Long-term outcomes following hospital admission for COVID-19 versus seasonal influenza: a cohort study

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Summary

Background Previous comparative analyses of people admitted to hospital for COVID-19 versus influenza evaluated the risk of death, hospital readmission, and a narrow set of health outcomes up to 6 months following infection. We aimed to do a comparative evaluation of both acute and long-term risks and burdens of a comprehensive set of health outcomes following hospital admission for COVID-19 or seasonal influenza.

Methods For this cohort study we used the health-care databases of the US Department of Veterans Affairs to analyse data from 81 280 participants admitted to hospital for COVID-19 between March 1, 2020, and June 30, 2022, and 10 985 participants admitted to hospital for seasonal influenza between Oct 1, 2015, and Feb 28, 2019. Participants were followed up for up to 18 months to comparatively evaluate risks and burdens of death, a prespecified set of 94 individual health outcomes, ten organ systems, overall burden across all organ systems, readmission, and admission to intensive care. Inverse probability weighting was used to balance the baseline characteristics. Cox and Poisson models were used to generate estimates of risk on both the relative scale and absolute scale as the event rate and disability-adjusted life-years (DALYs) per 100 persons.

Findings Over 18 months of follow-up, compared to seasonal influenza, the COVID-19 group had an increased risk of death (hazard ratio [HR] 1·51 [95% CI 1·45–1·58]), corresponding to an excess death rate of 8·62 (95% CI 7·55–9·44) per 100 persons in the COVID-19 group versus the influenza group. Comparative analyses of 94 prespecified health outcomes showed that COVID-19 had an increased risk of 68·1% (64 of 94) pre-specified health outcomes; seasonal influenza was associated with an increased risk of 6·4% (six of 94) pre-specified health outcomes, including three out of four pre-specified pulmonary outcomes. Analyses of organ systems showed that COVID-19 had a higher risk across all organ systems except for the pulmonary system, the risk of which was higher in seasonal influenza. The cumulative rates of adverse health outcomes across all organ systems were 615·18 (95% CI 605·17–624·88) per 100 persons in COVID-19 and 536·90 (527·38–544·90) per 100 persons in seasonal influenza, corresponding to an excess rate of 78·72 (95% CI 66·15–91·24) per 100 persons in COVID-19. The total number of DALYs across all organ systems were 287·43 (95% CI 281·10–293·59) per 100 persons in the COVID-19 group and 242·66 (236·75, 247·67) per 100 persons in the seasonal influenza group, corresponding to 45·03 (95% CI 37·15–52·90) higher DALYs per 100 persons in COVID-19. Decomposition analyses showed that in both COVID-19 and seasonal influenza, there was a higher burden of health loss in the post-acute than the acute phase; and comparatively, except for the pulmonary system, COVID-19 had a higher burden of health loss across all other organ systems than seasonal influenza in both the acute and post-acute phase. Compared to seasonal influenza, COVID-19 also had an increased risk of hospital readmission (excess rate 20·50 [95% CI 16·10–24·86] per 100 persons) and admission to intensive care (excess rate 9·23 [6·68–11·82] per 100 persons). The findings were consistent in analyses comparatively evaluating risks in seasonal influenza versus COVID-19 by individuals' respective vaccination status and in those admitted to hospital during the pre-delta, delta, and omicron eras.

Interpretation Although rates of death and adverse health outcomes following hospital admission for either seasonal influenza or COVID-19 are high, this comparative analysis shows that hospital admission for COVID-19 was associated with higher long-term risks of death and adverse health outcomes in nearly every organ system (except for the pulmonary system) and significant cumulative excess DALYs than hospital admission for seasonal influenza. The substantial cumulative burden of health loss in both groups calls for greater prevention of hospital admission for these two viruses and for greater attention to the care needs of people with long-term health effects due to either seasonal influenza or SARS-CoV-2 infection.

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Introduction

Both COVID-19 and influenza are associated with an increased risk of mortality and adverse health outcomes in multiple organ systems.[1–3] Previous comparative analyses of people admitted to hospital for COVID-19 versus influenza evaluated the risk of death, hospital readmission, and a narrow set of health outcomes up to 6 months following infection. These studies showed

Research in context

Evidence before this study

We searched PubMed for studies published between Dec 12, 2019, and Sept 10, 2023, using the search terms "COVID-19" and "SARS-CoV-2" in combination with the search terms "seasonal influenza", "flu", OR "influenza", with no language restrictions. Comparative studies of people admitted to hospital for COVID-19 versus influenza evaluated the risk of death, hospital readmission, and a narrow set of health outcomes up to 6 months following SARS-CoV-2 infection. These studies showed that, despite some decline during the course of the pandemic, COVID-19 was still associated with a higher risk of death and hospital readmission at 6 months than seasonal influenza. However, a comparative evaluation of both acute and long-term risks and burdens of death, a comprehensive set of health outcomes, and health-care utilisation (eg, hospital readmission) following hospital admission for COVID-19 or seasonal influenza has not been done.

Added value of this study

The findings of this cohort study show that the cumulative rates of death, adverse health outcomes, and health-care utilisation were high in both those admitted to hospital for COVID-19 and those admitted to hospital for seasonal influenza, but the risks and burdens were comparatively higher in people admitted to hospital for COVID-19. Risks were higher in COVID-19 for all organ systems except for the pulmonary system, the risk of which was higher in seasonal influenza in both the acute and post-acute phase of the infection, suggesting the possibility that seasonal influenza might have a higher affinity to affect the pulmonary system than SARS-CoV-2 infection and that SARS-CoV-2 infection manifests more systemically than seasonal influenza. Although COVID-19 had a comparatively higher burden of health loss than seasonal influenza in both the acute and post-acute phase, both COVID-19 and seasonal influenza had a higher burden of health loss in the post-acute phase of infection compared to their respective acute phases, suggesting that hospital admission for either COVID-19 or seasonal influenza has a greater long-term impact on health than the immediately manifested health effects during the acute phase.

Implications of all the available evidence

The findings illustrate the high toll of death and health loss following hospital admission for either seasonal influenza or COVID-19. The risks and burdens of death, health loss, and health-care utilisation are substantially higher for COVID-19 than for seasonal influenza. Our evaluation of health loss by organ systems showed some differentiating features, in that seasonal influenza had a higher risk of pulmonary system involvement, whereas COVID-19 was a multisystemic disease showing higher risks in all other organ systems. Hospital admission for both COVID-19 and seasonal influenza generated a higher burden of health loss in the post-acute phase, suggesting that conceptualisation of these infections solely as acute illnesses will overlook their larger post-acute health effects and underestimate their cumulative burden on human health. The substantial cumulative burden of health loss in both groups highlights the need for greater prevention of hospital admission for these two viruses and for greater attention towards the care needs of people with long-term health effects due to either seasonal influenza or SARS-CoV-2 infection.

that, despite some decline during the course of the pandemic, COVID-19 was still associated with a higher risk of death and hospital readmission at 6 months than seasonal influenza.[1–4] However, the comparative risks and burdens of death and health-care resource utilisation beyond 6 months after infection are largely unknown. And a comparative evaluation has not been done of both the acute and long-term risks and burdens of a comprehensive set of adverse health outcomes representing all major organ systems that could be affected following hospital admission for COVID-19 or seasonal influenza.

Comparative analyses of COVID-19 and influenza are useful because they juxtapose the relatively new COVID-19 and a respiratory viral illness that has been known for at least a century—allowing a better understanding of the similarities and differences between the acute and post-acute health trajectories of people infected with these two viruses.

We aimed to examine acute and long-term risks and burdens of death, health-care utilisation, and a comprehensive array of 94 health outcomes over an 18-month period in people admitted to hospital with COVID-9 and those admitted to hospital with seasonal influenza.

Methods

Study design and setting

This cohort study was conducted with the health-care databases of the US Department of Veterans Affairs (VA). The VA operates the largest integrated health-care system in the USA and provides health-care services to veterans of the US Armed Forces. The services included preventative and health maintenance, outpatient care, inpatient hospital care, prescriptions, mental health care, home health care, primary care, specialty care, geriatric and extended care, medical equipment, and prosthetics. The VA operates 1323 VA health-care facilities, which include 173 VA medical centres and 1137 outpatient sites.

Data sources

We used the health-care databases of the VA, which include information collected during patients' routine health-care encounters. Data were obtained from VA

Corporate Data Warehouse (CDW), which collected and managed electronic health records from all VA healthcare facilities. Data domains included outpatient, inpatient, pharmacy, laboratory, health factors, VA COVID-19 Shared Data Resource, and vital status. The Area Deprivation Index (ADI)—a composite measure of income, education, employment, and housing—was obtained from the Neighborhood Atlas and used as a summary measure of contextual disadvantage at participants' residential locations.[5] All data were accessed through the VA Informatics and Computing Infrastructure.

Cohort

The cohort flow of the study is presented in appendix 1 (p 2). 573 612 participants who had a positive SARS-CoV-2 test result between March 1, 2020, and June 30, 2022, were included in the COVID-19 group. We then selected those admitted to hospital with an admission diagnosis for COVID-19 within 5 days before or within 30 days after the positive test results (n=82 188). Because hospital admission for seasonal influenza was rare in the USA during the COVID-19 group enrolment period, we enrolled a historical seasonal influenza group; 50 509 participants who had a positive influenza test result between Oct 1, 2015, and Feb 28, 2019, were included in the seasonal influenza group. We then selected those admitted to hospital with an admission diagnosis for seasonal influenza within 5 days before or within 30 days after the positive test results (n=11 893). After removing 908 participants who were included in both the COVID-19 and seasonal influenza groups, the final cohort comprised 81 280 participants in the COVID-19 group and 10 985 participants in the seasonal influenza group. Within the seasonal influenza group, 8360 (76·1%) of 10 985 participants had influenza type A and 2625 (23·9%) had other types of influenza. The date of hospital admission was defined as T_0. The last date of follow-up for the COVID-19 group was set to be the first occurrence of 540 days after T_0 or July 20, 2023. The last date of follow-up for the seasonal influenza group was set to be the first occurrence of 540 days after T_0 or Feb 29, 2020.

For additional comparisons between different eras of the pandemic and seasonal influenza, the COVID-19 groups were further separated into three groups (pre-delta, delta, and omicron) based on the predominant SARS-CoV-2 variant at the date of infection according to the US Centers for Disease Control and Prevention (CDC).[6] There were 40 481 participants in the COVID-19 group who had a positive SARS-CoV-2 test before June 19, 2021, and were thus defined as the pre-delta group; 18 106 participants had a positive test between June 20, 2021, and Dec 18, 2021, and were thus defined as the delta group; and 22 693 participants had a positive test between Dec 19, 2021, and June 30, 2022, and were thus defined as the omicron group. To facilitate comparisons based on similar follow-up time across groups, we randomly assigned potential follow-up times to participants not in the omicron group based on values drawn from the follow-up distribution in the omicron group (the group with shortest potential follow-up time). Administrative censoring of the seasonal influenza, pre-delta, and delta groups based on the follow-up distribution of the omicron group resulted in a similar follow-up distribution across groups. After the application of administrative censoring, 100% of participants had at least 360 days of potential follow-up; 4620 (42·06%) of 10 985 participants in the seasonal influenza group, 17 027 (42·06%) of 40 481 in the pre-delta group, 7616 (42·06%) of 18 106 in the delta group, and 9545 (42·06%) of 22 693 in the omicron group had 540 days of follow-up.

See Online for appendix 1

Outcomes

A list of 94 pre-specified health outcomes that could be associated with COVID-19 or seasonal influenza were defined on the basis of the International Classification of Diseases 10th Revision (ICD-10) diagnosis codes, laboratory values, and prescription records.[1,4,7–11] Outcomes were also composited into ten organ systems: cardiovascular, coagulation and haematological, fatigue, gastrointestinal, kidney, mental health, metabolic, musculoskeletal, neurological, and pulmonary. Incident outcomes were defined as the first occurrence of outcomes during follow-up that was not present before T_0. A composite of adverse health outcomes across all organ systems was further defined as the number of incident organ systems affected. Outcomes were ascertained from T_0 until end of follow-up. To evaluate outcomes during the post-acute phase of infection, we separately ascertained outcomes from 30 days after T_0 until the end of follow-up. For the composite outcomes and to account for both the occurrence of individual outcomes and the influence of each outcome on overall health, we used the Global Burden of Disease Study (GBD) methodologies to estimate disability-adjusted life-years (DALYs) for the composite outcomes (in each organ system and across all organ systems).[7,12–14] For each composite outcome, DALYs were computed as the summation of the DALYs of all individual outcomes under the composite outcome (the product of the occurrence of the outcome and its associated health burden coefficient).[7,12–14] We also examined death (all-cause mortality) since hospital admission and health-care resource utilisation, including number of hospital readmissions and ICU admission after the index hospitalisation.

Covariates

Covariates were defined on the basis of previous knowledge and following directed acyclic graph (appendix 1 p 3).[1,8–11,15–17] Baseline covariates were collected from 1 year before T_0 until T_0. Demographic variables

including age, race (White, Black, and other), self-reported sex, area deprivation index based on residential address, smoking status (current, former, and never) and use of long-term care were used. We also selected laboratory and vital measurements including estimated glomerular filtration rate (eGFR), systolic and diastolic blood pressure and BMI; and diseases including cancer, cardiovascular disease, chronic lung disease, coronary artery disease, dementia, diabetes, hyperlipidaemia, HIV, immune dysfunction, liver diseases, and peripheral artery diseases. We selected the number of outpatient visits and hospital admissions, number of blood panel tests, number of medications received, and number of Medicare outpatient visits and hospital admissions to represent potential differences in health-care resource utilisation between the COVID-19 and the seasonal influenza groups. We also standardised vaccination rates in the COVID-19 group to the rate during the delta and omicron eras in the cohort. In this study, 4·32% of data on eGFR, 4·01% of data on BMI, and 0·06% of data on blood pressure were missing and imputed with multivariate imputation by chained equations and the predictive mean matching method conditional on all covariates. Continuous variables were transformed into restricted cubic spline functions to account for potential non-linear relationships, where four knots were placed at 5th, 35th, 65th, and 95th precentiles.[18]

Statistical analysis

We performed power analyses using 1000 simulations based on the parameters from the study cohort and power was defined by the proportion of simulations with a 95% CI of the hazard ratio that did not include 1. We varied the event rate from 1% to 20% and the strength of confounding based on C-statistics from 0·5 to 0·8. Given the study sample size, and under the setting of strong confounding, we observed a power of 99% to detect a hazard ratio (HR) of 0·70, a power of 91% to detect a HR of 0·80, and a power of 72% to detect a HR of 0·90, in a scenario where the event rate was 1%; and a power of 99% to detect a HR of 0·70, a power of 99% to detect a HR of 0·80, and a power of 99% to detect a HR of 0·90 in a scenario where the event rate was 20%.

Baseline characteristics of the COVID-19 and seasonal influenza groups were reported. Distributions of continuous variables were reported as means and SDs and categorical variables were described as frequencies and percentages. Differences of baseline characteristics between groups were measured with absolute standardised differences, where a value of less than 0·1 was considered evidence of good balance.

Inverse probability weighting based on propensity score was used to balance baseline differences between the COVID-19 and seasonal influenza groups. Logistic regression was applied to estimate the probability of being assigned to the seasonal influenza group (the propensity score), given all covariates previously described. In order to provide a comparative risk assessment based on the same underlying risk, the common reference group of seasonal influenza was selected as the target population. The inverse probability weight was computed as the propensity score divided by (1–propensity score) for the COVID-19 group and was defined as 1 for the seasonal influenza group. HRs of the occurrence of incident outcomes were estimated on the basis of the weighted Cox survival model, where death was considered as competing risk and cause-specific hazards were estimated for non-death outcomes. The estimated rate in each group and the difference between groups were generated on the basis of estimated survival probability. The relative and absolute risk of overall disease, DALYs, and health-care utilisation were estimated on the basis of weighted Poisson regression where the sums of the events during follow-up were set to be the dependent variables and follow-up times were set to be the offsets in the model. The cumulative difference between COVID-19 and seasonal influenza from T_0 until 30, 180, 360, and 540 days was estimated.

To examine the distributional contribution of acute and post-acute disease to the overall burden of disease after infection, we first examined the risk and risk difference between COVID-19 and seasonal influenza during the post-acute phase based on outcomes ascertained 30 days after T_0. We then evaluated the proportion of risk from the acute phase (0–30 days) and post-acute phase within the COVID-19 and seasonal influenza groups, as well as the difference between the two groups across each organ system and across all organ systems.

We then evaluated the comparative risks and burdens of death, organ system involvement, and health-care utilisation between those admitted to hospital for seasonal influenza and those admitted to hospital for COVID-19 during the pre-delta, delta, and omicron periods according to the CDC.[6] Propensity scores and inverse probability weights for each group were computed and applied.

To examine the influence of previous vaccination on the comparative risk between COVID-19 and seasonal influenza, we further separated COVID-19 groups on the basis of their COVID-19 vaccination status and the seasonal influenza group on the basis of their seasonal influenza vaccination status. Comparisons were conducted for unvaccinated individuals with COVID-19 compared to unvaccinated, and separately, vaccinated individuals with seasonal influenza, and for vaccinated individuals with COVID-19 compared to unvaccinated and vaccinated individuals with seasonal influenza. Propensity scores and inverse probability weights for each group were computed and applied.

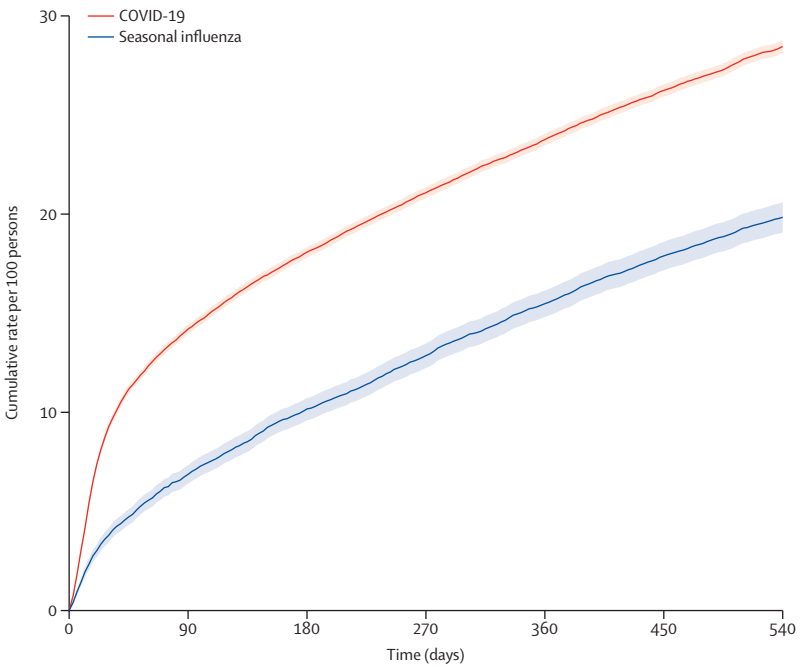
Multiple sensitivity analyses were conducted to test the robustness of the findings. First, because differences in screening practices for these infections during admission might have resulted in misspecification of exposure, we varied our definition of exposure by including those admitted to hospital within 5 days

	Overall (n=92 265)	COVID-19 (n=81 280)	Seasonal influenza (n=10 985)	SMD between seasonal influenza and COVID-19
Age, years	70·73 (12·74)	70·80 (12·70)	70·53 (12·71)	0·02
Race				
White	68 438 (74·2%)	60 084 (73·9%)	8116 (73·9%)	0·001
Black	19 400 (21·0%)	17 384 (21·4%)	2363 (21·5%)	0·003
Other	4427 (4·8%)	3812 (4·7%)	506 (4·6%)	0·004
Sex				
Male	87 627 (95·0%)	77 161 (94·9%)	10 426 (94·9%)	0·001
Female	4638 (5·0%)	4119 (5·1%)	559 (5·1%)	0·001
Smoking status				
Never	38 134 (41·3%)	33 368 (41·1%)	4541 (41·3%)	0·006
Former	24 388 (26·4%)	21 723 (26·7%)	2898 (26·4%)	0·008
Current	29 743 (32·2%)	26 189 (32·2%)	3546 (32·3%)	0·001
Area Deprivation Index*	51·32 (19·63)	51·52 (19·74)	51·81 (19·58)	0·02
Long-term care	7824 (8·5%)	6988 (8·6%)	908 (8·3%)	0·01
Vaccination	56 979 (61·8%)	49 719 (61·2%)	6712 (61·1%)	0·001
BMI	29·11 (7·32)	29·11 (7·38)	29·21 (7·33)	0·01
eGFR, mean (std), mL/min/1·73m^2	64·96 (26·37)	64·85 (26·40)	65·12 (26·33)	0·01
Systolic blood pressure, mmHg	133·58 (13·89)	133·61 (13·85)	133·60 (13·92)	0·001
Diastolic blood pressure, mmHg	74·69 (8·21)	74·69 (8·15)	74·80 (8·24)	0·01
Cancer	35 822 (38·8%)	31 511 (38·8%)	4209 (38·3%)	0·009
Chronic lung disease	61 771 (67·0%)	54 308 (66·8%)	7338 (66·8%)	<0·001
Dementia	30 836 (33·4%)	27 565 (33·9%)	3644 (33·2%)	0·02
Type 2 diabetes	51 182 (55·5%)	45 060 (55·4%)	6085 (55·4%)	0·001
Cardiovascular disease	62 972 (68·3%)	55 595 (68·4%)	7491 (68·2%)	0·004
Hyperlipidemia	36 436 (39·5%)	32 526 (40·0%)	4419 (40·2%)	0·004
Immune dysfunction	4690 (5·1%)	4310 (5·3%)	574 (5·2%)	0·003
Number of hospital admissions	0 (0–1)	0 (0–1)	0 (0–1)	0·02
Number of outpatient visits	3·67 (1·59)	3·70 (1·60)	3·66 (1·60)	0·03
Number of blood panel tests	18·57 (22·19)	19·02 (22·40)	18·42 (21·99)	0·03
Number of medications	14·02 (8·94)	14·05 (9·01)	13·93 (8·92)	0·01
Number of hospital admission from Medicare	0 (0–0)	0 (0–0)	0 (0–0)	0·01
Number of outpatient visits from Medicare	0 (0–0)	0 (0–0)	0 (0–0)	0·007
Predominant era				
Pre-delta	..	31 033 (38·2%)	..	..
Delta	..	20 680 (25·4%)	..	..
Omicron	..	29 568 (36·4%)	..	..

Data are n (%), mean (SD), or median (IQR). eGFR=estimated glomerular filtration rate. SMD=absolute standardised mean difference. An SMD of less than 0·1 was considered evidence of good balance. *Area Deprivation Index is a measure of socioeconomic disadvantage, with a range from low to high disadvantage of 0 to 100.

Table: **Demographic and health characteristics of the overall, COVID-19, and seasonal influenza groups after weighting**

before or after SARS-CoV-2 or seasonal influenza infection, and separately, included those admitted to hospital within 5 days after the infection, compared to the main approach where we included those admitted to hospital within 5 days before or 30 days after the infection. Second, we adjusted for ICU admission during the first hospital admission, compared to the main approach where no adjustments were made for variables after T_0. Third, we adjusted for the seasonal influenza vaccine in both groups, compared to the main approach in which it was not a covariate in the model. Fourth, we applied a doubly robust method that conducted adjustment in both the exposure model and outcome model to adjust for differences between groups,[19] compared to the main approach where only inverse probability weight was used in the outcome model. Fifth, we used the overlap weighting approach to balance baseline characteristics and estimated the



Period	0–30	0–180	0–360	0–540
Number at risk				
COVID-19	81280	67077	63647	25528
Seasonal influenza	10985	9858	9260	3125
Hazard ratio (95% CI)	2·51 (2·28–2·78)	1·86 (1·75–1·98)	1·61 (1·54–1·69)	1·51 (1·45–1·58)
Rate per 100 persons (95% CI)				
COVID-19	9·29 (9·09–9·48)	18·08 (17·81–18·34)	23·76 (23·47–24·05)	28·46 (28·14–28·78)
Seasonal influenza	3·80 (3·44–4·16)	10·17 (9·60–10·73)	15·48 (14·81–16·15)	19·84 (19·07–20·59)
Excess rate per 100 persons (95% CI)	5·48 (5·07–5·89)	7·91 (7·29–8·53)	8·28 (7·55–9·01)	8·62 (7·55–9·44)

Figure 1: **Event rates of death in COVID-19 and seasonal influenza**
Event rates per 100 persons are presented for COVID-19 (red) and seasonal influenza (blue). Shaded areas represent 95% CIs. The hazard ratio, rate, and rate difference per 100 persons during the periods of 0–30, 0–180, 0–360 and 0–540 days are also presented.

average treatment effect for the overlap population, compared to the main approach that used the inverse probability of treatment weighting.[20] Sixth, we estimated risk based on weighed Kaplan-Meier estimator, compared to the main approach that was based on the Cox model. Seventh, we censored participants at their date of reinfection and applied the inverse probability of censoring weight to account for informative censoring, compared to the main approach that continued following them up after reinfection. Finally, we compared COVID-19 with seasonal influenza A and, separately, with all other (non-A) seasonal influenza viruses, compared to the main approach that evaluated COVID-19 versus all seasonal influenza.

For all analyses, 95% CIs were estimated on the basis of the 2·5th and 97·5th percentile of 1000 times parametric bootstrapping. A risk on the relative scale with a 95% CI that does not cross 1 and a rate difference with a 95% CI that does not cross 0 were considered statistically significant. Analyses were done with SAS Enterprise Guide (version 8.3) and data visualisations were done in R (version 4.3.0). The study was approved, and a waiver of informed consent was granted, by the Institutional Review Board of St Louis Health Care System, US Department of Veteran Affairs.

See Online for appendix 2

Role of the funding source
The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results
There were 81280 people in the COVID-19 cohort and 10985 people in the seasonal influenza cohort. The COVID-19 cohort had a median follow-up of 1·46 (IQR 1·26–1·51) years and the seasonal influenza cohort had a median follow-up of 1·46 (1·18–1·53) years, altogether corresponding to 127640 person-years of follow up. The demographic and health characteristics of the two groups before weighting are presented in appendix 2 (supplementary table 1) and those after weighting are summarised in the table. The distribution of the propensity score before and after weighting is presented in appendix 1 (p 4). After inverse probability weighting, all baseline characteristics had an SMD less than 0·1, suggested good balance was achieved.

We examined the COVID-19 and seasonal influenza cohorts to comparatively evaluate the risks and burdens of death, 94 individual health outcomes, ten organ systems aggregated from individual health outcomes, a composite of adverse health outcomes across all ten organ systems, and readmission and admission to intensive care. Risks were estimated on both the relative scale as HRs or relative risks, and on the absolute scale as rates and DALYs per 100 persons in several time periods, including 0–30 days, 0–180 days, 0–360 days, and 0–540 days, where time zero was designated as the date of hospital admission.

The absolute death rate was higher in the COVID-19 group than in the influenza group in each time period (0–30 days, 0–180 days, 0–360 days, and 0–540 days); the cumulative death rates at 540 days were 28·46 (95% CI 28·14–28·78) per 100 persons for COVID-19 and 19·84 (19·07–20·59) per 100 persons for seasonal influenza; the excess death rate in the COVID-19 versus influenza group was 8·62 (95% CI 7·55–9·44) per 100 persons. Compared to the seasonal influenza group, the COVID-19 group had an increased risk of death in all time periods: 0–30 days (HR 2·51; 95% CI 2·28–2·78), 0–180 days (1·86; 1·75–1·98), 0–360 days (1·61; 1·54–1·69), and 0–540 days (1·51; 1·45–1·58; figure 1; appendix 2 supplementary table 2). We also examined the risk of death within non-overlapping time periods during follow-up (0–30 days, 31–180 days, 181–360 days, and 361–540 days); COVID-19 was associated with a higher risk of death within all these time periods (appendix 2 supplementary table 3).

We examined the comparative risks of 94 prespecified health outcomes across ten organ systems in people admitted to hospital for COVID-19 versus seasonal influenza in the following time periods: 0–30 days, 0–180 days, 0–360 days, and the overall follow-up of 0–540 days (figure 2; appendix 1 p 5, appendix 2 supplementary table 2).

Over the entire duration of follow-up (18 months; 540 days), COVID-19 was associated with a significantly increased risk of all pre-specified health outcomes (64 [68·1%] of 94), including cardiovascular outcomes (12 [70·6%] of 17), coagulation and haematological outcomes (five [100·0%] of five), fatigue (one [100·0%] of one), gastrointestinal outcomes (nine [64·3%] of 14), kidney outcomes (four [80·0%] of five), mental health outcomes (14 [87·5%] of 16), metabolic outcomes (two [66·7%] of three), musculoskeletal outcomes (three [75·0%] of four), neurological outcomes (13 [52·0%] of 25), and pulmonary outcomes (one [25·0%] of four; appendix 1 p 6; appendix 2 supplementary table 2).

Of all the 94 outcomes examined, compared to COVID-19, seasonal influenza was associated with an increased risk of six (6·4%) of 94 pre-specified health outcomes: angina, tachycardia, type 1 diabetes, and three of four pre-specified pulmonary outcomes (cough, hypoxaemia, and shortness of breath; appendix 1 p 6; appendix 2 supplementary table 2).

In analyses of comparative risks by organ system, COVID-19 had increased risks in all organ systems except for the pulmonary system (figure 3; appendix 2 supplementary table 4).

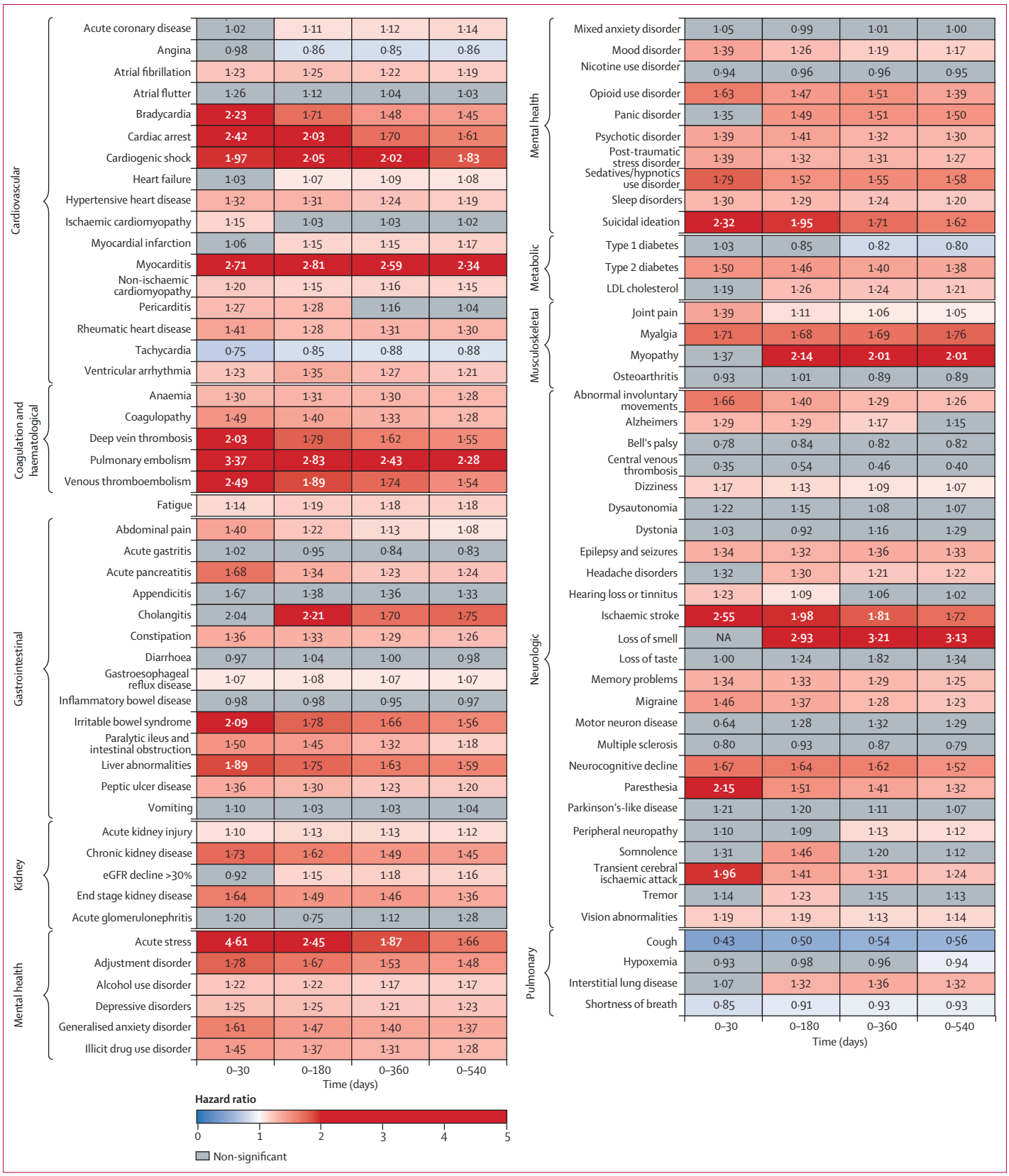
Cumulative incident rates of adverse health outcomes by organ system in the COVID-19 and influenza groups and the absolute differences between the two groups are presented in figure 4 and appendix 2 (supplementary table 4).

In the COVID-19 group, at 540 days there were cumulatively excess burdens of 1·62 (95% CI 0·81–2·61) cardiovascular outcomes per 100 persons, 8·00 (7·27–8·99) coagulation and haematological outcomes per 100 persons, 10·93 (10·84–11·81) gastrointestinal outcomes per 100 persons, 4·40 (3·14–5·36) outcomes of fatigue per 100 persons, 3·19 (2·18–4·20) kidney outcomes per 100 persons, 4·28 (3·53–5·26) mental health outcomes per 100 persons, 2·01 (1·19–2·82) metabolic outcomes per 100 persons, 12·24 (9·15–13·24) musculoskeletal outcomes per 100 persons, and 6·38 (5·62–7·40) neurological outcomes per 100 persons. In the seasonal influenza group, there was an excess burden of 7·23 (95% CI 6·23–8·03) pulmonary outcomes per 100 persons.

Over the entire duration of follow-up, the cumulative rate of adverse health outcomes across all organ systems was 615·18 (95% CI 605·17–624·88) per 100 persons in the COVID-19 group and 536·90 (527·38–544·90) per 100 persons in the seasonal influenza group, corresponding to an excess rate of 78·72 (95% CI 66·15–91·24) per 100 persons in the COVID-19 group (figure 4; appendix 2 supplementary table 4).

DALYs due to health outcomes in each organ system in the COVID-19 and influenza groups are provided in figures 3 and 4, and appendix 2 (supplementary table 5). The total number of DALYs across all organ systems were 287·43 (95% CI 281·10–293·59) per 100 persons in the COVID-19 group and 242·66 (236·75–247·67) per 100 persons in the influenza group, corresponding to 45·03 (95% CI 37·15–52·90) higher DALYs per 100 persons in the COVID-19 cohort compared to the seasonal influenza cohort (figure 4; appendix 2 supplementary table 5).

We conducted decomposition analyses to understand the distributional contribution of acute and post-acute disease to the overall burden of disease in people admitted to hospital with COVID-19 and seasonal influenza. Results of decomposition analyses of risks in the acute and post-acute phase in each organ system and across all organ systems are presented in figure 5 and appendix 2 (supplementary tables 6 and 7). Two key findings were identified. First, for all organ systems except for the gastrointestinal system, more than 50% of the total incident burden of disease in both the COVID-19 and seasonal influenza cohorts occurred in the post-acute phase of infection; and second, except for the pulmonary system, the COVID-19 cohort had a higher


Cardiovascular
Acute coronary disease 1·02 1·11 1·12 1·14
Angina 0·98 0·86 0·85 0·86
Atrial fibrillation 1·23 1·25 1·22 1·19
Atrial flutter 1·26 1·12 1·04 1·03
Bradycardia 2·23 1·71 1·48 1·45
Cardiac arrest 2·42 2·03 1·70 1·61
Cardiogenic shock 1·97 2·05 2·02 1·83
Heart failure 1·03 1·07 1·09 1·08
Hypertensive heart disease 1·32 1·31 1·24 1·19
Ischaemic cardiomyopathy 1·15 1·03 1·03 1·02
Myocardial infarction 1·06 1·15 1·15 1·17
Myocarditis 2·71 2·81 2·59 2·34
Non-ischaemic cardiomyopathy 1·20 1·15 1·16 1·15
Pericarditis 1·27 1·28 1·16 1·04
Rheumatic heart disease 1·41 1·28 1·31 1·30
Tachycardia 0·75 0·85 0·88 0·88
Ventricular arrhythmia 1·23 1·35 1·27 1·21
Coagulation and haematological
Anaemia 1·30 1·31 1·30 1·28
Coagulopathy 1·49 1·40 1·33 1·28
Deep vein thrombosis 2·03 1·79 1·62 1·55
Pulmonary embolism 3·37 2·83 2·43 2·28
Venous thromboembolism 2·49 1·89 1·74 1·54
Fatigue 1·14 1·19 1·18 1·18
Gastrointestinal
Abdominal pain 1·40 1·22 1·13 1·08
Acute gastritis 1·02 0·95 0·84 0·83
Acute pancreatitis 1·68 1·34 1·23 1·24
Appendicitis 1·67 1·38 1·36 1·33
Cholangitis 2·04 2·21 1·70 1·75
Constipation 1·36 1·33 1·29 1·26
Diarrhoea 0·97 1·04 1·00 0·98
Gastroesophageal reflux disease 1·07 1·08 1·07 1·07
Inflammatory bowel disease 0·98 0·98 0·95 0·97
Irritable bowel syndrome 2·09 1·78 1·66 1·56
Paralytic ileus and intestinal obstruction 1·50 1·45 1·32 1·18
Liver abnormalities 1·89 1·75 1·63 1·59
Peptic ulcer disease 1·36 1·30 1·23 1·20
Vomiting 1·10 1·03 1·03 1·04
Kidney
Acute kidney injury 1·10 1·13 1·13 1·12
Chronic kidney disease 1·73 1·62 1·49 1·45
eGFR decline >30% 0·92 1·15 1·18 1·16
End stage kidney disease 1·64 1·49 1·46 1·36
Acute glomerulonephritis 1·20 0·75 1·12 1·28
Mental health
Acute stress 4·61 2·45 1·87 1·66
Adjustment disorder 1·78 1·67 1·53 1·48
Alcohol use disorder 1·22 1·22 1·17 1·17
Depressive disorders 1·25 1·25 1·21 1·23
Generalised anxiety disorder 1·61 1·47 1·40 1·37
Illicit drug use disorder 1·45 1·37 1·31 1·28
0–30 0–180 0–360 0–540
Time (days)
Hazard ratio
0 1 2 3 4 5
Non-significant
Mental health
Mixed anxiety disorder 1·05 0·99 1·01 1·00
Mood disorder 1·39 1·26 1·19 1·17
Nicotine use disorder 0·94 0·96 0·96 0·95
Opioid use disorder 1·63 1·47 1·51 1·39
Panic disorder 1·35 1·49 1·51 1·50
Psychotic disorder 1·39 1·41 1·32 1·30
Post-traumatic stress disorder 1·39 1·32 1·31 1·27
Sedatives/hypnotics use disorder 1·79 1·52 1·55 1·58
Sleep disorders 1·30 1·29 1·24 1·20
Suicidal ideation 2·32 1·95 1·71 1·62
Metabolic
Type 1 diabetes 1·03 0·85 0·82 0·80
Type 2 diabetes 1·50 1·46 1·40 1·38
LDL cholesterol 1·19 1·26 1·24 1·21
Musculoskeletal
Joint pain 1·39 1·11 1·06 1·05
Myalgia 1·71 1·68 1·69 1·76
Myopathy 1·37 2·14 2·01 2·01
Osteoarthritis 0·93 1·01 0·89 0·89
Neurologic
Abnormal involuntary movements 1·66 1·40 1·29 1·26
Alzheimers 1·29 1·29 1·17 1·15
Bell's palsy 0·78 0·84 0·82 0·82
Central venous thrombosis 0·35 0·54 0·46 0·40
Dizziness 1·17 1·13 1·09 1·07
Dysautonomia 1·22 1·15 1·08 1·07
Dystonia 1·03 0·92 1·16 1·29
Epilepsy and seizures 1·34 1·32 1·36 1·33
Headache disorders 1·32 1·30 1·21 1·22
Hearing loss or tinnitus 1·23 1·09 1·06 1·02
Ischaemic stroke 2·55 1·98 1·81 1·72
Loss of smell NA 2·93 3·21 3·13
Loss of taste 1·00 1·24 1·82 1·34
Memory problems 1·34 1·33 1·29 1·25
Migraine 1·46 1·37 1·28 1·23
Motor neuron disease 0·64 1·28 1·32 1·29
Multiple sclerosis 0·80 0·93 0·87 0·79
Neurocognitive decline 1·67 1·64 1·62 1·52
Paresthesia 2·15 1·51 1·41 1·32
Parkinson's-like disease 1·21 1·20 1·11 1·07
Peripheral neuropathy 1·10 1·09 1·13 1·12
Somnolence 1·31 1·46 1·20 1·12
Transient cerebral ischaemic attack 1·96 1·41 1·31 1·24
Tremor 1·14 1·23 1·15 1·13
Vision abnormalities 1·19 1·19 1·13 1·14
Pulmonary
Cough 0·43 0·50 0·54 0·56
Hypoxemia 0·93 0·98 0·96 0·94
Interstitial lung disease 1·07 1·32 1·36 1·32
Shortness of breath 0·85 0·91 0·93 0·93
0–30 0–180 0–360 0–540
Time (days)

burden of disease across all other organ systems than the seasonal influenza cohort in both the acute and post-acute phase.

The COVID-19 group had a higher risk of hospital readmission than the seasonal influenza group in all time periods (0–30 days, 0–180 days, 0–360 days, and 0–540 days) examined. Over the entire 18 months of follow-up, the COVID-19 group had a higher risk (HR 1·11; 95% CI 1·08–1·13) of additional hospital readmission than the seasonal influenza group, corresponding to an excess of 20·50 (95% CI 16·10–24·86) hospital admissions per 100 persons (appendix 1 p 7, appendix 2 supplementary table 8).

The COVID-19 group had a higher risk of admission to the intensive care unit than the seasonal influenza group in all time periods (0–30 days, 0–180 days, 0–360 days, and 0–540 days) examined. Over the entire 18 months of follow-up, the COVID-19 group had a higher risk (HR 1·27; 95% CI 1·19–1·36) of admission to the intensive care unit than the influenza group, corresponding to excess admissions to the intense care unit of 9·23 (95% CI 6·68–11·82) per 100 persons (appendix 1 p 7, appendix 2 supplementary table 8).

Compared to the seasonal influenza group, the COVID-19 group had a higher risk of hospital readmission and admission to the intensive care unit within non-overlapping time periods during follow-up (0–30 days, 31–180 days, 181–360 days, and 361–540 days; appendix 2 supplementary table 9).

Over the entire duration of follow-up, hospital admission for COVID-19 in the pre-delta, delta, and omicron eras was associated with a higher risk of death, a higher risk of adverse health outcomes in each organ system except for the pulmonary system, adverse health outcomes across all organ systems, and hospital readmission and admission to intensive care compared to hospital admission for seasonal influenza (appendix 2 supplementary tables 10, 11, and 12). Analyses of the distributional contribution of acute and post-acute disease by era suggested that across all three eras examined, the disease burden was greater in the post-acute phase of the infection than in the acute phase; except for the pulmonary system, the COVID-19 cohort had a higher burden of disease across all other organ systems than the seasonal influenza cohort in both the acute and post-acute phase of infection (appendix 2 supplementary tables 13 and 14).

***Figure 2*: Risk of individual health outcomes in COVID-19 compared with seasonal influenza**

Hazard ratio of COVID-19 compared with seasonal influenza by days after hospital admission plotted for time periods of 0–30, 0–180, 0–360 and 0–540 days. Boxes are coloured in a graded fashion by the magnitude of risk on relative scale, with red shading indicating COVID-19 had a higher risk and blue shading indicating influenza had a higher risk. Risks that were not significantly different are coloured in grey. Outcomes are grouped by organ system. eGFR=estimated glomerular filtration rate.

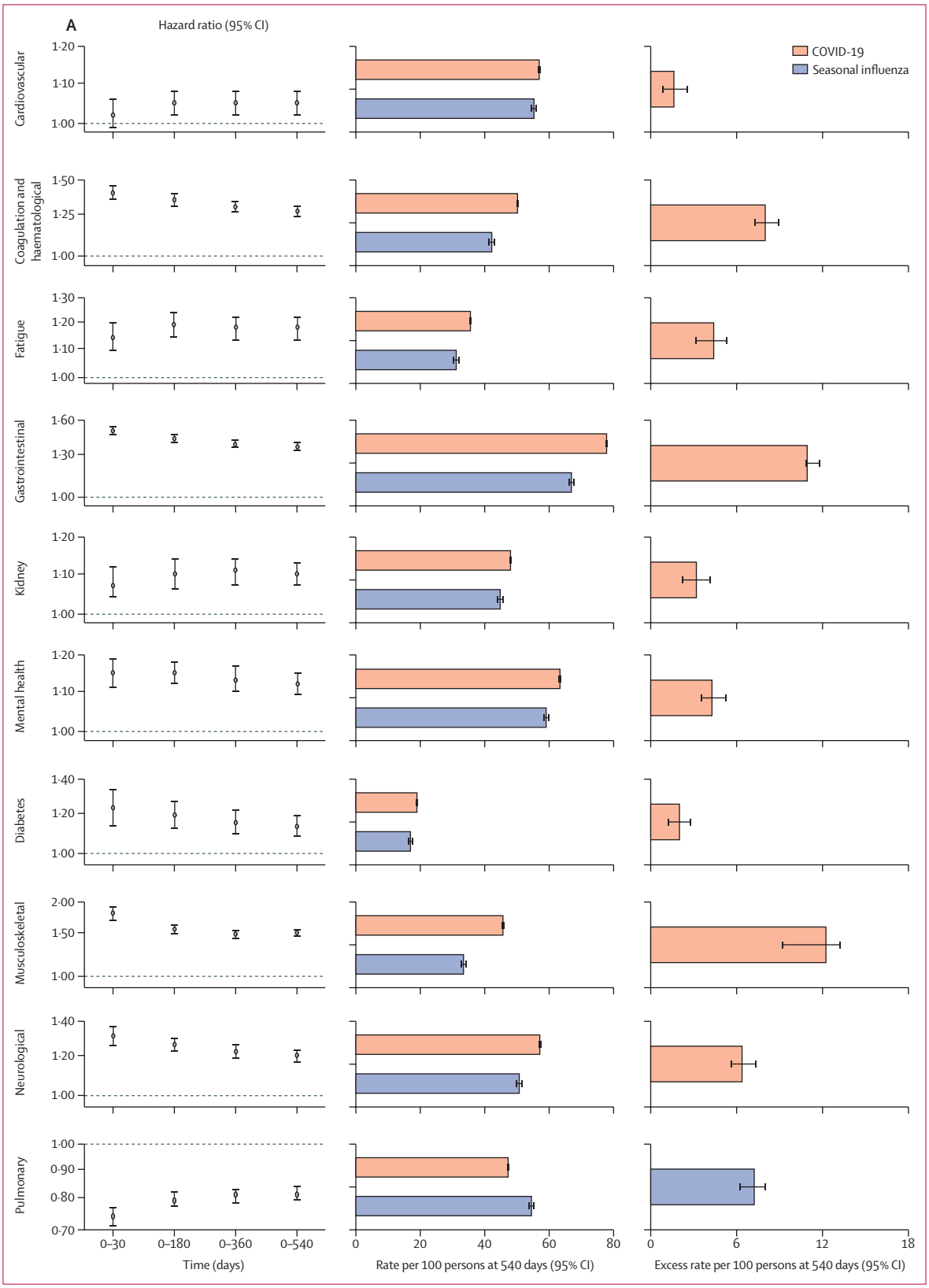
We conducted analyses to estimate the comparative risks of people admitted to hospital for COVID-19 and seasonal influenza by their respective vaccination status. Compared to seasonal influenza, COVID-19 had a higher risk of death and involvement in all organs except for the pulmonary system regardless of COVID-19 and seasonal influenza vaccination status (appendix 2 supplementary table 15).

We conducted multiple sensitivity analyses on outcome of death, each organ system, and across all organ systems. Results from all sensitivity analyses were consistent with the main results, showing that COVID-19 had a higher risk of death and disease across all organ systems except for the pulmonary system (appendix 2 supplementary table 16).

Discussion

In this comparative analysis of long-term health outcomes of people admitted to hospital for COVID-19 versus those admitted to hospital for seasonal influenza, we show that the absolute rates of death, adverse health outcomes, and health-care utilisation are high for both viruses, but significantly higher for COVID-19 compared to seasonal influenza. Our analyses of health burden by organ system show differential risks across organ systems, with a higher burden of pulmonary organ involvement in seasonal influenza and a higher burden of extrapulmonary organ involvement in COVID-19. Our decomposition analyses reveal two key findings: both SARS-CoV-2 infection and seasonal influenza result in a higher burden of health loss in the post-acute phase than their respective acute phases; and SARS-CoV-2 results in a higher burden of health loss in both the acute and post-acute phase than seasonal influenza. Altogether, these findings emphasise the high toll of death, health loss, and health-care utilisation following hospital admission for seasonal influenza and even a higher toll for SARS-CoV-2, and highlight the continued need to reduce the risk of hospital admission for these two viruses as a means to alleviate the burden of health loss in populations.

Our results show that, compared to seasonal influenza and despite changes in SARS-CoV-2 during the course of the pandemic (from pre-delta to delta to omicron), COVID-19 yielded a significantly higher burden of death, health loss across the spectrum of nine of ten organ systems (with the notable exception of pulmonary outcomes), and health-care utilisation. The excess burden per 100 people admitted to hospital for COVID-19 versus seasonal influenza should be interpreted in the context of a two to three times greater number of people being admitted to hospital for COVID-19 versus seasonal influenza in the USA during the same period.[21,22] This suggests that effort to reduce the risk of hospital admission for COVID-19 via prevention of infection and reinfection (especially in vulnerable populations), vaccination, and the use of antivirals should remain a core pillar of public health policy.[13,16,23–25]



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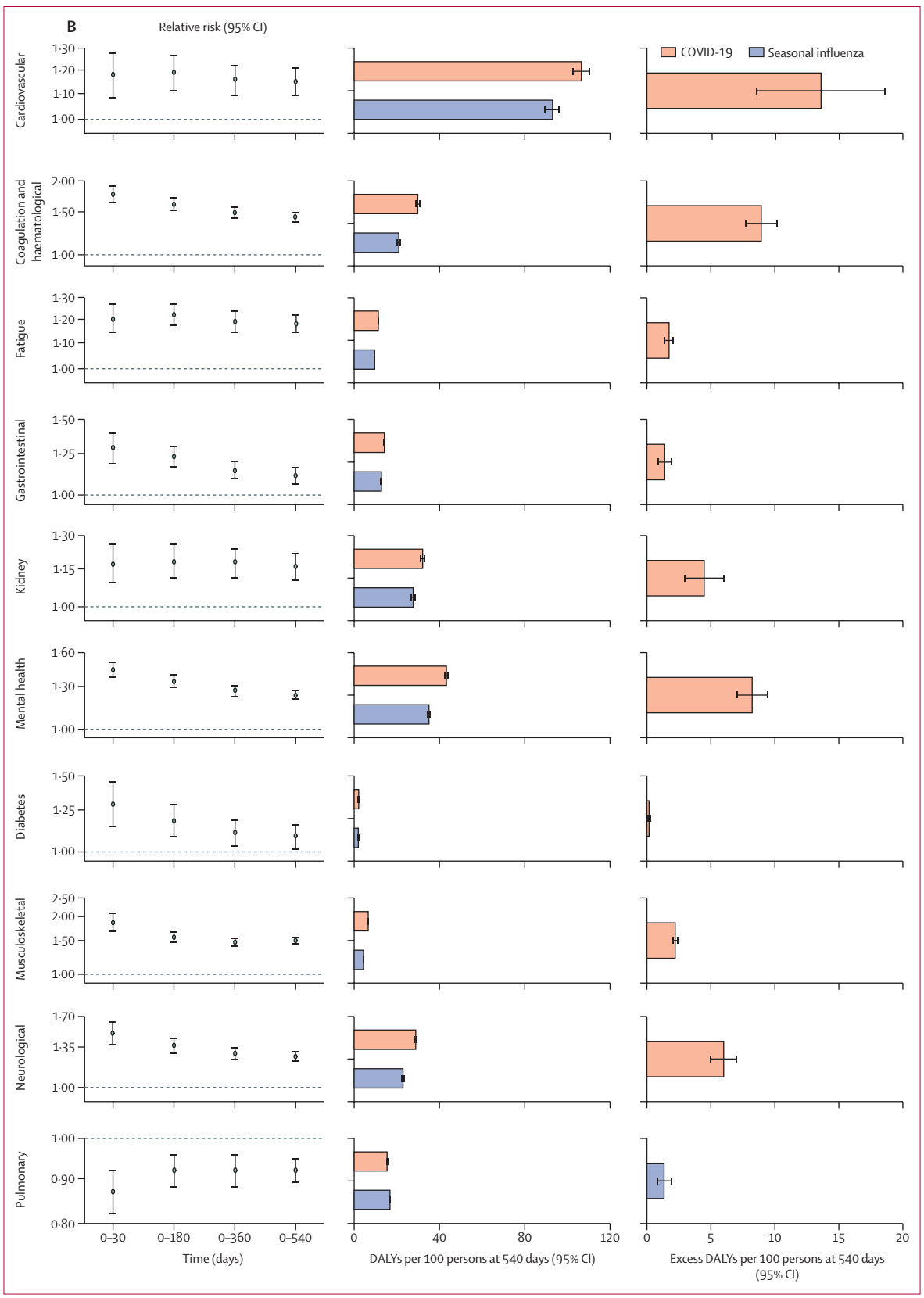
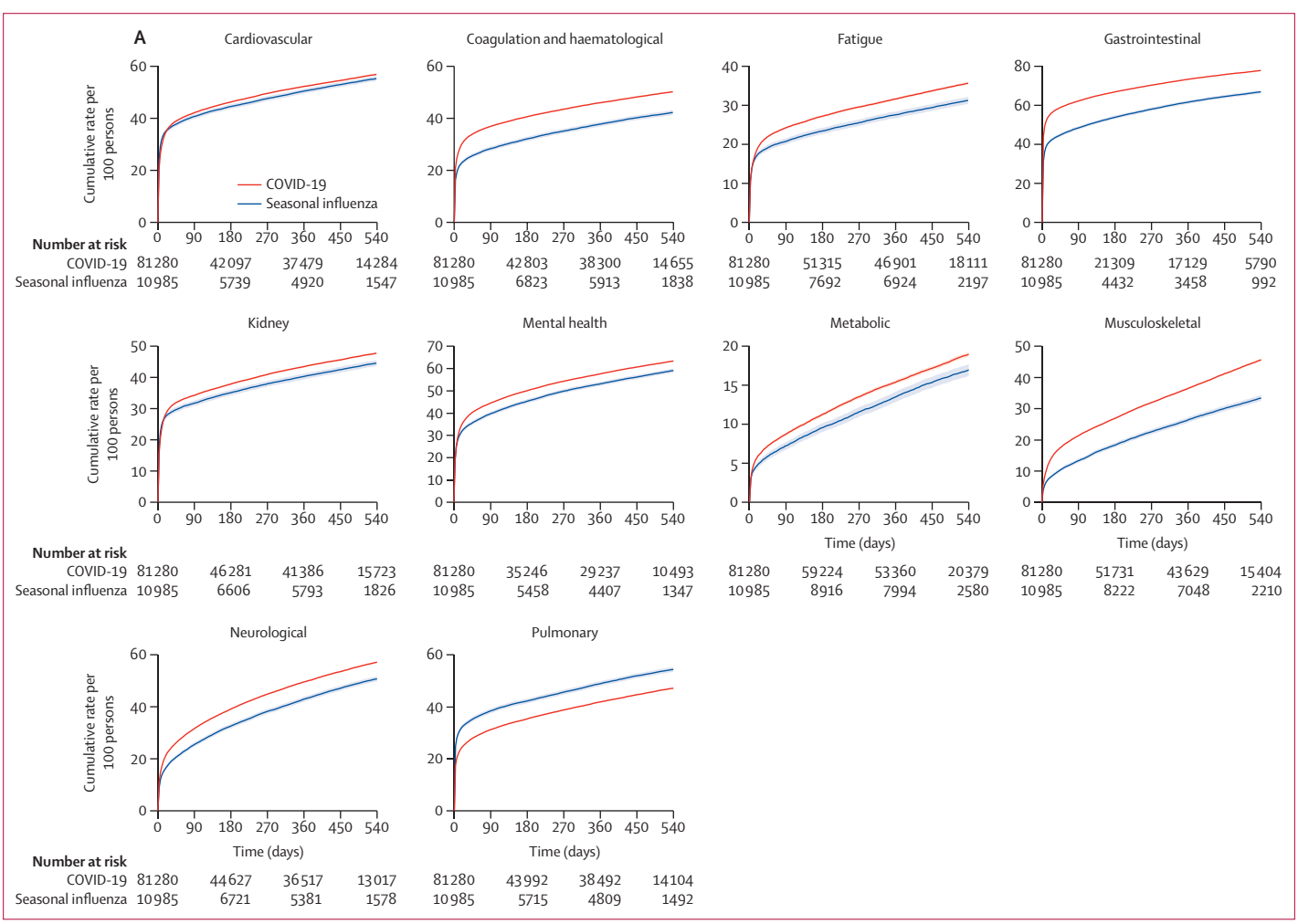


***Figure 3*: Risks and burdens of adverse health outcomes by organ system for COVID-19 versus seasonal influenza**
(A) Risk and burden estimated on the basis of event rate. (B) Risk and burden estimated on the basis of disability-adjusted life-years (DALYs). The first column in both panels includes risk on relative scale for COVID-19 compared to seasonal influenza on organ system by time periods of 0–30, 0–180, 0–360, and 0–540 days after hospital admission. The second column in both panels includes the cumulative burden per 100 persons at 540 days in the COVID-19 (red) and seasonal influenza (blue) groups. The third column in both panels presents the difference per 100 persons at 540 days. The difference for COVID-19 that excessed seasonal influenza was plotted in red and the difference for seasonal influenza that excessed COVID-19 was plotted in blue.

Our results also suggest that while both viruses exact a substantial toll of health loss across multiple organ systems, our comparative evaluation of the risks of adverse health outcomes across ten organ systems suggests that seasonal influenza is more of a respiratory virus than SARS-CoV-2 and that the latter is a more multisystemic virus than seasonal influenza. The mechanistic underpinnings of the multisystemic nature of SARS-CoV-2 sequelae are being elucidated;[26–29] these could provide insights into potential therapeutic interventions to ameliorate clinical outcomes. The multisystemic nature of SARS-CoV-2 also presents opportunities to provide integrated care across the various phases of illness (acute and post-acute).

We also show that both viruses yield a higher burden of health loss in the post-acute phase of illness than their respective acute phase, suggesting that focusing solely on the acute toll of these viruses obscures a larger portion of their overall effect and they should be conceptualised as infections leading to a high risk and burden of acute disease and even higher long-term risks of health loss. Furthermore, our comparative analyses of the burden of health loss emanating from both the acute and post-acute phase of COVID-19 and seasonal influenza showed a higher burden of health loss in both phases in COVID-19, resulting not only in a much larger cumulative burden of health loss but also implying a longer-term risk horizon for organ damage than seasonal influenza. This observation emphasises the need for provision of post-acute care following hospital admission for either COVID-19 or seasonal influenza, and that this need is likely to be greater for COVID-19; provision of post-acute care will not only facilitate the management of post-acute sequelae but could also improve health outcomes and reduce the need for costly health-care utilisation (repeat hospital admissions and intensive care).

This study has several strengths. We leveraged the vast databases of the VA, drawing on multiple data domains including demographics, diagnoses, laboratory tests, medications, vital signs, health-care utilisation, and contextual factors to build two large cohorts and follow



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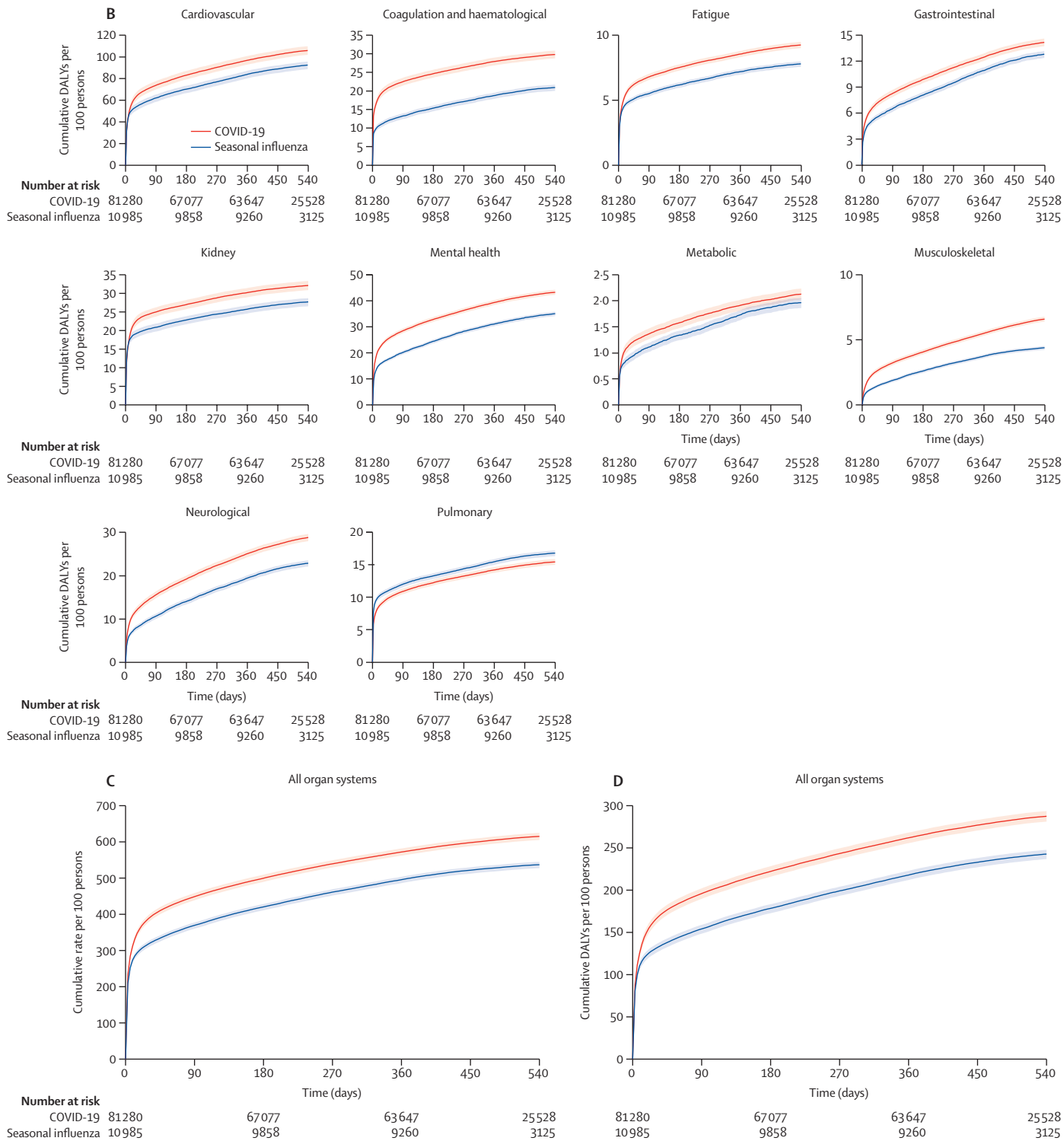
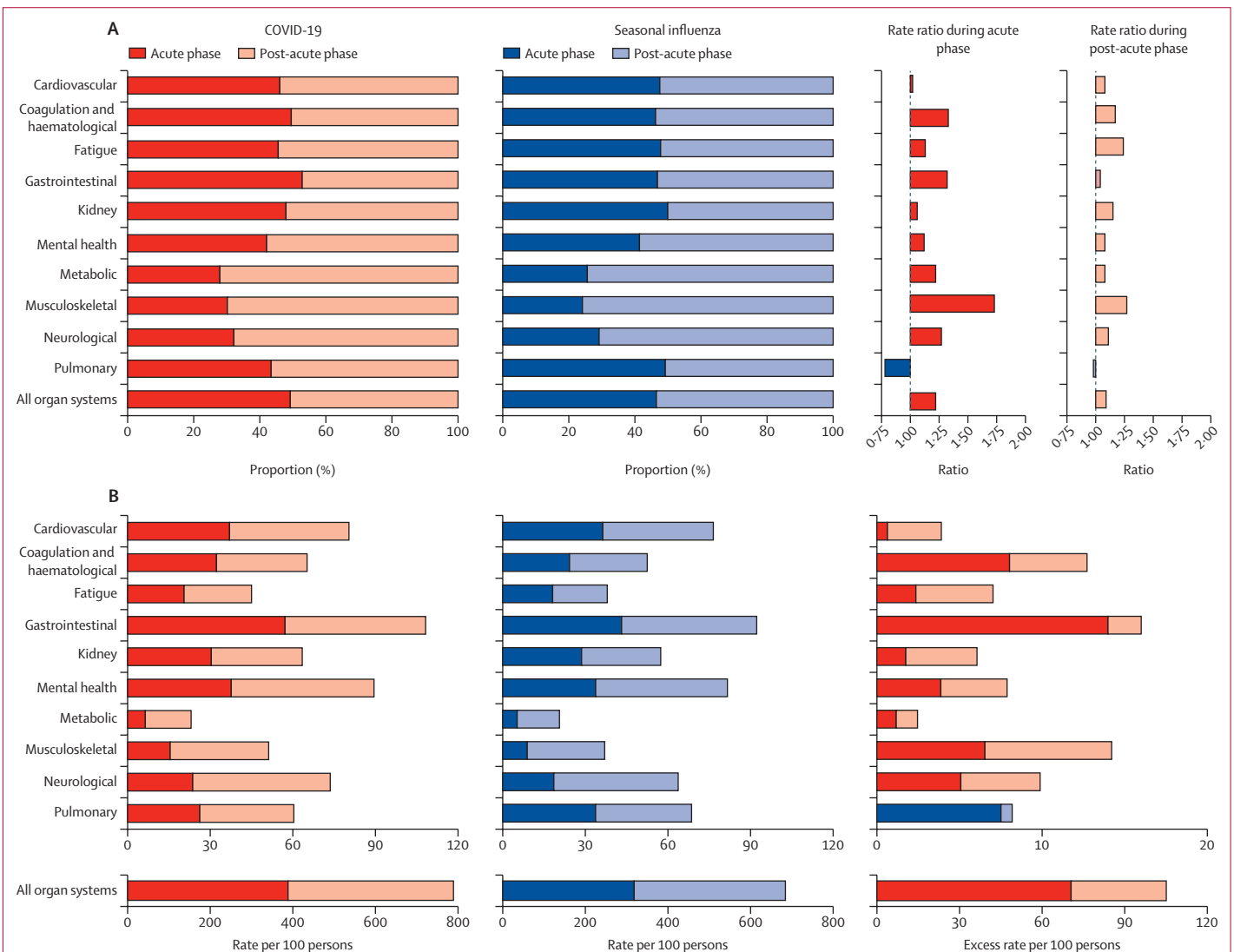


Figure 4: **Event rates of adverse health outcomes by organ system and across all organ systems in COVID-19 and seasonal influenza**
(A) Event rates per 100 persons presented for the COVID-19 (red) and seasonal influenza (blue) groups in each organ system. (B) Disability-adjusted life-years (DALYs) per 100 persons presented for the COVID-19 (red) and seasonal influenza (blue) groups in each organ system. (C) Event rates per 100 persons presented for COVID-19 (red) and seasonal influenza (blue). (D) DALYs per 100 persons presented for COVID-19 (red) and seasonal influenza (blue). Shaded areas are 95% CIs.

them up longitudinally over time to comparatively evaluate risks over several time intervals (including the acute phase and post-acute phase) and cumulatively over 18 months. We examined risk in 81 280 patients admitted to hospital for COVID-19 across different eras of the pandemic (pre-delta, delta, and omicron). We examined risk in 10 985 patients admitted to hospital for seasonal influenza and further examined comparative risk between COVID-19 and seasonal influenza type A (8360 [76·1%] of 10 985 in the influenza cohort) and other types of influenza (2625 [23·9%] of 10 985 in the influenza cohort). We evaluated the risks of death, health-care utilisation, and a comprehensive list of 94 pre-specified adverse health outcomes across ten organ systems. We reported estimates of risks on both the relative scale (HRs and relative risks) and absolute scale (rates). We also estimated DALYs, which took into account the occurrence of an outcome and its influence on overall health. We challenged the robustness of our primary approach in multiple sensitivity analyses; all yielded consistent results.

This study has several limitations. The study population predominantly comprised older white males and thus might not represent the general population admitted to hospital for COVID-19 and seasonal influenza, which could limit the generalisability of the findings. We evaluated risks in people admitted to hospital for COVID-19 versus those admitted to hospital for seasonal influenza; the results should not be extrapolated to those with milder infection that did not necessitate hospital admission. Because, as a byproduct of COVID-19 public health mitigation measures, hospital admission for seasonal influenza was rare in the USA during most of the COVID-19 cohort enrolment period, we enrolled a historical influenza cohort;



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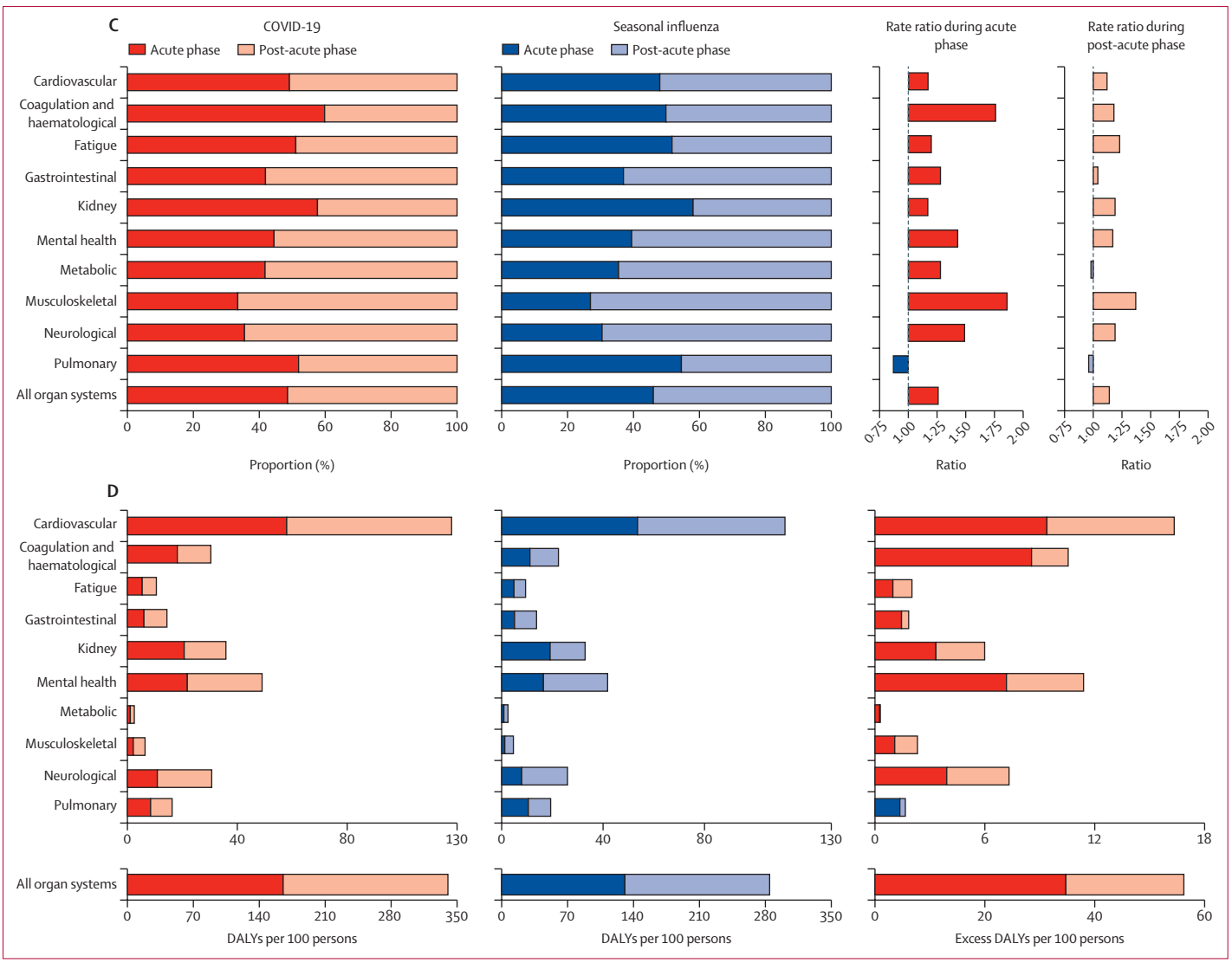

Figure 5: **Cumulative rate of adverse health outcomes by organ system and across all organ systems during acute and post-acute phase**
(A) Rate-based results presented on relative scale. From left to right: percentage of rate contributed from acute and post-acute phase in the COVID-19 group and in the seasonal influenza group, and rate ratio of COVID-19 compared to seasonal influenza during the acute phase and during the post-acute phase. (B) Rate-based results presented on absolute scale. From left to right: cumulative rate per 100 persons in the acute phase and post-acute phase in the COVID-19 group and in the seasonal influenza group, and excess rate per 100 persons between COVID-19 and seasonal influenza. (C) Results based on disability-adjusted life-years (DALYs) presented on relative scale. From left to right: percentage of DALYs contributed from the acute and post-acute phase in the COVID-19 group and in the seasonal influenza group, and rate ratio of COVID-19 compared to seasonal influenza during the acute phase and post-acute phase. (D) DALYs-based results presented on absolute scale. From left to right: DALYs per 100 persons in acute phase and post-acute phase in the COVID-19 group and in the seasonal influenza group, and excess DALYs per 100 persons between COVID-19 and seasonal influenza.

temporal changes in care and awareness of post-acute infection outcomes could confound the results. Although we balanced the two exposure groups through application of same inclusion and exclusion criteria and application of inverse probability weighting based on characteristics from multiple data dimensions including sociodemographics, health status (including baseline comorbidities), vital and laboratory measurements, and health-care utilisation, we cannot completely rule out the effect of biases, including residual confounding and misclassification of covariates such as smoking status or outcomes. We curated and pre-specified a comprehensive set of 94 health outcomes that could be associated with COVID-19 or seasonal influenza based on current knowledge, but there could be additional outcomes of importance—yet to be associated with either infection—that are not included in this analysis. Estimates of risk that are based on Cox models are sensitive to its underlying assumptions and prone to selection bias.[30] The absolute rates reflect the contribution of hospital admission to infection and the underlying baseline risk. Although we conducted a

comparative evaluation of risks between those admitted to hospital for seasonal influenza and those admitted to hospital for COVID-19 during the pre-delta, delta, and omicron eras, our study was not designed to assess differences in COVID-19 outcomes by era. We enrolled the seasonal influenza cohort between Oct 1, 2015, and Feb 28, 2019 and conducted comparisons for COVID-19 with seasonal influenza type A and other types as sensitivity analyses; we did not assess the comparative risks of various subtypes of influenza versus COVID-19. Our evaluation included a comparative assessment of clinical manifestations and outcomes of seasonal influenza and COVID-19; however, a pandemic influenza might have different clinical manifestations and a different outcome profile. Several factors could affect the comparative risk profiles, including changes in the virus, immunity, and changes in clinical care—all are still highly dynamic for SARS-CoV-2.

In sum, the burden of death, health loss, and healthcare utilisation is high among those admitted to hospital for seasonal influenza, but higher among those admitted to hospital for COVID-19 in the pre-delta, delta, and omicron eras. The risk of pulmonary involvement is higher in seasonal influenza while the risk of extrapulmonary organ system involvement is higher in COVID-19. Both infections lead to a higher burden of health loss in the post-acute phase than the acute phase of illness and, comparatively, COVID-19 has a higher burden of acute and post-acute health loss than seasonal influenza. Altogether, these findings emphasise the need to reduce the risk of infection and hospital admission due to SARS-CoV-2 and seasonal influenza and the need for post-acute care strategies to reduce the burden of health loss in populations.

Contributors

YX and ZA-A contributed to the research area and study design. YX, TC, and ZA-A contributed to data acquisition. YX, TC, and ZA-A contributed to data analysis and interpretation. YX, TC, and ZA-A contributed to statistical analysis. YX and ZA-A drafted the manuscript. YX, TC, and ZA-A contributed to critical revision of the manuscript. ZAA provided administrative, technical, or material support, as well as .supervision and mentorship. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. ZA-A takes responsibility for the fact that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted, and that any discrepancies from the study as planned have been explained. YX, TC, and ZA-A had full access to all the data in the study, and YX and ZA-A have verified the accuracy of all underlying data. All authors had final responsibility for the decision to submit the manuscript for publication.

Declaration of interests

YX and ZA-A report consulting (uncompensated) for Pfizer. YX reports consulting for Guidepoint. ZA-A reports consulting for Gilead Sciences and Tonix Pharmaceuticals. TC declares no competing interests.

Data sharing

The data that support the findings of this study are available from the US Department of Veterans Affairs, Office of Research and Development, VA Information Resource Center: VIReC@va.gov.

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