Long-term post-acute sequelae of COVID-19 infection: a retrospective, multi-database cohort study in Hong Kong and the UK

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Summary

Background Evidence on post-acute sequelae of SARS-CoV-2 (PASC) has shown inconsistent findings. This study aimed to generate coherent evidence on the post-acute sequelae of COVID-19 infection using electronic healthcare records across two regions.

Methods In this retrospective, multi-database cohort study, patients with COVID-19 aged 18 or above between April 1st 2020 and May 31st 2022 from the Hong Kong Hospital Authority (HKHA) and March 16th 2020 and May 31st 2021 from the UK Biobank (UKB) databases and their matched controls were followed for up to 28 and 17 months, respectively. Covariates between patients with COVID-19 and non-COVID-19 controls were adjusted using propensity score-based inverse probability treatment weighting. Cox proportional regression was used to estimate the hazard ratio (HR) of clinical sequelae, cardiovascular, and all-cause mortality 21 days after COVID-19 infection.

Findings A total of 535,186 and 16,400 patients were diagnosed with COVID-19 from HKHA and UKB, of whom 253,872 (47.4%) and 7613 (46.4%) were male, with a mean age (±SD) of 53.6 (17.8) years and 65.0 (8.5) years, respectively. Patients with COVID-19 incurred greater risk of heart failure (HR 1.82; 95% CI 1.65, 2.01), atrial fibrillation (1.31; 1.16, 1.48), coronary artery disease (1.32; 1.07, 1.63), deep vein thrombosis (1.74; 1.27, 2.37),

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chronic pulmonary disease (1.61; 1.40, 1.85), acute respiratory distress syndrome (1.89; 1.04, 3.43), interstitial lung disease (3.91; 2.36, 6.50), seizure (2.32; 1.12, 4.79), anxiety disorder (1.65; 1.29, 2.09), post-traumatic stress disorder (1.52; 1.23, 1.87), end-stage renal disease (1.76; 1.31, 2.38), acute kidney injury (2.14; 1.69, 2.71), pancreatitis (1.42; 1.10, 1.83), cardiovascular (2.86; 1.25, 6.51) and all-cause mortality (4.16; 2.11, 8.21) mortality during their post-acute phase of infection.

Interpretation The consistent greater risk of PASC highlighted the need for sustained multi-disciplinary care for COVID-19 survivors.

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Keywords: Post-acute sequelae of SARS-CoV-2; PASC; COVID-19; SARS-CoV-2

Research in context

Evidence before this study

We search PubMed and Embase on January 28th, 2023 for related articles, using the terms "COVID-19" or "SARS CoV-2" and "Post-acute sequelae of SARS-CoV-2" or "Clinical sequelae" with no date or language restrictions. A total of 25 studies which compared the risk of post-acute sequelae following COVID-19 infection amongst the general population were identified. Existing literatures provided evidence supporting an increased risks of cardiovascular, respiratory, neuropsychiatric, nephrological, endocrine disease and mortality amongst patients with COVID-19. Nevertheless, the risk of post-acute sequelae of COVID-19 estimated from previous comparative studies conducted with different study designs and population remained inconclusive owing to their inconsistent findings.

Added value of this study

This study evaluated the risk of long-term post-acute sequelae of COVID-19 infection using electronic healthcare records from the Hong Kong Hospital Authority and United Kingdom Biobank. This study reported consistent higher risk of diseases involving multiple-organ systems, cardiovascular and all-cause mortality amongst patients with COVID-19 across two regions with very different genetic compositions and healthcare systems. Such findings provided robust evidence on the risk of incident post-acute sequelae following COVID-19 infection.

Implications of all the available evidence

The current body of literature supported the greater risk of post-acute sequelae with multi-organ involvement and mortality amongst patients with COVID-19. Clinicians should be informed of such potential delayed sequelae. Sustained provision of healthcare services to COVID-19 survivors is also warranted to reduce the long-term implication of the COVID-19 pandemic.

Introduction

The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has demonstrated a broad spectrum of potential clinical presentations from asymptomatic to severe respiratory failure, myocardial injury, and death. Over 50 short and potential long-term sequelae of COVID-19 infection have been reported in previous review articles.[1,2] The internalization of SARS-CoV-2 virus through the angiotensin-converting enzyme 2 (ACE-2) receptors, provoking aggressive inflammatory response in various organs is widely speculated as the pathophysiological cause for the multi-organ dysfunction observed amongst patients with COVID-19.[3]

Post-acute sequelae of SARS-CoV-2 (PASC), also known as Post-Covid Syndrome or Long COVID, has been defined as a constellation of signs and symptoms involving multiple organ systems which persist for weeks or months after the initial COVID-19 infection.[4] Recently, PASC has gained interest amongst clinicians and researchers in understanding the clinical implication of COVID-19 beyond the acute-phase of infection. As the number of COVID-19 survivors amongst the global population continues to rise, the lingering symptoms of PASC emerge as a major public health concern with previous systematic reviews estimating that 54–80% of patients continue to experience one or more long term symptoms following acute infection.[2,5,6] Critically ill patients are at particular risk of developing respiratory impairment during the hospital stay compared to those with lower disease severity.[7] Persistent and delayed complications that arise from

acute and post-acute infection could negatively impact the disease prognosis of COVID-19 survivors.[8,9] A retrospective cohort study in the US evaluated the risk of clinical sequelae during the post-acute phase of COVID-19 infection. The study reported an approximately 5% increase in the proportion of adults with at least one new onset of respiratory, cardiovascular, hematologic or neurological sequelae requiring medical attention following COVID-19 infection compared to those without a COVID-19 diagnosis during the same period.[10] Recent evidences from the UK and US also reported that patients with COVID-19 are at a greater risk of incident cardiovascular related diseases, diabetes and all-cause mortality up to 19 months after initial infection whilst the risk of certain neurological and psychiatric diseases may persist for up to 2 years.[11–14]

Despite the extensive efforts aimed to characterize and evaluate the risk of PASC, evidence generated from previous studies remained inconclusive owing to the large variability in effect estimates from existing studies which differs in study design, population and selection of controls.[15] Contrasting evidences on the risk association of certain diseases including stroke and kidney injury have also been reported.[10,16,17] This study aims to generate coherent evidence on the risk of long-term clinical sequelae of patients recovering from COVID-19 infection using observational electronic healthcare records across two regions.

Methods

Data sources

In this retrospective, multi-database cohort study, inpatients and both in- and out-patients electronic medical records were retrieved from the Hong Kong Hospital Authority (HKHA) and United Kingdom Biobank (UKB) database, respectively. The Hospital Authority is a statutory body that manages all public hospitals and their ambulatory clinics in Hong Kong (HK), China. The service is available to all HK residents (>7.3 million) covering approximately 80% of all routine hospital admissions and all patients with COVID-19 in HK.[18] Electronic medical records from the HKHA database consisted of disease diagnoses recorded in planned or unplanned doctor consultations from hospital and emergency visits, thus allowing timely capture of all medical records of all users of the public health services in HK. The database has been used in previous study involving 17-year follow-up study of Severe acute respiratory syndrome survivors and COVID-19 vaccines safety surveillance and effectiveness.[19–23] Records were obtained from the Hong Kong Deaths Registry to identify mortality in this study. Information on vaccination status was provided by the Department of Health, The Government of Hong Kong Special Administrative Region.

UKB contains the medical records of 502,616 participants aged between 40 and 69 years, recruited between 2006 and 2010 for investigating health-related outcomes by collecting baseline data. Patients level data included primary care (GP) records from the Phoenix Partnership (TPP) and Egton Medical Information Systems (EMIS) Health GP system of England; hospital inpatient data, sourced from National Health Service (NHS) Digital; public death-registration records from the national death registry; and diagnostic COVID-19 test results from Public Health England (PHE), Public Health Scotland (PHS) and Secure Anonymized Information Linkage (SAIL).[24–26] Vaccination status was obtained from GP prescription records, including the date of receipt of each dose and the vaccine brand. dm + d codes (Dictionary of medicines and devices used across the UK's National Health Service) were used to identify BNT162b2 (39115611000001103) and ChAdOx1 (39114911000001105) Covid-19 vaccination.

Study design and patient population

A propensity-score weighted cohort study was conducted on patients aged 18 years or above. Patients with laboratory-confirmed SARS-CoV-2 infection (confirmed by positive polymerase chain reaction [PCR] test in throat swab, nasopharyngeal aspirate, or deep throat sputum specimens) between April 1st, 2020 to May 31st, 2022 were identified from the HKHA databases. Patients with COVID-19 from UKB were identified by a positive PCR test results or a hospital admission record with COVID-19-related diagnosis code (U07.1 or U07.2) between March 16th, 2020 and May 31st, 2021. Patients without a SARS-CoV-2 PCR positive record during the study period were selected as controls for analyses in HKHA, whilst patients without a positive SARS-CoV-2 PCR test record, COVID-19 diagnosis and/or record of COVID-19-related mortality till October 18th, 2021 (the date of the last valid record related to COVID-19 infection) were selected as controls for analyses in UKB. The index date of patients with COVID-19 was defined as 21 days after the first diagnosis date of COVID-19 infection. Controls were randomly matched to cases by birth-year and sex with the same index date assigned to individual controls of the same birth-year and sex as pseudo index date. The same matching process was applied in recruiting controls from the HKHA and UKB databases. All individuals were followed up from the index date until the date of death, outcome events or the latest date cut-off of the respective databases (August 15th, 2022 for HKHA and August 31st, 2021 for UKB), whichever occurred earlier.

Anonymized longitudinal clinical healthcare data since 2016 and the earliest date of data availability were obtained for all individuals from HKHA and UKB, respectively. Relevant data included baseline demographic (gender, age and Charlson Comorbidity Index); pre-existing morbidities captured by clinical

diagnosis codes (cardiovascular, cerebrovascular, respiratory, chronic kidney, liver diseases, rheumatoid arthritis and malignancy; Supplementary Table S1) and COVID-19 vaccination status before index date. Standardized mean difference (SMD) between cases and controls was estimated, SMD ≤0.1 was regarded as sufficient balance between case and control groups.[27]

Ethical approval for this study was granted by the Institutional Review Board of the University of HK/HA HK West Cluster (UW20-556 and UW21-149) and Department of Health, HK (L/M21/2021 and L/M175/2022) with an exemption for informed consent from participants as patients' confidentiality was maintained in this retrospective cohort study. Separate ethical approval was issued by the North West Multi-Centre Research Ethics Committee for the data extraction from UKB (Application No. 65688). All participants in UKB provided written consent upon recruitment, individuals withdrew from the study were removed from the analysis.

This study was reported according to the Reporting of studies Conducted using Observational Routinely-collected Data (RECORD), extended from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline.

Outcomes of clinical diagnosis

The outcomes of this study were selected based on previous evidence on the risk of PASC which includes incidences of major cardiovascular diseases (a composite outcome of stroke, heart failure and coronary heart disease), stroke, myocardial infarction (MI), heart failure, atrial fibrillation, coronary artery disease, deep vein thrombosis (DVT), chronic pulmonary disease, acute respiratory distress syndrome, interstitial lung disease, seizure, Bell's palsy, encephalitis and encephalopathy, anxiety disorder, post-traumatic stress disorder (PTSD), end-stage renal disease, acute kidney injury, pancreatitis, liver injury, cardiovascular and all-cause mortality.[10–13,28,29] Individuals with a history of outcome of interest were excluded from the analysis of specific conditions. Outcomes were identified from in-patients' hospital record based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) on the HKHA database and in- and out-patients primary care record based on International Classification of Diseases, Tenth Revision (ICD-10) and ICD-10 for World Health Organisation (ICD-10-WHO) system on the UKB database (Supplementary Table S1).

Statistical analysis

Consistent with previous studies on the long-term clinical outcome of COVID-19,[11,12,30] Inverse Probability Treatment Weighting (IPTW)[31] via propensity score was applied to account for the confounding factors. The propensity score for all individuals were estimated by logistic regression model conditioned to the probability of being infected with COVID-19 based on based on age, gender, Charlson Comorbidity index (CCI) and doses of COVID-19 vaccination received prior to index date. IPTW is conducted with respect to controls included from each separate database. The incidence rate (per 1000 person-years) of each outcome in patients with COVID-19 and controls was estimated. The hazard ratio (HR) and 95% confidence interval (CI) of each outcome were estimated using Cox proportional hazard regressions with COVID-19 infection as the covariate. A random effects meta-analysis model was fitted to combine the effect estimates of PASC measured across separate databases.[32,33]

Sensitivity analysis was performed by 1) defining the index date as 30 days and 2) 90 days after the first diagnosis date of COVID-19 infection and their corresponding controls, 3) adjusting for all-cause mortality as a competing risk using Fine–Gray competing risk analysis[34] 4) excluding patients with multiple records of COVID-19 infection at least 30 days apart and, 5) adjusting for characteristics with a SMD greater than 0.1 after IPTW as covariates in the regression model. Subgroup analyses were predefined taking account of the risk factors of PASC identified.[35] Patients were stratified by 1) Severe or non-severe COVID-19 infection, defined as cases requiring intensive care unit (ICU) or mechanical ventilation for the management of their COVID-19 infection within seven days of infection as defined by the ICD-9 and Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures (4th revision) (OPCS-4) procedure codes in the HKHA and UKB databases (Supplementary Table S2),[36] 2) age (<40, ≤65, >65), 3) gender, 4) Charlson Comorbidity index (<4, ≥4) and 5) COVID-19 vaccination status prior to the index date (0–1 doses, 2 doses, ≥3 doses).

All statistical analyses were performed using Stata version 15.1 (StataCorp LP, College Station, Texas) and R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria). All significance tests were two-tailed. 95% CI excluding 1.0 were taken to indicate statistical significance. At least two investigators (ICHL, RZ, and EYFW) conducted each of the statistical analyses independently for quality assurance.

Role of the funding source

The funders did not have any role in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

A total of 535,186 and 16,400 patients with a record of COVID-19 infection were identified from the HKHA

and UKB databases, of whom 253,872 (47.4%) and 7613 (46.4%) were male, with a mean age (±SD) of 53.6 (17.8) years and 65.0 (8.5) years, respectively. The median follow-up period for HKHA was 146 days (interquartile range 138–150 days) and 243 days (interquartile range 212–294 days) for the UKB. 4443 (0.8%) and none of the patients with COVID-19 from the HKHA and UKB database received subsequent diagnosis of COVID-19 at least 30 days after their first infection, respectively. The baseline characteristics of the weighted and unweighted study cohorts are summarized in Table 1 and Supplementary Table S3, respectively. The SMD of most baseline characteristics after weighting were <0.1 indicating that the variables were well-balanced between the cases and controls with the exception of cardiovascular and cerebrovascular disease between the two study cohorts in UKB.

Patients with a history of COVID-19 (cases) were found to have a higher risk of heart failure (HR 1.82; 95% CI 1.65, 2.01), atrial fibrillation (1.31; 1.16, 1.48), coronary artery disease (1.32; 1.07, 1.63), deep vein thrombosis (1.74; 1.27, 2.37), chronic pulmonary disease (1.61; 1.40, 1.85), acute respiratory distress syndrome (1.89; 1.04, 3.43), interstitial lung disease (3.91; 2.36, 6.50), seizure (2.32; 1.12, 4.79), anxiety disorder (1.65; 1.29, 2.09), post-traumatic stress disorder (1.52; 1.23, 1.87), end-stage renal disease (1.76; 1.31, 2.38), acute kidney injury (2.14; 1.69, 2.71), pancreatitis (1.42; 1.10, 1.83), cardiovascular (2.86; 1.25, 6.51) and all-cause mortality (4.16; 2.11, 8.21) compared to those without a history of COVID-19 infection (controls). Higher incidence of major cardiovascular event was observed in cases from both HKHA and UKB separately. Cases from HKHA showed a further increase in incidence of liver

Baseline characteristics	Hong Kong Hospital Authority (April 1st, 2020–August 15th, 2022)					United Kingdom Biobank (March 16th, 2020–August 31st, 2021)				
	Controls (N = 3,850,839)		Patients with COVID-19 (N = 3,849,967)		SMD[b]	Controls (N = 409,176)		Patients with COVID-19 (N = 406,734)		SMD[b]
	N/Mean	%/SD	N/Mean	%/SD		N/Mean	%/SD	N/Mean	%/SD	
Age, years[a]	54.2	(18.2)	54.1	(17.4)	0.003	68.1	(8.1)	68.1	(8.5)	0.006
Gender, male	1,695,166	(44.0)	1,698,670	(44.1)	0.002	182,804	(44.7)	183,091	(45.0)	0.007
Charlson Comorbidity Index[a]	1.7	(1.8)	1.7	(1.9)	0.001	3.7	(2.3)	3.8	(2.4)	0.044
Pre-existing morbidities										
Cardiovascular disease	292,096	(7.6)	317,829	(8.3)	0.025	56,491	(13.8)	77,327	(19.0)	0.141
Hypertension	905,830	(23.5)	950,890	(24.7)	0.027	159,316	(38.9)	177,696	(43.7)	0.097
Myocardiac Infarction	26,220	(0.7)	34,795	(0.9)	0.025	17,492	(4.3)	22,423	(5.5)	0.057
Chronic heart failure	35,940	(0.9)	53,082	(1.4)	0.042	6046	(1.5)	7816	(1.9)	0.034
Peripheral vascular disease	9987	(0.3)	11,705	(0.3)	0.008	14,032	(3.4)	18,061	(4.4)	0.052
Cerebrovascular disease	134,398	(3.5)	151,479	(3.9)	0.024	26,186	(6.4)	38,053	(9.4)	0.110
Respiratory disease	72,560	(1.9)	91,025	(2.4)	0.033	72,103	(17.6)	80,585	(19.8)	0.056
COPD	72,319	(1.9)	90,695	(2.4)	0.033	73,468	(18.0)	81,945	(20.1)	0.056
Paralysis	7855	(0.2)	10,060	(0.3)	0.012	6222	(1.5)	9858	(2.4)	0.065
Diabetes mellitus	443,509	(11.5)	483,096	(12.5)	0.032	45,367	(11.1)	56,664	(13.9)	0.086
Chronic kidney disease	43,347	(1.1)	58,004	(1.5)	0.033	35,392	(8.6)	37,379	(9.2)	0.019
Mild liver disease	3733	(0.1)	4646	(0.1)	0.007	18,447	(4.5)	22,868	(5.6)	0.051
Moderate-severe liver disease	3463	(0.1)	5194	(0.1)	0.013	899	(0.2)	1087	(0.3)	0.010
Ulcers	37,293	(1.0)	46,353	(1.2)	0.023	16,624	(4.1)	18,127	(4.5)	0.020
Rheumatoid arthritis and other Inflammatory polyarthropathies	16,043	(0.4)	17,806	(0.5)	0.007	20,768	(5.1)	22,959	(5.6)	0.025
Malignancy	110,006	(2.9)	115,530	(3.0)	0.009	62,155	(15.2)	51,090	(12.6)	0.076
Metastatic solid tumour	16,686	(0.4)	20,257	(0.5)	0.013	9019	(2.2)	5557	(1.4)	0.063
Doses of COVID-19 vaccines received					0.001					0.007
0	581,223	(15.1)	582,097	(15.1)		360,963	(88.2)	359,581	(88.4)	
1	304,370	(7.9)	304,403	(7.9)		42,984	(10.5)	41,879	(10.3)	
2	1,599,028	(41.5)	1,599,036	(41.5)		5229	(1.3)	5274	(1.3)	
3 or above	1,366,218	(35.5)	1,364,431	(35.4)		–	–	–	–	

Note: SMD: Standard mean difference; COPD: Chronic obstructive pulmonary disease. [a]Age, and Charlson Comorbidity Index are presented in mean ± Standard Deviation (SD). [b]SMD ≤0.1 is considered good balance between cohorts.

Table 1: **Baseline characteristics of patients with COVID-19 and controls from the Hong Kong Hospital Authority and the UK Biobank Database after propensity-score weighting.**

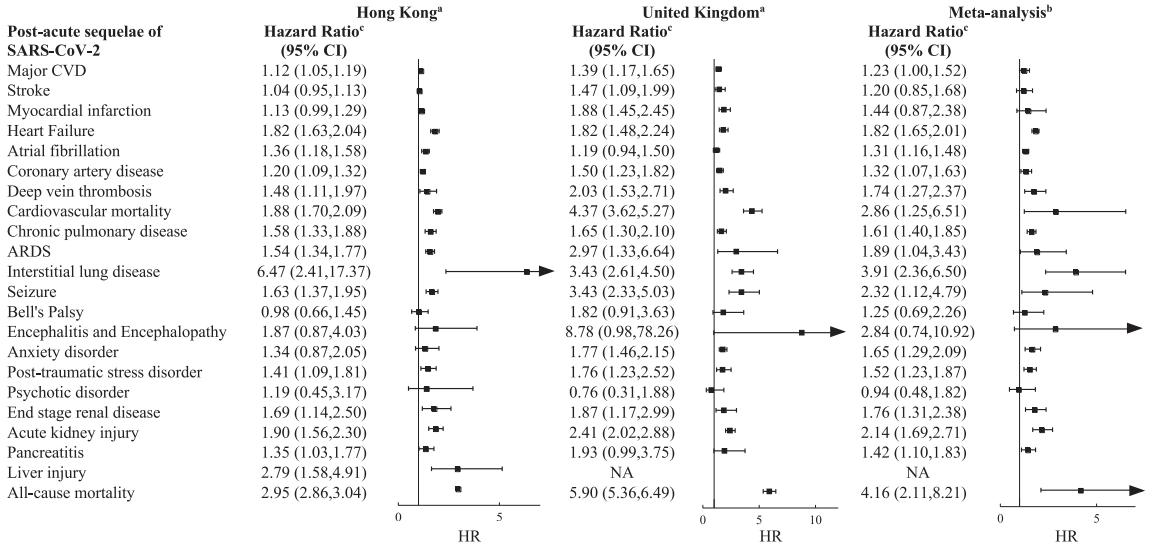

Fig. 1: Hazard ratio of post-acute sequelae of SARS-CoV-2 in the general population. [a]Data from Hong Kong and the United Kingdom (UK) were obtained from the Hong Kong Hospital Authority and UK Biobank, respectively. [b]Meta-analysis was performed using a random effects model. [c]Hazard Ratio (HR) and 95% Confidence Interval (95% CI) were estimated by Cox regression, HR > 1 (or <1) indicates patients with COVID-19 had higher (lower) risk of sequelae compared to the non-COVID-19 control cohort. The error bars denote the 95% CI of the respective HR. Note: Major CVD: Major Cardiovascular Disease; Composite outcome of stroke, heart failure and coronary artery disease; ARDS: Acute respiratory distress syndrome; NA: Not available due to insufficient number of events.

injury whilst a higher incidence of stroke, myocardial infarction and Bell's Palsy were observed amongst patients with COVID-19 infection from the UKB (Fig. 1 and Supplementary Table S4). Sensitivity analyses reported largely consistent results in all aforementioned outcomes (Supplementary Tables S5–S9).

Subgroup analysis conducted across two databases reported that patients with a severe COVID-19 infection, aged over 65 years, female, received less than two doses of COVID-19 vaccines or with a CCI of 4 or above have a higher risk of developing PASC than their opposing subgroup of patients (Supplementary Tables S10–S14).

Discussion

This study reported consistent increased incidence of PASC affecting the psychiatric, respiratory, cardiovascular, nephrological, hepatic system and all-cause mortality amongst patients with COVID-19 infection across two populations, demonstrating the multi-organ involvement of PASC following infection.

Patients with a history of severe COVID-19 infection, aged over 65 years, greater degree of multi-morbidities or received less than two doses of COVID-19 vaccines prior to infection were found to incur greater risk and may develop a more diverse range of post-acute sequelae during recovery. Clinicians should recognize the history of COVID-19 as a potential risk factor for various chronic diseases. Further studies on the disease prognosis of PASC amongst vulnerable groups of COVID-19 survivors is warranted to enhance the diagnosis and management of individual with clinical sequelae after acute COVID-19 infection.[28] Close monitoring and the provision of ongoing care for COVID-19 survivors especially in the vulnerable patient groups will presumptively incur greater utilisation of healthcare resources due to the increased number of healthcare visits and prescribed pharmaceutical treatment.[37] Follow-up care from dedicated clinics to triage patients for further diagnosis and specialist care would allow for more efficient use of resources.[38]

Cases of COVID-19 amongst the HK cohort were predominantly caused by the Omicron variant owing to the success in containing Alpha and Delta variant of the virus.[39,40] Compared to the pre-Omicron-strain dominant UKB cohort, a lower risk of all-cause mortality was observed amongst patients with COVID-19 from the Omicron-strain dorminant HK cohort. This concurs with the early evidence on the milder disease severity of Omicron variant characterized by a reduction in mortality, ICU admissions and shorter length of hospital stay.[41,42] Nevertheless, patients from two cohorts were observed to incur comparable risk of post-acute sequelae following COVID-19 infection indicating that the risk of PASC associated with this milder strain of virus might still be significant. Given the higher transmissibility of this dominant strain of virus which has led to record numbers of hospitalization in certain countries, such as in USA, the burden of long-term sequelae of COVID-19 remains a considerable threat to public health.

Previous studies have reported that individuals with COVID-19 are observed to incur a higher risk of incident cardiovascular disease (CVD) spanning from cerebrovascular disorders, dysrhythmias, inflammatory and ischemic heart disease, myocardial injuries, heart failure and thromboembolic disease beyond the acute infection. Such risk increase was evident in the majority of population with a history of COVID-19 and exhibited a graded risk increase across the severity spectrum of the acute phase of COVID-19, with severe cases admitted to the intensive care unit and patients not fully vaccinated reported to incur the greatest risk.[12,17,25] The findings on the higher risk of cardiovascular mortality in this study emphasised the significance of such major post-acute sequelae of COVID-19, new care strategies should be informed attending the treatment and prevention of major cardiovascular events and associated mortality. Strategies to monitor cardiovascular sequelae amongst the survivors of COVID-19 should also be considered even in patients with a low risk of CVD.

Findings of this study demonstrated an increased risk of several neuropsychiatric disorder including seizure, anxiety disorder and post-traumatic stress disorder for considerable period beyond acute COVID-19 infection. Such findings were largely consistent with previous findings on the trajectory of the neuropsychiatric diseases observed in patients within two years following COVID-19 infection.[13] The increased incidence of seizure was postulated to be caused by the lingering inflammatory and cytokine response resulting in impaired ion channel function and damage to the blood–brain barrier. In addition, our findings support the speculation of PTSD incidence arising from post-COVID-19 anxiety. Psychiatric disorder associated with COVID-19 was speculated to be associated with the psychological implications of a COVID-19 diagnosis rather than a direct manifestation of the illness. Nevertheless, such association highlighted the need for effective and accessible interventions to improve the prognosis of psychiatric related PASC.[43,44]

This study reported a considerably greater risk of incident post-infection sequelae amongst patients with severe COVID-19, suggesting potential poorer prognosis of PASC. Notably, the increase in risk of respiratory related disease was the greatest. Previous studies have reported that respiratory failure caused by fibrosis, interstitial thickening and vascular abnormalities may still persist in COVID-19 survivors 12 months following their acute infections.[45–47] Despite the gradual improvement in pulmonary physiology and exercise capacity, persistent physiological and radiographic abnormalities may still persist 12 months beyond hospital discharge.[46] The plausible burden of respiratory-related illnesses following COVID-19 recovery could be substantial given these observations and the huge number of individuals affected by COVID-19.

In view of the clinical complications arising from severe COVID-19 infection and those yet to be fully vaccinated, early administration of oral anti-viral drugs should be considered for eligible patients to reduce the risk of all-cause mortality, hospitalization and in-hospital disease progression.[48,49] Uptake of COVID-19 vaccine boosters is also encouraged to restore immunity against COVID-19 infection and reduce the risk of manifestation of severe complication following infection.[23,50]

The increased incidence of PASC could be attributed to the proposed physiological mechanism associated with respiratory, cardiovascular, hematological, nephrological and hepatic sequelae from COVID-19 infection reported in the early stage of this pandemic.[51–56] It was speculated that the internalization of the virus through the ACE-2 receptor is a major underlying pathway for the development of persistent symptoms and organ dysfunction.[57] The enriched expression of ACE-2 receptors in the proximal tubule of the kidney could mediate viral entry into tubular epithelial cells, causing acute tubular necrosis and proximal tubule dysfunction.[58,59] Kidney injuries arising from and following COVID-19 infection have the potential to evolve into cardiovascular complications resulting in both long- and short-term mortality.[60] Mass surveillance for acute kidney injury amongst patients with COVID-19 may be considered to identify asymptomatic individuals for earlier management.[61,62] Thrombotic complications in patients with COVID-19 were reported to be caused by the development of a cytokine storm, resulting in hyperinflammation, endothelial disruption, platelet activation, and coagulopathy.[55] Several randomized clinical trials have been conducted to evaluate the role of anticoagulant therapy in the management of thrombotic complications in patients with COVID-19.[63–67] The data supported the association of therapeutic heparin therapy with improved outcomes in hospitalized patients with COVID-19.[68] Despite the progression on understanding the plausible mechanism pathways, research on the pathogenesis of PASC is still in its infancy and remains a crucial area for research to further our understanding on the extra-pulmonary implication of COVID-19 infection, and identify treatments to reduce associated morbidity and mortality.[4]

This study reported highly consistent greater risk of diverse clinical sequelae between two population with very different ethnic background and healthcare systems evaluated systematically through adopting a comparable method in the analysis conducted on both databases, thus underpinning the robustness and generalizability of the results across healthcare systems with different ethnic composition. The meta-analysis of effect estimates generated reliable evidence supporting the association between COVID-19 infection and post-acute sequelae reported. These findings raise the importance of recognising the possibility of delayed illnesses from

COVID-19 infection as well as the need for sustained interdisciplinary care services to reduce the impact of PASC. Nevertheless, our study is subject to several limitations. Firstly, indication or detection bias might be inherent in this study, attributed to potential under-reporting of existing underlying conditions before receiving a diagnosis of COVID-19. In addition, under-capturing of COVID-19 diagnosis of asymptomatic cases would result in potential misclassification between existing co-morbidities and post-infection sequelae. For instance, asymptomatic cases presenting with sequelae may have developed certain diseases prior to their COVID-19 diagnosis; yet they did not receive a diagnosis for those conditions until a confirmed diagnosis of COVID-19, resulting in the misclassification of existing undiagnosed co-morbidities as post-infection sequelae of COVID-19. Nevertheless, such error should have a minimal effect on sequelae observed during the post-acute phase of infection. As demonstrated in previous study,[69] the history of chronic diseases in the HKHA has been recorded with high completeness whilst the disease history recorded from the UKB were extracted from both hospital and primary care services under the National Health Services (NHS), thus ensuring the accuracy and reliability of data to distinguish existing co-morbidities and sequelae of COVID-19. Given the sufficiently long observation period, any existing co-morbidities of individuals that were not captured in their respective databases are considered unlikely. Furthermore, sequelae reported in this study including stroke, MI and seizure were largely of great disease severity which would typically result in distinct symptoms upon the onset of disease. Thus, the incidence of such sequelae would not be affected by the increased surveillance on patients following COVID-19 infection. Secondly, owing to the in-patient medical record used to identify disease outcomes in the HKHA, the number events and incidence rate of certain diseases including anxiety and kidney disorders which may not require hospitalization may be under-estimated. Thirdly, certain important research questions including the potential benefit against PASC from receiving the fourth booster dose of COVID-19 vaccines and the risk of mild symptoms such as chronic fatigue remains due to the insufficient sample size and lack of corresponding diagnosis codes to capture such symptoms in the study databases. Fourthly, the hazard ratio of certain condition estimated could not reach statistical significance due to the scarcity of diseases amongst the population. Lastly, residual confounding bias can remain even after weighing individuals according to their propensity scores. Several important unmeasured confounders, namely socioeconomic status, educational level, health awareness and strains of COVID-19 found in individual patient, could not be accounted for in this study owing to data availability, which may have introduced bias to our results and variability in effect estimates measured between the two separate databases. Readers are encouraged to interpret the meta-analysed effect estimates when evaluating the risk of PASC through the findings of this study.

In conclusion, our study reported highly consistent increased incidences of a diverse range long-term sequelae involving multiple organ systems and all-cause mortality during the post-acute phase of COVID-19 infection in HK and UK. Findings from this study emphasize the importance of sustained interdisciplinary follow-up for patients recovering from COVID-19 to improve their clinical outcomes and reduce morbidity of PASC.

Contributors

ICHL, EYFW and ICKW had the original idea for the study, contributed to the development of the study, extracted data from the source database, constructed the study design and the statistical model, reviewed the literature, and act as guarantors for the study. ICHL, RZ and EYFW accessed and verified the data, performed statistical analysis. ICHL, RZ, EYFW and ICKW wrote the first draft of the manuscript. ICKW is the principal investigator and provided oversight for all aspects of this project. CKHW, CSLC, FTTL, XL, EWYC, LH, QZ, KKCM, BMYC, SCWT, CSL, EYFW and ICKW 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. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Data sharing statement

The Hospital Authority electronic medical record data underlying the results presented in the study are available from Administrative Assessment of External Data Requests, Hong Kong Hospital Authority Head Office (contact via hacpaaedr@ha.org.hk). Data from the UK Biobank analysed in this study are available through open application (via https://www.ukbiobank.ac.uk/register-apply/).

Declaration of interests

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102000.

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