Title: The short-, medium- and long-term risk and the multi-organ involvement of clinical sequelae following COVID-19 infection: a multinational network cohort study

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Declarations

Competing Interests Statement

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former director of Therakind in England, outside of the submitted work. ICKW reports role as member of Pharmacy and Poisons Board in Hong Kong, the Expert Committee on Clinical Events Assessment Following COVID-19 Immunisation, and the Advisory Panel on COVID-19 Vaccines of the Hong Kong Government. The remaining authors declare no competing interests.

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Ethical approval

The data partners have obtained institutional review board approvals (for UK IMRD) or exemption (for all other databases) for their participation in this study as patients' confidentiality was maintained in this retrospective cohort study.

Guarantor

ICK Wong and EYF Wan

Contributorship

ICH Lam, Y Chai, EYF Wan and ICK Wong had the original idea for the study, contributed to the development of the study, constructed the study design and the statistical model, reviewed the literature. ICH Lam, Y Chai, X Lin, C Yin, EYF Wan and ICK Wong accessed, verified the data, performed statistical analysis. ICH Lam, Y Chai, EYF Wan and ICK Wong wrote the first draft of the manuscript. ICK Wong is

the principal investigator and provided oversight for all aspects of this project. KKC Man, WCY Lau, X Lin, C Yin, CSL Chui, X Li, Q Zhang, EWY Chan, EYF Wan and ICK Wong provided critical input to the analyses, study design, and discussion. All authors contributed to the interpretation of the analysis, critically reviewed and revised the manuscript, and approved the final manuscript to be submitted.

Abstract

Objectives

To generate comprehensive evidence on the risk of clinical sequelae involving different organ systems over time following COVID-19 infection.

Design

Multinational retrospective cohort study

Setting

Electronic medical records from the US, UK, France, Germany and Italy standardised to the Observational Medical Outcomes Partnership Common Data Model

Participants

303,251 individuals with a COVID-19 infection between December 01, 2019 and December 01, 2020 and propensity score matched non-COVID-19 comparators from 22,108,925 eligible candidates

Main outcome measures

Incidence of 73 clinical sequelae involving multiple organ systems including the respiratory, cardiovascular, dermatological and endocrine systems over the short (0-6 months), medium (6-12 months) and long-term (1-2 years) following COVID-19 infection. The hazard ratio (HR) and 95% confidence interval (95% CI) of individual disease outcomes were estimated using Cox proportional hazard regression.

Results

Individuals with COVID-19 incurred a greater risk of clinical sequelae involving multiple organ systems including respiratory [France HR 2.23, 95%CI (2.10,2.37) to Italy 13.13 (11.80,14.63)], cardiovascular [Germany 1.39 (1.30,1.50) to US 1.79 (1.74,1.85)] and dermatological [UK 1.13 (1.01,1.25) to Italy 1.77 (1.42,2.21)] disorder over the short-term. Whilst the risk of clinical sequelae have largely subsided during

the medium-term, the risk of cardiovascular [US 1.16 (1.11,1.21), France 1.10 (1.01,1.19)] and endocrine [US 1.18 (1.12,1.24), Germany 1.15 (1.03,1.29)] related complications may continue to persist for up to two years.

Conclusion

Through a network of multinational healthcare databases, this study generated comprehensive and robust evidence supporting the extensive multi-organ involvement of post-COVID-19 condition over the short-term period and the subside in risk for most complications over the medium and long-term.

Keywords

COVID-19; SARS-CoV-2; Post-COVID-19 conditions; Long COVID; Post-acute sequelae of SARS-CoV-2

Introduction

COVID-19 infection caused by the SARS-CoV-2 virus has posed unprecedented challenges and clinical burden from its diverse potential clinical presentations, ranging from asymptomatic infection to life-threatening manifestations including severe respiratory failure, myocardial injury, and even death. Although a substantial proportion of patients recovered from the initial infection within the first four weeks, up to 80% of patients continued to experience lingering or newly developed symptoms beyond the acute illnesses of COVID-19, conditions known as post-acute sequelae of SARS-CoV-2 (PASC) or Long COVID.[1] Given the widespread of the virus globally, the evaluation of potential clinical sequelae associated with COVID-19 emerged as a major public health priority.

COVID-19 infection has been widely associated with respiratory-related complications ranging from mild upper respiratory tract symptoms to severe manifestations including acute respiratory distress syndrome (ARDS) and viral pneumonia, which may require mechanical ventilation support.[2] Beyond the respiratory-related complications, thromboinflammation, dysregulation of immune responses, and maladaptation of angiotensin-converting enzyme 2 receptor (ACE-2) related pathways from the initial infection may contribute to a spectrum of extra-pulmonary manifestations.[3, 4] Previous research efforts have systematically characterised the diverse extrapulmonary sequelae of COVID-19 infection including nervous system, neurocognitive, metabolic, cardiovascular, gastrointestinal disorders, and several other clinical conditions at 6 months of infection.[5] Subsequent evidence have further demonstrated the prolonged involvement of incident clinical sequelae involving a diverse range of organ systems resulting in the higher incidence of mortality and healthcare burden associated with COVID-19.[6-8] Despite a gradual reduction in risks over time, the risk of certain conditions continued to perisist at two years after initial infection.[8, 9]

Nevertheless, few studies have examined the evolving risk of associated clinical sequelae, particularly over the long-term following COVID-19 infection.[10, 11] The existing evidence predominantly based on findings from single database, with under-representative study populations, such as discharged hospitalised or older patients, has led to limited generalisability across the general population.[12] This study aims to generate

comprehensive evidence on the risk of clinical sequelae over the short-, medium-, and long-term, spanning up to two years following COVID-19 infection through leaveraging population-based electronic medical records and claims data from five countries.

Method

Data sources

Population-based electronic health records were extracted from IQVIA Longitudinal Patient Database France (France LPD), IQVIA Disease Analyzer Germany (Germany DA), IQVIA Longitudinal Patient Database Italy (Italy LPD), and IQVIA Medical Research Data UK (UK IMRD) and insurance claims data from IQVIA US PharMetrics Plus in the US (US PharMetrics Plus). Due to the computational power limitation, a stratified random sampling approach was employed to select 20% of targets and comparators within each age and sex stratum for the US PharMetrics Plus database. These databases were quality-controlled for research purposes and used extensively in high-quality, large-scale epidemiological studies.[13, 14] Details of each data source are presented in Supplementary Method 1 and have been reported previously.[15]

Study design and population

In this retrospective cohort study, the target cohort was defined as all individuals who received an incident diagnosis of COVID-19 or a first positive screening test result for SARS-Cov-2 between December 01, 2019, and December 01, 2020. This time frame predated the availability of COVID-19 vaccines and or oral antiviral therapies for COVID-19 including Molnupiravir and Paxlovid, ensuring that the protective effects against COVID-19 conferred by these later-introduced interventions could not impact the course of the initial infection. Nevertheless, patients may have received supportive treatments from prophylactic anticoagulation, dexamethasone and repurposed antiviral treatments towards the early phase of infection. The earliest date of COVID-19 confirmation was designated as the index date. Patients with a negative result for SARS-CoV-2 screening test within three days of their index date were excluded. The full

definition of patients with COVID-19 is detailed in Supplementary method 2 and Supplementary table 1. Individuals without any diagnosis or positive test results of COVID-19 throughout the entire study period were identified as eligible comparators. Targets and comparators were initially matched by month, year of birth and sex. The identical index date of targets was assigned to their corresponding matched comparators as the pseudo-index date.

Individuals with a continuous observation in their respective databases for at least 365 days before their index date and at least one day at risk were eligible for this study. All subjects were followed up for up to two years to observe any incident clinical sequelae over the short (0-6 months), medium (6-12 months) and long-term (1-2 years) periods following COVID-19 infection, or the last healthcare encounter or continuous enrolment (for UK IMRD), whichever occurred earlier. The index date of subjects for analysis over the medium and long-term observation period were defined as 180 and 365 days of their initial infection, respectively.

This study was reported according to the Reporting of studies Conducted using Observational Routinely-collected Data (RECORD).

Outcome of interest

Outcomes of this study were the incident diagnoses of 73 pre-specified post-infection sequelae of COVID-19 involving 10 organ systems including neurological, respiratory, cardiovascular, hematologic, endocrine, nephrological, hepatic, gastrointestinal, and dermatologic disorders and malignancies referenced from existing literature (Supplementary table 2).[1, 3, 16, 17] For each outcome, individuals with a history of the condition examined before the index date were excluded from the analysis.

Statistical analysis

Propensity score matching was employed to balance the measured confounding variables between targets and comparators. Propensity score was estimated as the probability of COVID-19 infection conditional on observed covariates. A separate propensity score model was developed for the evaluation of each outcome

in each database. A data-driven large-scale regularised regression was fitted to perform the covariate selection on combinations of a large set of predefined baseline patient characteristics (>30,000 factors), including demographics, diagnoses, drug exposures, measurements of laboratory tests, vital signs, quantitative findings from pathology reports and medical procedures observed 365 days prior to and on the index date.[18] Up to ten comparators were randomly selected based on the propensity scores matching approach with a calliper width of 0.2.[19]

The standardised mean difference (SMD) on baseline characteristics was presented to evaluate cohort balance before and after propensity score matching. Incidence rates (per 1,000 person-years) of each outcome in each database were calculated for all temporal phases. Cox proportional hazard regression model was fitted to estimate the hazard ratio (HR) and 95% confidence interval (95% CI) of the short-, medium-, and long-term risks of the outcomes associated with the COVID-19 infection. Subgroup analyses stratified by sex (male and female) and age (<18 years, 18-24 years, 25-44 years, 45-64 years, and 65+ years) were conducted.[20] Sensitivity analysis was performed by controlling for the false discovery rate at 0.05 through Benjamin-Hochberg procedure.[21]

All statistical analyses were performed using the open-source OHDSI CohortMethod with large-scale analytics from the Cyclops R package as part of the Health-Analytics Data to Evidence Suite (HADES).[22] The study protocol and analytical package are publicly accessible (https://github.com/QuickyIvan/ACESO_COVID19.git).

Results

A total of 8,111,859 individuals from US PharMetrics Plus, 3,174,005 from France LPD, 2,522,462 from UK IMRD, 7,561,205 from Germany DA and 1,042,645 from Italy LPD were included as study population. The majority of individuals with COVID-19 were identified from US with 161,018 individuals, followed by 66,433 from France, 35,882 from UK, 20,193 from Germany and 19,725 from Italy. Supplementary figure 1 illustrated the process of study cohort selection. The proportion of female subjects across the

databases ranges from 52.2% (US) to 56.0% (France). The majority of subjects from France LPD, Germany and UK were aged 50-54. Whilst the majority of subjects from US and Italy were aged 45-49 and 20-24, respectively. The baseline characteristics of study individuals across separate databases were summarised in Table 1 and supplementary Tables 3-7. The SMDs of all baseline characteristics after matching were less than 0.1, indicating a good balance between patients with COVID-19 and comparators. The median time of follow-up over the short and medium-term observation windows were 181 (Interquartile range 181-181) and 185 (185-185) days for patients included across all the databases, respectively. The median time of follow-up over the long-term observation window ranges from 238 (215-365) in Italy LPD to 258 (230-365) days in France LPD.

Short-term

Patients with COVID-19 incurred a considerable greater risk of at least one clinical sequelae involving cardiovascular, respiratory, neurological, endocrine, hematological, immunological, renal, and hepatic system over the short-term observation period (Table2, Supplementary figure 2). Among the organ systems evaluated, respiratory-related sequelae exhibited the greatest difference in risk, with an observed increase in risk ranging from two to 13-fold among patients with COVID-19 infection [US HR 3.62, 95%CI (3.54,3.71); UK 3.17 (2.95,3.39); France 2.17 (2.04,2.31); Germany 2.65 (2.48,2.83); Italy 13.13(11.80,14.63)]. Meanwhile, a consistent increase in cardiovascular [US 1.79 (1.74,1.85); UK 1.50 (1.35,1.67); France 1.44 (1.34,1.55); Germany 1.39 (1.30,1.50); Italy 1.71 (1.49,1.96)] and dermatological [US 1.15 (1.11,1.19); UK 1.13 (1.01,1.25); France 1.17 (1.09,1.26); Germany 1.25 (1.12,1.40); Italy 1.77 (1.42,2.21)] related sequelae were observed across all the databases. An increased risk of neurological related disorder was observed in the US [1.57 (1.51,1.64)], UK [1.30 (1.13,1.49)], France [1.28 (1.17,1.40)] and Italy [1.81 (1.38,2.35)]. The associated risk of clinical sequelae observed ranged from mild symptoms, such as olfactory and gustatory disorder, to severe diseases including myocardial infarction and acute respiratory distress. (Figure 1a-1e, Table 2, Supplementary table 7)

Medium-term

Patients with COVID-19 exhibited comparable risk of the majority of clinical sequelae as their matched comparators. However, an increased risk of cardiovascular [US 1.16 (1.11,1.21), France1.19 (1.09,1.30)], respiratory [UK 1.16 (1.03,1.30), France 1.22 (1.11,1.33), Italy 2.61 (2.11,3.21)], neurological [France 1.17 (1.05,1.31), Italy 1.54 (1.11,2.09)] and endocrine conditions [US 1.16 (1.10,1.22), Germany 1.21 (1.08,1.36)] were continuously observed among patients with COVID-19 in certain databases. Nonetheless, the associated risk of clinical sequlae was comparatively lower compared to that observed over the short-term window. (Figure 1a-1e, Table 2, Supplementary Table 8)

Long-term

Patients with COVID-19 demonstrated a comparable or further reduced risk of the majority of clinical sequelae examined compared to the risks observed over the medium-term period. Despite the further lower in risk of clinical sequelae observed, an increased risk of cardiovascular [US 1.16 (1.11,1.21), France 1.10 (1.01,1.20)], endocrine [US 1.18 (1.12,1.24), Germany 1.15 (1.03,1.29)] and respiratory related clinical sequelae [UK 1.14 (1.02,1.27), France 1.19 (1.10,1.29), Italy 1.33 (1.06,1.65)] was continuously observed over the long-term. Notably, a gradual increase in risk of certain clinical sequelae including lung fibrosis [UK short- 1.00 (0.37-2.26), medium- 2.03 (0.86-4.28), long-term 5.86 (2.91-11.45)] was observed, indicating the possible delayed onset of certain diseases. (Figure 1a-1e, Table 2, Supplementary Table 9)

Subgroup and sensitivity analyses

Older patients aged 65 years or older exhibited a considerably higher risk of clinical sequelae following COVID-19 infection than their younger counterpart of patients aged 44 or below and between 45 and 64. More specifically, a greater risk of cardiovascular [US aged 25-44 1.55 (1.46,1.64), 45-64 1.64 (1.57,1.71), 65 or over 1.83 (1.65, 2.03)] and endocrine [US aged 25-44 1.43 (1.32,1.55), 45-64 1.40 (1.32,1.48), 65 or over 1.72 (1.53, 1.94)] related sequelae were observed over the short-term across the aforementioned age groups. A broadly comparable risk of sequelae was observed between males and females. (Supplementary

Tables 10-30). Sensitivity analysis reported largely consistent findings as the main analysis. (Supplementary Table 32)

Discussion

Principal findings

This multinational network study examined the risk of a comprehensive array of clinical sequelae over short-, medium- and long-term periods following COVID-19 infection among individuals with COVID-19 infection and their non-infected controls. Cases of COVID-19 observed were presumably caused by the wild-type of SARS-CoV-2 as the first variants of concern, namely Alpha, emerged globally in late 2020. Patients with COVID-19 incurred significant greater risk of various clinical sequelae spanning multiple organ systems particularly during the first six month following infection. The considerable increase in the incidence of several severe conditions including ARDS, myocardial infarction and could be triggered by respiratory tissue damage and immune response from the acute infection. A substantial reduction in the risk of the majority of clinical sequelae, to a level comparable between patients with COVID-19 and their controls, was observed over the medium and long-term period. Nevertheless, the diverse array of clinical outcomes associated with PASC and the persistent higher risk of certain complications underscore the need for continuous monitoring and care for higher risk patients recovering from COVID-19 infection.

Findings in context

COVID-19 infection, especially cases resulting from the early variant of SARS-CoV-2, were found to be associated with respiratory-related sequelae of varying severity, ranging from mild symptoms to severe conditions including pneumonia, ARDS and other chronic respiratory illnesses. Critically ill patients who developed ARDS are also susceptible to substantial long-term respiratory morbidity due to the reduction in pulmonary diffusion capacity, resulting in lingering symptoms associated with Long COVID, such as breathlessness.[23] Given the far-reaching respiratory consequences of SARS-CoV-2 infection, careful assessment to identify the specific need for treatment and rehabilitation strategies for individuals with

related post-COVID-19 conditions, especially those who suffered from severe respiratory distress during the acute infection.[2, 10]

The findings of this study provided further evidence supporting the association of a diverse spectrum of extrapulmonary clinical sequelae with COVID-19 infection resulting in long-term, post-acute clinical conditions reported.[1, 4, 6, 7, 24] Cardiovascular and neurological sequelae are among the commonly observed manifestations associated with PASC, encompassing acute myocardial infarction, myocarditis, stroke and cognitive disturbance.[1] Previous studies have shown that patients with COVID-19, particularly those with a severe illness, are prone to developing myocardial injuries, as evidenced by elevated troponin levels and cardiac MRI abnormalities.[25] These cardiac abnormalities may offer insights into the potential acute myocardial injury caused by the initial infection, which could, in turn, lead to long-term sequelae such as arrhythmias, heart failure and even associated mortality. Patients with COVID-19 and signs of acute cardiac injury should be closely monitored for any potential long-term prognosis.

Consistent with previous studies examining the persistence in risk of health consequences associated with COVID-19, the risk of most clinical sequelae in patients with COVID-19 was shown to have largely subsided 6 months following the initial infection. Nonetheless, fluctuation in Long COVID symptoms and the gradual progression in risk of certain diseases underscores the potential for latent development or relapse of certain clinical outcomes.[8, 9, 26] Going forward, clinicians should take account of the differences in trajectories of disease progression and the potential latent onset or diagnosis of complication over time. Although the risk and symptoms of which may gradually subside over time, certain individuals may experience worsening or alternating courses of health impairment and recovery. The resumption of routine care, including screening and follow-up appointments, should be carefully planned for the management of clinical sequelae arised.[27]

The pathophysiology of the multi-organ involvement in post-COVID-19 sequelae was hypothesised to be multifaceted leading to tissue dysfunction and damage.[17] A growing body of evidence have shown that SARS-CoV-2 produces its RNA and proteins in a wide range of cell types across various organ systems

resulting in subsequent clinical complications.[28] Local inflammatory response to SARS-CoV-2 in one organ can also cause lasting alterations in distant tissues and organs as shown in previous study where even mild lung-restricted COVID-19 may induce prolonged changes in the central nervous system after infection.[29] Acknowledging the multi-systemic implication of post-COVID-19 sequelae is crucial for enhancing the development of effective treatments and management strategies. In line with this effort, future researches should be promoted to deepen our understanding on the extensive clinical implications of COVID-19, encompassing the mechanisms and risk factors associated with potential adverse clinical outcomes.[27]

Strengths and limitations

Through a multi-national network, this study leaveraged electronic healthcare records across multiple countries and practice settings to comprehensively evaluate the risk of clinical sequelae associated with COVID-19. Given the global implication of the COVID-19 pandemic and the heterogeneity in the phenotype of individuals who may experience post-infection sequelae after COVID-19, the recruitment of patients with a diverse demographic and practice settings provided generalisable evidence on the risk of a wide spectrum of diseases associated with COVID-19, as well as the risk progression following infection. The highly consistent findings observed across separate databases further supported the association of the diverse clinical implication with COVID-19 and ensured the robustness of the findings. The resources from this study serve as a platform to foster future network research studies on post-infection outcome of communicable diseases.

This study is subject to several limitations. Firstly, detection bias might be inherent in this study due to the increased healthcare contacts amongst patients diagnosed with COVID-19 infection due to further examinations they may receive, potentially resulting in the increased diagnosis of conditions which might have already existed prior to their infection. However, given the sufficiently long continuous follow-up prior to the inclusion of individuals, any existing comorbidities not captured are considered unlikely. Secondly, patients with COVID-19 in this study were likely to be a result of the early variants of SARS-CoV-2 associated with greater disease severity compared to variants emerged later stage of the pandemic.

Regardless, a previous study have demonstrated the substantial risk of post-acute sequelae associated with later variant of SARS-CoV-2 despite its milder disease severity.[30] Thirdly, the potential false negative screening test particularly in SARS-CoV-2 infectants with low viral load could lead to the misclassification of patients infected as controls resulting underestimation of the risk of clinical sequelae observed. Fourthly, the COVID-19 vaccination status of individual participants cannot be accounted for due to the incomplete relevant records from the source data. Fifth, the risk estimates reported were based on selected groups of comparators with a comparable baseline characteristics as the target population. Given the disparities in baseline characteristics between study populations, comparison of risk estimates observed in separate databases should be interpreted with caution. Lastly, despite the use of a large-scale regression model to estimate the propensity score of individuals, certain unmeasured confounders including lifestyle factors and socioeconomic status cannot be accounted for owing to data availability, which could introduce bias to the results and variability in effect estimates measured across separate databases.

Conclusion

This multinational network study evaluated the risk associated with post-COVID-19 sequelae among participants from five countries. Patients with COVID-19 incurred greater risk of a diverse spectrum of clinical sequelae involving multiple organ systems over the short-term before the subside in risk of the majority of clinical sequelae over the medium and long-term period. The findings provided a comprehensive evidence base to facilitate further understanding in the risk of clinical sequelae associated with COVID-19 infection in supporting clinical and policy decision making.

Data availability statement

Patient level data cannot be shared without approval from data custodians owing to local information governance and data protection regulations.

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Table 1. Baseline patient characteristics for patients with COVID-19 and non-COVID-19 comparators in US PharMetrics Plus, UK IMRD, France LPD, Germany DA and Italy LPD after PS adjustment

Characteristic	US PharMetrics Plus			UK IMRD			France LPD			Germany DA			Italy LPD		
	Target (%)	Comparator (%)	SMD	Target (%)	Comparator (%)	SMD	Target (%)	Comparator (%)	SMD	Target (%)	Comparator (%)	SMD	Target (%)	Comparator (%)	SMD
Age groups															
0-19	11.3	15.3	0.10	13.8	13.6	0.01	11.0	12.2	0.04	11.2	14.9	0.09	12.9	14.2	0.04
20-44	42.4	43.7	0.03	38.6	39.0	0.01	39.5	36.1	0.03	38.5	37.6	0.02	40.7	42.4	0.02
45-64	39.0	33.8	0.05	31.4	31.7	0.00	35.6	35.3	0.02	35.0	32.4	0.04	31.4	28.6	0.06
65 or above	7.4	7.3	0.02	15.6	15.0	0.01	12.8	14.8	0.03	13.2	12.8	0.03	9.9	9.7	0.02
Sex															
Male	47.1	45.2	0.04	43.3	41.7	0.03	42.7	43.4	0.01	46.0	46.8	0.02	38.5	38.4	0.00
Medical history															
Acute respiratory disease	37.1	42.1	0.10	4.4	4.7	0.02	16.1	19.0	0.08	59.6	60.8	0.03	25.4	30.8	0.12
Chronic liver disease	0.4	0.4	0.01	0.7	0.9	0.02	0.1	0.1	0.00	0.2	0.2	0.02	2.0	2.2	0.01
Dementia	1.2	1.6	0.04	0.4	0.5	0.01	0.2	0.3	0.03	1.2	1.8	0.04	0.7	0.7	0.00
Depressive disorder	10.1	11.9	0.06	1.5	1.6	0.01	6.4	8.0	0.06	7.3	7.8	0.02	6.9	7.4	0.02
Diabetes mellitus	10.5	9.2	0.04	0.7	0.8	0.01	5.5	7.1	0.06	4.2	5.3	0.05	7.8	7.9	0.00
Gastroesophageal reflux disease	10.2	10.7	0.02	0.3	0.4	0.01	4.5	5.7	0.06	1.4	1.6	0.01	9.1	9.7	0.02
Gastrointestinal hemorrhage	1.5	1.7	0.02	0.5	0.6	0.01	0.5	0.6	0.01	0.6	0.7	0.01	0.3	0.4	0.01
Hyperlipidemia	20.8	19.3	0.04	0.2	0.2	0.00	4.3	5.1	0.04	5.7	6.7	0.04	11.5	11.0	0.02
Hypertensive disorder	24.8	23.1	0.04	0.9	1.0	0.01	12.7	16.2	0.10	12.1	14.6	0.07	26.0	25.1	0.02
Lesion of liver	0.4	0.5	0.01	0.1	0.2	0.01	0.1	0.1	0.01	0.2	0.3	0.02	0.3	0.4	0.02
Obesity	10.8	10.3	0.02	0.2	0.2	0.00	0.3	0.4	0.00	2.6	2.6	0.00	0.4	0.4	0.01
Osteoarthritis	10.7	10.6	0.00	0.8	0.8	0.00	3.9	4.9	0.05	5.5	6.3	0.03	8.0	8.6	0.02
Pneumonia	5.0	3.5	0.08	1.0	1.1	0.00	0.8	1.1	0.03	3.0	3.3	0.01	4.4	3.8	0.03
Renal impairment	3.8	3.9	0.00	1.1	1.2	0.01	0.3	0.5	0.03	1.6	2.2	0.05	2.4	2.4	0.00
Rheumatoid arthritis	1.0	1.0	0.00	0.1	0.1	0.00	0.3	0.3	0.01	0.6	0.8	0.02	0.6	0.5	0.01
Urinary tract infectious disease	5.1	5.5	0.02	2.1	2.3	0.01	1.5	1.9	0.03	4.2	5.4	0.06	2.8	3.3	0.03
Medication use															
Agents acting on the renin-angiotensin system	10.7	9.6	0.04	12.6	12.8	0.01	11.5	14.5	0.09	19.6	21.6	0.05	21.4	20.7	0.02
Antibacterials for systemic use	36.7	38.7	0.04	38.4	40.7	0.05	35.5	40.0	0.09	27.4	32.7	0.12	41.8	44.9	0.06
Antidepressants	12.3	14.2	0.06	22.1	24.1	0.05	7.8	9.7	0.07	6.4	8.1	0.06	11.2	11.3	0.00
Antiepileptics	5.6	6.3	0.03	5.9	6.5	0.03	2.6	3.5	0.06	2.4	3.0	0.04	4.9	5.1	0.01

Anti-inflammatory and antirheumatic products	18.2	18.0	0.01	20.5	21.6	0.03	36.2	41.1	0.10	33.7	35.3	0.04	29.4	31.9	0.06
Antineoplastic agents	2.7	2.9	0.01	1.0	1.0	0.00	1.1	1.1	0.01	1.0	1.2	0.02	2.1	2.1	0.00
Antipsoriatics	1.9	2.0	0.01	4.5	4.9	0.02	0.5	0.7	0.02	0.3	0.3	0.00	1.4	1.3	0.01
Antithrombotic agents	4.2	4.4	0.01	10.1	10.4	0.01	8.7	11.1	0.08	10.3	12.4	0.07	16.6	15.8	0.02
Beta blocking agents	6.4	6.2	0.01	9.9	10.4	0.01	6.9	8.6	0.06	12.5	14.1	0.05	15.1	14.4	0.02
Calcium channel blockers	4.8	4.4	0.02	8.2	8.2	0.00	6.4	8.2	0.07	8.8	9.7	0.03	10.0	9.1	0.03
Diuretics	8.0	7.5	0.02	6.8	7.0	0.00	5.9	7.7	0.07	11.4	13.3	0.06	14.6	14.1	0.01
Drugs for acid related disorders	11.9	12.5	0.02	25.7	27.7	0.04	25.4	29.5	0.09	20.8	23.4	0.06	25.8	26.1	0.01
Drugs for obstructive airway diseases	22.5	23.7	0.03	23.7	25.0	0.03	23.4	27.4	0.09	15.7	20.0	0.11	19.0	21.2	0.06
Drugs used in diabetes	6.2	5.4	0.03	6.4	6.7	0.01	5.9	7.4	0.06	6.0	6.5	0.02	6.8	6.8	0.00
Immunosuppressants	1.5	1.6	0.00	1.0	1.0	0.00	0.4	0.4	0.01	0.6	0.7	0.01	1.0	0.8	0.02
Opioids	12.2	13.1	0.03	17.6	18.9	0.04	57.0	58.5	0.03	9.1	10.6	0.05	8.1	8.7	0.02
Psycholeptics	12.7	14.2	0.04	10.2	11.4	0.04	15.8	19.0	0.09	5.3	6.8	0.06	13.0	13.4	0.01
Psychostimulants, agents used for ADHD and nootropics	3.6	4.2	0.04	0.2	0.3	0.01	4.5	5.3	0.04	0.3	0.3	0.00	0.9	1.3	0.04

Note: PS: Propensity Score; SMD: Standard mean difference; SMD ≤ 0.1 is considered good balance between cohorts

US PharMetrics Plus: IQVIA US PharMetrics Plus in the US; UK IMRD: IQVIA Medical Research Data UK; France LPD: IQVIA Longitudinal Patient Database France; Germany DA: IQVIA Disease Analyzer Germany; Italy LPD: IQVIA Longitudinal Patient Database Italy

Table 2. Hazard ratio of clinical sequelae in COVID-19 and non-COVID-19 comparators estimated from US PharMetrics Plus, UK IMRD, France LPD, Germany DA and Italy LPD databases

Clinical sequelae	US PharMetrics Plus	UK IMRD	France LPD	Germany DA	Italy LPD
Cardiovascular disorder					
Short-term	1.79 (1.74,1.85)	1.50 (1.35,1.67)	1.44 (1.34,1.54)	1.39 (1.30,1.50)	1.71 (1.49,1.96)
Medium-term	1.16 (1.11,1.21)	0.92 (0.79,1.05)	1.17 (1.07,1.29)	1.08 (0.98,1.19)	1.14 (0.94,1.37)
Long-term	1.16 (1.11,1.21)	1.12 (0.99,1.27)	1.10 (1.01,1.19)	1.03 (0.94,1.13)	1.07 (0.89,1.27)
Dermatological disorder					
Short-term	1.15 (1.11,1.19)	1.13 (1.01,1.25)	1.16 (1.08,1.24)	1.25 (1.12,1.40)	1.77 (1.42,2.21)
Medium-term	0.95 (0.91,0.99)	1.17 (1.05,1.30)	1.04 (0.95,1.12)	1.05 (0.92,1.20)	1.07 (0.80,1.41)
Long-term	0.94 (0.90,0.98)	1.12 (1.01,1.25)	1.05 (0.97,1.13)	0.95 (0.83,1.09)	0.62 (0.45,0.84)
Endocrine disorder					
Short-term	1.53 (1.47,1.59)	1.12 (0.98,1.28)	1.30 (1.17,1.43)	1.20 (1.09,1.31)	1.38 (1.14,1.66)
Medium-term	1.16 (1.10,1.22)	0.95 (0.81,1.09)	1.08 (0.95,1.22)	1.21 (1.08,1.36)	1.00 (0.78,1.27)
Long-term	1.18 (1.12,1.24)	1.14 (0.99,1.30)	1.03 (0.92,1.16)	1.15 (1.03,1.29)	1.05 (0.84,1.31)
Gastrointestinal disorder					
Short-term	1.05 (0.99,1.11)	1.06 (0.87,1.27)	1.29 (1.15,1.45)	1.23 (1.00,1.48)	1.36 (1.01,1.82)
Medium-term	0.95 (0.88,1.01)	0.89 (0.71,1.10)	1.12 (0.97,1.28)	1.06 (0.84,1.33)	1.61 (1.16,2.21)
Long-term	0.97 (0.91,1.04)	1.19 (0.97,1.43)	1.10 (0.97,1.25)	1.22 (0.97,1.51)	0.87 (0.60,1.23)
Hematologic disorder					
Short-term	1.04 (0.89,1.21)	1.93 (1.40,2.61)	2.42 (1.00,5.39)	1.56 (1.09,2.18)	1.90 (1.11,3.12)
Medium-term	0.92 (0.79,1.08)	1.22 (0.74,1.92)	3.25 (0.67,12.08)	0.95 (0.57,1.50)	0.74 (0.30,1.60)
Long-term	1.89 (1.70,2.10)	1.54 (0.95,2.39)	0.95 (0.30,2.44)	1.22 (0.75,1.90)	1.13 (0.53,2.18)
Immunological disorder					
Short-term	0.92 (0.80,1.04)	2.18 (1.68,2.80)	1.67 (1.29,2.14)	1.11 (0.74,1.62)	0.94 (0.30,2.45)
Medium-term	3.15 (2.96,3.36)	0.82 (0.53,1.21)	1.29 (0.95,1.73)	0.65 (0.29,1.26)	2.33 (0.87,5.49)
Long-term	0.95 (0.84,1.06)	1.33 (0.88,1.95)	1.18 (0.88,1.56)	1.09 (0.60,1.86)	0.80 (0.17,2.68)
Malignant diseases					
Short-term	1.01 (0.94,1.10)	1.13 (0.95,1.35)	1.07 (0.92,1.24)	0.95 (0.81,1.12)	1.38 (1.08,1.73)
Medium-term	1.04 (0.97,1.11)	0.91 (0.73,1.13)	1.05 (0.88,1.25)	0.97 (0.79,1.17)	1.00 (0.74,1.32)
Long-term	0.98 (0.91,1.06)	0.90 (0.72,1.11)	1.14 (0.97,1.33)	0.91 (0.75,1.09)	0.90 (0.68,1.18)
Neurological disorder					
Short-term	1.57 (1.51,1.64)	1.30 (1.13,1.49)	1.30 (1.19,1.43)	1.11 (0.99,1.25)	1.81 (1.38,2.35)
Medium-term	0.97 (0.92,1.03)	0.95 (0.79,1.12)	1.14 (1.02,1.27)	1.01 (0.88,1.16)	1.54 (1.11,2.09)
Long-term	1.01 (0.95,1.07)	0.96 (0.80,1.13)	1.23 (1.11,1.36)	1.00 (0.87,1.14)	1.07 (0.77,1.47)
Renal and Hepatic disorder					
Short-term	2.05 (1.94,2.16)	1.95 (1.67,2.27)	1.36 (1.00,1.84)	1.14 (0.93,1.38)	1.87 (1.36,2.53)
Medium-term	0.95 (0.87,1.03)	0.77 (0.59,0.99)	0.94 (0.64,1.36)	0.96 (0.74,1.24)	1.16 (0.75,1.72)
Long-term	0.97 (0.89,1.05)	1.17 (0.93,1.46)	1.14 (0.81,1.57)	0.97 (0.77,1.21)	1.11 (0.76,1.58)
Respiratory disorder					
Short-term	3.62 (3.54,3.71)	3.17 (2.95,3.39)	2.23 (2.10,2.37)	2.65 (2.48,2.83)	13.13 (11.80,14.63)
Medium-term	0.98 (0.93,1.02)	1.16 (1.03,1.30)	1.19 (1.08,1.30)	0.98 (0.87,1.10)	2.61 (2.11,3.21)
Long-term	1.05 (1.00,1.09)	1.14 (1.02,1.27)	1.19 (1.10,1.29)	0.91 (0.82,1.01)	1.33 (1.06,1.65)

Hazard ratio (HR) and 95% confidence interval (95% CI) were estimated by Cox regression, HR > 1 (or <1) indicates patients with COVID-19 had a higher (lower) risk of sequelae compared to the non-COVID-19 control cohort.

Effect estimates were derived from IQVIA US PharMetrics Plus in the US (US PharMetrics Plus), IQVIA Medical Research Data UK (UK IMRD), IQVIA Longitudinal Patient Database France (France LPD), IQVIA Disease Analyzer Germany (Germany DA) and IQVIA Longitudinal Patient Database Italy (Italy LPD) databases

Short-, medium-, long-term observation windows refers to the 0-6 months, 6-12 months and 1-2 years following COVID-19 infection, respectively

Figure Legends

Figure 1a. Hazard ratio of clinical sequelae in COVID-19 and non-COVID-19 comparators over the short-,medium-, and long-term estimated from IQVIA US PharMetrics Plus

Short-, medium-, long-term observation windows refers to the 0-6 months, 6-12 months and 1-2 years following COVID-19 infection, respectively

Figure 1b. Hazard ratio of clinical sequelae in COVID-19 and non-COVID-19 comparators over the short-,medium-, and long-term estimated from IQVIA Medical Research Data UK (UK IMRD)

Short-, medium-, long-term observation windows refers to the 0-6 months, 6-12 months and 1-2 years following COVID-19 infection, respectively

Figure 1c. Hazard ratio of clinical sequelae in COVID-19 and non-COVID-19 comparators over the short-,medium-, and long-term estimated from IQVIA Longitudinal Patient Database France (France LPD)

Short-, medium-, long-term observation windows refers to the 0-6 months, 6-12 months and 1-2 years following COVID-19 infection, respectively

Figure 1d. Hazard ratio of clinical sequelae in COVID-19 and non-COVID-19 comparators over the short-,medium-, and long-term estimated from IQVIA Disease Analyzer Germany (Germany DA)

Short-, medium-, long-term observation windows refers to the 0-6 months, 6-12 months and 1-2 years following COVID-19 infection, respectively

Figure 1e. Hazard ratio of clinical sequelae in COVID-19 and non-COVID-19 comparators over the short-,medium-, and long-term estimated from IQVIA Longitudinal Patient Database Italy (Italy LPD)

Short-, medium-, long-term observation windows refers to the 0-6 months, 6-12 months and 1-2 years following COVID-19 infection, respectively