Rates of serious clinical outcomes in survivors of hospitalisation with COVID-19: a descriptive cohort study within the OpenSAFELY platform

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Abstract

Background

Patients with COVID-19 are thought to be at higher risk of cardiometabolic and pulmonary complications, but quantification of that risk is limited. We aimed to describe the overall burden of these complications in survivors of severe COVID-19.

Methods

Working on behalf of NHS England we used data from the OpenSAFELY platform linking primary care records to death certificate and hospital data. We constructed two cohorts: a COVID-19 cohort consisting of patients discharged following hospitalisation with COVID-19, and a comparison population of patients discharged following hospitalisation with pneumonia in 2019. Outcomes included DVT, PE, ischaemic stroke, MI, heart failure, AKI and new type 2 diabetes diagnosis. Outcome rates from hospital discharge were measured in each cohort, stratified by patient demographics and 30-day period. We fitted Cox regression models to estimate crude and age/sex adjusted hazard ratios comparing outcome rates between the two cohorts.

Results

Amongst the population of 31,569 patients discharged following hospitalisation with COVID-19, the highest rates were observed for heart failure (199.3; 95% CI: 191.8 - 207.1) and AKI (154.5; 95% CI: 147.9 - 161.4). Rates of DVT, heart failure, ischaemic stroke, MI, PE and diabetes were high over the four months post discharge, especially in the first month. Patterns were broadly similar to those seen in patients discharged with pneumonia but somewhat higher in the COVID-19 population for stroke (adj-HR 1.78; 95% CI: 1.53 - 2.08), PE (adj-HR 1.38; 95% CI: 1.21 - 1.58), MI (adj-HR 1.46; 95% CI: 1.20 - 1.76), AKI (adj-HR 1.27; 95% CI: 1.19 - 1.36) and T2DM (adj-HR 1.28; 95% CI: 1.08 - 1.50).

Conclusions

In this descriptive study of survivors of severe COVID-19, rates of the measured outcomes are at least as high, though in some cases slightly higher, than in patients discharged after hospitalisation with pneumonia. Further work is needed to identify what characteristics of COVID-19 patients put them at highest risk of adverse events.

Introduction

Cardiometabolic and pulmonary complications, especially thrombotic events, have been described as a key feature of the severe acute phase of COVID-19. A recent systematic review estimated the risk of venous thromboembolism (VTE) to be ~15% in hospitalised COVID-19 patients, with higher risks observed in people admitted to intensive care (~30%[1–3]). Underlying reasons for this increased risk are likely to be multifactorial, including immobility following illness/hospitalisation as well as the known association with infection in general, mediated through interactions with general inflammatory and other immune pathways[4]. The possibility that SARS-CoV-2 may directly trigger pulmonary thrombi via vascular damage and inflammatory effects in the lung has also been raised[5].

As the COVID-19 pandemic has progressed, it is increasingly reported that some patients who recover from the acute disease phase go on to experience a range of post-recovery clinical problems. This post-acute COVID-19 syndrome is currently not well described or understood, with the UK National Institute for Health and Care Excellence stating that any body system could be affected, for an undetermined period of time[6]. Any such syndrome now needs to be defined and quantified so that patients and health services can know what outcomes may be expected, and plan accordingly[6,7]. It is also unclear whether COVID-19 is exceptional in its association with cardiometabolic events, or comparable to other respiratory pathogens.

Work to date on cardiometabolic outcomes with COVID-19 has largely focused on risks during hospitalisation, with a lack of evidence on how these risks evolve in survivors of severe COVID-19. We therefore measured the rates of cardiometabolic outcomes in people in England with COVID-19, focusing on those who were discharged from hospital following the acute phase of COVID-19. For context, we compared these rates with those seen amongst people discharged following hospitalization for non-COVID-19 pneumonia prior to the pandemic.

Methods

Study design and data sources

We conducted an observational cohort study using electronic health record (EHR) data from primary care practices using The Phoenix Partnership (TPP) software linked to Office for National Statistics (ONS) death registrations and Secondary Uses Service (SUS) data (containing hospital records) through OpenSAFELY. This is a data analysis platform developed during the COVID-19 pandemic, on behalf of NHS England, to allow near real-time analysis of pseudonymised primary care records at scale, covering approximately 40% of the population in England, operating within the EHR vendor's highly secure data centre.[8,9] Details on Information Governance for the OpenSAFELY platform can be found in the Appendix.

Population

We included all adults aged ≥18 years registered with a general practice for ≥1 year on the index date with information on age, sex, and socioeconomic deprivation. From this source population we selected two cohorts: all patients hospitalised with COVID-19 in 2020, and a comparison cohort containing all patients hospitalised with non-COVID pneumonia across the equivalent period in 2019. The COVID-19 and pneumonia cohorts were selected as anyone hospitalised with an associated diagnostic code for COVID-19 or pneumonia respectively (referred to as the "index hospitalisation").

Outcomes and follow-up

We measured eight outcomes: deep vein thrombosis (DVT), pulmonary embolism (PE), ischaemic stroke, myocardial infarction (MI), heart failure, acute kidney injury (AKI) and new type 2 diabetes diagnosis.

The study periods ran between 1st February and 1st November in either 2019 or 2020, depending on the population (as defined above). The follow-up period began on the discharge date of the index COVID-19 or pneumonia hospital stay. For each analysis, follow-up ended on the earliest of: the first recorded outcome event, the study end date, or the date of death of the patient. For the AKI outcome, we excluded patients who were receiving dialysis before the index date (defined as presence of a dialysis code or eGFR < 15ml/min). For diabetes, we excluded any patients who had a previous diabetes event, to ensure only incident diagnoses were measured.

Outcomes were defined primarily as the presence of a diagnostic code for each of the respective outcomes, either in the general practice record, in hospital, or as a cause of death on a death certificate. For AKI, the outcome was restricted just to events recorded in hospital or on the death certificate. For the primary analysis, we excluded use of a GP record if the patient had a recent outcome recorded within three months before the index date (including if they had been recorded during the index hospitalisation). This was to prevent double counting of the same

event, for example where a GP updates the record of a patient, recording an event that occurred during a recent hospitalisation.

Statistical Methods

We described the demographics of patients discharged from an admission with COVID-19 and pneumonia.

Rates were reported for each outcome, per 10,000 person months, initially for the whole follow-up time, then stratified into time windows: 0-29 days, 30-59 days, 60-89 days, 90-120 days and 120+ days post discharge, to determine how the rate of outcomes changed over time. Rates were also stratified by age, sex and ethnicity.

We used Cox regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) to compare the rates of each outcome between the hospitalised COVID-19 group and the hospitalised pneumonia group. We investigated crude univariable and age and sex adjusted models. The same patient can contribute person-time to both exposure groups, however these periods are non-overlapping. Theoretically this will lead to narrower confidence intervals, therefore we applied robust standard errors.

In sensitivity analyses we tested the effect of including a) previously omitted outcomes recorded in the primary care record when there was a recorded outcome within 3 months before the index date, and b) only events recorded in hospital or as a cause of death on a death certificate.

Software and reproducibility

Data management was performed using the OpenSAFELY software, Python 3.8 and SQL, and analysis using Stata 16.1. All codelists alongside code for data management and analyses can be found at: https://github.com/opensafely/post-covid-thrombosis-research. All software for the OpenSAFELY platform is available for review and re-use at https://github.com/opensafely.

Results

We identified 31,569 patients discharged following an admission with COVID-19 and 68,303 patients discharged with pneumonia in 2019. Demographics for the cohorts studied are summarised in Table 1. Compared to the COVID-19 cohort, the pneumonia cohort had a higher proportion aged over 70. The ethnic breakdown was broadly similar between the two groups, COVID-19 patients had a higher proportion of patients who are Asian and Asian British.

Overall rates of each outcome per 10,000 person months for the whole follow-up are presented in Table 2. For the majority of outcomes we observed higher rates of serious cardiometabolic and pulmonary complications in discharged COVID-19 patients compared to discharged pneumonia patients (Table 2, Figure 1). For both cohorts, the largest absolute rates were for AKI and heart failure. Overall rates stratified by age, sex and ethnicity are present in the appendix (Tables A5-A12). For COVID-19 patients, rates of stroke, heart failure MI and AKI were consistently higher amongst the over 80s, although the pattern of results was not consistent across other ages groups. Similarly, rates were not constant by ethnic group, for example, the rate of new T2DM diagnoses were slightly higher amongst black patients discharged following an admission with COVID-19.

Stratified overall rates in 30-day time windows are shown in Figure 1. For discharged COVID-19 patients we observed the highest rates for all outcomes in the first 30 days post-discharge, with a gradual decline in subsequent periods. This was remarkably consistent with the pattern of rates observed for patients discharged with pneumonia in 2019. For both cohorts, we observed pronounced rates of AKI and heart failure in the first 30 days post-discharge (Figure 1).

Cox regression models were used to estimate HRs comparing the hazards of each outcome between the discharged COVID-19 and pneumonia groups (Table 3, Figure 2). After age and sex adjustment, we observed an increased risk in the majority of outcomes for discharged COVID-19 patients compared to discharged pneumonia patients. We observed modest increases in risks for stroke (HR 1.78; 95% CI: 1.53 - 2.08), PE (HR 1.38; 95% CI: 1.21 - 1.58), MI (HR 1.46; 95% CI: 1.20 - 1.76), AKI (HR 1.27; 95% CI: 1.19 - 1.36) and T2DM (HR 1.28; 95% CI: 1.08 - 1.50).

Results from a sensitivity analysis investigating robustness of absolute and relative rates to outcome definition are presented in the Appendix. Change in outcome definitions did not meaningfully alter conclusions.

Table 1: Patient demographics amongst patients discharged with COVID-19 in 2020 and all patients discharged with non-COVID pneumonia in 2019

Demographic (%)	Discharged Pneumonia (2019)	Discharged COVID-19
Total	68,303	31,569
Age		
18 - 49	8,277 (12.1)	6,427 (20.4)
50 - 59	7,153 (10.5)	4,910 (15.6)
60 - 69	11,190 (16.4)	5,208 (16.5)
70 -79	17,818 (26.1)	6,347 (20.1)
80 +	23,865 (34.9)	8,677 (27.5)
Sex		
Male	34,485 (50.5)	14,944 (47.3)
Female	33,818 (49.5)	16,625 (52.7)
Ethnicity		
White	45,647 (66.8)	19,353 (62.1)
Mixed	273 (0.4)	306 (1.0)
Asian /Asian British	2,670 (3.9)	3,285 (10.4)
Black	687 (1.0)	1,040 (3.3)
Other	429 (0.6)	521 (1.6)
Unknown	18,597 (27.2)	7,073 (22.4)

Table 2: Overall rates of outcomes amongst patients discharged with COVID-19 in 2020 and all patients discharged with non-COVID pneumonia in 2019

Outcome	Analysis Group	Person Time (per 10,000 person months)	Number of events	Rate (95% CI)
Stroke	Discharged COVID-19	13.7	535	39.1 (35.9-42.6)
	Discharged Pneumonia	31.4	634	20.2 (18.7-21.8)
DVT	Discharged COVID-19	13.7	256	18.7 (16.5-21.1)
	Discharged Pneumonia	31.4	530	16.9 (15.5-18.4)
PE	Discharged COVID-19	13.6	515	37.8 (34.7-41.2)
	Discharged Pneumonia	31.3	793	25.3 (23.6-27.1)
Heart Failure	Discharged COVID-19	13.1	2607	199.3 (191.8-207.1)
	Discharged Pneumonia	29.2	6958	238.7 (233.1-244.3)
MI	Discharged COVID-19	13.7	294	21.4 (19.1-24.0)
	Discharged Pneumonia	31.4	534	17.0 (15.6-18.5)
AKI	Discharged COVID-19	13	2012	154.5 (147.9-161.4)
	Discharged Pneumonia	29.8	3933	131.8 (127.7-136.0)
T2DM	Discharged COVID-19	9.3	291	31.2 (27.8-35.0)
	Discharged Pneumonia	22.3	627	28.1 (26.0-30.4)

Table 3: Estimated hazard ratios from univariable and age and sex adjusted Cox regression models comparing the risk of outcomes in patients who were discharged with COVID-19 patients compared to patients who had pneumonia in 2019

Outcome	Discharged COVID-19 Person Time	Discharged COVID-19 Number of events	Discharged Pneumonia Person Time	Discharged Pneumonia Number of events	Crude HR (95% CI)	Age/Sex adjusted HR (95% CI)
Stroke	13.7	535	31.4	634	1.92 (1.71-2.15)	1.78 (1.53-2.08)
DVT	13.7	256	31.4	530	1.10 (0.95-1.28)	1.06 (0.88-1.28)
PE	13.6	515	31.3	793	1.50 (1.34-1.68)	1.38 (1.21-1.58)
Heart failure	13.1	2607	29.2	6958	0.84 (0.81-0.88)	0.98 (0.93-1.05)
MI	13.7	294	31.4	534	1.26 (1.09-1.46)	1.46 (1.20-1.76)
AKI	13	2012	29.8	3933	1.17 (1.11-1.24)	1.27 (1.19-1.36)
T2DM	9.3	291	22.3	627	1.13 (0.98-1.30)	1.28 (1.08-1.50)

Figure 1: Rate of outcomes (events per 10,000 person months) in time periods following hospital discharge for COVID-19/pneumonia.

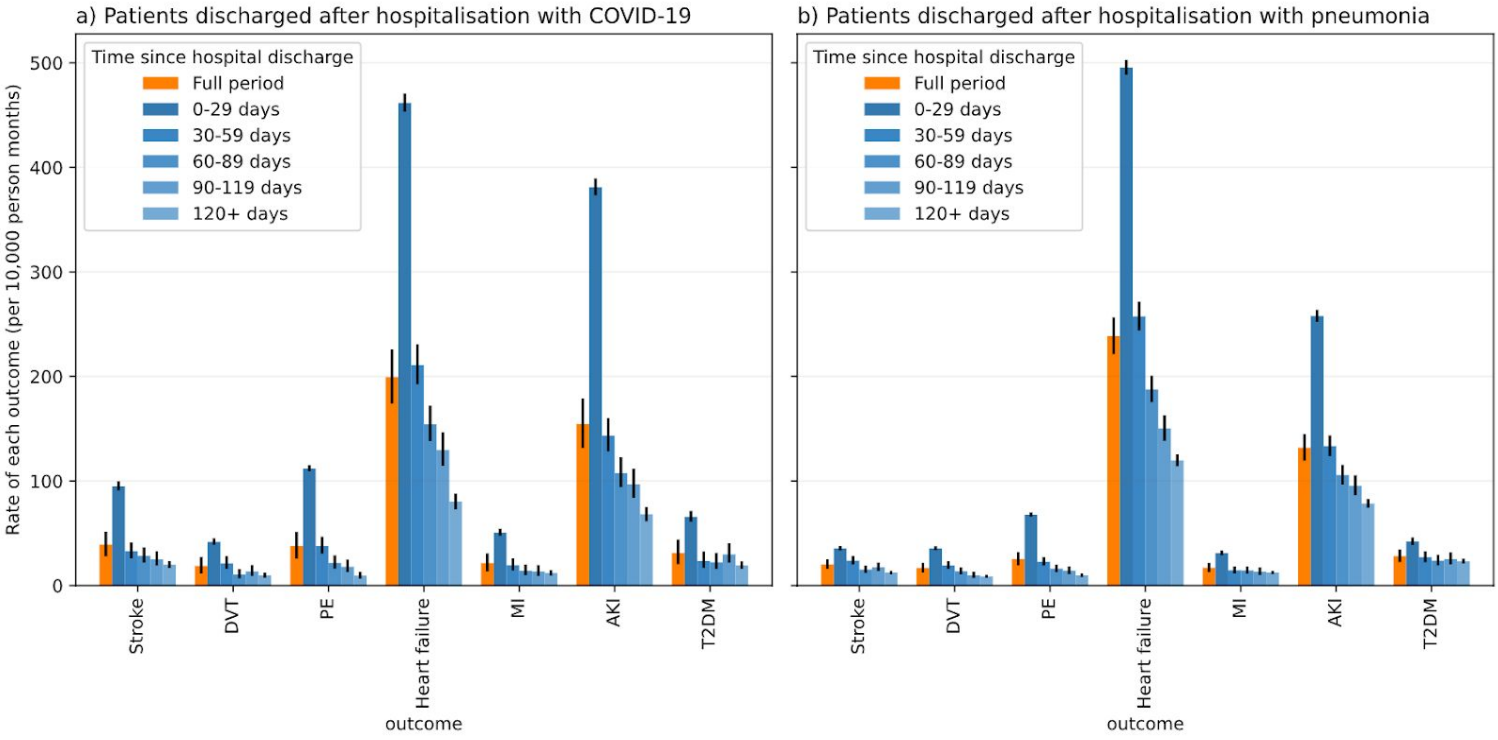
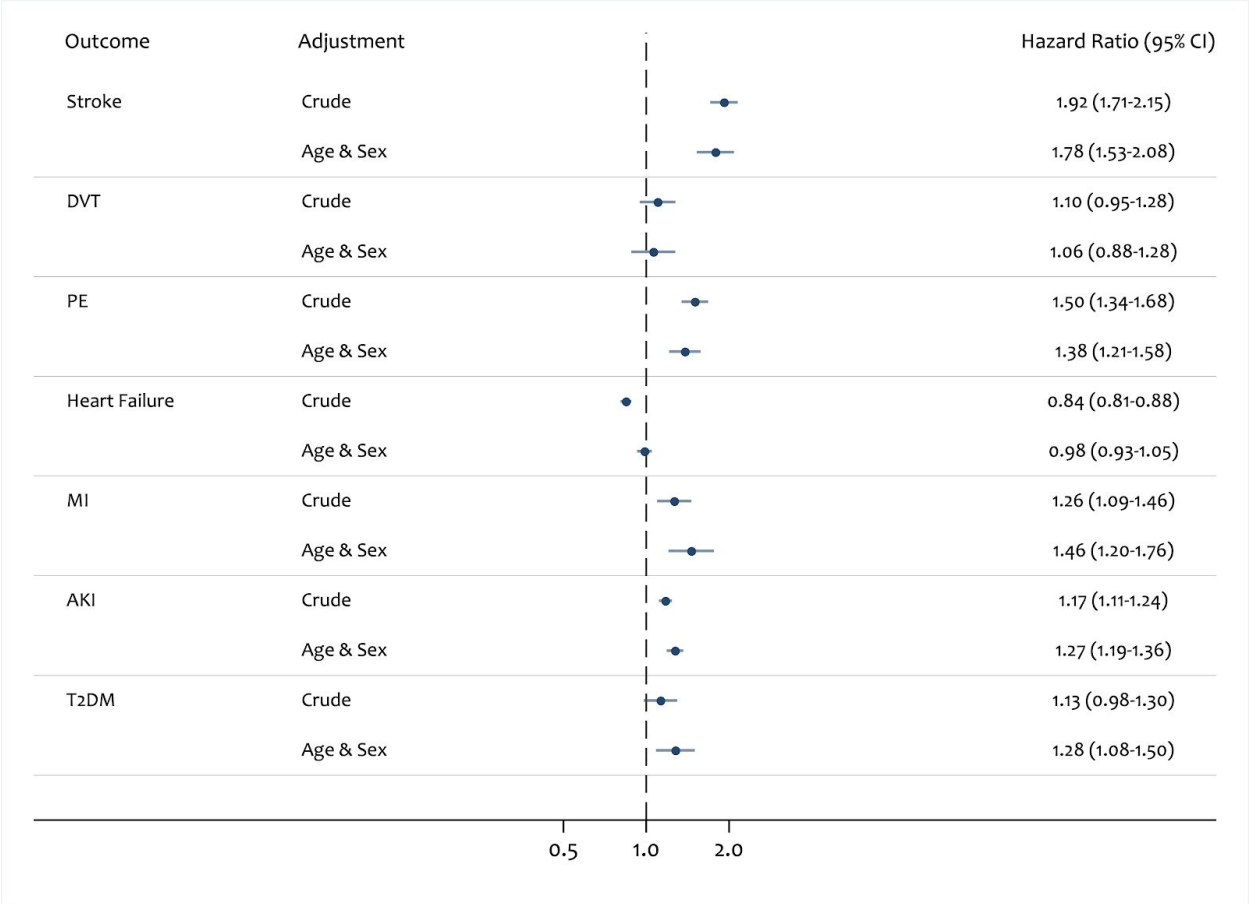


Figure 2: Hazard ratios for risk of outcomes in patients who were hospitalised with COVID-19 and then discharged, compared to patients who were hospitalised with pneumonia in 2019 and then discharged.



Discussion

Key findings

In this descriptive study, we set out to report the overall rates of outcomes in each of the cohorts, regardless of their cause. We found that the rate of cardiometabolic and pulmonary complications following discharge from hospitalisation with COVID-19 followed a broadly similar pattern of elevated rates to those discharged from hospital after pneumonia in 2019. Some outcomes, such as stroke, PE, AKI and T2DM showed a modestly higher rate in discharged COVID-19 patients than discharged pneumonia patients, while the other outcomes we measured were not measurably different. The pattern of change in the rate of outcomes over time following discharge from hospital was also broadly similar between the COVID-19 and pneumonia patients, with a high rate in the initial 30 days of follow-up, then a 2-3 fold drop in the next 30 days, followed by a more gradual decline. In both cohorts discharged after hospitalisation, rates remained substantial even after more than 120 days.

Strengths and limitations

We were able to source our cohorts from the OpenSAFELY platform, which contains over 17m adults. This gave us a population of patients who were discharged following hospitalisation with COVID-19 of 31,569, allowing us to obtain precise estimates of the rate of each outcome. We were also able to draw on multiple linked data sources, including primary care records, hospitalisations and death certificates. This allows a more complete picture to be presented of the clinical activity surrounding each outcome.

We believe that our use of an active control population of patients hospitalised with pneumonia in 2019 provides useful context for the rates of these outcomes in COVID-19 patients who survive hospitalisation. A comparison cohort could also have been attained by matching patients from the general population on various attributes such as age, sex and comorbidities. However, such a cohort would be lacking the exposure of an acute respiratory illness event requiring hospitalisation. We think presenting the rates in this context is more informative than within a general population.

We note that our study aimed to describe clinical events that occurred *after* discharge from hospital, and therefore may not reflect the true additional morbidity burden of COVID-19 hospitalisation: specifically we did not set out to describe events that occurred *during* hospital admission with COVID-19 or pneumonia. However, in our view reliable analysis of in-hospital events may only be achievable with bespoke collections of detailed hospital data, due to shortcomings in routinely collected administrative data that are widely used for such analyses. For example, SUS and HES data contain a list of diagnostic codes associated with each hospitalisation, but they do not contain sufficient information to determine the exact timing of all events within each hospitalisation episode. This means that time-to event analyses are not possible. Furthermore it is not possible in SUS or HES to reliably determine the sequence of events during the hospitalisation: so a patient hospitalised with COVID-19, who later had a stroke, may be coded in a similar way to a patient who was hospitalised with a stroke, and then infected with SARS-CoV-2 while in hospital. In addition, routine PCR testing on hospitalised

patients during the pandemic may lead to very high ascertainment of infection with SARS-CoV-2, which may not have occurred to the same extent in the comparison population for pneumonia admissions.

We did not attempt to determine here whether any observed differences were due to a particular feature of the pathophysiology associated with SARS-CoV-2 infection, or whether other factors might have had a greater influence, such as competing risk of death, pre-existing patient comorbidities, changes in healthcare provision during the pandemic or differing likelihood of ascertainment of pre-existing conditions. In the context of the rapidly changing pandemic, we aimed to provide an overview of the rates of outcomes after discharge from hospitalisation with COVID-19, compared with pneumonia, to inform health services.

It has been reported that there was a marked reduction in hospital activity during the first wave of the pandemic, for example a 40% reduction in admissions for acute coronary syndrome[10]. This may be in part explained by a reluctance of patients to present at hospitals for fear of contracting the virus. As a result, we believe population-level rates of many outcomes will be under-ascertained during 2020 compared with 2019. It is unknown whether this applies in the same way to patients who have already had severe COVID-19; if ascertainment is lower, then this would result in a possible under-estimate of outcome events associated with COVID-19 in our study.

Findings in context

A recent observational study measured similar outcome events in a population of patients discharged from hospital following COVID-19[11]. They observed elevated rates in the COVID-19 population compared to a matched general population control group. Our findings are consistent in showing high increased rates of outcomes in patients post-discharge with COVID-19. However, importantly we show that these increased rates of outcomes are broadly comparable, if not slightly lower, in people discharged from hospital following pneumonia, selected as a major non-COVID respiratory infection.

The impact of the post COVID-19 hospitalisation events described in this study upon the NHS in England is substantial. Though the absolute number of events is lower than in the post pneumonia hospitalisation cohort, it is likely that the COVID-19 related events will continue to make up a substantial proportion of the total hospitalisations for these conditions for some time. Future work will also investigate any association between non-hospitalised SARS-CoV-2 infection and these outcomes, and quantify any likely population level impact.

Summary

The rate of cardiometabolic and pulmonary events in COVID-19 survivors discharged from hospitalisation was elevated in a similar manner to patients discharged from hospitalisation with pre-pandemic pneumonia, with some outcomes observed to have a slightly higher rate in the COVID-19 survivors population. Next steps include seeing whether patients at highest risk of post-covid outcomes can be identified and determining whether higher risk groups could be early targeted for possible preventative action.

Acknowledgements

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Conflicts of interest

BG has received research funding from the Laura and John Arnold Foundation, the Wellcome Trust, the NIHR Oxford Biomedical Research Centre, the NHS National Institute for Health Research School of Primary Care Research, the Mohn-Westlake Foundation, Health Data Research UK (HDR-UK), the Good Thinking Foundation, the Health Foundation, and the World Health Organisation; he also receives personal income from speaking and writing for lay audiences on the misuse of science. IJD has received unrestricted research grants and holds shares in GlaxoSmithKline (GSK).

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Funders had no role in the study design, collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Data Sharing

All data were linked, stored and analysed securely within the OpenSAFELY platform (https://opensafely.org/). Detailed pseudonymized patient data are potentially re-identifiable and therefore not shared. We rapidly delivered the OpenSAFELY data analysis platform without prior funding to deliver timely analyses of urgent research questions in the context of the global COVID-19 health emergency: now that the platform is established, we are developing a formal process for external users to request access in collaboration with NHS England. Details of this process will be published in due course on the OpenSAFELY website.

Ethical Approval

This study was approved by the Health Research Authority (REC 20/LO/0651) and by the LSHTM Ethics Board (#21863).

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Appendix

Sensitivity analyses

Figure A1: As Figure 1 but including all GP outcomes rather than censoring if the patient had an outcome within the 3 months before index date. AKI and diabetes are unchanged from figure 1.

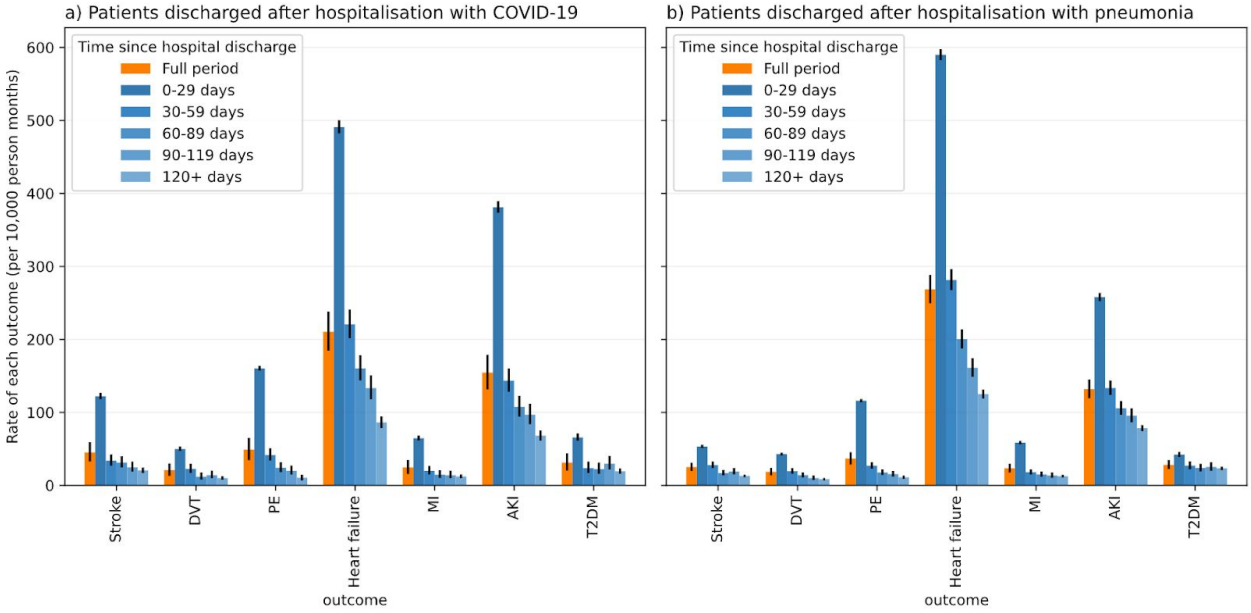

Figure A2: As Figure 1, but without using GP as an outcome (only hospitalisations and death certificate records). AKI and diabetes are unchanged from figure 1.

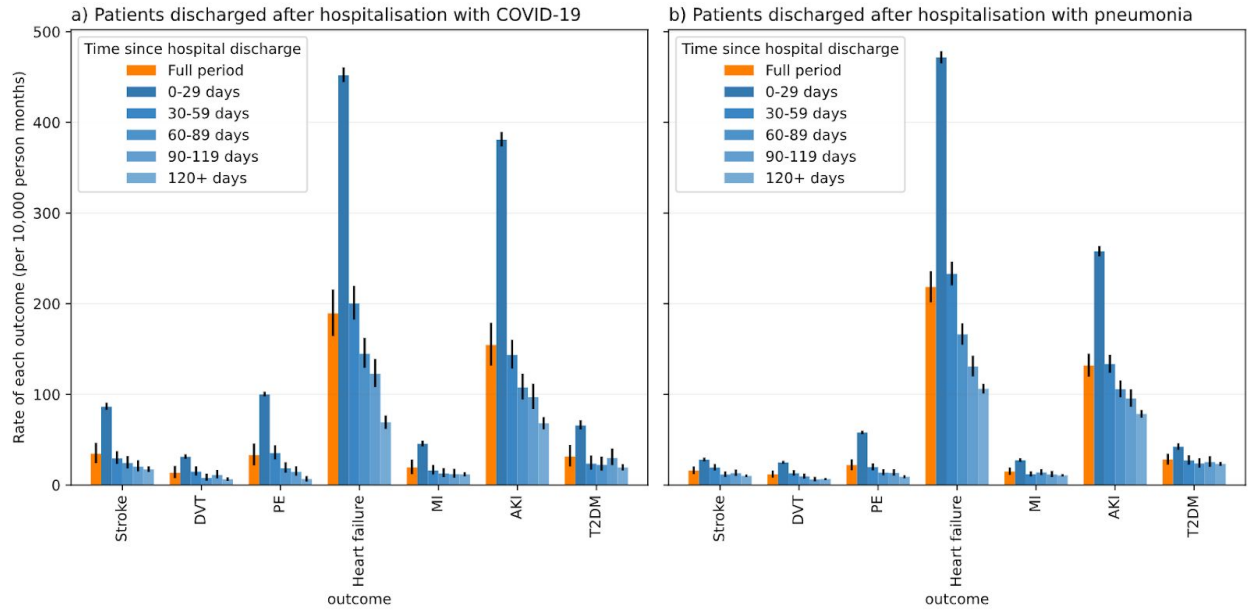

Figure A3: As Figure 2, but outcomes recorded in GP records are not censored if the patient had an outcome within the 3 months before index date.

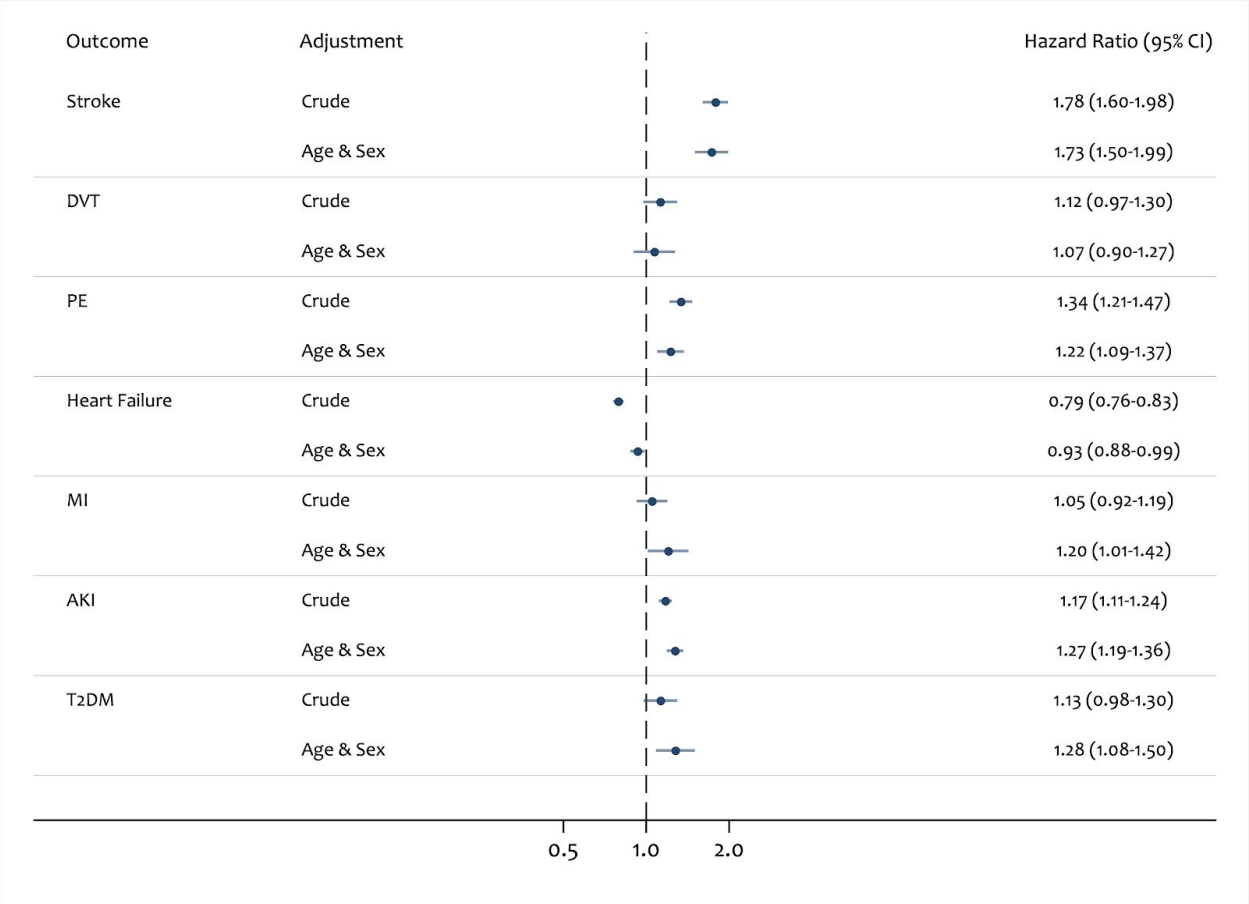

Figure A4: As Figure 2, but without using GP as an outcome (only hospitalisations and death certificate records).

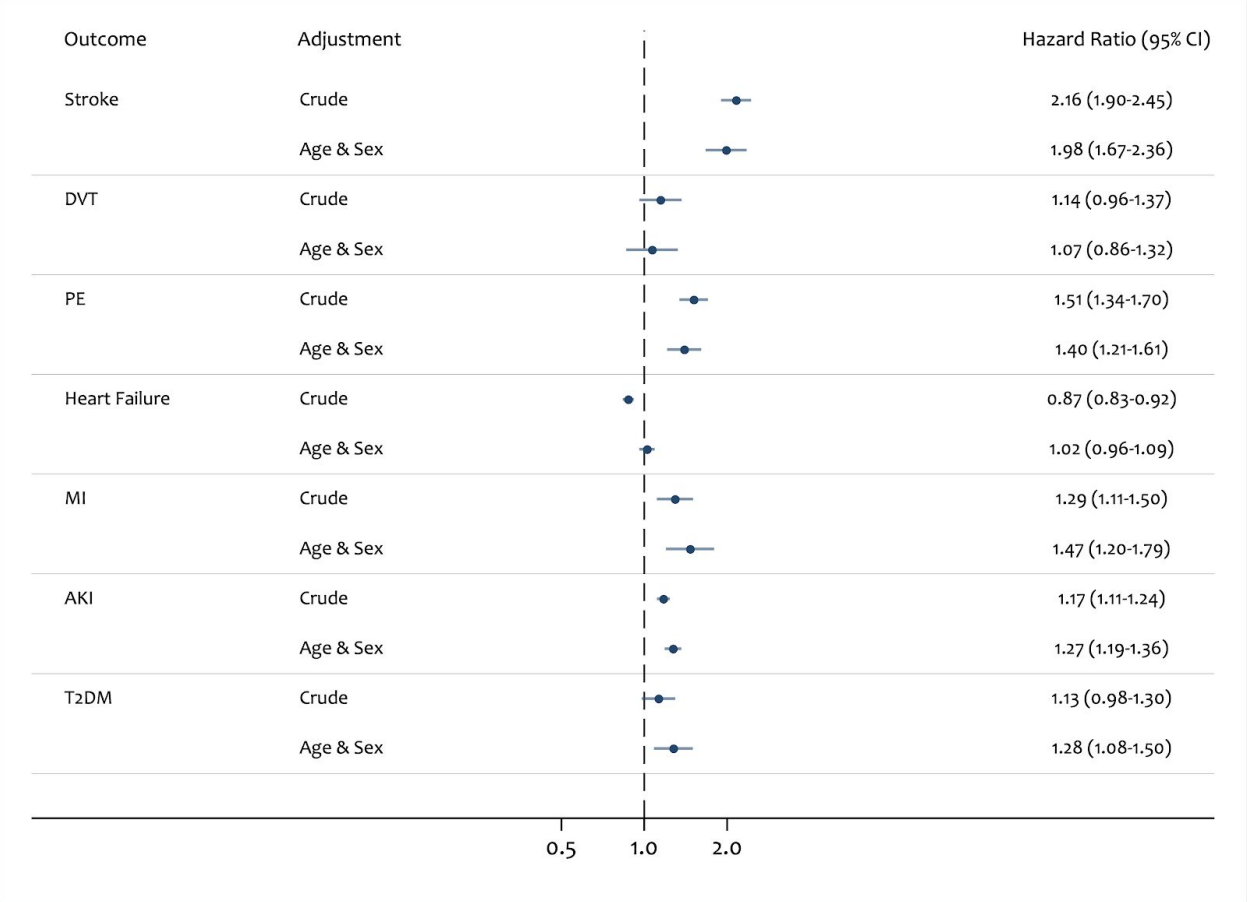

Table A1: As Table 2, but outcomes recorded in GP records are not censored if the patient had an outcome within the 3 months before index date.

Outcome	Analysis Group	Person Time (per 10,000 person months)	Number of events	Rate (95% CI)
Stroke	Discharged COVID-19	13.6	617	45.2 (41.8-48.9)
	Discharged Pneumonia	31.3	787	25.1 (23.4-26.9)
DVT	Discharged COVID-19	13.7	286	20.9 (18.6-23.5)
	Discharged Pneumonia	31.4	578	18.4 (17.0-20.0)
PE	Discharged COVID-19	13.6	665	49.1 (45.5-52.9)
	Discharged Pneumonia	31.2	1143	36.7 (34.6-38.8)
Heart Failure	Discharged COVID-19	13	2742	210.4 (202.7-218.4)
	Discharged Pneumonia	28.8	7745	268.6 (262.7-274.6)
MI	Discharged COVID-19	13.7	336	24.5 (22.0-27.3)
	Discharged Pneumonia	31.3	730	23.3 (21.7-25.0)
AKI	Discharged COVID-19	13	2012	154.5 (147.9-161.4)
	Discharged Pneumonia	29.8	3933	131.8 (127.7-136.0)
T2DM	Discharged COVID-19	9.3	291	31.2 (27.8-35.0)
	Discharged Pneumonia	22.3	627	28.1 (26.0-30.4)

Table A2: As Table 2, but without using GP as an outcome (only hospitalisations and death) certificate records.

Outcome	Analysis Group	Person Time (per 10,000 person months)	Number of events	Rate (95% CI)
Stroke	Discharged COVID-19	13.7	473	34.5 (31.5-37.8)
	Discharged Pneumonia	31.4	500	15.9 (14.6-17.4)
DVT	Discharged COVID-19	13.7	186	13.6 (11.7-15.7)
	Discharged Pneumonia	31.5	370	11.8 (10.6-13.0)
PE	Discharged COVID-19	13.6	450	33.0 (30.1-36.2)
	Discharged Pneumonia	31.4	690	22.0 (20.4-23.7)
Heart Failure	Discharged COVID-19	13.1	2482	189.2 (181.9-196.8)
	Discharged Pneumonia	29.3	6408	218.4 (213.2-223.9)
MI	Discharged COVID-19	13.7	265	19.3 (17.1-21.8)
	Discharged Pneumonia	31.5	466	14.8 (13.5-16.2)
AKI	Discharged COVID-19	13	2012	154.5 (147.9-161.4)
	Discharged Pneumonia	29.8	3933	131.8 (127.7-136.0)
T2DM	Discharged COVID-19	9.3	291	31.2 (27.8-35.0)
	Discharged Pneumonia	22.3	627	28.1 (26.0-30.4)

Table A3: As Table 3, but without using GP as an outcome (only hospitalisations and death) certificate records.

Outcome	Discharged COVID-19 Person Time	Discharged COVID-19 Number of events	Discharged Pneumonia Person Time	Discharged Pneumonia Number of events	Crude HR (95% CI)	Age/Sex adjusted HR(95% CI)
Stroke	13.7	473	31.4	500	2.16 (1.90-2.45)	1.98 (1.67-2.36)
DVT	13.7	186	31.5	370	1.14 (0.96-1.37)	1.07 (0.86-1.32)
PE	13.6	450	31.4	690	1.51 (1.34-1.70)	1.40 (1.21-1.61)
Heart Failure	13.1	2482	29.3	6408	0.87 (0.83-0.92)	1.02 (0.96-1.09)
MI	13.7	265	31.5	466	1.29 (1.11-1.50)	1.47 (1.20-1.79)
AKI	13	2012	29.8	3933	1.17 (1.11-1.24)	1.27 (1.19-1.36)
T2DM	9.3	291	22.3	627	1.13 (0.98-1.30)	1.28 (1.08-1.50)

Table A4: As Table 3, but outcomes recorded in GP records are not censored if the patient had an outcome within the 3 months before index date.

Outcome	Discharged COVID-19 Person Time	Discharged COVID-19 Number of events	Discharged Pneumonia Person Time	Discharged Pneumonia Number of events	Crude HR (95% CI)	Age/Sex adjusted HR (95% CI)
Stroke	13.6	617	31.3	787	1.78 (1.60-1.98)	1.73 (1.50-1.99)
DVT	13.7	286	31.4	578	1.12 (0.97-1.30)	1.07 (0.90-1.27)
PE	13.6	665	31.2	1143	1.34 (1.21-1.47)	1.22 (1.09-1.37)
Heart Failure	13	2742	28.8	7745	0.79 (0.76-0.83)	0.93 (0.88-0.99)
MI	13.7	336	31.3	730	1.05 (0.92-1.19)	1.20 (1.01-1.42)
AKI	13	2012	29.8	3933	1.17 (1.11-1.24)	1.27 (1.19-1.36)
T2DM	9.3	291	22.3	627	1.13 (0.98-1.30)	1.28 (1.08-1.50)

Table A5: Rates of stroke amongst patients discharged with COVID-19 in 2020 and all patients discharged with non-COVID pneumonia in 2019 stratified by age, sex and ethnicity.

Variable	Category	Analysis Group	Person Time (per 10,000 person months)	Number of events	Rate (95% CI)
Overall	-	Discharged COVID-19	13.7	535	39.1 (35.9-42.6)
		Discharged Pneumonia	31.4	634	20.2 (18.7-21.8)
Age	18 -49	Discharged COVID-19	2.9	25	8.6 (5.8-12.8)
		Discharged Pneumonia	3.9	40	10.4 (7.6-14.1)
	50-59	Discharged COVID-19	2.3	34	14.6 (10.4-20.4)
		Discharged Pneumonia	3.4	41	12.2 (8.9-16.5)
	60-69	Discharged COVID-19	2.3	68	29.0 (22.9-36.8)
		Discharged Pneumonia	5.2	93	17.8 (14.5-21.8)
	70-79	Discharged COVID-19	2.7	128	47.2 (39.7-56.2)
		Discharged Pneumonia	8.2	184	22.3 (19.3-25.8)
	80+	Discharged COVID-19	3.4	280	82.3 (73.2-92.5)
		Discharged Pneumonia	10.7	276	25.8 (23.0-29.1)
Sex	Female	Discharged COVID-19	6.4	243	37.8 (33.3-42.8)
		Discharged Pneumonia	16	272	17.0 (15.1-19.2)
	Male	Discharged COVID-19	7.2	292	40.3 (35.9-45.2)
		Discharged Pneumonia	15.4	362	23.4 (21.2-26.0)
Ethnicity	White	Discharged COVID-19	8.3	354	42.5 (38.3-47.2)
		Discharged Pneumonia	20.9	417	19.9 (18.1-21.9)
	Mixed	Discharged COVID-19	0.1	<5	20.2 (6.5-62.5)
		Discharged Pneumonia	0.1	<5	39.7 (16.5-95.5)
	Asian/Asian British	Discharged COVID-19	1.4	40	29.5 (21.6-40.2)
		Discharged Pneumonia	1.3	18	14.1 (8.9-22.4)
	Black	Discharged COVID-19	0.5	14	26.7 (15.8-45.2)
		Discharged Pneumonia	0.3	14	44.6 (26.4-75.3)
	Other	Discharged COVID-19	0.3	<5	3.9 (0.5-27.7)
		Discharged Pneumonia	0.2	<5	24.8 (10.3-59.5)
	Unknown	Discharged COVID-19	3.1	123	40.0 (33.5-47.7)
		Discharged Pneumonia	8.5	175	20.5 (17.7-23.8)

Table A6: Rates of DVT amongst patients discharged with COVID-19 in 2020 and all patients discharged with non-COVID pneumonia in 2019 stratified by age, sex and ethnicity.

Variable	Category	Analysis Group	Person Time (per 10,000 person months)	Number of events	Rate (95% CI)
Overall	-	Discharged COVID-19	13.7	256	18.7 (16.5-21.1)
		Discharged Pneumonia	31.4	530	16.9 (15.5-18.4)
Age	18 -49	Discharged COVID-19	2.9	43	14.9 (11.0-20.1)
		Discharged Pneumonia	3.9	77	20.0 (16.0-25.0)
	50-59	Discharged COVID-19	2.3	28	12.0 (8.3-17.4)
		Discharged Pneumonia	3.4	61	18.1 (14.1-23.3)
	60-69	Discharged COVID-19	2.3	43	18.3 (13.6-24.7)
		Discharged Pneumonia	5.2	82	15.7 (12.6-19.5)
	70-79	Discharged COVID-19	2.7	66	24.3 (19.1-31.0)
		Discharged Pneumonia	8.3	122	14.8 (12.4-17.6)
	80+	Discharged COVID-19	3.4	76	22.3 (17.8-27.9)
		Discharged Pneumonia	10.7	188	17.6 (15.2-20.3)
Sex	Female	Discharged COVID-19	6.4	117	18.2 (15.2-21.8)
		Discharged Pneumonia	16	285	17.9 (15.9-20.1)
	Male	Discharged COVID-19	7.3	139	19.2 (16.2-22.6)
		Discharged Pneumonia	15.5	245	15.8 (14.0-18.0)
Ethnicity	White	Discharged COVID-19	8.3	169	20.3 (17.4-23.6)
		Discharged Pneumonia	21	359	17.1 (15.4-19.0)
	Mixed	Discharged COVID-19	0.1	6	40.8 (18.3-90.9)
		Discharged Pneumonia	0.1	<5	7.9 (1.1-55.9)
	Asian/Asian British	Discharged COVID-19	1.4	12	8.8 (5.0-15.5)
		Discharged Pneumonia	1.3	11	8.6 (4.8-15.5)
	Black	Discharged COVID-19	0.5	6	11.5 (5.1-25.5)
		Discharged Pneumonia	0.3	9	28.7 (14.9-55.2)
	Other	Discharged COVID-19	0.3	<5	3.9 (0.5-27.7)
		Discharged Pneumonia	0.2	<5	4.9 (0.7-35.0)
	Unknown	Discharged COVID-19	3.1	62	20.2 (15.7-25.9)
		Discharged Pneumonia	8.5	149	17.4 (14.8-20.5)

Table A7: Rates of PE amongst patients discharged with COVID-19 in 2020 and all patients discharged with non-COVID pneumonia in 2019 stratified by age, sex and ethnicity.

Variable	Category	Analysis Group	Person Time (per 10,000 person months)	Number of events	Rate (95% CI)
Overall	-	Discharged COVID-19	13.6	515	37.8 (34.7-41.2)
		Discharged Pneumonia	31.3	793	25.3 (23.6-27.1)
Age	18 -49	Discharged COVID-19	2.9	71	24.7 (19.5-31.1)
		Discharged Pneumonia	3.8	114	29.7 (24.7-35.7)
	50-59	Discharged COVID-19	2.3	82	35.5 (28.6-44.1)
		Discharged Pneumonia	3.4	89	26.5 (21.6-32.7)
	60-69	Discharged COVID-19	2.3	101	43.4 (35.7-52.8)
		Discharged Pneumonia	5.2	158	30.3 (26.0-35.5)
	70-79	Discharged COVID-19	2.7	117	43.3 (36.1-51.9)
		Discharged Pneumonia	8.2	225	27.4 (24.0-31.2)
	80+	Discharged COVID-19	3.4	144	42.3 (35.9-49.8)
		Discharged Pneumonia	10.7	207	19.3 (16.9-22.2)
Sex	Female	Discharged COVID-19	6.4	227	35.4 (31.1-40.3)
		Discharged Pneumonia	15.9	408	25.7 (23.3-28.3)
	Male	Discharged COVID-19	7.2	288	39.9 (35.6-44.8)
		Discharged Pneumonia	15.4	385	25.0 (22.6-27.6)
Ethnicity	White	Discharged COVID-19	8.3	321	38.7 (34.7-43.2)
		Discharged Pneumonia	20.9	523	25.0 (23.0-27.3)
	Mixed	Discharged COVID-19	0.1	<5	20.3 (6.5-62.8)
		Discharged Pneumonia	0.1	<5	23.8 (7.7-73.7)
	Asian/Asian British	Discharged COVID-19	1.4	47	34.7 (26.1-46.2)
		Discharged Pneumonia	1.3	16	12.5 (7.7-20.4)
	Black	Discharged COVID-19	0.5	19	36.6 (23.4-57.4)
		Discharged Pneumonia	0.3	16	51.6 (31.6-84.2)
	Other	Discharged COVID-19	0.3	8	31.5 (15.8-63.0)
		Discharged Pneumonia	0.2	<5	14.8 (4.8-45.9)
	Unknown	Discharged COVID-19	3.1	117	38.3 (31.9-45.9)
		Discharged Pneumonia	8.5	232	27.3 (24.0-31.0)

Table A8: Rates of heart failure amongst patients discharged with COVID-19 in 2020 and all patients discharged with non-COVID pneumonia in 2019 stratified by age, sex and ethnicity.

Variable	Category	Analysis Group	Person Time (per 10,000 person months)	Number of events	Rate (95% CI)
Overall	-	Discharged COVID-19	13.1	2607	199.3 (191.8-207.1)
		Discharged Pneumonia	29.2	6958	238.7 (233.1-244.3)
Age	18 -49	Discharged COVID-19	2.9	75	26.0 (20.7-32.6)
		Discharged Pneumonia	3.8	187	49.0 (42.5-56.6)
	50-59	Discharged COVID-19	2.3	146	63.6 (54.1-74.8)
		Discharged Pneumonia	3.3	322	98.6 (88.4-110.0)
	60-69	Discharged COVID-19	2.3	317	140.1 (125.5-156.4)
		Discharged Pneumonia	4.9	911	184.2 (172.6-196.5)
	70-79	Discharged COVID-19	2.5	694	273.4 (253.8-294.5)
		Discharged Pneumonia	7.6	2031	267.9 (256.5-279.8)
	80+	Discharged COVID-19	3.1	1375	443.4 (420.5-467.4)
		Discharged Pneumonia	9.5	3507	367.4 (355.4-379.7)
Sex	Female	Discharged COVID-19	6.2	1191	193.3 (182.6-204.6)
		Discharged Pneumonia	14.8	3384	227.9 (220.4-235.7)
	Male	Discharged COVID-19	6.9	1416	204.7 (194.3-215.6)
		Discharged Pneumonia	14.3	3574	249.8 (241.7-258.1)
Ethnicity	White	Discharged COVID-19	7.9	1757	222.0 (211.8-232.6)
		Discharged Pneumonia	19.5	4540	233.0 (226.3-239.8)
	Mixed	Discharged COVID-19	0.1	10	68.8 (37.0-127.9)
		Discharged Pneumonia	0.1	29	244.6 (170.0-351.9)
	Asian/Asian British	Discharged COVID-19	1.3	148	111.9 (95.2-131.4)
		Discharged Pneumonia	1.2	329	282.1 (253.2-314.3)
	Black	Discharged COVID-19	0.5	47	91.9 (69.0-122.3)
		Discharged Pneumonia	0.3	63	214.8 (167.8-275.0)
	Other	Discharged COVID-19	0.3	16	63.5 (38.9-103.7)
		Discharged Pneumonia	0.2	49	261.6 (197.7-346.1)
	Unknown	Discharged COVID-19	2.9	629	214.4 (198.3-231.9)
		Discharged Pneumonia	7.9	1948	246.6 (235.9-257.8)

Table A9: Rates of MI amongst patients discharged with COVID-19 in 2020 and all patients discharged with non-COVID pneumonia in 2019 stratified by age, sex and ethnicity.

Variable	Category	Analysis Group	Person Time (per 10,000 person months)	Number of events	Rate (95% CI)
Overall	-	Discharged COVID-19	13.7	294	21.4 (19.1-24.0)
		Discharged Pneumonia	31.4	534	17.0 (15.6-18.5)
Age	18 -49	Discharged COVID-19	2.9	9	3.1 (1.6-6.0)
		Discharged Pneumonia	3.9	18	4.6 (2.9-7.4)
	50-59	Discharged COVID-19	2.3	28	12.0 (8.3-17.4)
		Discharged Pneumonia	3.4	29	8.6 (6.0-12.3)
	60-69	Discharged COVID-19	2.3	40	17.0 (12.5-23.2)
		Discharged Pneumonia	5.2	96	18.3 (15.0-22.4)
	70-79	Discharged COVID-19	2.7	78	28.7 (23.0-35.8)
		Discharged Pneumonia	8.2	163	19.8 (17.0-23.0)
	80+	Discharged COVID-19	3.4	139	40.7 (34.5-48.1)
		Discharged Pneumonia	10.7	228	21.3 (18.7-24.3)
Sex	Female	Discharged COVID-19	6.5	120	18.6 (15.5-22.2)
		Discharged Pneumonia	16	222	13.9 (12.2-15.8)
	Male	Discharged COVID-19	7.3	174	24.0 (20.6-27.8)
		Discharged Pneumonia	15.5	312	20.2 (18.1-22.6)
Ethnicity	White	Discharged COVID-19	8.4	178	21.3 (18.4-24.7)
		Discharged Pneumonia	21	362	17.3 (15.6-19.1)
	Mixed	Discharged COVID-19	0.1	<5	33.9 (14.1-81.5)
		Discharged Pneumonia	0.1	<5	7.9 (1.1-55.8)
	Asian/Asian British	Discharged COVID-19	1.4	25	18.4 (12.4-27.2)
		Discharged Pneumonia	1.3	25	19.6 (13.2-29.0)
	Black	Discharged COVID-19	0.5	<5	9.5 (4.0-22.8)
		Discharged Pneumonia	0.3	<5	12.7 (4.8-33.7)
	Other	Discharged COVID-19	0.3	<5	15.7 (5.9-41.8)
		Discharged Pneumonia	0.2	<5	4.9 (0.7-35.1)
	Unknown	Discharged COVID-19	3.1	77	25.0 (20.0-31.3)
		Discharged Pneumonia	8.6	141	16.5 (14.0-19.4)

Table A10: Rates of AKI amongst patients discharged with COVID-19 in 2020 and all patients discharged with non-COVID pneumonia in 2019 stratified by age, sex and ethnicity.

Variable	Category	Analysis Group	Person Time (per 10,000 person months)	Number of events	Rate (95% CI)
Overall	-	Discharged COVID-19	13	2012	154.5 (147.9-161.4)
		Discharged Pneumonia	29.8	3933	131.8 (127.7-136.0)
Age	18 -49	Discharged COVID-19	2.8	130	45.8 (38.5-54.4)
		Discharged Pneumonia	3.8	239	63.7 (56.1-72.3)
	50-59	Discharged COVID-19	2.2	160	71.1 (60.9-83.1)
		Discharged Pneumonia	3.2	265	81.8 (72.5-92.2)
	60-69	Discharged COVID-19	2.2	303	136.3 (121.8-152.6)
		Discharged Pneumonia	5	547	109.6 (100.8-119.1)
	70-79	Discharged COVID-19	2.5	514	203.0 (186.2-221.3)
		Discharged Pneumonia	7.8	1156	148.6 (140.3-157.4)
	80+	Discharged COVID-19	3.2	905	284.4 (266.5-303.6)
		Discharged Pneumonia	10.1	1726	171.3 (163.4-179.6)
Sex	Female	Discharged COVID-19	6.2	863	139.8 (130.8-149.4)
		Discharged Pneumonia	15.3	1848	121.1 (115.7-126.7)
	Male	Discharged COVID-19	6.9	1149	167.7 (158.3-177.7)
		Discharged Pneumonia	14.6	2085	143.0 (137.0-149.3)
Ethnicity	White	Discharged COVID-19	7.9	1327	167.4 (158.6-176.6)
		Discharged Pneumonia	20	2575	128.9 (124.0-133.9)
	Mixed	Discharged COVID-19	0.1	6	41.0 (18.4-91.3)
		Discharged Pneumonia	0.1	17	144.0 (89.5-231.6)
	Asian/Asian British	Discharged COVID-19	1.3	114	87.3 (72.7-104.9)
		Discharged Pneumonia	1.2	176	149.9 (129.3-173.7)
	Black	Discharged COVID-19	0.5	53	108.6 (83.0-142.2)
		Discharged Pneumonia	0.3	39	134.1 (98.0-183.6)
	Other	Discharged COVID-19	0.2	8	32.1 (16.0-64.2)
		Discharged Pneumonia	0.2	25	134.7 (91.0-199.3)
	Unknown	Discharged COVID-19	2.9	504	173.4 (158.9-189.2)
		Discharged Pneumonia	8.1	1101	136.1 (128.3-144.4)

Table A11: Rates of T2DM amongst patients discharged with COVID-19 in 2020 and all patients discharged with non-COVID pneumonia in 2019 stratified by age, sex and ethnicity.

Variable	Category	Analysis Group	Person Time (per 10,000 person months)	Number of events	Rate (95% CI)
Overall	-	Discharged COVID-19	9.3	291	31.2 (27.8-35.0)
		Discharged Pneumonia	22.3	627	28.1 (26.0-30.4)
Age	18 -49	Discharged COVID-19	2.4	49	20.3 (15.3-26.8)
		Discharged Pneumonia	3.4	57	16.7 (12.8-21.6)
	50-59	Discharged COVID-19	1.6	55	33.7 (25.9-43.9)
		Discharged Pneumonia	2.6	64	24.8 (19.4-31.6)
	60-69	Discharged COVID-19	1.5	59	40.6 (31.5-52.5)
		Discharged Pneumonia	3.5	130	36.7 (30.9-43.6)
	70-79	Discharged COVID-19	1.6	54	33.0 (25.3-43.1)
		Discharged Pneumonia	5.4	191	35.1 (30.5-40.5)
	80+	Discharged COVID-19	2.2	74	33.8 (26.9-42.5)
		Discharged Pneumonia	7.3	185	25.2 (21.9-29.2)
Sex	Female	Discharged COVID-19	4.6	134	29.3 (24.7-34.7)
		Discharged Pneumonia	11.7	303	25.8 (23.1-28.9)
	Male	Discharged COVID-19	4.8	157	33.0 (28.3-38.6)
		Discharged Pneumonia	10.6	324	30.6 (27.5-34.1)
Ethnicity	White	Discharged COVID-19	5.9	180	30.7 (26.5-35.5)
		Discharged Pneumonia	15.1	403	26.7 (24.2-29.5)
	Mixed	Discharged COVID-19	0.1	0	0.0 (0.0-0.0)
		Discharged Pneumonia	0.1	<5	38.4 (12.4-119.0)
	Asian/Asian British	Discharged COVID-19	0.7	25	34.9 (23.6-51.7)
		Discharged Pneumonia	0.6	37	67.0 (48.5-92.5)
	Black	Discharged COVID-19	0.3	17	60.5 (37.6-97.3)
		Discharged Pneumonia	0.2	<5	21.9 (8.2-58.2)
	Other	Discharged COVID-19	0.2	<5	30.2 (12.6-72.7)
		Discharged Pneumonia	0.1	<5	17.3 (4.3-69.4)
	Unknown	Discharged COVID-19	2.2	64	29.2 (22.8-37.3)
		Discharged Pneumonia	6.3	178	28.2 (24.4-32.7)

Information governance and ethics

NHS England is the data controller; TPP is the data processor; and the key researchers on OpenSAFELY are acting on behalf of NHS England. OpenSAFELY is hosted within the TPP environment which is accredited to the ISO 27001 information security standard and is NHS IG Toolkit compliant;[12,13] patient data are pseudonymised for analysis and linkage using industry standard cryptographic hashing techniques; all pseudonymised datasets transmitted for linkage onto OpenSAFELY are encrypted; access to the platform is via a virtual private network (VPN) connection, restricted to a small group of researchers who hold contracts with NHS England and only access the platform to initiate database queries and statistical models. Pseudonymised structured data include demographics, medications prescribed from primary care, diagnoses, and laboratory measures. No free text data are included. All database activity is logged; only aggregate statistical outputs leave the platform environment following best practice for anonymisation of results such as statistical disclosure control for low cell counts.[14] The OpenSAFELY research platform adheres to the obligations of the UK General Data Protection Regulation (GDPR) and the Data Protection Act 2018. In March 2020, the Secretary of State for Health and Social Care used powers under the UK Health Service (Control of Patient Information) Regulations 2002 (COPI) to require organisations to process confidential patient information for the purposes of protecting public health, providing healthcare services to the public and monitoring and managing the COVID-19 outbreak and incidents of exposure; this sets aside the requirement for patient consent.[15] Taken together, these provide the legal bases to link patient datasets on the OpenSAFELY platform. GP practices, from which the primary care data are obtained, are required to share relevant health information to support the public health response to the pandemic, and have been informed of the OpenSAFELY analytics platform. This study was approved by the Health Research Authority (REC reference 20/LO/0651) and by the LSHTM Ethics Board (ref 21863).