: a language and environment for statistical computing*. Vienna, Austria; 2016. Available from: https://www.R-project.org/. Accessed February 10, 2023.

41 Lederer DJ, Martinez FJ. Idiopathic pulmonary fibrosis. *N Engl J Med*. 2018;379(8):797–798. https://doi.org/10.1056/NEJMra1705751.

42 Raghu G, Chen SY, Hou Q, Yeh WS, Collard HR. Incidence and prevalence of idiopathic pulmonary fibrosis in US adults 18-64 years old. *Eur Respir J*. 2016;48(1):179–186. https://doi.org/10.1183/13993003.01653-2015.

43 Steele MP, Peljto AL, Mathai SK, et al. Incidence and progression of fibrotic lung disease in an at-risk cohort. *Am J Respir Crit Care Med*. 2022;207(5):587–593. https://doi.org/10.1164/rccm.202206-1075OC.

44 Skeoch S, Weatherley N, Swift AJ, et al. Drug-Induced interstitial lung disease: a systematic review. *J Clin Med*. 2018;7(10):356. https://doi.org/10.3390/jcm7100356.

45 Idiopathic Pulmonary Fibrosis Clinical Research N, Raghu G, Anstrom KJ, King TE Jr, Lasky JA, Martinez FJ. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. *N Engl J Med*. 2012;366(21):1968–1977. https://doi.org/10.1056/nejmoa1113354.

46 Wiertz IA, Wuyts WA, van Moorsel CHM, et al. Unfavourable outcome of glucocorticoid treatment in suspected idiopathic pulmonary fibrosis. *Respirology*. 2018;23(3):311–317. https://doi.org/10.1111/resp.13230.

47 Andersen KM, Bates BA, Rashidi ES, et al. Long-term use of immunosuppressive medicines and in-hospital COVID-19 outcomes: a retrospective cohort study using data from the National COVID-19 Cohort Collaborative. *Lancet Rheumatol*. 2022;4(1):e33–e41. https://doi.org/10.1016/S2665-9913(21)00325-8.

48 Citera G, Mysler E, Madariaga H, et al. Incidence rates of interstitial lung disease events in tofacitinib-treated rheumatoid arthritis patients: post hoc analysis from 21 clinical trials. *J Clin Rheumatol*. 2021;27(8):e482–e490. https://doi.org/10.1097/RHU.0000000000001552.

49 Vacchi C, Manfredi A, Cassone G, Erre GL, Salvarani C, Sebastiani M. Efficacy and safety of rituximab in the treatment of connective tissue disease-related interstitial lung disease. *Drugs Context*. 2021;10. https://doi.org/10.7573/dic.2020-8-7.

50 Naqibullah M, Shaker SB, Bach KS, Bendstrup E. Rituximab-induced interstitial lung disease: five case reports. *Eur Clin Respir J*. 2015;2. https://doi.org/10.3402/ecrj.v2.27178.

51 Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol*. 2020;21(3):335–337. https://doi.org/10.1016/S1470-2045(20)30096-6.

52 Zhang L, Zhu F, Xie L, et al. Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China. *Ann Oncol*. 2020;31(7):894–901. https://doi.org/10.1016/j.annonc.2020.03.296.

53 Al-Shamsi HO, Alhazzani W, Alhuraiji A, et al. A practical approach to the management of cancer patients during the novel coronavirus disease 2019 (COVID-19) pandemic: an international collaborative group. *Oncologist*. 2020;25(6):e936–e945. https://doi.org/10.1634/theoncologist.2020-0213.

54 Yekeduz E, Utkan G, Urun Y. A systematic review and meta-analysis: the effect of active cancer treatment on severity of COVID-19. *Eur J Cancer*. 2020;141:92–104. https://doi.org/10.1016/j.ejca.2020.09.028.

55 Castelo-Branco L, Tsourti Z, Gennatas S, et al. COVID-19 in patients with cancer: first report of the ESMO international, registry-based, cohort study (ESMO-CoCARE). *ESMO Open*. 2022;7(3):100499. https://doi.org/10.1016/j.esmoop.2022.100499.

56 Pinato DJ, Scotti L, Gennari A, et al. Determinants of enhanced vulnerability to coronavirus disease 2019 in UK patients with cancer: a European study. *Eur J Cancer*. 2021;150:190–202. https://doi.org/10.1016/j.ejca.2021.03.035.

57 Lan L, Xu D, Ye G, et al. Positive RT-PCR test results in patients recovered from COVID-19. *JAMA*. 2020;323(15):1502–1503. https://doi.org/10.1001/jama.2020.2783.

58 O'Sullivan JM, Huddart RA, Norman AR, Nicholls J, Dearnaley DP, Horwich A. Predicting the risk of bleomycin lung toxicity in patients with germ-cell tumours. *Ann Oncol*. 2003;14(1):91–96. https://doi.org/10.1093/annonc/mdg020.

59 Williams SD, Birch R, Einhorn LH, Irwin L, Greco FA, Loehrer PJ. Treatment of disseminated germ-cell tumors with cisplatin, bleomycin, and either vinblastine or etoposide. *N Engl J Med*. 1987;316(23):1435–1440. https://doi.org/10.1056/NEJM198706043162302.

60 Spagnolo P, Bonniaud P, Rossi G, Sverzellati N, Cottin V. Drug-induced interstitial lung disease. *Eur Respir J*. 2022;60(4):2102776. https://doi.org/10.1183/13993003.02776-2021.

61 Guzy RD, Stoilov I, Elton TJ, Mecham RP, Ornitz DM. Fibroblast growth factor 2 is required for epithelial recovery, but not for pulmonary fibrosis, in response to bleomycin. *Am J Respir Cell Mol Biol*. 2015;52(1):116–128. https://doi.org/10.1165/rcmb.2014-0184OC.

62 Fatherree JP, Guarin JR, McGinn RA, Naber SP, Oudin MJ. Chemotherapy-Induced collagen IV drives cancer cell motility through activation of src and focal adhesion kinase. *Cancer Res*. 2022;82(10):2031–2044. https://doi.org/10.1158/0008-5472.CAN-21-1823.

63 Lu Y, Azad N, Wang L, et al. Phosphatidylinositol-3-kinase/akt regulates bleomycin-induced fibroblast proliferation and collagen production. *Am J Respir Cell Mol Biol*. 2010;42(4):432–441. https://doi.org/10.1165/rcmb.2009-0002OC.