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Original Article

Increased risk of hospitalization for various disorders after COVID-19 infection: A Cohort study of the UK biobank spanning over a hundred disease categories

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ABSTRACT

Background: COVID-19 is one of the most pressing public health issues worldwide. The sequelae of COVID-19 however remains unclear. We performed a systematic assessment of sequelae across all body systems, focusing on whether COVID-19 is associated with increased risk of hospitalization for various diseases.
Methods: In this cohort study, we examined 135 disorders in UK biobank (UKBB) (N = 412,096; age: 50–87). We also conducted analysis for new-onset and recurrent cases, and employed the prior event rate adjustment (PERR) approach to minimize effects of unmeasured confounders. Time-dependent effects were also tested.
Results: Compared to individuals with no known COVID-19 history, those with severe COVID-19 (hospitalized) exhibited increased hazards of hospitalization due to multiple disorders (median follow-up = 261 days), including disorders of respiratory, cardiovascular, neurological, gastrointestinal, genitourinary, musculoskeletal systems, as well as injuries, infections and non-specific symptoms. Notably, severe COVID-19 was associated with increased hospitalization risks in 77 out of the 107 disease categories with ≥ 5 events in both groups. These results remained largely consistent in sensitivity analyses.
Mild (non-hospitalized) COVID-19 was associated with increased risk of hospitalization for several disorders: aspiration pneumonitis, musculoskeletal pain and other general signs/symptoms. The risk of hospitalizations following infection was generally higher during the pre-vaccination era.
Conclusion: This study revealed increased risk of hospitalization from a wide variety of pulmonary and extra-pulmonary diseases after COVID-19, especially for severe infections. The findings may have important clinical implications, such as the need for closer monitoring and risk assessment of relevant sequelae, and allocating more resources toward prevention and treatment of such sequelae.

1. Introduction

There are more than 767 million[1] documented cases of COVID-19 and over 6.9 million fatalities worldwide (till 7-Jun-2023). Notably, accumulating evidence have shown that COVID-19 is associated with a wide range of sequelae. For example, respiratory disorders were reported frequently post-infection, like dyspnoea and cough,[2] lung function impairment,[3] and bronchiectasis.[4] Relatively less attention has been paid on other organ systems. For example, studies reported that neurological manifestations could persist in COVID-19 survivors.[5,6]

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Table 1
The four sets of analyses performed in this study.

Cohort	Cohort Exposed group ('case')	$N_{cohort\ case}$	Cohort Non-exposed group ('control')	$N_{cohort\ control}$	$N_{in\ total}$
A	Hospitalized or fatal (U07.1)	6484	Non-hospitalized infection	18976	25460
B	Hospitalized or fatal (U07.1)	6484	UKBB subjects with no known infection*	386636	393120
C	All subjects with infection	25460	UKBB subjects with no known infection*	386636	412096
D	Non-hospitalized infection	18976	UKBB subjects with no known infection*	386636	405612

Cohort A was restricted to infected patients. Other Cohorts also involve UKBB subjects with no known history of infection.
U07.1 is the code for fatal (laboratory-confirmed) COVID-19 infection based on the latest ICD coding. Dx, diagnosis.
*Inclusion criteria for "UKBB subjects with no known infection": all UKBB participants without a known COVID-19 diagnosis or those tested negative were included, regardless of hospitalization status.
Please refer to the following abbreviations used in all main tables.
HR, hazard ratio (with adjustment for covariates); p.adj*, FDR-adjusted p-value; Lower and upper CI represent the lower and upper 95 % confidence interval of HR.
Raw_HR, HR without adjustment for covariates.
CCSR, Clinical Classifications Software Refined, a method to classify disease categories. Sig., significant with FDR-adjusted $p < 0.05$.
HR_PERR, hazard ratio in comparing two analysis performed before and after the onset of pandemic to adjust for baseline differences between the infected and non-infected groups (see main text), two hundred bootstraps were performed to derive the standard error; pval_PERR, corresponding p-value in final analysis after PERR adjustment.
t.stat_diff: the t statistic corresponding to the comparison between the pre-vaccination (pre_vac) and whole FU period; diff.beta.p: the p value for the difference between the pre_vac period and the whole period; diff.beta.p.adj: the FDR corrected diff.beta.p.
Significance: * indicates a diff.beta.p.adj value between 0.01 and 0.05, ** indicates between 0.001 and 0.01, while *** indicates a value smaller than 0.001.
"∼3 m" represents the results from stratified analysis considering outcomes within 3 months of infection; "3m ∼ 6m" represents results considering outcomes from 3 to 6 months after infection; "6m ∼" represents results considering outcomes from 6 months post-infection until the end of follow-up.

Increased risks of cardiovascular diseases were also observed.[7] Several other studies also investigated the COVID-19 sequelae across different systems.[8–10] Nevertheless, the full spectrum of COVID-19 sequelae remains unclear, and there are still very limited studies that comprehensively examined the sequelae from *all* body systems.

Given the huge number of COVID-19 cases worldwide, additional studies are still very much needed to delineate clearly the COVID-19 sequelae. There are also some limitations of existing studies. For example, some studies[10] are of relatively small sample sizes, limiting the power to detect moderate associations. One of the most similar studies is conducted by Al-Aly et al.,[9] however the study was restricted to veterans (predominantly males), and findings may not generalize to the general population,[11] since higher rates of physical and mental comorbidities were reported among veterans.[12] Moreover, the study[9] focused on new-onset (incident) diagnoses only, and individuals with a history of the studied diseases were excluded.

To our knowledge, *this is the first study to comprehensively and systematically study COVID-19 sequelae covering all systems and >130 disease categories, with consideration of both new-onset and recurrent diseases, in a large general population sample*[*].

Additionally, while many studies focused on post-infection symptoms,[13] here we studied the more severe end of the diseases that requiring hospitalization, which is still an under-researched area. For a review of relevant studies, please refer to other works.[14–16]

We also performed PERR adjustment analysis, a type of negative outcome control, to minimize the impact of measured and *unmeasured* confounders. To our knowledge, this is *the first COVID-19 sequelae study that also rigorously accounts for unmeasured/unknown confounding using PERR*. Furthermore, we conducted several sensitivity analyses, including assessments of hospitalization risks for new-onset and recurrent diseases, and risk of sequelae across different follow-up periods.

2. Methods

Please also refer to Supplementary Text for details.

2.1. Study design

This prospective cohort study utilizes data from the UKBB (ID-28732), comprising approximately 500,000 participants. Exposure to SARS-CoV-2 was identified through positive PCR test results or hospitalization records with diagnosis code U071. Outcomes were defined based on the primary cause of hospitalization. The analysis period spanned from January-31-2020 (date of the first confirmed COVID-19 case in the UK) to September-30-2021 (last date for available hospitalization records at the time of analysis). The primary analysis focuses on assessing hazard ratios (HRs) for hospitalization due to various diseases after COVID-19 infection.

2.2. Study setting, participants and study size

The study included UKBB participants with available hospitalization records who were alive at follow-up commencement. Four sets of cohorts were considered (Table_1). Cohort_A examined severe versus mild COVID-19 among infected patients. Cohorts_B, C, and D compared exposed (COVID-19 positive) and unexposed (no recorded infection) individuals to evaluate the sequelae of severe (cohort_B), any (cohort_C), and mild (cohort_D) COVID-19 infections, respectively. Participants were followed from their entry date until the occurrence of an outcome of interest, mortality, or the end of follow-up, whichever came first. Any tests/events occurring after the study end-dates were censored. Regarding the total study size, we included totally 412,096 individuals who met the inclusion criteria. Sample size of each of the four cohorts are detailed in Table_1.

2.3. Outcome variables and covariates

The main study outcomes were hospitalization due to 135 clinically meaningful disease categories based on the Clinical Classifications Software Refined (CCSR; version-2022). Our multivariable regression analysis included 31 covariates, which were potentially related to COVID-19 infection and complications (Table_S1). These covariates encompassed basic demographics, major cardiovascular risk factors, immunological factors, comorbidities, general health/multimorbidity indicators, obesity measures, socioeconomic status, and smoking status (see Supplementary Text). Missing values for covariates were imputed using "missRanger",[17] with missing rates and out-of-bag (OOB) errors detailed in Table_S2.

[*] This study was based on an earlier draft first posted on MedRxiv (https://doi.org/10.1101/2022.03.23.22272811) on 23 March 2022.

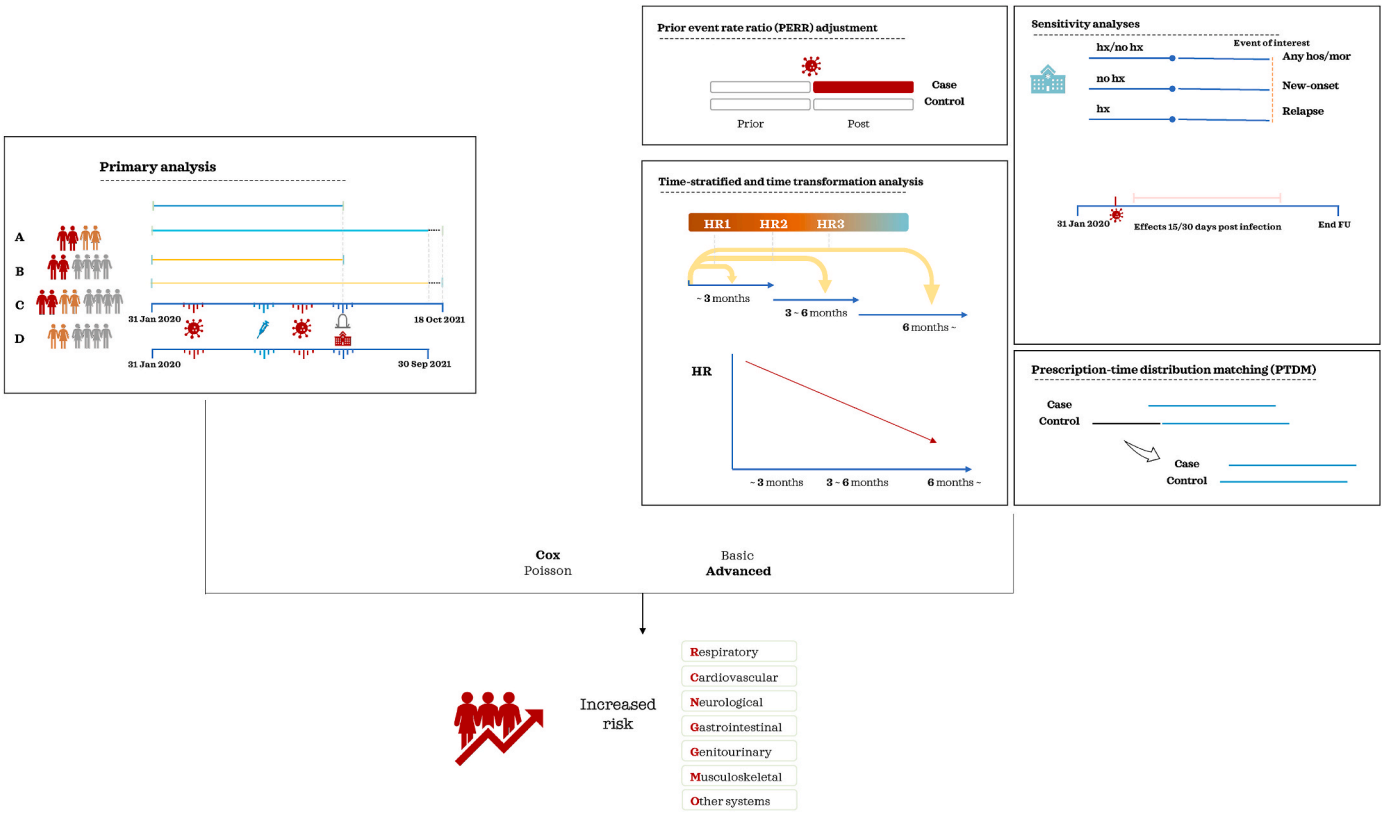

Fig. 1. An overview of analysis flow.
Legend: We investigated the associations between COVID-19 and subsequent risks of hospital admission in our primary analysis. For details please also refer to the Methods section in main text. We conducted analyses within infected patients (comparing outcomes of hospitalized vs non-hospitalized patients), and also compared hospitalized (severe) and non-hospitalized (mild) patients with subjects with no known history of infection. We conducted a comprehensive survey on disorders from all systems (up to 135 disease categories). Multivariable Cox and Poisson regression was conducted controlling for main confounders. For sensitivity analysis, we also conducted separate analysis for new-onset and recurrent cases, and other sensitivity analysis such as the prior event rate adjustment (PERR) approach to minimize effects of unmeasured confounders. Time-dependent effects on subsequent hospitalization were also tested.

Table 2
The proportion of significant results (FDR-adjusted $p < 0.05$) with increased risks of hospitalization for each cohort.

	No. of (unique) CCSR categories with sig. results[a] (increased hospitalization risks)	No. of CCSR categories studied[a]	Proportion of sig. results
Cohort A (hospitalization)	40	78	51.28 %
Cohort B (hospitalization)	77	107	71.96 %
Cohort C (hospitalization)	66	135	48.89 %
Cohort D (hospitalization)	11	85	12.94 %
A to D combined (hospitalization)	90	135	66.67 %

CCSR, Clinical Classifications Software Refined, a method to classify disease categories. Sig., significant with FDR adjusted $p < 0.05$.
[a] The no. of total CCSR categories studied and significant categories was computed by only including the disease categories with *number of events* ≥ 5 *in both exposed and non-exposed groups.*

2.4. Data sources and measurement

Data sources include baseline assessments, follow-up questionnaires, COVID-19 test results, GP records, linked electronic health records, and death registries. Outcomes and covariates were identified through ICD-10 codes in GP or hospitalization records.

2.5. Addressing bias

To address potential biases, we employed prescription-time distribution matching (PTDM) to account for survival bias, multivariable models to adjust for potential confounders, and the PERR adjustment to account for unmeasured confounders. Details are provided below.

2.6. Statistical analysis

2.6.1. Primary analysis

Cox and Poisson regression were employed for each cohort. For study outcomes, we primarily focused on any hospitalization, regardless of past medical history. We followed the methodology of Zhao et al.[18] to avoid convergence issues. Briefly, we first included standard variables like age, sex, hospitalizations/medications in the past year into the regression model. We then performed univariate testing to identify additional significant predictors ($p < 0.05$) for inclusion in the final model. All statistical analysis were performed by R (version-3.6.1). False discovery rate (FDR)[19] was used to control for multiple testing. The overall analytic flow is presented in Fig. 1.

2.6.2. Advanced analysis to control for bias/unmeasured confounding

- The PERR approach exploits a before-and-after design to minimize the effects of unmeasured confounders.[20–22] The basic idea is to compare the differences in HRs between the exposed and unexposed groups before and after the pandemic onset, as differences in

Table 3
Associations of COVID-19 with subsequent hospitalization due to various disorders (results with FDR-adjusted $p < 0.05$ are shown).

a. Compared to subjects with no known history of COVID-19, associations of severe COVID-19 with hospitalization due to various disorders (i.e. Cohort B)

Outcome	Raw_HR	HR	P-value	p.adj*	Lower CI	Upper CI	CCSR Category Description
BLD010	5.687	3.832	4.39E-03	**1.81E-02**	1.52	9.659	Other specified and unspecified hematologic conditions
BLD003	5.166	1.887	1.25E-04	**8.82E-04**	1.364	2.611	Aplastic anemia
BLD001	4.191	1.568	4.40E-03	**1.81E-02**	1.151	2.137	Nutritional anemia
CIR021	7.344	4.244	5.04E-08	**8.17E-07**	2.524	7.138	Acute hemorrhagic cerebrovascular disease
CIR031	9.520	3.512	5.02E-11	**1.16E-09**	2.415	5.109	Hypotension
CIR026	7.573	3.166	7.39E-06	**7.52E-05**	1.913	5.24	Peripheral and visceral vascular disease
CIR020	6.586	3.028	4.87E-08	**7.99E-07**	2.034	4.508	Cerebral infarction
CIR019	7.854	2.797	1.98E-06	**2.30E-05**	1.831	4.273	Heart failure
CIR009	4.072	2.369	1.38E-05	**1.34E-04**	1.606	3.494	Acute myocardial infarction
CIR017	3.229	2.162	1.53E-05	**1.45E-04**	1.524	3.066	Cardiac dysrhythmias
CIR012	2.931	1.843	1.37E-02	**4.68E-02**	1.133	2.998	Nonspecific chest pain
DIG016	6.862	4.264	8.60E-08	**1.30E-06**	2.508	7.251	Peritonitis and intra-abdominal abscess
DIG020	4.571	2.98	8.22E-05	**6.20E-04**	1.731	5.132	Pancreatic disorders (excluding diabetes)
DIG017	4.815	2.977	4.63E-06	**5.02E-05**	1.867	4.749	Biliary tract disease
DIG025	4.585	2.895	3.74E-04	**2.24E-03**	1.612	5.199	Other specified and unspecified gastrointestinal disorders
DIG001	5.362	2.721	3.57E-10	**7.95E-09**	1.99	3.72	Intestinal infection
DIG012	4.636	2.435	4.28E-04	**2.52E-03**	1.484	3.996	Intestinal obstruction and ileus
DIG015	2.904	2.14	8.70E-04	**4.55E-03**	1.367	3.349	Anal and rectal conditions
DIG022	3.027	2.052	1.14E-02	**3.99E-02**	1.176	3.581	Noninfectious gastroenteritis
DIG021	3.409	1.979	6.86E-05	**5.40E-04**	1.414	2.77	Gastrointestinal hemorrhage
DIG014	2.447	1.899	3.86E-03	**1.63E-02**	1.229	2.935	Hemorrhoids
DIG004	2.249	1.626	1.49E-02	**4.98E-02**	1.1	2.405	Esophageal disorders
END015	8.706	2.991	2.75E-05	**2.44E-04**	1.792	4.991	Other specified and unspecified endocrine disorders
END011	6.540	2.746	1.65E-06	**1.96E-05**	1.817	4.15	Fluid and electrolyte disorders
EYE002	1.771	1.495	9.26E-03	**3.37E-02**	1.104	2.024	Cataract and other lens disorders
FAC010	2.682	1.937	3.03E-03	**1.32E-02**	1.251	2.997	Other aftercare encounter
GEN001	11.604	6.508	2.36E-05	**2.14E-04**	2.731	15.507	Nephritis; nephrosis; renal sclerosis
GEN002	15.561	5.285	5.02E-37	**5.07E-35**	4.089	6.832	Acute and unspecified renal failure
GEN004	8.415	3.262	1.76E-27	**1.44E-25**	2.635	4.037	Urinary tract infections
GEN003	12.681	2.711	1.45E-05	**1.40E-04**	1.727	4.256	Chronic kidney disease
GEN006	4.128	2.693	2.01E-04	**1.34E-03**	1.597	4.54	Other specified and unspecified diseases of kidney and ureters
GEN005	3.186	2.284	8.88E-04	**4.63E-03**	1.403	3.716	Calculus of urinary tract
INF002	11.207	4.089	2.89E-32	**2.71E-30**	3.238	5.164	Septicemia
INF003	10.404	4.04	7.00E-39	**7.66E-37**	3.275	4.983	Bacterial infections
INF009	4.975	2.559	2.27E-07	**3.20E-06**	1.793	3.653	Parasitic, other specified and unspecified infections
INJ006	6.793	3.708	3.75E-13	**1.12E-11**	2.604	5.282	Fracture of the neck of the femur (hip)
INJ002	6.694	3.643	1.08E-04	**7.80E-04**	1.893	7.01	Fracture of the spine and back
INJ005	4.346	3.368	2.20E-04	**1.44E-03**	1.769	6.413	Fracture of the lower limb (except hip)
INJ073	4.649	2.985	1.19E-46	**1.57E-44**	2.571	3.466	Injury, sequela
INJ004	2.720	2.526	3.30E-05	**2.85E-04**	1.631	3.912	Fracture of the upper limb
MBD002	10.057	5.329	4.73E-05	**3.93E-04**	2.38	11.929	Depressive disorders
MUS002	17.646	5.095	5.51E-06	**5.79E-05**	2.524	10.283	Osteomyelitis
MUS010	4.749	2.593	3.68E-11	**8.77E-10**	1.955	3.439	Musculoskeletal pain, not low back pain
MUS038	4.410	2.444	2.41E-05	**2.15E-04**	1.615	3.701	Low back pain
NEO048	7.065	5.443	8.05E-05	**6.11E-04**	2.345	12.636	Nervous system cancers - brain
NEO013	6.306	3.787	3.69E-04	**2.22E-03**	1.82	7.879	Gastrointestinal cancers - stomach
NEO072	3.901	2.912	6.03E-05	**4.83E-04**	1.727	4.908	Neoplasms of unspecified nature or uncertain behavior
NEO015	3.605	2.664	1.95E-07	**2.78E-06**	1.842	3.853	Gastrointestinal cancers - colorectal
NEO070	3.568	2.37	8.66E-05	**6.42E-04**	1.54	3.646	Secondary malignancies
NVS013	30.580	9.848	4.68E-07	**6.03E-06**	4.045	23.972	Coma; stupor; and brain damage
NVS011	15.914	4.364	3.50E-17	**1.39E-15**	3.098	6.146	Neurocognitive disorders
NVS004	8.833	3.877	2.83E-05	**2.49E-04**	2.056	7.312	Parkinson's disease
NVS017	4.764	2.804	8.53E-03	**3.14E-02**	1.301	6.046	Nerve and nerve root disorders
NVS012	4.515	2.649	2.85E-04	**1.79E-03**	1.565	4.484	Transient cerebral ischemia
NVS010	3.013	1.968	1.34E-02	**4.60E-02**	1.15	3.366	Headache; including migraine
RSP014	22.183	12.799	3.71E-09	**7.07E-08**	5.485	29.867	Pneumothorax
RSP012	18.915	7.442	3.53E-11	**8.58E-10**	4.109	13.48	Respiratory failure; insufficiency; arrest
RSP010	25.762	7.332	3.50E-28	**3.06E-26**	5.142	10.453	Aspiration pneumonitis
RSP008	10.129	3.013	3.96E-12	**1.06E-10**	2.206	4.114	Chronic obstructive pulmonary disease and bronchiectasis
RSP002	8.505	2.886	3.49E-27	**2.70E-25**	2.381	3.498	Pneumonia (except that caused by tuberculosis)
RSP016	6.329	2.694	3.11E-09	**6.07E-08**	1.941	3.739	Other specified and unspecified lower respiratory disease
SYM016	13.021	7.383	0.00E+00	**0.00E+00**	6.797	8.019	Other general signs and symptoms
SYM017	5.763	3.605	4.03E-09	**7.56E-08**	2.352	5.526	Abnormal findings without diagnosis
SYM002	6.742	3.343	7.40E-05	**5.70E-04**	1.84	6.073	Fever
SYM014	4.211	2.66	1.27E-02	**4.39E-02**	1.232	5.741	Skin/Subcutaneous signs and symptoms
SYM010	4.731	2.508	3.87E-07	**5.09E-06**	1.758	3.577	Nervous system signs and symptoms
SYM001	4.366	2.455	6.86E-07	**8.58E-06**	1.722	3.5	Syncope
SYM013	3.955	2.107	2.28E-03	**1.05E-02**	1.305	3.401	Respiratory signs and symptoms

b. Compared to subjects with mild COVID-19, the associations of severe COVID-19 with hospitalization due to various disorders (i.e. Cohort A)

Outcome	Raw_HR	HR	P-value	p.adj*	Lower CI	Upper CI	CCSR Category Description
BLD003	7.572	3.606	1.57E-04	**1.08E-03**	1.854	7.014	Aplastic anemia

(*continued on next page*)

Table 3 (*continued*)

b. Compared to subjects with mild COVID-19, the associations of severe COVID-19 with hospitalization due to various disorders (i.e. Cohort A)

Outcome	Raw_HR	HR	P-value	p.adj*	Lower CI	Upper CI	CCSR Category Description
CIR020	14.127	6.307	2.87E-04	**1.79E-03**	2.331	17.061	Cerebral infarction
CIR017	6.436	4.364	1.65E-05	**1.54E-04**	2.232	8.531	Cardiac dysrhythmias
CIR031	8.762	3.965	3.39E-04	**2.07E-03**	1.867	8.423	Hypotension
CIR009	5.747	3.674	3.98E-04	**2.36E-03**	1.788	7.549	Acute myocardial infarction
DIG001	7.984	5.237	5.42E-07	**6.91E-06**	2.74	10.008	Intestinal infection
DIG022	5.478	4.5	4.32E-03	**1.81E-02**	1.602	12.643	Noninfectious gastroenteritis
DIG016	5.809	4.432	2.17E-03	**1.01E-02**	1.711	11.483	Peritonitis and intra-abdominal abscess
DIG020	4.446	4.172	2.44E-03	**1.10E-02**	1.656	10.508	Pancreatic disorders (excluding diabetes)
DIG017	6.404	3.899	2.44E-03	**1.10E-02**	1.617	9.4	Biliary tract disease
DIG021	3.137	2.156	4.54E-03	**1.86E-02**	1.268	3.665	Gastrointestinal hemorrhage
END015	9.800	3.955	1.33E-02	**4.58E-02**	1.331	11.756	Other specified and unspecified endocrine disorders
FAC009	7.144	5.582	1.71E-03	**8.30E-03**	1.906	16.342	Implant, device or graft related encounter
GEN002	15.355	7.009	1.14E-09	**2.38E-08**	3.744	13.119	Acute and unspecified renal failure
GEN006	6.055	5.353	4.91E-04	**2.81E-03**	2.084	13.748	Other specified and unspecified diseases of kidney and ureters
GEN003	12.890	4.769	5.32E-04	**3.01E-03**	1.97	11.542	Chronic kidney disease
GEN004	8.857	4.533	1.94E-11	**4.85E-10**	2.915	7.048	Urinary tract infections
GEN005	4.251	2.992	8.62E-03	**3.16E-02**	1.321	6.777	Calculus of urinary tract
INF002	11.769	6.039	1.96E-11	**4.85E-10**	3.571	10.212	Septicemia
INF003	10.959	5.801	1.06E-13	**3.46E-12**	3.649	9.222	Bacterial infections
INF009	7.856	5.438	5.81E-06	**6.05E-05**	2.615	11.31	Parasitic, other specified and unspecified infections
INJ006	10.761	5.489	1.37E-05	**1.34E-04**	2.548	11.824	Fracture of the neck of the femur (hip)
INJ073	4.743	3.269	1.87E-19	**8.49E-18**	2.527	4.228	Injury, sequela
MUS010	2.657	1.81	5.83E-03	**2.34E-02**	1.187	2.76	Musculoskeletal pain, not low back pain
NEO070	7.746	5.095	2.11E-04	**1.40E-03**	2.153	12.056	Secondary malignancies
NEO015	4.725	3.593	5.74E-05	**4.66E-04**	1.927	6.701	Gastrointestinal cancers - colorectal
NVS011	18.642	10.081	2.30E-07	**3.21E-06**	4.201	24.193	Neurocognitive disorders
RSP002	10.103	5.226	6.93E-15	**2.46E-13**	3.446	7.924	Pneumonia (except that caused by tuberculosis)
RSP011	6.126	4.552	8.17E-03	**3.07E-02**	1.481	13.996	Pleurisy, pleural effusion and pulmonary collapse
RSP008	9.944	3.633	9.15E-05	**6.71E-04**	1.904	6.935	Chronic obstructive pulmonary disease and bronchiectasis
RSP010	7.008	3.573	5.74E-05	**4.66E-04**	1.921	6.644	Aspiration pneumonitis
RSP016	6.116	3.559	3.52E-05	**3.00E-04**	1.95	6.495	Other specified and unspecified lower respiratory disease
SYM016	11.618	8.231	1.65E-121	**3.62E-119**	6.901	9.817	Other general signs and symptoms
SYM017	4.906	3.294	1.65E-03	**8.13E-03**	1.567	6.921	Abnormal findings without diagnosis
SYM001	3.954	2.542	1.69E-03	**8.24E-03**	1.42	4.55	Syncope
SYM010	2.776	2.073	8.95E-03	**3.27E-02**	1.2	3.582	Nervous system signs and symptoms

The above results are based on analyses without PTDM adjustment.

HR, hazard ratio (with adjustment for covariates); Raw_HR: HR without adjustment for covariates; p.adj*, FDR-adjusted p-value; Lower and upper CI represent the lower and upper 95 % confidence interval of HR.
Only results with FDR-adjusted p-value<0.05 are shown.

hospitalization risks prior to the pandemic may reflect baseline differences (unmeasured confounders) between the two groups.

- The PTDM approach was designed to control for survival bias. In this study, the start-date (time0) for the exposed group was the first date of being tested positive, while an artificial time0 was randomly assigned to the unexposed group. Imbalance of 'prescription time' (here 'prescription' refers to SARS-CoV-2 infection) distribution may lead to survival bias, which can be corrected by PTDM.

2.6.3. Sensitivity analysis

While primarily focusing on all hospitalizations, we also performed stratified analysis for new-onset and recurrent/relapsed diseases. Additionally, since vaccination may change the risk of sequelae, we also performed analysis during pre-vaccination period (before 8-Dec-2020). Furthermore, we examined associations with subsequent hospitalizations 15 or 30 days *after* being tested positive.

2.6.4. Additional analyses to study changes in HRs over time

We compared the HR of sequelae in the pre-vaccination era against the HR considering the whole follow-up period.

Additionally, we tested the proportional hazards (PH) assumption and examined the effect of COVID-19 on hospitalization risks across different follow-up periods. Moreover, we evaluated continuous time-dependent coefficients, assuming they follow a linear function of log (t), i.e. $\beta(t) = a + b\log(t)$.

3. Results

All supplementary tables/figures are available at the journal's website and at https://drive.google.com/drive/folders/1RtSoNTxUPQ90KTqMt7112smuL_Nsma1o?usp=drive_link.

3.1. Overview

In this study, we found that COVID-19, particularly severe infection, was associated with elevated HRs of hospitalization due to various diseases involving the pulmonary, cardiovascular, digestive, genitourinary, musculoskeletal, neurological and other systems after infection. The proportion of significant results (FDR-adjusted $p < 0.05$) for each cohort are summarized in Table_2. For example, under cohort B, severe COVID-19 was associated with increased hospitalization risks in 77 out of 107 (~72 %) disease categories studied.

Our findings were largely consistent across multiple sensitivity analyses and after PERR and PTDM adjustment. Notably, hospitalization risks were generally higher in the pre-vaccination period. Time-dependent analyses revealed that although the hospitalization risk decreases over time, it remains elevated beyond 6 months post-infection for a number of sequalae.

3.2. Severe (hospitalized) COVID-19 vs population (no evidence of infection)

3.2.1. Association with hospitalizations from different disorders

Severe infection (median follow-up = 261 days) was associated with

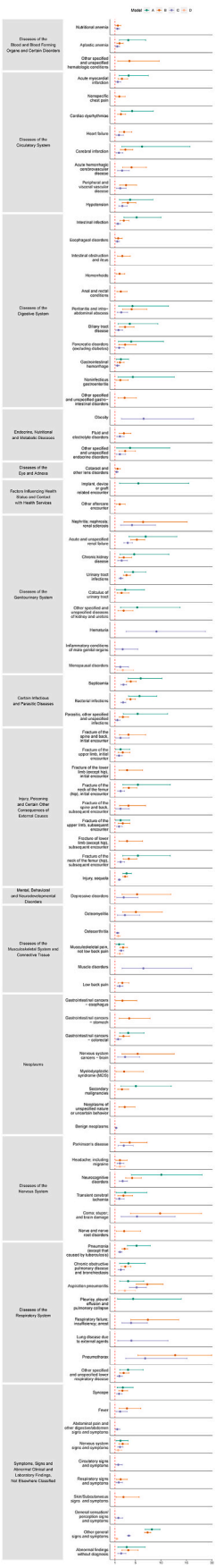

Fig. 2. Significant association of COVID-19 with hospitalization due to various diseases, Cohorts A to D (containing analysis on all hospitalizations, and without PTDM).
Legend: The red dashed line stands for the line of no effect (hazard ratio = 1). Y-axis indicates the HR (hazard ratio) of hospitalization post COVID-19. X-axis indicates each specific diagnoses category. Confidence intervals are also shown in the figure. Arrows in the confidence intervals (CIs) indicate that the (upper) CI was truncated for better visualization. Please refer to the supplementary Tables for the exact CIs. The same applies to Figs. 2–4. We only present the results if the number of events ≥ 5 for both exposed and unexposed groups.

(caption on next column)

higher hazards of hospitalization from various diseases across multiple systems. The top disorders included (for each system, up to 3 sequelae with the largest HRs are shown).

- **Respiratory**: Pneumothorax, respiratory failure, insufficiency, arrest, and aspiration pneumonitis.
- **Cardiovascular**: Acute hemorrhagic cerebrovascular disease, hypotension, and peripheral/visceral vascular disease.
- **Genitourinary**: Nephritis, nephrosis, renal sclerosis, acute/unspecified renal failure (RF), and urinary tract infection (UTI).
- **Neurological**: Coma, stupor, brain damage, neurocognitive disorders, and Parkinson's disease.
- **Digestive**: Peritonitis, intra-abdominal abscess, pancreatic disorders (excluding diabetes), and biliary tract disease.
- **Musculoskeletal (including injuries, fractures)**: Osteomyelitis, neck of femur fractures, fracture of the spine and back.
- **Neoplasms**: Brain, stomach, and colorectal cancers.
- **Infectious**: Septicemia, bacterial, and parasitic infections.
- **Hematological**: Other hematologic conditions, aplastic and nutritional anemia.
- **Endocrine:** Other endocrine disorders, fluid and electrolyte disorders
- **Psychiatric**: Depressive disorders.
- **Others**: General signs/symptoms, abnormal findings without diagnosis and fever.

Demographic characteristics for each cohort are summarized in Table_S1. Main results are presented in Table_3a and Fig_2, with full results in Table_S3. A summary of the overall results, including findings from advanced analyses, is presented in Table_7.

When we restricted the outcome to hospitalization from *new-onset/recurrent* diseases, most results were similar (Fig. S1). Higher hospitalization risks from a few additional disorders (new-onset) were found, including coronary atherosclerosis, other heart diseases, and other specified hereditary and degenerative nervous system conditions.

We also repeated the analysis using Poisson regression which models the incidence hospitalization rate. The results were similar to those from Cox regression (Table_S3).

3.2.2. Analysis restricted to sequelae 15 or 30 days post-infection

In a sensitivity analysis restricting outcomes to those occurring 15/30 days after infection (Table_S4), the overall patterns of sequelae remained similar.

3.3. Mild (non-hospitalized) COVID-19 vs population

A history of 'mild' (non-hospitalized) COVID-19 (Cohort_D; median follow-up: 243 days) were associated with significantly increased hazards of hospitalization due to musculoskeletal pain (excluding low back pain), aspiration pneumonitis, and other general signs/symptoms (Table_S3 and Fig. 2).

3.4. Any COVID-19 infection vs population

The results from this analysis (Cohort_C; median follow-up: 248

Table 4
The associations of any hospitalization with severe COVID-19 due to various disorders, *with PERR adjustment* (results with pval_PERR<0.05 are shown).

Outcome	Cohort	HR_PERR	Pval_PERR	Lower CI	Upper CI	CCSR Category Description
CIR020	B	4.12	**1.39E-04**	1.989	8.535	Cerebral infarction
CIR017	A	3.524	**1.42E-02**	1.288	9.646	Cardiac dysrhythmias
CIR026	B	3.331	**2.93E-02**	1.129	9.825	Peripheral and visceral vascular disease
CIR009	B	2.432	**3.91E-02**	1.045	5.658	Acute myocardial infarction
CIR017	B	2.219	**6.57E-03**	1.249	3.941	Cardiac dysrhythmias
CIR031	C	2.069	**1.66E-02**	1.142	3.751	Hypotension
DIG016	B	4.503	**3.24E-03**	1.653	12.262	Peritonitis and intra-abdominal abscess
DIG025	B	4.255	**3.78E-03**	1.597	11.336	Other specified and unspecified gastrointestinal disorders
DIG001	A	3.18	**1.37E-02**	1.268	7.974	Intestinal infection
DIG001	B	2.707	**9.63E-04**	1.499	4.889	Intestinal infection
DIG017	B	2.468	**3.17E-02**	1.082	5.627	Biliary tract disease
DIG016	C	2.211	**1.64E-02**	1.157	4.225	Peritonitis and intra-abdominal abscess
DIG021	B	2.1	**1.90E-02**	1.13	3.904	Gastrointestinal hemorrhage
DIG001	C	1.584	**1.94E-02**	1.077	2.329	Intestinal infection
DIG021	C	1.517	**2.07E-02**	1.066	2.16	Gastrointestinal hemorrhage
END015	B	5.323	**4.19E-03**	1.695	16.716	Other specified and unspecified endocrine disorders
EYE002	C	1.463	**4.16E-03**	1.128	1.898	Cataract and other lens disorders
GEN002	B	4.941	**2.73E-09**	2.918	8.364	Acute and unspecified renal failure
GEN002	A	4.025	**1.87E-02**	1.26	12.854	Acute and unspecified renal failure
GEN004	B	3.569	**1.20E-07**	2.228	5.716	Urinary tract infections
GEN002	C	3.229	**8.00E-08**	2.105	4.955	Acute and unspecified renal failure
GEN004	A	2.296	**1.96E-02**	1.142	4.614	Urinary tract infections
GEN004	C	2.135	**2.83E-06**	1.554	2.933	Urinary tract infections
INF003	B	3.61	**1.20E-10**	2.442	5.335	Bacterial infections
INF002	B	2.73	**7.10E-06**	1.761	4.231	Septicemia
INF003	C	2.427	**6.80E-08**	1.759	3.35	Bacterial infections
INF009	B	2.052	**4.54E-02**	1.015	4.148	Parasitic, other specified and unspecified infections
INF002	C	2.037	**1.17E-04**	1.418	2.926	Septicemia
INJ073	B	2.339	**7.21E-11**	1.812	3.021	Injury, sequela
INJ073	A	2.306	**4.72E-05**	1.542	3.449	Injury, sequela
INJ004	C	1.626	**3.39E-02**	1.038	2.548	Fracture of the upper limb, initial encounter
INJ041	C	1.626	**4.22E-02**	1.017	2.599	Fracture of the upper limb, subsequent encounter
INJ073	C	1.561	**4.66E-06**	1.29	1.888	Injury, sequela
MUS002	B	8.64	**5.12E-03**	1.909	39.096	Osteomyelitis
MUS002	C	5.033	**9.86E-03**	1.475	17.173	Osteomyelitis
MUS010	B	2.531	**3.65E-05**	1.629	3.934	Musculoskeletal pain, not low back pain
MUS038	B	2.023	**2.40E-02**	1.097	3.728	Low back pain
MUS010	C	1.962	**2.16E-07**	1.521	2.531	Musculoskeletal pain, not low back pain
MUS006	C	1.388	**5.50E-03**	1.101	1.75	Osteoarthritis
NEO015	B	2.36	**1.43E-02**	1.187	4.692	Gastrointestinal cancers - colorectal
NVS012	B	2.829	**3.42E-02**	1.08	7.409	Transient cerebral ischemia
NVS011	B	2.786	**2.19E-02**	1.16	6.689	Neurocognitive disorders
NVS010	C	1.818	**2.82E-02**	1.066	3.102	Headache; including migraine
RSP012	B	5.496	**7.01E-03**	1.593	18.966	Respiratory failure; insufficiency; arrest
RSP012	C	4.184	**3.15E-02**	1.135	15.421	Respiratory failure; insufficiency; arrest
RSP010	C	2.842	**3.68E-03**	1.405	5.752	Aspiration pneumonitis
RSP002	B	2.528	**1.98E-06**	1.725	3.705	Pneumonia (except that caused by tuberculosis)
RSP010	B	2.521	**2.91E-02**	1.099	5.786	Aspiration pneumonitis
RSP002	A	2.17	**1.83E-02**	1.14	4.129	Pneumonia (except that caused by tuberculosis)
RSP016	B	1.908	**1.47E-02**	1.136	3.207	Other specified and unspecified lower respiratory disease
RSP002	C	1.785	**6.86E-05**	1.342	2.374	Pneumonia (except that caused by tuberculosis)
RSP016	C	1.708	**1.18E-02**	1.126	2.59	Other specified and unspecified lower respiratory disease
RSP008	C	1.635	**4.55E-02**	1.01	2.648	Chronic obstructive pulmonary disease and bronchiectasis
SYM017	B	7.835	**6.65E-07**	3.48	17.64	Abnormal findings without diagnosis
SYM016	B	7.456	**7.69E-110**	6.248	8.899	Other general signs and symptoms
SYM016	A	5.828	**2.05E-22**	4.088	8.31	Other general signs and symptoms
SYM017	C	3.726	**5.32E-06**	2.115	6.566	Abnormal findings without diagnosis
SYM002	B	3.688	**3.64E-02**	1.086	12.524	Fever
SYM016	C	3.553	**5.22E-81**	3.119	4.048	Other general signs and symptoms
SYM010	B	2.436	**8.20E-03**	1.259	4.714	Nervous system signs and symptoms
SYM013	C	2.153	**1.17E-02**	1.186	3.906	Respiratory signs and symptoms
SYM010	C	1.673	**1.95E-02**	1.086	2.577	Nervous system signs and symptoms

HR_PERR, hazard ratio in comparing two analysis performed before and after the onset of pandemic to adjust for baseline differences between the infected and non-infected groups (see main text), two hundred bootstraps were performed to derive the standard error; pval_PERR, corresponding p-value in final analysis after PERR adjustment. Considering that the traits under investigation using the PERR method were selected based on FDR-corrected p-values less than 0.05 from the original tests, and taking into account the inherently conservative nature of the PERR method, we did not apply further FDR correction to the P-values obtained from PERR.

days) were largely similar to those from Cohort_B (Table_S3 and Fig. 2). In addition to findings from Cohort_B, we also found increased hospitalization risks from essential hypertension, obesity, haematuria, osteoarthritis, muscle disorders, lung diseases, and general signs/symptoms.

3.5. Severe vs mild COVID-19

Compared to mild COVID-19, severe infection was associated with higher hazards of hospitalization across multiple diseases, involving cardiovascular, digestive, genitourinary and respiratory disorders, various infections, injuries, as well as general signs/symptoms

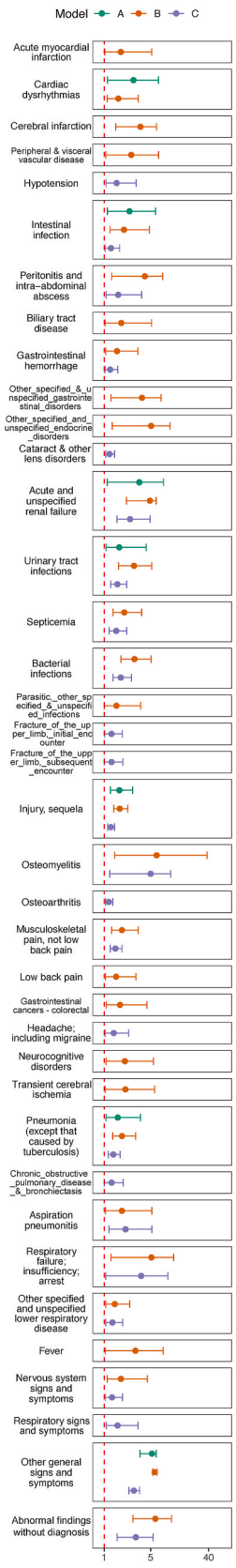

Fig. 3. Association of hospitalization with COVID-19 with PERR adjustment. Legend: Associations COVID-19 with hospitalization from other diseases with prior event rate ratio (PERR) adjustment. Significant results in the primary analysis were further selected for analysis with PERR adjustment. The red dashed line stands for the line of no effect. We only present the results if the number of events ≥ 5 for both exposed and unexposed groups.

(Table_3b, Fig_2).

3.6. Association results with PTDM adjustment

Results with PTDM adjustment are shown in Table_S3 and Fig. S2. Under PTDM adjustment, increased hospitalization risks for severe COVID-19 remained for various disorders, such as pulmonary (e.g. non-COVID-19 pneumonia, COPD, aspiration pneumonitis), cardiovascular (e.g. acute myocardial infarction (AMI), heart failure, thromboembolism), cerebrovascular (e.g. infarction, hemorrhage), renal (e.g. nephritis, acute/chronic renal failure [ARF/CRF]) disorders, and certain infections, injuries and neoplasms. Elevated hospitalization risks were also observed for many hematological, endocrine, musculoskeletal, and neurological disorders.

3.7. Association results with PERR adjustment

The primary results with PERR adjustment (with prior exposure period restricted to 30-Jan-2018 - 30-Jan-2020) are listed in Table_4 and Fig. 3. Compared to those without known infections, severe COVID-19 was associated with increased hazards of hospitalization for both pulmonary (e.g., pneumonia, respiratory failure) and extra-pulmonary conditions (e.g., AMI, dysrhythmias, transient ischemic attack[TIA], cerebral infarction, ARF, UTI, peripheral/visceral vascular disease, neurocognitive disorders, osteomyelitis etc.).

Compared to mild COVID-19, severe COVID-19 was associated with higher hospitalization risks for pneumonia, cardiac dysrhythmias, ARF, UTI, injuries, and intestinal infections. When comparing any COVID-19 infection to the general population, elevated hospitalization risks were also observed for COPD, hypotension, osteoarthritis and other respiratory symptoms, in addition to most associations reported for Cohort_B.

3.8. Risk of sequelae during the pre-vaccination period

The associations of hospitalization after COVID-19 during the pre-vaccination period are presented in Table_5 (also see Fig. 4 and Table_S5). The sequelae spectrum remained similar.

Generally, HRs were higher in the pre-vaccination period for a variety of diseases (Table_5). We also tested the proportion of conditions with higher pre-vaccination HRs for each system. Our analysis revealed higher hospitalization risks during the pre-vaccination period across various body systems for Cohort_B and C (Table_6).

In Cohort_B, other general signs/symptoms and injury sequelae exhibited the most significant differences. Overall, higher pre-vaccination hospitalization risks were observed for 55 out of 65 disorders (binomial test, one-tailed $p = 5.88E\text{-}09$; binomial test serves as an approximate inference guide considering the potential dependency among disorders), including disorders of circulatory (8/9), respiratory (5/5), and several other systems.

In Cohort_C, in addition to other general signs/symptoms and injury sequelae, significant differences were noted in the pre-vaccination period for cerebral infarction, biliary tract disease, acute/unspecified RF, bacterial infections, and various fracture conditions. Overall, higher pre-vaccination HRs was observed for 62 out of 73 conditions.

Note that we restricted the analysis to disorders with ≥5 events in each group for a meaningful comparison. Details are presented in Table_7 and Table_S5.

3.9. HRs changes with time since infection

Test for PH assumption were listed in Table_S6. We performed time-stratified and time-transformation analysis to estimate time-dependent HRs. We observed larger effects and more significant associations in the first 3 months; generally, the effects of infection attenuated over time (Table_8, Table_S7 and Fig. S3).

Nevertheless, even after 6 months, COVID-19 infections, particularly

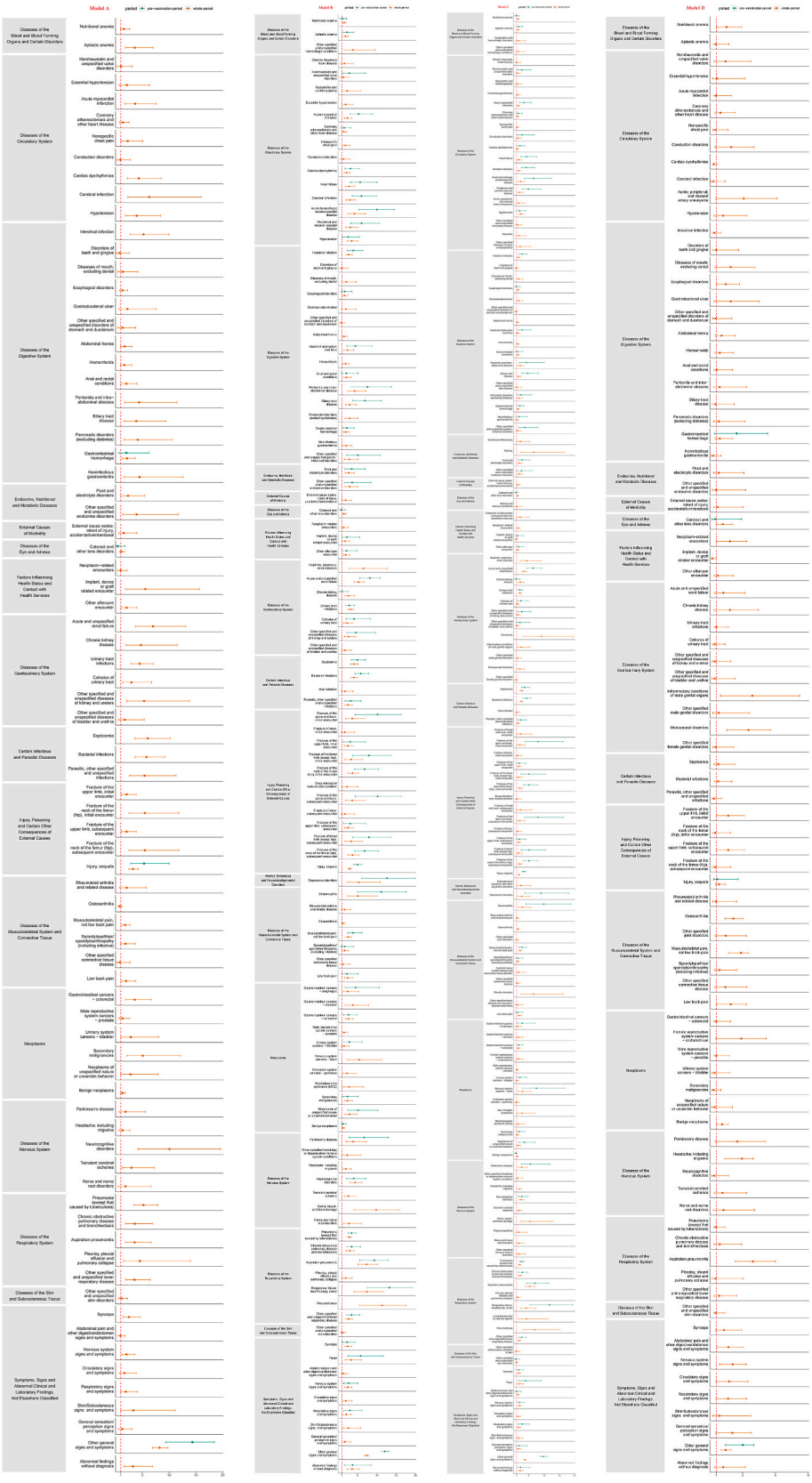

Fig. 4. Association of COVID-19 with hospitalization due to various diseases, models A to D, restricted to pre-vaccination period (before Dec 8, 2020)
Legend: Associations COVID-19 with hospitalization from other diseases, restricted to pre-vaccination period were shown. The red dashed line stands for the line of no effect. We only present the results if the number of events ≥ 5 for both exposed and unexposed groups.

Table 5
Association of COVID-19 with hospitalization due to various diseases, cohorts A to D, restricted to pre-vaccination period (before Dec 8, 2020) (results with significant difference between the pre-vaccination and the whole FU period are shown).

Outcome	HR	P-value	Lower CI	Upper CI	Cohort	t. stat_diff	diff.beta.p	diff.beta.p.adj	Significance	CCSR Category Description
CIR009	5.278	5.60E-10	3.12	8.929	B	2.402	8.16E-03	6.66E-02		Acute myocardial infarction
CIR009	3.457	3.69E-06	2.045	5.846	C	2.562	5.20E-03	5.68E-02		Acute myocardial infarction
CIR017	2.146	6.92E-03	1.233	3.735	C	1.732	4.16E-02	1.48E-01		Cardiac dysrhythmias
CIR019	5.698	3.94E-09	3.192	10.169	B	1.943	2.60E-02	1.12E-01		Heart failure
CIR019	4.254	8.99E-07	2.387	7.581	C	2.435	7.46E-03	6.66E-02		Heart failure
CIR020	5.994	5.84E-12	3.6	9.98	B	2.069	1.93E-02	1.01E-01		Cerebral infarction
CIR020	4.226	1.12E-08	2.577	6.93	C	2.788	2.65E-03	**4.54E-02**	*	Cerebral infarction
CIR021	10.048	2.07E-12	5.28	19.118	B	2.042	2.06E-02	1.01E-01		Acute hemorrhagic cerebrovascular disease
CIR021	6.585	8.03E-09	3.471	12.494	C	2.501	6.18E-03	6.27E-02		Acute hemorrhagic cerebrovascular disease
CIR026	4.857	4.30E-07	2.632	8.964	C	2.234	1.27E-02	9.05E-02		Peripheral and visceral vascular disease
DIG001	2.836	1.27E-05	1.776	4.529	C	2.147	1.59E-02	1.00E-01		Intestinal infection
DIG012	2.877	2.34E-03	1.457	5.684	C	1.9	2.87E-02	1.14E-01		Intestinal obstruction and ileus
DIG017	6.935	1.79E-10	3.825	12.574	B	2.191	1.42E-02	9.62E-02		Biliary tract disease
DIG017	4.627	1.50E-07	2.612	8.195	C	2.858	2.13E-03	**4.32E-02**	*	Biliary tract disease
DIG025	3.708	8.69E-04	1.714	8.02	C	2.072	1.91E-02	1.01E-01		Other specified and unspecified gastrointestinal disorders
GEN002	8.191	1.70E-27	5.605	11.971	B	1.875	3.04E-02	1.17E-01		Acute and unspecified renal failure
GEN002	6.404	5.96E-23	4.428	9.262	C	2.718	3.29E-03	**4.66E-02**	*	Acute and unspecified renal failure
GEN005	2.449	8.61E-03	1.255	4.777	C	1.736	4.13E-02	1.48E-01		Calculus of urinary tract
INF003	5.854	6.62E-31	4.338	7.899	B	1.987	2.34E-02	1.04E-01		Bacterial infections
INF003	4.237	8.14E-22	3.155	5.691	C	2.761	2.88E-03	**4.54E-02**	*	Bacterial infections
INJ002	10.43	1.13E-07	4.386	24.803	B	1.899	2.88E-02	1.14E-01		Fracture of the spine and back
INJ002	8.068	4.07E-07	3.597	18.098	C	2.648	4.05E-03	**4.79E-02**	*	Fracture of the spine and back
INJ005	7.98	1.82E-07	3.657	17.413	B	1.671	4.73E-02	1.56E-01		Fracture of the lower limb (except hip)
INJ005	5.079	1.21E-05	2.453	10.515	C	2.389	8.45E-03	6.66E-02		Fracture of the lower limb (except hip)
INJ006	6.842	5.55E-15	4.224	11.083	B	2.007	2.24E-02	1.02E-01		Fracture of the neck of the femur (hip)
INJ006	5.063	7.17E-13	3.251	7.885	C	3.167	7.69E-04	**1.82E-02**	*	Fracture of the neck of the femur (hip)
INJ073	5.009	1.32E-45	4.008	6.259	B	3.781	7.81E-05	**2.77E-03**	**	Injury, sequela
INJ073	3.351	5.93E-30	2.72	4.127	C	4.899	4.82E-07	**2.28E-05**	***	Injury, sequela
MBD002	15.353	6.72E-09	6.098	38.654	B	1.692	4.53E-02	1.56E-01		Depressive disorders
MBD002	9.007	2.18E-06	3.627	22.368	C	2.042	2.06E-02	1.01E-01		Depressive disorders
MUS002	9.893	3.92E-07	4.081	23.981	C	2.122	1.69E-02	1.00E-01		Osteomyelitis
NEO072	3.578	2.17E-04	1.821	7.033	C	2.04	2.07E-02	1.01E-01		Neoplasms of unspecified nature or uncertain behavior
RSP002	2.653	3.23E-12	2.016	3.49	C	1.764	3.88E-02	1.45E-01		Pneumonia (except that caused by tuberculosis)
RSP012	11.777	3.44E-10	5.453	25.434	C	2.131	1.65E-02	1.00E-01		Respiratory failure; insufficiency; arrest
SYM016	14.348	9.34E-35	9.385	21.935	A	2.369	8.91E-03	6.66E-02		Other general signs and symptoms
SYM016	14.196	0.00E+00	12.59	16.008	B	8.789	7.55E-19	**5.36E-17**	***	Other general signs and symptoms
SYM016	9.736	0.00E+00	8.673	10.93	C	13.773	1.85E-43	**2.63E-41**	***	Other general signs and symptoms

Note: CCSR: Clinical Classifications Software Refined (CCSR) - HCUP. t.stat_diff: the t statistic of the comparison between pre_vac and whole FU period; diff.beta.p: the p value for the difference between the pre_vac period and the whole period; diff.beta.p.adj: the FDR corrected diff.beta.p; HR, hazard ratio (with adjustment for covariates); Lower and upper CI represent the lower and upper 95 % confidence interval of HR.
Significance: * indicates a diff.beta.p.adj value between 0.01 and 0.05, ** indicates between 0.001 and 0.01, while *** indicates a value smaller than 0.001, all suggesting significant difference betweens the pre_vac and the whole period.

severe cases, were still associated with elevated hospitalization risks from numerous conditions (Table_8, Table_S7). These included higher hospitalization risks for ARF, septicemia (with the leading cause being sepsis from unspecified organisms), bacterial infections, musculoskeletal pain, pneumonia, UTI, and other general signs/symptoms. Furthermore, mild COVID-19 cases were associated with a significantly increased risk of hospitalization due to aspiration pneumonitis at 3–6 months and after 6 months.

However, the limited sample size for follow-up beyond six months resulted in relatively modest statistical power, implying that there may be additional disorders with persistent elevated risks after this period. Tests for PH for time-stratified analyses are shown in Table_S8.

Analyses using time-transformation are presented in Table_S9. For most outcomes, the baseline risk was the highest, decreasing over time. However, the estimated time taken (assuming a linear reduction of hazard on log(t) scale) for the adverse effects of infection to wane to zero was generally >6 months. For example, the median time was 403.8 days for severe infections (Cohort_B).

4. Discussion

Overall, we found that COVID-19, especially severe disease, was associated with increased risks of hospitalization due to pulmonary, cardiovascular, digestive, neurological, genitourinary and musculoskeletal disorders. These results were largely consistent and robust to multiple sensitivity analysis, and after PERR and PTDM adjustment.

4.1. Context of findings considering previous research

The COVID-19 sequelae have been investigated in several previous studies.[8,11,23] Some studies focused on specific organ systems.[3,4] Two previous studies on US veterans[7,9] revealed that COVID-19 was associated with cardiovascular disorders. Besides, adverse cardiovascular disorders,[24] cerebrovascular disorders involvement were also commonly reported.[25,26] Also, renal involvement,[27] and deterioration of renal function following acute infection were reported. Moreover, neurocognitive impairment was also observed,[6,28] although the mechanisms remain poorly understood. Our study also revealed similar cardiovascular sequelae in a general population cohort based on an independent sample. We also observed that COVID-19 patients were more likely to be admitted for *other bacterial/viral infections* post-infection and several musculoskeletal problems, especially fractures, which is not widely recognized.

While this is an observational study, it is interesting to note that

Table 6
Test of the proportion of conditions (from each system) for which the HR from the pre-vaccination period is higher than that from the whole follow-up period.

(One-tailed binomial test was employed; the alternative hypothesis is that the proportion K/N is larger than 0.5)

CCSR category	Total no. of comparisons that can be made (N)	No. of times that pre-vaccination HR is higher (K)	% of times pre-vaccination HR higher	Binomial test p-value (K/N greater than 0.5)	Cohort
Cohort A all disorders	4	2	50 %	0.6875	A
Diseases of the Blood and Blood Forming Organs and Certain Disorders	2	1	50 %	0.7500	B
Diseases of the Circulatory System	**9**	**8**	**89 %**	**0.0195**	**B**
Diseases of the Digestive System	**8**	**7**	**88 %**	**0.0352**	**B**
Endocrine, Nutritional and Metabolic Diseases	2	2	100 %	0.2500	B
Diseases of the Eye and Adnexa	1	1	100 %	0.5000	B
Factors Influencing Health Status and Contact with Health Services	2	2	100 %	0.2500	B
Diseases of the Genitourinary System	5	3	60 %	0.5000	B
Certain Infectious and Parasitic Diseases	3	3	100 %	0.1250	B
Injury, Poisoning and Certain Other Consequences of External Causes	**9**	**9**	**100 %**	**0.0020**	**B**
Mental, Behavioral and Neurodevelopmental Disorders	1	1	100 %	0.5000	B
Diseases of the Musculoskeletal System and Connective Tissue	4	2	50 %	0.6875	B
Neoplasms	**6**	**6**	**100 %**	**0.0156**	**B**
Diseases of the Nervous System	2	1	50 %	0.7500	B
Diseases of the Respiratory System	**5**	**5**	**100 %**	**0.0313**	**B**
Symptoms, Signs and Abnormal Clinical and Laboratory Findings	6	5	83 %	0.1094	B
Cohort B all disorders	**65**	**55**	**85 %**	**0.0000**	**B**
Diseases of the Blood and Blood Forming Organs and Certain Disorders	2	1	50 %	0.7500	C
Diseases of the Circulatory System	**10**	**9**	**90 %**	**0.0107**	**C**
Diseases of the Digestive System	10	8	80 %	0.0547	C
Endocrine, Nutritional and Metabolic Diseases	2	2	100 %	0.2500	C
Diseases of the Eye and Adnexa	1	0	0 %	1.0000	C
Factors Influencing Health Status and Contact with Health Services	2	2	100 %	0.2500	C
Diseases of the Genitourinary System	6	4	67 %	0.3437	C
Certain Infectious and Parasitic Diseases	3	3	100 %	0.1250	C
Injury, Poisoning and Certain Other Consequences of External Causes	**9**	**9**	**100 %**	**0.0020**	**C**
Mental, Behavioral and Neurodevelopmental Disorders	1	1	100 %	0.5000	C
Diseases of the Musculoskeletal System and Connective Tissue	4	3	75 %	0.3125	C
Neoplasms	7	6	86 %	0.0625	C
Diseases of the Nervous System	2	2	100 %	0.2500	C
Diseases of the Respiratory System	**5**	**5**	**100 %**	**0.0313**	**C**
Diseases of the Skin and Subcutaneous Tissue	1	1	100 %	0.5000	C
Symptoms, Signs and Abnormal Clinical and Laboratory Findings	**8**	**7**	**88 %**	**0.0352**	**C**
Cohort C all disorders	**73**	**62**	**85 %**	**0.0000**	**C**
Cohort D all disorders	4	2	50 %	0.6875	D

Note: HR, hazard ratio (with adjustment for covariates); note that the binomial test is approximate here as some diseases within the listed categories are correlated.

Mendelian randomization studies, a causal inference approach less prone to confounding, also showed that COVID-19 may be a causal risk factor for various cardiometabolic and neuropsychiatric disorders.[29,30]

Interestingly, we observed preliminary evidence that the risks of certain sequelae were higher in the pre-vaccination period. Additionally, we revealed higher pre-vaccination hospitalization risks across different body systems for Cohorts_B and C. However, this study is not primarily designed for COVID-19 vaccinations, and future studies are needed.

4.2. Strengths of the study

Our work has unique strengths and contributes important additional insights to existing evidence. Firstly, the sample size of the UKBB cohort is large, with detailed health records and a sufficient period of follow-up. Notably, this is one of the very few studies that *systematically cover all organ systems and disorders*, providing a comprehensive picture of COVID-19 sequelae. Furthermore, we focused on the more severe end of the sequelae spectrum, rather than emergence of various symptoms post-infection. We also revealed elevated hospitalization risks of several body systems/disease categories that were less well-studied or unreported before. Another noteworthy finding is that 'mild' infections were associated with a significantly increased risk of hospitalization due to some disorders, which is not a well-known phenomenon. Other strengths of this study include additional stratified analyses on new-onset and recurrent cases, analysis of time-dependent HRs, advanced methodologies such as PTDM and PERR adjustments to reduce residual bias and confounding, as well as a relatively long follow-up period. The median follow-up among the infected was ~ 8–9 months, which is among the longest among all similar studies on COVID-19 sequelae described earlier.

4.3. Limitations

There are several limitations of this study. Firstly, this is an observational study. Confounding effects cannot be excluded completely, and causality cannot be concluded. However, many results remained significant after PERR adjustment, which further supports our findings.

Table 7
Summary of hazard ratios for each cohort and overview of findings from other advanced and sensitivity analysis.

Outcome	HR_A	HR_B	HR_C	HR_D	PERR	15days after	30days after	Sig larger in pre vaccination
BLD001	1.58	**1.57**	**1.48**	1.39	N	Y	Y	N
BLD003	**3.61**	**1.89**	**1.44**	0.87	N	Y	Y	N
BLD010		**3.83**	1.58		N			
CIR009	**3.67**	**2.37**	**1.55**	0.91	Y	N	N	Y
CIR012	2.30	**1.84**	1.21	0.83	N	N	N	
CIR017	**4.36**	**2.16**	1.23	0.62	Y	Y	Y	N
CIR019		**2.80**	**1.77**		N	Y	Y	Y
CIR020	**6.31**	**3.03**	**1.76**	0.55	Y	N	N	Y
CIR021		**4.24**	**2.40**		N	N	N	Y
CIR026		**3.17**	**2.04**		Y	Y	Y	Y
CIR031	**3.97**	**3.51**	**2.44**	1.26	Y	N	N	N
DIG001	**5.24**	**2.72**	**1.57**	0.69	Y	Y	Y	Y
DIG004	1.33	**1.63**	**1.45**	1.36	N	Y	Y	N
DIG012		**2.44**	1.31		N	N	N	Y
DIG014	1.66	**1.90**	1.37	1.13	N	Y	Y	
DIG015	2.04	**2.14**	1.40	1.01	N	Y	Y	N
DIG016	**4.43**	**4.26**	**2.23**	1.12	Y	Y	Y	N
DIG017	**3.90**	**2.98**	**1.68**	0.83	Y	Y	Y	Y
DIG020	**4.17**	**2.98**	**1.82**	1.10	N	N	N	N
DIG021	**2.16**	**1.98**	**1.47**	1.13	Y	Y	N	N
DIG022	**4.50**	**2.05**	1.07	0.53	N	N	N	N
DIG025		**2.89**	1.38		Y	N	N	Y
END011	2.37	**2.75**	**1.95**	1.10	N	Y	Y	N
END015	**3.96**	**2.99**	**1.96**	0.93	Y	Y	N	N
EYE002	1.12	**1.50**	**1.34**	1.24	Y	Y	Y	N
FAC010	2.09	**1.94**	1.38	1.06	N	Y	Y	N
GEN001		**6.51**	**4.34**		N	Y	Y	
GEN002	**7.01**	**5.29**	**3.49**	1.27	Y	Y	Y	Y
GEN003	**4.77**	**2.71**	**2.31**	1.52	N	Y	Y	N
GEN004	**4.53**	**3.26**	**2.13**	1.00	Y	Y	Y	N
GEN005	**2.99**	**2.28**	1.24	0.73	N	N	N	N
GEN006	**5.35**	**2.69**	1.44	0.73	N	N	N	N
INF002	**6.04**	**4.09**	**2.66**	1.07	Y	Y	Y	N
INF003	**5.80**	**4.04**	**2.59**	1.07	Y	Y	Y	Y
INF009	**5.44**	**2.56**	**1.47**	0.66	Y	Y	Y	N
INJ002		**3.64**	2.08		N	N	N	Y
INJ004	2.09	**2.53**	**1.79**	1.45	Y	Y	Y	N
INJ005		**3.37**	1.68		N	N	N	Y
INJ006	**5.49**	**3.71**	**2.10**	0.80	N	N	N	Y
INJ073	**3.27**	**2.99**	**1.84**	1.10	Y	Y	Y	Y
MBD002		**5.33**	**2.71**		N			Y
MUS002		**5.10**	**2.94**		Y	Y	Y	Y
MUS010	**1.81**	**2.59**	**2.21**	**1.94**	Y	Y	Y	N
MUS038	2.01	**2.44**	**1.91**	1.55	Y	Y	Y	N
NEO013		**3.79**	1.60		N	Y	Y	
NEO015	**3.59**	**2.66**	**1.61**	0.95	Y	Y	Y	N
NEO048		**5.44**	**2.97**		N	Y	Y	N
NEO070	**5.10**	**2.37**	1.29	0.59	N	Y	Y	N
NEO072	2.81	**2.91**	1.54	0.72	N	Y	Y	Y
NVS004	1.91	**3.88**	**2.71**	1.80	N	Y	Y	N
NVS010	1.34	**1.97**	**1.96**	**1.97**	Y	Y	Y	
NVS011	**10.08**	**4.36**	**2.50**	0.65	Y	Y	Y	N
NVS012	2.99	**2.65**	**1.84**	1.23	Y	N	N	
NVS013		**9.85**	**5.31**		N			
NVS017	1.89	**2.80**	1.84	1.27	N	N	N	
RSP002	**5.23**	**2.89**	**1.98**	0.93	Y	Y	Y	N
RSP008	**3.63**	**3.01**	**2.14**	1.13	Y	Y	Y	N
RSP010	**3.57**	**7.33**	**5.24**	**2.93**	Y	Y	Y	N
RSP012		**7.44**	**4.15**		Y	Y	Y	Y
RSP014		**12.80**	**6.91**		N	Y	Y	
RSP016	**3.56**	**2.69**	**1.86**	1.10	Y	Y	Y	N
SYM001	**2.54**	**2.46**	**1.79**	1.29	N	Y	Y	N
SYM002		**3.34**	**2.01**		Y	Y	Y	N
SYM010	**2.07**	**2.51**	**1.98**	**1.62**	Y	Y	Y	N
SYM013	1.95	**2.11**	**1.73**	1.45	Y	Y	N	N
SYM014	3.34	**2.66**	1.67	1.12	N	N	N	
SYM016	**8.23**	**7.38**	**3.72**	**1.35**	Y	Y	Y	Y
SYM017	**3.29**	**3.60**	**2.22**	1.26	Y	Y	Y	N

HR* refers to the hazard ratio (HR) of infection on the corresponding sequelae, obtained from the corresponding cohort (note that the HR refers to any hospitalizations as the outcome, without PTDM adjustment); HR with FDR-adjusted $p < 0.05$ are in bold.

PERR, prior event rate ratio adjustment; 15 or 30 days after: the association analyses were restricted to events that occurred 15 or 30 days *after* the first date of being tested positive for COVID-19 infection. "Sig larger in pre vaccination": whether the HR is significantly larger in the pre-vaccination era, with FDR-adjusted $p < 0.1$. For the last three columns, "Y" denotes whether the selected outcome showed significant results (FDR-adjusted $p < 0.05$) under the corresponding analysis, for at least one of the cohorts (A to D).

For each analysis, we require the number of events in both exposed and non-exposed groups (see Table 1) to be ≥ 5 to be included in the above table, hence some cells are empty.
Please refer to Tables 2–4 for the abbreviations of the outcome (coded by CCSR).

Table 8
Significant association of COVID-19 infection and risk of subsequent hospitalization within different time periods.

Cohort	Outcome	Time_period	HR	P-value	p.adj	Lower CI	Upper CI	CCSR Category Description
B	GEN002	~3m	11.470	7.94E-37	5.69E-35	7.866	16.726	Acute and unspecified renal failure
B	GEN002	3m ~ 6m	2.795	1.14E-03	3.03E-03	1.505	5.191	Acute and unspecified renal failure
B	GEN002	6m ~	3.412	1.56E-07	7.49E-07	2.157	5.397	Acute and unspecified renal failure
B	INF002	~3m	6.596	2.01E-28	8.65E-27	4.721	9.215	Septicemia
B	INF002	3m ~ 6m	3.986	1.35E-08	8.39E-08	2.473	6.423	Septicemia
B	INF002	6m ~	2.319	2.60E-04	7.76E-04	1.477	3.641	Septicemia
C	INF002	~3m	3.740	3.65E-16	1.02E-14	2.723	5.136	Septicemia
C	INF002	3m ~ 6m	2.653	5.55E-06	3.63E-05	1.741	4.042	Septicemia
C	INF002	6m ~	1.806	2.62E-03	7.55E-03	1.229	2.653	Septicemia
B	INF003	~3m	6.502	5.36E-35	2.88E-33	4.830	8.753	Bacterial infections
B	INF003	3m ~ 6m	4.215	1.22E-11	1.19E-10	2.781	6.389	Bacterial infections
B	INF003	6m ~	2.084	7.80E-04	2.15E-03	1.358	3.199	Bacterial infections
C	INF003	~3m	3.498	5.56E-18	1.82E-16	2.633	4.647	Bacterial infections
C	INF003	3m ~ 6m	2.817	1.99E-08	1.86E-07	1.962	4.045	Bacterial infections
C	INF003	6m ~	1.701	3.21E-03	9.12E-03	1.195	2.422	Bacterial infections
C	MUS010	~3m	1.961	4.41E-04	1.68E-03	1.347	2.854	Musculoskeletal pain, not low back pain
C	MUS010	3m ~ 6m	3.992	6.60E-15	1.44E-13	2.818	5.655	Musculoskeletal pain, not low back pain
C	MUS010	6m ~	1.619	5.61E-03	1.46E-02	1.151	2.278	Musculoskeletal pain, not low back pain
A	RSP002	~3m	7.826	4.69E-11	1.31E-09	4.240	14.443	Pneumonia (except that caused by tuberculosis)
A	RSP002	3m ~ 6m	4.428	3.25E-04	1.82E-03	1.967	9.968	Pneumonia (except that caused by tuberculosis)
A	RSP002	6m ~	3.054	2.35E-03	8.97E-03	1.487	6.268	Pneumonia (except that caused by tuberculosis)
B	RSP002	~3m	3.507	6.04E-21	1.30E-19	2.699	4.557	Pneumonia (except that caused by tuberculosis)
B	RSP002	3m ~ 6m	3.158	8.19E-08	4.10E-07	2.074	4.808	Pneumonia (except that caused by tuberculosis)
B	RSP002	6m ~	1.992	2.96E-04	8.72E-04	1.372	2.894	Pneumonia (except that caused by tuberculosis)
C	RSP002	~3m	2.205	1.15E-10	1.41E-09	1.734	2.805	Pneumonia (except that caused by tuberculosis)
C	RSP002	3m ~ 6m	2.192	2.98E-05	1.72E-04	1.516	3.168	Pneumonia (except that caused by tuberculosis)
C	RSP002	6m ~	1.572	5.73E-03	1.46E-02	1.140	2.166	Pneumonia (except that caused by tuberculosis)
B	RSP016	~3m	2.819	1.17E-05	4.19E-05	1.774	4.481	Other specified and unspecified lower respiratory disease
B	RSP016	3m ~ 6m	3.696	1.84E-04	5.81E-04	1.863	7.332	Other specified and unspecified lower respiratory disease
B	RSP016	6m ~	2.080	1.76E-02	3.82E-02	1.136	3.808	Other specified and unspecified lower respiratory disease
A	SYM016	~3m	16.162	1.49E-106	1.26E-104	12.603	20.726	Other general signs and symptoms
A	SYM016	3m ~ 6m	3.048	1.36E-06	1.78E-05	1.939	4.790	Other general signs and symptoms
A	SYM016	6m ~	2.254	1.63E-06	1.78E-05	1.617	3.143	Other general signs and symptoms
B	SYM016	~3m	23.425	0.00E+00	0.00E+00	21.031	26.092	Other general signs and symptoms
B	SYM016	3m ~ 6m	2.878	4.82E-12	5.45E-11	2.132	3.883	Other general signs and symptoms
B	SYM016	6m ~	1.762	2.67E-07	1.23E-06	1.420	2.186	Other general signs and symptoms
C	SYM016	~3m	10.232	0.00E+00	0.00E+00	9.242	11.327	Other general signs and symptoms
C	SYM016	3m ~ 6m	1.888	7.18E-08	5.86E-07	1.498	2.379	Other general signs and symptoms
C	SYM016	6m ~	1.292	2.00E-03	6.14E-03	1.098	1.521	Other general signs and symptoms
B	GEN004	~3m	5.196	2.43E-27	8.70E-26	3.857	7.002	Urinary tract infections
B	GEN004	3m ~ 6m	2.605	2.25E-04	6.92E-04	1.566	4.332	Urinary tract infections
B	GEN004	6m ~	2.140	8.91E-05	2.99E-04	1.463	3.131	Urinary tract infections
C	GEN004	~3m	2.660	2.19E-11	2.87E-10	1.997	3.542	Urinary tract infections
C	GEN004	3m ~ 6m	1.939	1.70E-03	5.65E-03	1.282	2.931	Urinary tract infections
C	GEN004	6m ~	1.801	1.76E-04	8.00E-04	1.325	2.449	Urinary tract infections
B	RSP010	~3m	10.966	8.72E-19	1.70E-17	6.452	18.636	Aspiration pneumonitis
B	RSP010	3m ~ 6m	7.877	3.76E-07	1.69E-06	3.553	17.463	Aspiration pneumonitis
B	RSP010	6m ~	4.797	1.57E-07	7.49E-07	2.670	8.618	Aspiration pneumonitis
C	RSP010	~3m	6.871	2.80E-14	5.50E-13	4.182	11.290	Aspiration pneumonitis
C	RSP010	3m ~ 6m	5.941	3.10E-07	2.33E-06	3.002	11.756	Aspiration pneumonitis
C	RSP010	6m ~	3.939	3.31E-08	2.82E-07	2.422	6.406	Aspiration pneumonitis
D	RSP010	~3m	25.902	3.53E-16	5.47E-15	11.847	56.634	Aspiration pneumonitis
D	RSP010	3m ~ 6m	5.083	7.75E-05	3.43E-04	2.270	11.386	Aspiration pneumonitis
D	RSP010	6m ~	3.050	1.85E-04	6.38E-04	1.700	5.473	Aspiration pneumonitis
C	MUS006	~3m	0.512	1.98E-03	6.14E-03	0.335	0.782	Osteoarthritis
C	MUS006	3m ~ 6m	10.691	1.57E-38	1.54E-36	7.476	15.290	Osteoarthritis
C	MUS006	6m ~	1.669	6.18E-05	3.19E-04	1.299	2.144	Osteoarthritis

Notes: HR, hazard ratio (with adjustment for covariates); p.adj, FDR-adjusted p-value; Lower and upper CI represent the lower and upper 95 % confidence interval of HR. "~3 m" represents the results from stratified analysis considering outcomes within 3 months of infection; "3m ~ 6m" represents results considering outcomes from 3 to 6 months after infection; "6m ~" represents results considering outcomes from 6 months post-infection until the end of follow-up.
The time-split analysis outcomes were selected based on 1): the number of events in both cases and controls is ≥ 5 across all time periods; 2): significant FDR-adjusted p-value (p.adj <0.05) across *all* time periods with consistent directions of effect.

Secondly, some disorders may be too rare to be included for further analysis. Additionally, due to the relatively small number of events for some disorders, absence of significant associations can also be due to inadequate statistical power.

The PTDM and PERR methods also have limitations: PTDM may reduce observed events in the unexposed group, causing a loss of statistical power. PERR also may lead to less precise effect size estimates. Please refer to Supplementary Text for further discussions.

Besides, variant information is not known, although we expect the Alpha/Delta variants are likely the predominant variants during the

study period. Due to limitations of data access at the time of analysis, the sequelae from later viral variants were not analysed. However, it was hypothesized that the associations of COVID-19 with various sequelae might extend to Omicron or other emerging variants, based on existing evidence.[31–35]

4.4. Clinical implications

Our findings may have important clinical implications. Given the large number of infections globally, the overall burden and disabilities from hospitalizations related to COVID-19 could be substantial. Patients recovering from COVID-19, particularly severe cases, may therefore require appropriate follow-up, monitoring, and risk assessment for potential complications. Notably, we also observed that the risk of COVID-19 sequelae is generally elevated in the pre-vaccination period. This observation suggests that COVID-19 vaccination may partially ameliorate the burden of these sequelae.

Public health policies should focus on addressing the post-infection impact of COVID-19 by allocating resources for prevention and treatment of relevant complications, as well as increasing public awareness. Further studies are needed to replicate these findings and investigate the underlying mechanisms of sequelae, as well as strategies for prevention and treatment.

CRediT authorship contribution statement

Yong Xiang: Writing – review & editing, Writing – original draft, Validation, Software, Resources, Methodology, Formal analysis. **Ruoyu Zhang:** Writing – review & editing, Visualization, Validation, Software, Formal analysis. **Jinghong Qiu:** Writing – review & editing, Visualization, Validation, Formal analysis. **Hon-Cheong So:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Funding acquisition, Data curation, Conceptualization.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2025.02.001.

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