bmjmedicine

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Risk of admission to hospital with arterial or venous thromboembolism among patients diagnosed in the ambulatory setting with covid-19 compared with influenza: retrospective cohort study

Vincent Lo Re III [1,2] Sarah K Dutcher [3] John G Connolly [4,5] Silvia Perez-Vilar [3] Dena M Carbonari [2] Terese A DeFor,[6] Djeneba Audrey Djibo [7] Laura B Harrington [8] Laura Hou [4,5] Sean Hennessy [2] Rebecca A Hubbard [2] Maria E Kempner,[4,5] Jennifer L Kuntz [9] Cheryl N McMahill-Walraven [7] Jolene Mosley,[4,5] Pamala A Pawloski [6] Andrew B Petrone [4,5] Allyson M Pishko [1] Meighan Rogers Driscoll [4,5] Claudia A Steiner,[10] Yunping Zhou,[11] Noelle M Cocoros [4,5]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjmed-2022-000421).

For numbered affiliations see end of article.
Correspondence to: Dr Vincent Lo Re III, Department of Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA; vincentl@pennmedicine.upenn.edu

Cite this as: *BMJMED* 2023;2:e000421. doi:10.1136/bmjmed-2022-000421

Received: 1 November 2022
Accepted: 3 May 2023

ABSTRACT

OBJECTIVE To measure the 90 day risk of arterial thromboembolism and venous thromboembolism among patients diagnosed with covid-19 in the ambulatory (ie, outpatient, emergency department, or institutional) setting during periods before and during covid-19 vaccine availability and compare results to patients with ambulatory diagnosed influenza.

DESIGN Retrospective cohort study.

SETTING Four integrated health systems and two national health insurers in the US Food and Drug Administration's Sentinel System.

PARTICIPANTS Patients with ambulatory diagnosed covid-19 when vaccines were unavailable in the US (period 1, 1 April-30 November 2020; n=272 065) and when vaccines were available in the US (period 2, 1 December 2020-31 May 2021; n=342 103), and patients with ambulatory diagnosed influenza (1 October 2018-30 April 2019; n=118 618).

MAIN OUTCOME MEASURES Arterial thromboembolism (hospital diagnosis of acute myocardial infarction or ischemic stroke) and venous thromboembolism (hospital diagnosis of acute deep venous thrombosis or pulmonary embolism) within 90 days after ambulatory covid-19 or influenza diagnosis. We developed propensity scores to account for differences between the cohorts and used weighted Cox regression to estimate adjusted hazard ratios of outcomes with 95% confidence intervals for covid-19 during periods 1 and 2 versus influenza.

RESULTS 90 day absolute risk of arterial thromboembolism with covid-19 was 1.01% (95% confidence interval 0.97% to 1.05%) during period 1, 1.06% (1.03% to 1.10%) during period 2, and with influenza was 0.45% (0.41% to 0.49%). The risk of arterial thromboembolism was higher for patients with covid-19 during period 1 (adjusted hazard ratio 1.53 (95% confidence interval 1.38 to 1.69)) and period 2 (1.69 (1.53 to 1.86)) than for patients with influenza. 90 day absolute risk of venous thromboembolism with covid-19 was 0.73% (0.70% to 0.77%) during period 1, 0.88% (0.84 to 0.91%) during period 2, and with influenza was 0.18% (0.16% to 0.21%). Risk of venous thromboembolism was higher with covid-19 during period 1 (adjusted hazard ratio 2.86 (2.46 to 3.32)) and period 2 (3.56 (3.08 to 4.12)) than with influenza.

CONCLUSIONS Patients diagnosed with covid-19 in the ambulatory setting had a higher 90 day risk of admission to hospital with arterial thromboembolism and venous thromboembolism both before and after covid-19 vaccine availability compared with patients with influenza.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Case series and cohort studies of patients admitted to hospital with covid-19 have suggested that SARS-CoV-2 infection promotes hypercoagulability that could lead to arterial thromboembolism or venous thromboembolism
⇒ Incidence and determinants of thrombotic complications after diagnosis of covid-19 in the ambulatory setting remain unclear
⇒ Using propensity scores to account for differences between people with covid-19 or influenza who were admitted to hospital, risk of venous thromboembolism, but not arterial thromboembolism, was significantly higher with covid-19, before and during vaccine availability, compared with influenza

WHAT THIS STUDY ADDS

⇒ Patients diagnosed with covid-19 in the ambulatory setting had a higher 90 day risk of admission to hospital with arterial thromboembolism and venous thromboembolism, before and after covid 19 vaccine availability, compared with patients with ambulatory diagnosed influenza

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ Risk factors for arterial thromboembolism and venous thromboembolism could be used to identify subgroups at high risk of these thrombotic complications, for whom closer monitoring for events may be warranted, and could help to inform interventions to prevent their development

Introduction

Reports have suggested that SARS-CoV-2 infection promotes hypercoagulability that could lead to arterial thromboembolism (ATE) or venous

thromboembolism (VTE).[1–5] Studies evaluating thrombotic complications with covid-19 have focused mainly on patients admitted to hospital. We previously reported a significantly higher risk of VTE, but not ATE, among patients admitted to hospital with covid-19 before (April-November 2020) and during (December 2020-May 2021) periods of covid-19 vaccine availability compared with patients admitted to hospital with influenza during the 2018-19 season within the US Food and Drug Administration (FDA) Sentinel System.[6] However, few studies have examined the incidence of ATE or VTE among patients diagnosed with covid-19 in the ambulatory (ie, outpatient, emergency department, or institutional) setting.[7 8] Moreover, whether the risk of admission to hospital with ATE or VTE after ambulatory diagnosed covid-19 differs from that after ambulatory diagnosed influenza is unclear. These data can help to determine if biological differences exist in the risk of thrombosis after SARS-CoV-2 infection compared with another common respiratory viral infection.

To address these knowledge gaps, we measured the 90 day absolute risk of admission to hospital with ATE and VTE among patients initially diagnosed with covid-19 in the ambulatory setting both before and during covid-19 vaccine availability in the US. The risk of admission to hospital with ATE and VTE in patients with covid-19 during each of these periods was compared with the risk among patients initially diagnosed with influenza in the ambulatory setting prior to the covid-19 pandemic. We selected patients with influenza as the comparator because this pathogen also causes pandemics, precipitates admission to hospital when severe, and is associated with increased risk of acute myocardial infarction,[9] ischemic stroke,[10] and VTE.[11 12] Among patients with ambulatory diagnosed covid-19, we also examined characteristics present prior to covid-19 diagnosis as risk factors for admission to hospital with ATE or VTE.

Methods

Study design and data sources

In this retrospective cohort study, we investigated patients diagnosed with covid-19 or influenza who were in the US FDA Sentinel System. Sentinel is a multi-site distributed data network with standardized, quality-checked administrative claims and electronic health record data.[13 14] Data include health plan enrollment dates, demographics, diagnoses (recorded using International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes), laboratory results, and dispensed outpatient medications.

We used data from six Data Partners: two national health insurers (Aetna, a CVS Health company and Humana Healthcare Research, Inc) and four regional integrated health systems (HealthPartners Institute; Kaiser Permanente Colorado; Kaiser Permanente Northwest; and Kaiser Permanente Washington).[13] We used the routine data quality processes and programmes used within Sentinel.[15–17] The study protocol and statistical analysis plan were reviewed, approved, and posted on the FDA Sentinel website prior to study implementation.[18] This Sentinel study was a public health surveillance activity conducted under FDA authority and was not subject to Institutional Review Board oversight.[19 20]

Study population

The covid-19 cohort eligibility criteria included: (1) initial covid-19 ICD-10-CM diagnosis U07.1 or positive SARS-CoV-2 nucleic acid test recorded in the ambulatory (ie, outpatient, emergency department, or institutional (eg, nursing home)) setting between 1 April 2020 and 31 May 2021; (2) age at least 18 years at diagnosis; and (3) at least 365 days of continuous prior medical and pharmacy coverage at diagnosis. The influenza cohort eligibility criteria included: (1) initial influenza ICD-10-CM diagnosis or positive influenza nucleic acid test recorded in the ambulatory setting between 1 October 2018 and 30 April 2019; (2) age 18 years or older at diagnosis; and (3) at least 365 days of continuous prior medical and pharmacy coverage at diagnosis. The approach that we used to identify patients with covid-19 and influenza has been previously reported.[21 22] Patients with ambulatory diagnosed covid-19 or influenza who were subsequently admitted to hospital on the same date were classified as admitted to hospital and considered not eligible for inclusion. To ensure that patients with influenza were not co-infected with covid-19, we included patients diagnosed during the 2018-19 influenza season (moderate in severity[23]), which was prior to the first detection of SARS-CoV-2 in the US. We allowed patients previously diagnosed with influenza during the 2018-19 season to be included in the covid-19 cohort because prior influenza infection was unlikely to affect subsequent thrombosis risk with covid-19.

We defined the index date as the earliest date of diagnosis or positive laboratory test for covid-19 or influenza during the corresponding period. Within each cohort, we excluded patients with diagnostic or laboratory evidence of their infection within 90 days prior to the index date to ensure inclusion of incident infections. We also excluded patients diagnosed with another respiratory virus (ie, adenovirus, enterovirus, metapneumovirus, parainfluenza, respiratory syncytial virus, and rhinovirus) within 14 days before or after their index date; those in the covid-19 cohorts were excluded if they had evidence of influenza within 14 days before or after their index date. The 365 days prior to the index date represented the baseline period. Follow-up began on the index date and continued until an ATE or VTE event (defined below), disenrollment from medical or pharmacy coverage, death, or 90 days after index date, whichever occurred first.

Main study outcomes

We evaluated two primary endpoints: admission to hospital with ATE, defined by a principal or contributory hospital discharge diagnosis of acute myocardial infarction or ischemic stroke; and admission to hospital with VTE, defined by a principal or contributory hospital discharge diagnosis of acute deep vein thrombosis or pulmonary embolism. We chose to ascertain inpatient ATE and VTE events as primary endpoints to identify severe thrombotic outcomes that required treatment in the hospital setting. Events were ascertained using ICD-10-CM diagnoses, as previously defined,[6] mapped from ICD-9-CM diagnoses for ATE[24–27] and VTE[28 29] that had been validated within Sentinel against medical record review. Prior to the current analysis, mapped ICD-10-CM diagnoses underwent clinical review to ensure appropriate inclusion within ATE and VTE endpoint algorithms.

We examined three secondary outcomes. We evaluated an expanded ATE endpoint that included emergency department or hospital discharge diagnoses of acute myocardial infarction, ischemic stroke, angina, transient ischemic attack, or peripheral arterial disease. We also evaluated an expanded VTE endpoint that included emergency department or hospital discharge diagnoses of acute deep vein thrombosis, pulmonary embolism, or venous thrombosis of devices, implants, or grafts. Additionally, we examined all cause mortality within 30 days after an inpatient ATE or VTE event.

Covariates

We collected age at diagnosis, sex, race and ethnic group (both obtained by self-report via closed-ended questionnaires or health plan enrollment forms), geographical location of care setting, month of covid-19 diagnosis, and number of medical encounters in the year before index diagnosis. During the baseline period, we identified diagnoses that might affect SARS-CoV-2 or influenza infection, or thrombosis risk, as defined previously.[6] We collected hemoglobin and platelet counts during the baseline period from dates closest to (or on) the index date. We identified dispensed outpatient fills for anticoagulants, antiplatelet drugs, statins, and other products possibly affecting coagulation in the three to 183 days prior to the index date as a measure of recent use of these treatments.[6] To estimate infection severity, we collected data on admission to hospital for any reason within 14 days after index diagnosis of covid-19 or influenza.

Statistical analysis

Since covid-19 vaccination might affect risk of thrombosis after SARS-CoV-2 infection,[30] we separately evaluated patients with ambulatory diagnosed covid-19 during a period when vaccines were unavailable (period 1, 1 April 2020-30 November 2020) and during a period when they were available in the US (period 2, 1 December 2020-31 May 2021). In the US, covid-19 and influenza vaccination often occurs in the community or workplace, outside of healthcare settings and without reimbursement by health plans. As a result, documentation of immunization is not complete within US administrative claims and electronic medical record databases.[31 32] Consequently, we evaluated periods of ambulatory diagnosed covid-19 stratified by availability of covid-19 vaccination. We assessed differences between the covid-19 and influenza cohorts using standardized differences, of which an absolute value of ≥0.1 indicated meaningful imbalance.[33] For each cohort, we estimated the unadjusted 90 day absolute risk and incidence rates of ATE and VTE with 95% confidence intervals separately and stratified results by demographic characteristics, history of cardiovascular disease or prior VTE, and month at diagnosis (for patients with covid-19 since SARS-CoV-2 variants evolved over time and evaluation for thrombotic complications changed during the course of the pandemic). For all cohorts, we performed a sensitivity analysis accounting for death as a competing risk using the cumulative incidence function.[34]

We developed propensity scores to control for differences in characteristics between the influenza cohort and each covid-19 cohort. Within each Data Partner, we estimated for each patient a single propensity score using logistic regression, with covid-19 (versus influenza) status as the dependent variable. We excluded patients from each covid-19 cohort whose score exceeded the maximum or minimum values in the influenza cohort and vice versa (ie, trimmed the tails). We used fine stratification of propensity scores to retain the maximum number of patients.[35] We assigned patients to one of 50 propensity score strata based on quantiles of the score distribution among patients with covid-19. We calculated stratum-specific weights using the distribution of exposure within each stratum to create a weighted population reflecting the characteristics of the overall sample.[36] We implemented weighted propensity score fine stratification, since traditional unweighted propensity score stratification would likely not provide sufficiently strong confounding control.[35 36]

We used weighted Cox regression accounting for propensity scores and adjusted for Data Partner to calculate hazard ratios with robust 95% confidence intervals of primary and secondary thrombotic outcomes comparing covid-19 during period 1 or 2 versus influenza.[37] We performed sensitivity analyses to assess the robustness of the results of the primary analyses to unmeasured confounding using E-values, which represent the minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need to have with both exposure and outcome to explain an observed association.[38]

Additionally, for primary endpoints, we stratified results by cardiovascular disease (ATE analysis) or prior VTE (VTE analysis). Among patients who had an inpatient ATE or VTE event, we used weighted Cox regression accounting for propensity scores and adjusted for Data Partner to estimate hazard ratios for mortality in the 30 days after the event during each covid-19 period versus influenza.

Among patients diagnosed with covid-19 in the ambulatory setting, we evaluated baseline characteristics as risk factors for ATE and VTE on the basis of their potential to promote stasis of circulation, endothelial injury, or hypercoagulability.[6] Variables included diagnoses of alcohol dependence or misuse, antiphospholipid antibody syndrome, atrial fibrillation or flutter, cancer, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, heart failure, cardiovascular disease (for ATE analysis) or VTE (for VTE analysis), hypertension, hyperlipidemia, inherited thrombophilia, neurological diseases that promote immobility (Alzheimer's disease, amyotrophic lateral sclerosis, dementia, Guillain-Barre syndrome, multiple sclerosis, muscular dystrophy, Parkinson's disease), obesity, pregnancy, polycythemia (diagnosis or hemoglobin >16.0 g/dL), rheumatological disease, thrombocytosis (diagnosis or platelet count >450 000/µL), and tobacco use. We also evaluated by older age group, sex, and outpatient dispensing of an anticoagulant, antiplatelet, or statin within three to 183 days prior to the index date. We used multivariable Cox regression to estimate hazard ratios with 95% confidence intervals of inpatient ATE and VTE for each risk factor during period 1 and period 2 that was adjusted for all other risk factors. Data were analyzed using SAS 9.4 (SAS Institute Inc, Cary, NC).

Patient and public involvement

We did not involve patients or members of the public in the study design, conduct, interpretation of results, or development of a dissemination strategy because this study was retrospective and used existing healthcare system data. On publication, we plan to share our results with clinicians and researchers through professional societies.

Results

Cohort characteristics

We identified 272 065 patients with ambulatory diagnosed covid-19 during period 1; 342 103 patients with ambulatory diagnosed covid-19 during period 2; and 118 618 patients with ambulatory diagnosed influenza during the 2018-19 season (table 1, figure 1). Patients with covid-19 were admitted more frequently to hospital for any reason within 14 days after ambulatory diagnosis during period 1 (17 879 (6.6%)) and period 2 (23 321 (6.8%)) than were patients with ambulatory diagnosed influenza (2421 (2.0%)).

Prior to propensity score fine stratification and weighting, patients with covid-19 in both periods were older; more frequently male and white; more commonly diagnosed with specific comorbidities, including atrial fibrillation or flutter, cardiovascular disease, chronic kidney disease, diabetes, hypertension, hyperlipidemia, and heart failure; and were more frequently dispensed statins, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, and anticoagulants during baseline compared with patients with influenza (table 1, online supplemental table 1). Patients with influenza more commonly had asthma and chronic obstructive pulmonary disease and more frequently received corticosteroids during baseline. After propensity score fine stratification and weighting, we did not observe standardized differences in characteristics of 0.1 or more between the cohorts for variables in propensity score models; some variables that were not included in propensity score models (ie, ethnic group and geographical location of care) had standardized differences ≥0.1 (table 1, online supplemental table 1). No data were missing in variables included in propensity scores and outcome models. No observations were excluded due to missing data. Data for ethnic group, race, and geographical location (online supplemental table 1) did have missingness associated with these variables, but they are reported only for descriptive purposes and were not included within propensity scores or examined in primary or secondary analyses.

Risk of ATE with covid-19 versus influenza

The unadjusted 90 day absolute risk of ATE was 1.01% (95% confidence interval 0.97% to 1.05%) for covid-19 during period 1, 1.06% (1.03% to 1.10%) for covid-19 during period 2, and 0.45% (0.41% to 0.49%) for influenza. After accounting for death as a competing risk, estimates of the absolute risk of ATE remained similar (online supplemental table 2). Within each cohort, the unadjusted 90 day risk of ATE was higher in patients who were older (≥65 years), male, or had cardiovascular disease (table 2). Among patients with covid-19, 90 day absolute risk of ATE varied by month of infection (online supplemental table 3). Unadjusted incidence rates of ATE for each cohort are reported in online supplemental table 4.

After propensity score fine stratification and weighting, the risk of ATE was significantly higher among patients with covid-19 during period 1 (adjusted hazard ratio 1.53 (1.38 to 1.69)) and period 2 (1.69 (1.53 to 1.86)) compared with patients with influenza (table 3). E-values for the point estimate and lower bound of the 95% confidence interval for period 1 were 2.43 and 2.10, and for period 2 were 2.77 and 2.43. Associations were attenuated when evaluating the secondary (expanded) ATE endpoint during period 1 (adjusted hazard ratio 1.20 (1.14 to

Table 1 | Demographic and clinical characteristics of ambulatory patients diagnosed with covid-19 in period 1 (1 April 2020-30 November 2020) and period 2 (1 December 2020-31 May 2021) compared with ambulatory patients diagnosed with influenza (1 October 2018-30 April 2019)

	Overall			Standardized difference after PS fine stratification and weighting	
Characteristic	Covid-19 period 1 cohort (n=272 065)*	Covid-19 period 2 cohort (n=342 103)*	Influenza cohort (n=118 618)*	Covid-19 period 1 *v* influenza	Covid-19 period 2 *v* influenza
Age, years:					
Mean† (SD)	55.6 (17.5)	56.1 (17.0)	51.0 (16.5)	0.084	0.079
18-44	86 564 (31.8)	105 220 (30.8)	49 028 (41.3)	−0.079	−0.066
45-54	38 454 (14.1)	48 596 (14.2)	18 920 (16.0)	−0.032	−0.032
55-64	42 182 (15.5)	53 241 (15.6)	18 190 (15.3)	−0.001	−0.020
65-74	57 089 (21.0)	76 909 (22.5)	19 539 (16.5)	0.079	0.086
75-84	33 535 (12.3)	43 320 (12.7)	10 131 (8.5)	0.035	0.038
≥85	14 241 (5.2)	14 817 (4.3)	2810 (2.4)	0.036	0.017
Sex†:					
Male	121 048 (44.5)	154 283 (45.1)	47 776 (40.3)	−0.005	−0.005
Female	151 017 (55.5)	187 820 (54.9)	70 842 (59.7)	0.005	0.005
Intensity of health service utilization, mean (SD):					
Ambulatory encounters†	14.8 (19.4)	15.0 (19.2)	13.7 (16.4)	0.013	0.016
Hospital encounters†	0.1 (0.5)	0.1 (0.5)	0.1 (0.5)	0.018	0.016
Comorbidities:					
Charlson/Elixhauser comorbidity score†, ‡, §, mean (SD)	1.4 (2.5)	1.3 (2.4)	1.0 (1.9)	0.041	0.039
Alcohol dependence/misuse†, §	5525 (2.0)	6597 (1.9)	1744 (1.5)	0.009	0.008
Antiphospholipid antibody syndrome†, §	352 (0.1)	426 (0.1)	144 (0.1)	−0.001	−0.000
Asthma†, §	24 484 (9.0)	31 245 (9.1)	13 424 (11.3)	−0.003	0.001
Atrial fibrillation or flutter†, §	19 861 (7.3)	24 740 (7.2)	5749 (4.8)	0.023	0.022
Cancer (excluding non-melanoma skin cancers)†, §	33 201 (12.2)	42 611 (12.5)	12 140 (10.2)	0.020	0.020
Chronic kidney disease†, §	39 610 (14.6)	49 497 (14.5)	12 089 (10.2)	0.032	0.030
Chronic liver disease†, §	16 010 (5.9)	20 507 (6.0)	5996 (5.1)	0.007	0.009
Chronic obstructive pulmonary disease†, §	30 803 (11.3)	37 272 (10.9)	14 778 (12.5)	0.029	0.033
Diabetes mellitus†, §	61 249 (22.5)	77 890 (22.8)	20 334 (17.1)	0.028	0.030
Type 1 diabetes§	3801 (1.4)	4410 (1.3)	1600 (1.3)	−0.025	−0.031
Type 2 diabetes§	60 297 (22.2)	76 854 (22.5)	19 915 (16.8)	0.029	0.032
Diabetes, unspecified§	4006 (1.5)	4813 (1.4)	1284 (1.1)	−0.001	−0.005
Heart failure†, §	21 430 (7.9)	26 131 (7.6)	5834 (4.9)	0.027	0.026
HIV†, §	1062 (0.4)	1096 (0.3)	390 (0.3)	−0.001	0.000
Hypertension†, §	125 942 (46.3)	162 357 (47.5)	45 757 (38.6)	0.056	0.056
Hyperlipidemia†, §	119 851 (44.1)	156 966 (45.9)	44 101 (37.2)	0.044	0.046
Inherited (primary) thrombophiliat†, §	1921 (0.7)	3364 (1.0)	569 (0.5)	0.010	0.015
Neurological disease†, §	18 184 (6.7)	17 356 (5.1)	3090 (2.6)	0.021	0.023
Obesity†, §	66 051 (24.3)	88 942 (26.0)	27 174 (22.9)	0.019	0.023
Pregnancy†, ¶	5289 (1.9)	7161 (2.1)	2866 (2.4)	−0.005	−0.006
Polycythemia vera§	262 (0.1)	369 (0.1)	107 (0.1)	−0.001	−0.000
Rheumatological disease†, §	11 658 (4.3)	15 568 (4.6)	5214 (4.4)	0.007	0.009
Tobacco use†, §	43 570 (16.0)	57 044 (16.7)	18 610 (15.7)	0.033	0.031
Cardiovascular disease†, **	61 737 (22.7)	77 702 (22.7)	19 353 (16.3)	0.045	0.041
Prior myocardial infarction**	10 344 (3.8)	13 228 (3.9)	3323 (2.8)	0.009	0.011
Prior stroke**	8636 (3.2)	9765 (2.9)	2119 (1.8)	0.030	0.022
Prior coronary artery disease**	44 684 (16.4)	56 767 (16.6)	14 415 (12.2)	0.029	0.025
Prior cerebrovascular disease, other**	17 608 (6.5)	21 209 (6.2)	5360 (4.5)	0.011	0.004
Prior PAD or acute limb ischemia**	20 961 (7.7)	25 458 (7.4)	5234 (4.4)	0.058	0.057
With recent outpatient anticoagulant use††	13 143 (4.8)	17 391 (5.1)	3814 (3.2)	0.014	0.013
Prior VTE†, **	5979 (2.2)	7454 (2.2)	1867 (1.6)	0.012	0.009

Continued

Table 1 Continued

Characteristic	Overall			Standardized difference after PS fine stratification and weighting	
	Covid-19 period 1 cohort (n=272 065)*	Covid-19 period 2 cohort (n=342 103)*	Influenza cohort (n=118 618)*	Covid-19 period 1 *v* influenza	Covid-19 period 2 *v* influenza
Prior deep vein thrombosis**	4098 (1.5)	5035 (1.5)	1278 (1.1)	0.010	0.006
Prior pulmonary embolism**	2385 (0.9)	3150 (0.9)	757 (0.6)	0.004	0.009
Prior venous thrombosis, other**	430 (0.2)	470 (0.1)	116 (0.1)	0.007	0.003
With recent outpatient anticoagulant use††	3762 (1.4)	4855 (1.4)	1121 (0.9)	0.011	0.008
Polycythemia (diagnosis code or hemoglobin >16.0 g/dL)†, §	6782 (2.5)	9309 (2.7)	3184 (2.7)	−0.003	−0.001
Thrombocytosis (diagnosis code or platelet count >450 000/µL)†, §	17 275 (6.3)	21 789 (6.4)	5230 (4.4)	0.012	0.012
Positive nucleic acid test at cohort entry	61 899 (22.7)	66 614 (19.5)	2149 (1.8)	–‡‡	–‡‡

PAD=peripheral artery disease; PS=propensity score; SD=standard deviation; VTE=venous thromboembolism.

*No. of patients are presented prior to weighting. Data presented as n (%) unless otherwise specified.

†Included in the propensity score logistic regression model. Additional included characteristics are in online supplemental table 1.

‡The Charlson/Elixhauser Combined Comorbidity Score is calculated based on comorbidities observed during a requester defined window around the exposure episode start date.[44]

§Determined from 365 days before through the date of index diagnosis.

¶Determined from 90 days before through the date of index diagnosis.

**Determined from 365 days before through one day prior to the date of index diagnosis.

††Determined from 183 days before through three days prior to the date of index diagnosis.

‡‡No standardized differences are reported because the method of identification was not included within the propensity score.

1.25)) and period 2 (1.28 (1.22 to 1.33)). Associations between covid-19 and ATE among groups stratified by history of cardiovascular disease were similar to those in the primary analysis (table 3). After an inpatient ATE event, 30 day all cause mortality was higher in patients with covid-19 during period 1 (2.65 (1.88 to 3.73)) and period 2 (2.53 (1.82 to 3.51)) compared patients with influenza.

Risk of VTE with covid-19 versus influenza

The unadjusted 90 day absolute risk of VTE was 0.73% (95% confidence interval 0.70% to 0.77%) for covid-19 during period 1, 0.88% (0.84% to 0.91%) for covid-19 during period 2, and 0.18% (0.16% to 0.21%) for influenza. After accounting for death as a competing risk, estimates of the absolute risk of VTE remained similar (online supplemental table 2). Within each cohort, the unadjusted 90 day risk of VTE was higher for patients who had prior history of VTE (table 2). Among patients with covid-19, 90 day absolute risk of VTE was variable by month of infection (online supplemental table 3). Unadjusted incidence rates of VTE for each cohort are reported in online supplemental table 4.

After propensity score fine stratification and weighting, the risk of VTE was higher with covid-19 during period 1 (adjusted hazard ratio 2.86 (2.46 to 3.32)) and period 2 (3.56 (3.08 to 4.12); table 3) than with influenza. E-values for the point estimate and lower bound of the 95% confidence interval for period 1 were 5.17 and 4.36, and for period 2 were 6.58 and 5.61. Associations were attenuated when evaluating the secondary (expanded) VTE endpoint during period 1 (2.49 (2.20 to 2.82)) and period 2 (3.14 (2.79 to 3.53)). Associations between covid-19 and VTE among groups stratified by history of prior VTE were similar to those in the primary analysis (table 3). After an inpatient VTE event, 30 day all cause mortality was higher for patients with covid-19 during period 1 (2.36 (1.34 to 4.18)) and period 2 (2.58 (1.48 to 4.50)) compared with influenza.

Risk factors for ATE and VTE in people with covid-19

Within fully adjusted models examining the primary ATE outcome, older age, male sex, chronic kidney disease, cardiovascular disease, diabetes, heart failure, hypertension, neurological disease, thrombocytosis, tobacco use, and recent outpatient antiplatelet drug use were associated with significantly higher risk of ATE during both periods (table 4).

Within fully-adjusted models examining the primary VTE outcome, older age, male sex, cancer, chronic kidney disease, chronic obstructive pulmonary disease, diabetes, heart failure, hypertension, prior history of VTE, inherited thrombophilia, obesity, and thrombocytosis were associated with significantly higher risk of VTE during both periods (table 4).

Discussion

Principal findings

Among patients initially diagnosed with covid-19 in the ambulatory setting during periods when covid-19 vaccines were unavailable (April-November 2020) and available (December 2020-May 2021), the 90 day risk of admission to hospital with ATE was 1.01-1.06%, and the 90 day risk of admission to hospital with VTE was 0.73-0.88%. The absolute

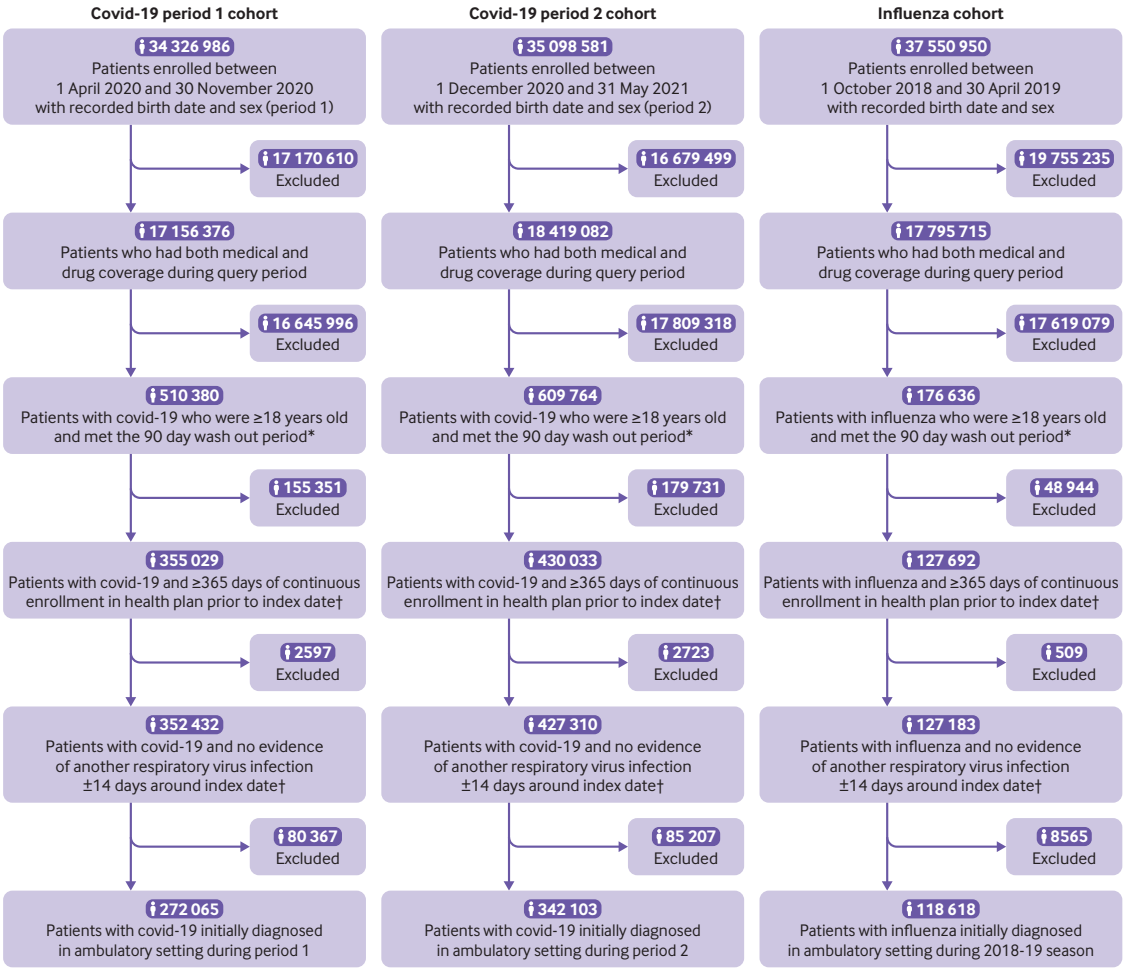

Figure 1 | Selection of patients diagnosed with covid-19 and influenza virus infection in the ambulatory setting. *Covid-19 and influenza were defined by a positive nucleic acid amplification test or diagnosis code in the ambulatory care setting. †Index date was defined as earliest date of first positive nucleic acid amplification test or diagnosis date in the ambulatory care setting

risk of ATE and VTE remained stable across both periods, despite differences in SARS-CoV-2 variants, covid-19 vaccine availability, access to SARS-CoV-2 testing, and potential changes in awareness and approaches to diagnosis of thrombotic complications related to covid-19. The 90 day risk of ATE and VTE was higher for patients with ambulatory diagnosed covid-19 than in patients with influenza prior to and during covid-19 vaccine availability. After an inpatient ATE or VTE event during either period, the risk of death was higher for patients with covid-19 than for patients with influenza. We identified characteristics associated with stasis of circulation, endothelial injury, or hypercoagulability that increased risk of ATE and VTE among individuals with ambulatory diagnosed covid-19.

Comparison with other studies and explanation of findings

Few studies have examined the risk of ATE or VTE among patients diagnosed with covid-19 in the ambulatory setting. One cohort study from Denmark found that the 30 day risk of VTE was 0.4% (40/9460) among patients not admitted to hospital and diagnosed with covid-19 between 27 February 2020 and 4 May 2020 compared with 1.0% (158/16 281) for patients not admitted to hospital and diagnosed with influenza between 2010 and 2018.[7] The higher absolute risk of VTE among patients with influenza in this study compared with our results might be due to inclusion of outpatient VTE events in their outcome definition. Another cohort study of 909 473 people who were not admitted to hospital but identified with covid-19 from Europe and the United Kingdom between 1 September 1 2020 and 31 July 2021 found that the 90 day incidence of ATE was 0.06-0.79%, and the 90 day incidence of VTE was 0.21-0.80%.[8] Our study found similar estimates of risk of ATE and VTE among US patients with ambulatory diagnosed covid-19.

Several reasons are possible for the observed higher ATE and VTE risk among patients with an ambulatory diagnosis of covid-19 compared with influenza. The inflammatory response generated by SARS-CoV-2 infection of endothelial cells can trigger endotheliitis, marked activation of coagulation cascades, and

Table 2 | Unadjusted 90 day absolute risk of inpatient arterial and venous thromboembolism events among patients who were diagnosed in the ambulatory setting with covid-19 in period 1 (1 April 2020-30 November 2020) and period 2 (1 December 2020-31 May 2021) compared with patients diagnosed in the ambulatory setting with influenza (1 October 2018-30 April 2019)

	Covid-19 period 1 cohort			Covid-19 period 2 cohort			Influenza cohort		
Characteristic	No. of patients*	No. of events*	Absolute risk, % (95% CI)	No. of patients*	No. of events*	Absolute risk, % (95% CI)	No. of patients*	No. of events*	Absolute risk, % (95% CI)
Arterial thromboembolism									
Overall	272 065	2752	1.01 (0.97 to 1.05)	342 103	3629	1.06 (1.03 to 1.10)	118 618	535	0.45 (0.41 to 0.49)
Age, years:									
18-44	86 564	41	0.05 (0.03 to 0.06)	105 220	75	0.07 (0.06 to 0.09)	49 028	15	0.03 (0.02 to 0.05)
45-54	38 454	109	0.28 (0.23 to 0.34)	48 596	152	0.31 (0.27 to 0.37)	18 920	32	0.17 (0.12 to 0.24)
55-64	42 182	313	0.74 (0.66 to 0.83)	53 241	409	0.77 (0.70 to 0.85)	18 190	92	0.51 (0.41 to 0.62)
65-74	57 089	912	1.60 (1.50 to 1.70)	76 909	1158	1.51 (1.42 to 1.59)	19 539	173	0.89 (0.76 to 1.03)
75-84	33 535	911	2.72 (2.55 to 2.90)	43 320	1249	2.88 (2.73 to 3.05)	10 131	145	1.43 (1.21 to 1.69)
≥85	14 241	466	3.27 (2.99 to 3.58)	14 817	586	3.95 (3.65 to 4.28)	2810	78	2.78 (2.21 to 3.47)
Sex:									
Male	121 048	1535	1.27 (1.21 to 1.33)	154 283	1981	1.28 (1.23 to 1.34)	47 776	271	0.57 (0.50 to 0.64)
Female	151 017	1217	0.81 (0.76 to 0.85)	187 820	1648	0.88 (0.84 to 0.92)	70 842	264	0.37 (0.33 to 0.42)
Cardiovascular disease†:	61 737	1917	3.11 (2.97 to 3.25)	77 702	2425	3.12 (3.00 to 3.25)	19 353	351	1.81 (1.63 to 2.01)
Recent outpatient anticoagulant use‡	13 143	596	4.53 (4.19 to 4.91)	17 391	818	4.70 (4.40 to 5.03)	3814	116	3.04 (2.53 to 3.65)
No recent outpatient anticoagulant use‡	48 594	1321	2.72 (2.58 to 2.87)	60 311	1607	2.66 (2.54 to 2.80)	15 539	235	1.51 (1.33 to 1.72)
Venous thromboembolism									
Overall:	272 065	1994	0.73 (0.70 to 0.77)	342 103	2994	0.88 (0.84 to 0.91)	118 618	219	0.18 (0.16 to 0.21)
Age, years:									
18-44	86 564	97	0.11 (0.09 to 0.14)	105 220	110	0.10 (0.09 to 0.13)	49 028	14	0.03 (0.02 to 0.05)
45-54	38 454	133	0.35 (0.29 to 0.41)	48 596	197	0.41 (0.35 to 0.47)	18 920	18	0.10 (0.06 to 0.15)
55-64	42 182	288	0.68 (0.61 to 0.77)	53 241	440	0.83 (0.75 to 0.91)	18 190	32	0.18 (0.12 to 0.25)
65-74	57 089	700	1.23 (1.14 to 1.32)	76 909	1052	1.37 (1.29 to 1.45)	19 539	61	0.31 (0.24 to 0.40)
75-84	33 535	557	1.66 (1.53 to 1.80)	43 320	877	2.02 (1.89 to 2.16)	10 131	75	0.74 (0.59 to 0.93)
≥85	14 241	219	1.54 (1.35 to 1.76)	14 817	318	2.15 (1.92 to 2.40)	2810	19	0.68 (0.42 to 1.08)
Sex:									
Male	121 048	1093	0.90 (0.85 to 0.96)	154 283	1628	1.06 (1.01 to 1.11)	47 776	104	0.22 (0.18 to 0.26)
Female	151 017	901	0.60 (0.56 to 0.64)	187 820	1366	0.73 (0.69 to 0.77)	70 842	115	0.16 (0.13 to 0.20)
Prior venous thromboembolism†:	5979	326	5.45 (4.90 to 6.07)	7454	452	6.06 (5.54 to 6.64)	1867	62	3.32 (2.58 to 4.26)
Recent outpatient anticoagulant use‡	3762	228	6.06 (5.33 to 6.88)	4855	341	7.02 (6.33 to 7.79)	1121	47	4.19 (3.13 to 5.58)
No recent outpatient anticoagulant use‡	2217	98	4.42 (3.62 to 5.38)	2599	111	4.27 (3.54 to 5.14)	746	15	2.01 (1.17 to 3.37)

CI=confidence interval.

*No. of patients and events are presented prior to weighting.

†Determined from 365 days before through one day prior to the date of index diagnosis.

‡Determined from 183 days before through three days prior to the date of index diagnosis.

Table 3 | Hazard ratios for 90 day inpatient arterial and venous thromboembolism events among ambulatory patients diagnosed with covid-19 in period 1 (1 April 2020-30 November 2020) and period 2 (1 December 2020-31 May 2021) compared with ambulatory patients diagnosed with influenza (1 October 2018-30 April 2019)

Cohort	No. of Patients*	No. of events*	Risk per 100 patients	Difference in risk per 100 patients with influenza cohort (95% CI)	Unweighted HR (95% CI)	Weighted HR† (95% CI)
Arterial thromboembolism						
Primary ATE outcome:						
Covid-19 period 1 cohort	272 065	2752	1.01	0.56 (0.51 to 0.61)	2.09 (1.90 to 2.29)	1.53 (1.38 to 1.69)
Covid-19 period 2 cohort	342 103	3629	1.06	0.61 (0.56 to 0.66)	2.22 (2.03 to 2.43)	1.69 (1.53 to 1.86)
Influenza cohort	118 618	535	0.45	Reference	Reference	Reference
With cardiovascular disease:						
Covid-19 period 1 cohort	61 737	1917	3.11	1.29 (1.06 to 1.52)	1.78 (1.59 to 1.99)	1.49 (1.31 to 1.69)
Covid-19 period 2 cohort	77 702	2425	3.12	1.31 (1.08 to 1.53)	1.78 (1.59 to 1.99)	1.61 (1.42 to 1.81)
Influenza cohort	19 353	351	1.81	Reference	Reference	Reference
Without cardiovascular disease:						
Covid-19 period 1 cohort	210 328	835	0.40	0.21 (0.17 to 0.25)	1.98 (1.69 to 2.32)	1.62 (1.37 to 1.91)
Covid-19 period 2 cohort	264 401	1204	0.46	0.27 (0.23 to 0.31)	2.31 (1.98 to 2.70)	1.87 (1.58 to 2.20)
Influenza cohort	99 265	184	0.19	Reference	Reference	Reference
All cause mortality within 30 days after inpatient ATE event:						
Covid-19 period 1 cohort	2752	534	19.40	10.81 (8.01 to 13.60)	2.43 (1.79 to 3.28)	2.65 (1.88 to 3.73)
Covid-19 period 2 cohort	3629	703	19.37	10.77 (8.07 to 13.47)	2.42 (1.80 to 3.27)	2.53 (1.82 to 3.51)
Influenza cohort	535	46	8.60	Reference	Reference	Reference
Secondary (expanded) ATE outcome‡‡:						
Covid-19 period 1 cohort	272 065	11 523	4.24	1.77 (1.65 to 1.89)	1.58 (1.52 to 1.65)	1.20 (1.14 to 1.25)
Covid-19 period 2 cohort	342 103	15 064	4.40	1.94 (1.83 to 2.05)	1.67 (1.61 to 1.74)	1.28 (1.22 to 1.33)
Influenza cohort	118 618	2924	2.47	Reference	Reference	Reference
Venous thromboembolism						
Primary VTE outcome:						
Covid-19 period 1 cohort	272 065	1994	0.73	0.55 (0.51 to 0.59)	3.74 (3.25 to 4.30)	2.86 (2.46 to 3.32)
Covid-19 period 2 cohort	342 103	2994	0.88	0.69 (0.65 to 0.73)	4.55 (3.96 to 5.22)	3.56 (3.08 to 4.12)
Influenza cohort	118 618	219	0.18	Reference	Reference	Reference
With prior VTE:						
Covid-19 period 1 cohort	5979	326	5.45	2.13 (1.14 to 3.13)	1.71 (1.31 to 2.25)	1.47 (1.08 to 2.00)
Covid-19 period 2 cohort	7454	452	6.06	2.74 (1.77 to 3.72)	1.92 (1.48 to 2.51)	1.64 (1.19 to 2.24)
Influenza cohort	1867	62	3.32	Reference	Reference	Reference
Without prior VTE:						
Covid-19 period 1 cohort	266 086	1668	0.63	0.49 (0.46 to 0.53)	4.38 (3.72 to 5.17)	3.51 (2.94 to 4.19)
Covid-19 period 2 cohort	334 649	2542	0.76	0.63 (0.59 to 0.66)	5.41 (4.60 to 6.36)	4.42 (3.73 to 5.24)
Influenza cohort	116 751	157	0.13	Reference	Reference	Reference
All cause mortality within 30 days after inpatient VTE event:						
Covid-19 period 1 cohort	1994	316	15.85	9.00 (5.29 to 12.71)	2.34 (1.39 to 3.93)	2.36 (1.34 to 4.18)
Covid-19 period 2 cohort	2994	527	17.60	10.75 (7.14 to 14.37)	2.68 (1.61 to 4.49)	2.58 (1.48 to 4.50)
Influenza cohort	219	15	6.85	Reference	Reference	Reference
Secondary (expanded) VTE outcome§:						
Covid-19 period 1 cohort	272 065	2555	0.94	0.65 (0.61 to 0.70)	3.13 (2.79 to 3.51)	2.49 (2.20 to 2.82)
Covid-19 period 2 cohort	342 103	3934	1.15	0.86 (0.82 to 0.91)	3.88 (3.48 to 4.34)	3.14 (2.79 to 3.53)
Influenza cohort	118 618	338	0.28	Reference	Reference	Reference

ATE=arterial thromboembolism; CI=confidence interval; HR=hazard ratio; VTE=venous thromboembolism event.

*No. of patients and events are presented prior to weighting.

†Hazard ratios calculated after adjustment for Data Partner and propensity score fine stratification with stratum specific weighting.

‡Secondary (expanded) ATE outcome defined by emergency department or hospital discharge diagnoses of acute myocardial infarction, ischemic stroke, angina, transient ischemic attack, or peripheral arterial disease.

§Secondary (expanded) VTE outcome defined by emergency department or hospital discharge diagnoses of acute upper or lower deep venous thrombosis, pulmonary embolism, or venous thrombosis of devices, implants, or grafts.

Table 4 | Hazard ratios (HRs), adjusted for all risk factors, for inpatient arterial and venous thromboembolism events among patients diagnosed with covid-19 in the ambulatory (ie, outpatient, emergency department, institutional) setting during period 1 (1 April 2020-30 November 2020) and period 2 (1 December 2020-31 May 2021)

	Adjusted HR (95% CI) of arterial thromboembolism		Adjusted HR (95% CI) of venous thromboembolism	
Characteristic	Period 1	Period 2	Period 1	Period 2
Age, years:				
45-54	4.04 (2.81 to 5.81)	3.08 (2.33 to 4.08)	2.52 (1.93 to 3.29)	3.22 (2.55 to 4.08)
55-64	6.85 (4.88 to 9.60)	4.99 (3.86 to 6.46)	4.11 (3.23 to 5.24)	5.54 (4.46 to 6.89)
65-74	10.07 (7.21 to 14.05)	7.31 (5.68 to 9.41)	6.22 (4.90 to 7.89)	8.40 (6.78 to 10.40)
75-84	12.62 (9.01 to 17.69)	10.66 (8.26 to 13.76)	7.58 (5.91 to 9.71)	11.59 (9.30 to 14.44)
≥85	13.87 (9.82 to 19.61)	12.95 (9.94 to 16.89)	7.63 (5.80 to 10.04)	13.06 (10.26 to 16.63)
Sex	1.45 (1.34 to 1.56)	1.36 (1.27 to 1.45)	1.54 (1.41 to 1.69)	1.49 (1.38 to 1.61)
Pregnancy*	1.29 (1.01 to 1.64)	1.13 (0.90 to 1.41)	1.35 (1.01 to 1.80)	1.10 (0.84 to 1.44)
Prior cardiovascular disease†	1.76 (1.59 to 1.94)	1.67 (1.53 to 1.82)	—	—
Prior venous thromboembolism†	—	—	3.98 (3.46 to 4.58)	3.85 (3.42 to 4.33)
Obesity‡	0.94 (0.87 to 1.03)	0.99 (0.92 to 1.06)	1.43 (1.30 to 1.58)	1.36 (1.26 to 1.48)
Alcohol dependence/misuse‡	1.24 (1.03 to 1.49)	1.06 (0.89 to 1.27)	1.08 (0.85 to 1.37)	1.04 (0.84 to 1.28)
Tobacco use‡	1.10 (1.01 to 1.20)	1.17 (1.09 to 1.26)	1.10 (0.99 to 1.23)	1.12 (1.03 to 1.22)
Chronic kidney disease‡	1.43 (1.31 to 1.56)	1.46 (1.35 to 1.57)	1.33 (1.19 to 1.47)	1.24 (1.14 to 1.36)
Cancer‡ (excluding non-melanoma skin cancers)	0.91 (0.83 to 1.00)	0.98 (0.91 to 1.06)	1.20 (1.08 to 1.33)	1.10 (1.01 to 1.20)
Chronic obstructive pulmonary disease‡	1.07 (0.98 to 1.17)	1.14 (1.05 to 1.23)	1.28 (1.15 to 1.43)	1.21 (1.11 to 1.33)
Diabetes mellitus‡	1.65 (1.52 to 1.79)	1.48 (1.37 to 1.59)	1.14 (1.03 to 1.26)	1.27 (1.17 to 1.38)
Heart failure‡	1.50 (1.36 to 1.65)	1.47 (1.36 to 1.60)	1.24 (1.09 to 1.40)	1.16 (1.05 to 1.29)
Hyperlipidemia‡	0.81 (0.73 to 0.91)	0.90 (0.82 to 1.00)	0.90 (0.80 to 1.02)	0.89 (0.80 to 0.98)
Hypertension‡	1.73 (1.49 to 2.00)	1.57 (1.39 to 1.77)	1.22 (1.07 to 1.40)	1.25 (1.12 to 1.39)
Rheumatological disease‡	0.98 (0.84 to 1.14)	1.07 (0.94 to 1.21)	1.05 (0.88 to 1.26)	1.13 (0.98 to 1.31)
Neurological disease‡	1.35 (1.22 to 1.49)	1.33 (1.21 to 1.46)	1.07 (0.94 to 1.23)	1.06 (0.94 to 1.19)
Atrial fibrillation or flutter‡	1.25 (1.13 to 1.39)	1.08 (0.99 to 1.19)	0.74 (0.64 to 0.85)	0.68 (0.60 to 0.77)
Antiphospholipid antibody syndrome‡	1.24 (0.56 to 2.78)	0.61 (0.23 to 1.63)	0.86 (0.38 to 1.93)	0.52 (0.19 to 1.38)
Inherited (primary) thrombophilia‡	1.03 (0.80 to 1.34)	1.09 (0.91 to 1.32)	1.37 (1.05 to 1.80)	1.36 (1.11 to 1.67)
Polycythemia‡ (diagnosis code or hemoglobin >16.0 g/dL)	0.97 (0.76 to 1.23)	1.04 (0.86 to 1.27)	1.05 (0.81 to 1.35)	1.00 (0.81 to 1.24)
Thrombocytosis‡ (diagnosis code or platelets >450 000/μL)	1.46 (1.33 to 1.62)	1.45 (1.33 to 1.59)	1.32 (1.16 to 1.50)	1.27 (1.14 to 1.42)
Recent outpatient anticoagulant use§	1.09 (0.98 to 1.21)	1.18 (1.07 to 1.29)	1.10 (0.96 to 1.27)	1.16 (1.03 to 1.30)
Recent outpatient antiplatelet use§	1.62 (1.47 to 1.79)	1.47 (1.35 to 1.61)	0.93 (0.79 to 1.09)	1.05 (0.93 to 1.19)
Recent outpatient statin use§	1.06 (0.96 to 1.15)	1.00 (0.92 to 1.08)	0.97 (0.88 to 1.08)	0.92 (0.84 to 1.00)

Reference for age was 18-44 years; reference for sex was female; all other reference groups were no. CI=confidence interval; HR=hazard ratio.

*Determined from 90 days before through the date of index diagnosis.

†Determined from 365 days before through one day prior to the date of index diagnosis.

‡Determined from 365 days before through the date of index diagnosis.

§Determined from 183 days before through three days prior to the date of index diagnosis.

platelet hyper-reactivity.[39] This process, referred to as thromboinflammation, might be more marked with covid-19 than influenza. Differences in characteristics in the populations being infected, tested, and diagnosed in the ambulatory setting might also have contributed to the higher risk of thromboses among patients with covid-19 than influenza.

The 90 day absolute risk of ATE and VTE among patients with an ambulatory diagnosis of covid-19 did not substantially change between periods 1 and 2 despite covid-19 vaccine availability and evolution of SARS-CoV-2 variants. Recent data suggest that breakthrough SARS-CoV-2 infection in individuals who are vaccinated is associated with lower risk of coagulation disorders (eg, acute deep vein thrombosis and pulmonary embolism) compared with people with the infection who were not vaccinated.[30] It is possible that most patients diagnosed with covid-19 during period 2 could have been unvaccinated; however, covid-19 vaccination status was incomplete in our data because many patients in the US received covid-19 vaccines outside of healthcare settings.

We also found that the risk of 30 day mortality after an inpatient ATE or VTE event was more than twofold higher for people with covid-19 than influenza. One explanation could be that the thromboinflammatory response to SARS-CoV-2 infection might be more exaggerated than with influenza, producing a higher frequency of microvascular and

macrovascular thromboses leading to hypoxemia, multi-organ failure, and death.[40 41] Differences in the severity of infection at inpatient ATE or VTE diagnosis between patients with covid-19 and influenza might also have contributed to these findings. Additional research is needed to determine the mechanisms for this observation.

We identified demographic and clinical characteristics present before ambulatory diagnosis of covid-19 that were associated with an increased risk of ATE and VTE. These risk factors were examined because of their potential to promote stasis of circulation, endothelial injury, or hypercoagulability, each of which might contribute to thrombosis. These factors could be used to identify subgroups at high risk of ATE and VTE, for whom closer monitoring for events may be warranted, and could help to inform interventions to prevent their development.

Limitations and strengths

This study has several potential limitations. Misclassification of thrombotic outcomes was possible. To minimise potential for misclassification, we evaluated inpatient events using diagnoses previously validated within the Sentinel System.[24–29] However, clinicians could have been more likely to assign ATE or VTE diagnoses among patients with covid-19 based on clinical suspicion because confirmatory tests might not have been performed due to isolation measures. Additionally some thrombotic events or deaths might have been missed because of delays in data availability or because they were diagnosed and managed exclusively in the outpatient setting. Prior influenza infection could also have affected risk of ATE or VTE. We did not include data for covid-19 or influenza immunisation status because vaccination against both infections may have occurred outside of healthcare settings. Infection among vaccinated individuals might have affected risk of thrombotic events. Analyses examining risk factors for ATE and VTE might have been subject to selection bias due to its focus on patients diagnosed in the ambulatory setting who may not be representative of the broader population of patients with infections, which could have created or altered existing associations.[42] Our analyses used a distributed data framework in which only summary level data are shared, as such, we were unable to evaluate the proportional hazards assumption for relative hazards of outcomes between patients with covid-19 and influenza.

Our sample was comprised of predominantly commercially insured health plan members and might not be generalizable to people with no insurance. Our study is also not representative of patients with covid-19 or seasonal influenza who did not undergo outpatient testing due to mild symptoms. Furthermore, results might not be generalizable to patients with covid-19 who were infected with SARS-CoV-2 during later waves of the pandemic. Additionally, few patients in each of the cohorts had positive nucleic acid tests at cohort entry.

Residual confounding by unmeasured factors (eg, tobacco and obesity) is possible. We did not have access to medications administered within the hospital, such as prophylactic or therapeutic anticoagulation, which can affect thrombotic risk. We calculated E-values to examine the risk of bias due to unmeasured confounders. E-values for the point estimate of the hazard ratio and lower bound of the 95% confidence interval of ATE associated with covid-19 for period 1 were 2.43 and 2.10, and for period 2 were 2.77 and 2.43, meaning that residual confounding could explain the observed association if there exists an unmeasured covariate having an association at least as large as 2.10 with both ATE and with covid-19.[38 43] In table 4, the hazard ratios for the known ATE risk factors did not exceed 2.0 with the exception of higher age. These results indicate that an unmeasured confounder is unlikely to be present that would negate the observed associations between covid-19 and ATE. E-values for the point estimate of the hazard ratio and lower bound of the 95% confidence interval of VTE associated with covid-19 for periods 1 and 2 were substantially higher, exceeding 4.0. With the exception of prior VTE, hazard ratios for known VTE risk factors were not larger than 2.0, suggesting that that an unmeasured confounder that would negate the observed associations between covid-19 and VTE is also unlikely.

Lastly, our study focused on whether SARS-CoV-2 differed from seasonal influenza with regards to the risk of arterial and venous thrombotic complications. Future studies should consider alternative study approaches, such as self-controlled case series or cohort designs that compare patients who tested positive for covid-19 to those who tested negative, to continue to examine the risk of thrombosis associated with covid-19 as the pandemic evolves.

Our study has various strengths. We included large cohorts of patients diagnosed with covid-19 and influenza in the ambulatory setting from two national health insurers and four regional integrated health systems. We implemented weighted propensity score fine stratification to account for differences between the influenza and covid-19 cohorts and provide strong confounding control. We stratified results of ATE analyses by pre-existing cardiovascular disease status and VTE analyses by prior VTE to enhance understanding of the effects of these pre-existing conditions on thrombotic outcomes. Additionally, we assessed the robustness of results to unmeasured confounding using E-values.

Conclusions

Among patients initially diagnosed with covid-19 in the ambulatory setting, our cohort study found that the 90 day risk of admission to hospital with ATE

ranged from 1.01% to 1.06% and the 90 day risk of admission to hospital with VTE ranged from 0.73% to 0.88%. In the ambulatory setting, people who were diagnosed with covid-19 during periods when covid-19 vaccines were unavailable or were available had a higher 90 day risk of admission to hospital with ATE or VTE compared with people diagnosed with influenza. We identified characteristics that promote stasis of circulation, endothelial injury, or hypercoagulability as risk factors for ATE and VTE during covid-19. Future studies should develop prognostic models to identify people diagnosed with covid-19 in the ambulatory setting who might be at high risk for admission to hospital with ATE or VTE.

AUTHOR AFFILIATIONS

[1]Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA
[2]Department of Biostatistics, Epidemiology, and Informatics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA
[3]Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, USA
[4]Department of Population Medicine, Harvard Medical School, Boston, MA, USA
[5]Department of Population Medicine, Harvard Pilgrim Health Care Inc, Wellesley, MA, USA
[6]HealthPartners Institute, Bloomington, MN, USA
[7]CVS Health Clinical Trial Services, an affiliate of Aetna, CVS Health Company, Blue Bell, PA, USA
[8]Kaiser Permanente Washington Health Research Institute and Department of Epidemiology, University of Washington, Seattle, WA, USA
[9]Kaiser Permanente Northwest Center for Health Research, Portland, OR, USA
[10]Kaiser Permanente Colorado Institute for Health Research, Aurora, CO, USA
[11]Humana Healthcare Research, Inc, Louisville, KY, USA

Acknowledgements We thank the following individuals who each received financial support for their contributions to this work: Brian Kit (clinical subject matter expert), formerly at US Food and Drug Administration; Catherine Cleveland (research data integration architect), Daniel Vaughn (database architect), and Celeste Machen (project manager) at Kaiser Permanente Northwest Center for Health Research; Ron Johnson (data reporting and analytics consultant), Vina Graham (programmer analyst), and Monica Fujii (project manager) at Kaiser Permanente Washington Health Research Institute; Thomas Harkins (project director) and Vinit Nair, BPharm (principal investigator) at Humana Healthcare Research, Inc; Anne Marie Kline (data specialist) and Carla Brannan (project manager) at CVS Health; Mahesh Maiyani (data specialist) and Karen Glenn (programmer) at Kaiser Permanente Colorado Institute for Health Research; Jacob Zillhardt (senior research informatics programmer analyst), Dianne Eggen (research nurse), and Laurie VanArman (research nurse) at HealthPartners Institute; and Jenice Ko (research analyst) at Harvard Pilgrim Health Care Institute. We also thank the following individuals who did not receive financial support for their contributions to this work: John Weeks, MBA (senior research data warehouse engineer), Roy Pardee (principal engineer), and Yonah Karp (manager of data projects and programs) at Kaiser Permanente Washington Health Research Institute and Laura Shockro (project manager), Tawil Contreras (research analyst), Suzanne Carter (research analyst), Daniel Kiernan (research analyst), and Candace Fuller (research scientist) at Harvard Pilgrim Health Care Institute. We thank the following organizations that provided data and/or support for this work: CVS Health Clinical Trial Services, an affiliate of Aetna, a CVS Health Company, Blue Bell, PA, USA; Harvard Pilgrim Health Care Institute, Boston, MA, USA; HealthPartners Institute, Minneapolis, MN, USA; Humana Healthcare Research, Inc, Louisville, KY, USA; Kaiser Permanente Colorado Institute for Health Research, Aurora, CO, USA; Kaiser Permanente Northwest Center for Health Research, Portland, OR, USA; and Kaiser Permanente Washington Health Research Institute, Seattle, WA, USA.

Contributors TAD, DAD, LBH, JLK, CNM-W, PAP, CAS, and YZ had full access to all of the data in this study from their respective site and take responsibility for the integrity of the data. VLR and NMC are the guarantors and take responsibility for the conduct of the study. VLR, SKD, JGC, SP-V, DMC, SH, RAH, AMP, and NMC created the concept and design. All authors were involved in acquisition, analysis, or interpretation of data. VLR, DMC, and NMC drafted the manuscript. All authors critically revised the manuscript for important intellectual content. JGC, LH, and RAH did the statistical analysis. VLR, DMC, TAD, DAD, LBH, MEK, JLK, CNM-W, JM, PAP, ABP, MRD, and NMC provided administrative, technical, or material support. VLR, SKD, MRD, and NMC provided supervision. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. Transparency: The lead author (the guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Funding This project was supported by Task Order 75F40119F19001 under Master Agreement 75F40119D10037 from the US Food and Drug Administration (FDA). The FDA approved the study protocol, including the statistical analysis plan, and reviewed and approved this manuscript. Coauthors from the FDA participated in the results interpretation and in the preparation and decision to submit the manuscript for publication.

Disclaimer The views expressed in this paper reflect those of the authors and should not be construed to represent US Food and Drug Administration views or policies.

Competing interests All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: VLR reports research grants to his institution from the US Food and Drug Administration (FDA) during the conduct of the study and personal consulting fees from Takeda outside the submitted work. DAD reports contract research funding from FDA Sentinel Initiative via Harvard Pilgrim Health Care Institute. LBH reports contract research funding from FDA Sentinel Initiative during the conduct of the study and grants from Kaiser Permanente Garfield Memorial Fund for covid-19 related research outside the submitted work. SH reports grants from FDA, Pfizer, and Johnson & Johnson during the conduct of the study, consulting for Novo Nordisk, Arbor Pharmaceuticals, the Medullary Thyroid Cancer Consortium (Novo Nordisk, AstraZeneca, GlaxoSmithKline, and Eli Lilly), Biogen, Intercept Pharmaceuticals, Provention Bio, bluebird bio, and Amylyx Pharmaceuticals, and is a special government employee of the FDA. RAH reports grants from FDA during the conduct of the study and grants from Merck, Pfizer, and Johnson & Johnson outside of the submitted work. CNM-W works for CVS Health Clinical Trial Services LLC, an affiliate of CVS Health. She is responsible for CVS Health Clinical Trial Services activities with the FDA Sentinel Initiative, including both the Sentinel Program and BEST Program, and other Distributed Research Networks that use Sentinel infrastructure to analyze health claims data administered by Aetna, also a CVS Health affiliate. The Distributed Research Networks include Academy of Managed Care Pharmacy's Biologics and Biosimilars Collective Intelligence Collaborative; Reagan-Udall's Foundation IMEDS multisite research service agreements funded by Abbvie, Merck, Novartis, and Pfizer; Patient Centered Outcomes Research Institute; Research Action for Health Network; TherapeuticsMD; National Evaluation System for Health Technology Coordinating Center; and, Harvard Pilgrim Health Care Institute multisite research subcontracts funded by FDA, National Institutes of Health, Pfizer, Janssen, and GSK. To the best of her knowledge, CNM-W is not aware that any of these professional roles or activities create a conflict of interest with this project; however, she is itemizing them here for purposes of full disclosure. PAP reports contract funding support from HPHCI during the conduct of the study and outside the submitted work. AMP reports research funding to her institution from FDA during the conduct of the study and research funding from Sanofi Genzyme Research to her institution outside of the submitted work. NMC reports research funding from FDA via an HHS contract during the conduct of the study and funding from Harvard Pilgrim Health Care Institute (a non-profit organization that conducts work for government and private organizations, including pharmaceutical companies) outside of the submitted work. All other authors report no competing interest.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Patient consent for publication Patient consent not required (patient anonymised, dead, or hypothetical).

Ethics approval This study was a public health surveillance activity conducted under the authority of the US Food and Drug Administration and, accordingly, was not subject to Institutional Review Board oversight.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The data generated in this study are not publicly available. Sentinel uses a distributed data approach in which Data Partners maintain physical and operational control of their own electronic health data after transforming it into a common data model. Sentinel does not save, maintain, or post individual level datasets in order to preserve patient privacy.

ORCID iDs

Vincent Lo Re III http://orcid.org/0000-0001-7955-0600
Sarah K Dutcher http://orcid.org/0000-0003-0574-2890
John G Connolly http://orcid.org/0000-0003-1916-557X
Silvia Perez-Vilar http://orcid.org/0000-0003-1272-1502
Dena M Carbonari http://orcid.org/0000-0003-0310-270X
Djeneba Audrey Djibo http://orcid.org/0000-0003-3378-0691
Laura B Harrington http://orcid.org/0000-0001-5951-8291
Laura Hou http://orcid.org/0000-0003-0847-2574
Sean Hennessy http://orcid.org/0000-0003-4726-9413
Rebecca A Hubbard http://orcid.org/0000-0003-0879-0994
Jennifer L Kuntz http://orcid.org/0000-0002-0017-6853
Cheryl N McMahill-Walraven http://orcid.org/0000-0002-3765-6527
Pamala A Pawloski http://orcid.org/0000-0002-1005-5764
Andrew B Petrone http://orcid.org/0000-0001-8413-6236
Allyson M Pishko http://orcid.org/0000-0001-9997-454X
Meighan Rogers Driscoll http://orcid.org/0000-0003-1371-9658
Noelle M Cocoros http://orcid.org/0000-0001-7090-2761

REFERENCES

1 Zhang Y, Xiao M, Zhang S, *et al.* Coagulopathy and Antiphospholipid antibodies in patients with COVID-19. N Engl J Med 2020;382:e38. 10.1056/NEJMc2007575
2 Al-Samkari H, Karp Leaf RS, Dzik WH, *et al.* COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-Cov-2 infection. Blood 2020;136:489–500. 10.1182/blood.2020006520
3 Panigada M, Bottino N, Tagliabue P, *et al.* Hypercoagulability of COVID-19 patients in intensive care unit: a report of thromboelastography findings and other parameters of hemostasis. J Thromb Haemost 2020;18:1738–42. 10.1111/jth.14850
4 Spiezia L, Boscolo A, Poletto F, *et al.* COVID-19-related severe hypercoagulability in patients admitted to intensive care unit for acute respiratory failure. Thromb Haemost 2020;120:998–1000. 10.1055/s-0040-1710018
5 Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood 2020;135:2033–40. 10.1182/blood.2020006000
6 Lo Re V III, Dutcher SK, Connolly JG, *et al.* Association of COVID-19 vs influenza with risk of arterial and venous thrombotic events among hospitalized patients. JAMA 2022;328:637. 10.1001/jama.2022.13072
7 Dalager-Pedersen M, Lund LC, Mariager T, *et al.* Venous thromboembolism and major bleeding in patients with Coronavirus disease 2019 (COVID-19): a nationwide, population-based cohort study. Clin Infect Dis 2021;73:2283–93. 10.1093/cid/ciab003
8 Burn E, Duarte-Salles T, Fernandez-Bertolin S, *et al.* Venous or arterial thrombosis and deaths among COVID-19 cases: a European network cohort study. Lancet Infect Dis 2022;22:1142–52. 10.1016/S1473-3099(22)00223-7
9 Kwong JC, Schwartz KL, Campitelli MA, *et al.* Acute myocardial infarction after laboratory-confirmed influenza infection. N Engl J Med 2018;378:345–53. 10.1056/NEJMoa1702090
10 Boehme AK, Luna J, Kulick ER, *et al.* Influenza-like illness as a trigger for ischemic stroke. Ann Clin Transl Neurol 2018;5:456–63. 10.1002/acn3.545
11 Bunce PE, High SM, Nadjafi M, *et al.* Pandemic H1N1 influenza infection and vascular thrombosis. Clin Infect Dis 2011;52:e14–7. 10.1093/cid/ciq125
12 Dimakakos E, Grapsa D, Vathiotis I, *et al.* H1N1-induced venous thromboembolic events? Results of a single-institution case series. Open Forum Infect Dis 2016;3:ofw214. 10.1093/ofid/ofw214
13 Cocoros NM, Fuller CC, Adimadhyam S, *et al.* A COVID-19-ready public health surveillance system: The Food and Drug Administration's sentinel system. Pharmacoepidemiol Drug Saf 2021;30:827–37. 10.1002/pds.5240
14 Curtis LH, Weiner MG, Boudreau DM, *et al.* Design considerations, architecture, and use of the mini-sentinel distributed data system. Pharmacoepidemiol Drug Saf 2012;21:23–31. 10.1002/pds.2336
15 Sentinel Operations Center. Sentinel data quality assurance practices compliance with "guidance for industry and FDA staff: best practices for conducting and reporting Pharmacoepidemiology safety studies using electronic Healthcare data". Available: https://www.sentinelinitiative.org/sites/default/files/data/distributed-database/Sentinel_DataQAPractices_Memo.pdf [Accessed 1 Feb 2023].
16 Sentinel Operations Center. Data quality review and characterization programs: quality assurance (QA) package. Available: https://dev.sentinelsystem.org/projects/QA/repos/qa_package/browse [Accessed 1 Feb 2023].
17 Maro JC. Medical product safety surveillance: data quality in the sentinel initiative. Available: https://www.sentinelinitiative.org/sites/default/files/communications/publications-presentations/Sentinel_Canadian-Society-Pharmaceutical-Sciences_Presentation_Medical-Product-Safety-Surveillance-Data-Quality.pdf [Accessed 1 Feb 2023].
18 Sentinel Operations Center. Study Synopsis: natural history of coagulopathy in COVID-19. Version 2.0. 2021. Available: https://www.sentinelinitiative.org/sites/default/files/documents/Coagulopathy_COVID19_Study_Synopsis_v2.0_0.pdf
19 Rosati K, Jorgensen N, Soliz M, *et al.* Sentinel initiative principles and policies: HIPAA and common rule compliance in the sentinel initiative. Available: https://www.sentinelinitiative.org/sites/default/files/communications/publications-presentations/HIPAA-Common-Rule-Compliance-in-Sentinel-Initiative.pdf [Accessed 31 Oct 2021].
20 Basic HHS policy for protection of human research subjects, 45 CFR §46.102(L)(2). Available: https://www.ecfr.gov/current/title-45/subtitle-A/subchapter-A/part-46/subpart-A#46.102 [Accessed 2 Nov 2021].
21 Kluberg SA, Hou L, Dutcher SK, *et al.* Validation of diagnosis codes to identify hospitalized COVID-19 patients in health care claims data. Pharmacoepidemiol Drug Saf 2022;31:476–80. 10.1002/pds.5401
22 United States Food and Drug Administration Sentinel Initiative. Master protocol development: COVID-19 natural history. Available: https://www.sentinelinitiative.org/sentinel/methods/master-protocol-development-covid-19-natural-history [Accessed 27 Oct 2021].
23 Xu X, Blanton L, Elal AIA, *et al.* Update: Influenza activity in the United States during the 2018-19 season and composition of the 2019-20 influenza vaccine. MMWR Morb Mortal Wkly Rep 2019;68:544–51. 10.15585/mmwr.mm6824a3
24 Ammann EM, Schweizer ML, Robinson JG, *et al.* Chart validation of inpatient ICD-9-CM administrative diagnosis codes for acute myocardial infarction (AMI) among intravenous immune globulin (IGIV) users in the sentinel distributed database. Pharmacoepidemiol Drug Saf 2018;27:398–404. 10.1002/pds.4398
25 Cutrona SL, Toh S, Iyer A, *et al.* Validation of acute myocardial infarction in the Food and Drug Administration's mini-sentinel program. Pharmacoepidemiol Drug Saf 2013;22:40–54. 10.1002/pds.3310
26 Roumie CL, Mitchel E, Gideon PS, *et al.* Validation of ICD-9 codes with a high positive predictive value for incident strokes resulting in hospitalization using Medicaid health data. Pharmacoepidemiol Drug Saf 2008;17:20–6. 10.1002/pds.1518
27 Wahl PM, Rodgers K, Schneeweiss S, *et al.* Validation of claims-based diagnostic and procedure codes for cardiovascular and gastrointestinal serious adverse events in a commercially-insured population. Pharmacoepidemiol Drug Saf 2010;19:596–603. 10.1002/pds.1924

28 Ammann EM, Cuker A, Carnahan RM, *et al*. Chart validation of inpatient International classification of diseases, ninth revision, clinical modification (ICD-9-CM) administrative diagnosis codes for venous thromboembolism (VTE) among intravenous immune globulin (IGIV) users in the sentinel distributed database. Medicine (Baltimore) 2018;97:e9960. 10.1097/MD.0000000000009960
29 Yih WK, Greene SK, Zichittella L, *et al*. Evaluation of the risk of venous thromboembolism after quadrivalent human papillomavirus vaccination among US females. Vaccine 2016;34:172–8. 10.1016/j.vaccine.2015.09.087
30 Al-Aly Z, Bowe B, Xie Y. Long COVID after breakthrough SARS-CoV-2 infection. Nat Med 2022;28:1461–7. 10.1038/s41591-022-01840-0
31 Haynes K. Preparing for COVID-19 vaccine safety surveillance: a United States perspective. Pharmacoepidemiol Drug Saf 2020;29:1529–31. 10.1002/pds.5142
32 Lo Re V, Klungel OH, Chan KA, *et al*. Global COVID-19 vaccine rollout and safety surveillance-how to keep pace. BMJ 2021;373:1416. 10.1136/bmj.n1416
33 Mamdani M, Sykora K, Li P, *et al*. Reader's guide to critical appraisal of cohort studies: 2. Assessing potential for confounding. BMJ 2005;330:960–2. 10.1136/bmj.330.7497.960
34 Marubini E, Valsecchi M. Analysing survival data from clinical trials and observational studies. Chichester, England: John Wiley & Sons, 1995: 331–64.
35 Desai RJ, Rothman KJ, Bateman BT, *et al*. A propensity-score-based fine stratification approach for confounding adjustment when exposure is infrequent. Epidemiology 2017;28:249–57. 10.1097/EDE.0000000000000595
36 Desai RJ, Franklin JM. Alternative approaches for confounding adjustment in observational studies using weighting based on the propensity score: a Primer for practitioners. BMJ 2019;367:l5657. 10.1136/bmj.l5657
37 Shu D, Yoshida K, Fireman BH, *et al*. Inverse probability weighted cox model in multi-site studies without sharing individual-level data. Stat Methods Med Res 2020;29:1668–81. 10.1177/0962280219869742
38 VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. Ann Intern Med 2017;167:268–74. 10.7326/M16-2607
39 Varga Z, Flammer AJ, Steiger P, *et al*. Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020;395:1417–8. 10.1016/S0140-6736(20)30937-5
40 Ackermann M, Verleden SE, Kuehnel M, *et al*. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in COVID-19. N Engl J Med 2020;383:120–8. 10.1056/NEJMoa2015432
41 Levi M, Thachil J, Iba T, *et al*. Coagulation abnormalities and thrombosis in patients with COVID-19. Lancet Haematol 2020;7:e438–40. 10.1016/S2352-3026(20)30145-9
42 Holmberg MJ, Andersen LW. Collider bias. JAMA 2022;327:1282. 10.1001/jama.2022.1820
43 Haneuse S, VanderWeele TJ, Arterburn D. Using the E-value to assess the potential effect of Unmeasured confounding in observational studies. JAMA 2019;321:602–3. 10.1001/jama.2018.21554
44 Gagne JJ, Glynn RJ, Avorn J, *et al*. A combined comorbidity score predicted mortality in elderly patients better than existing scores. J Clin Epidemiol 2011;64:749–59. 10.1016/j.jclinepi.2010.10.004

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjmed-2022-000421).