



Hospitalized Arterial and Venous Thrombotic Events in Patients Diagnosed in the Ambulatory Setting with COVID-19 Compared to Influenza

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Background

- Case series and other analyses of hospitalized COVID-19 patients have indicated risk of **arterial** or **venous** thrombotic complications
- Our prior work on individuals initially diagnosed in the hospital setting with COVID-19 vs influenza demonstrated:
 - Increased risk of **venous** thrombotic events with COVID-19
 - Suggestion of more **arterial** thrombotic events with COVID-19
 - Increased mortality among those with an **arterial** or **venous** thrombotic event and COVID-19
- The incidence of these events among patients **diagnosed with COVID-19 vs influenza in the ambulatory** (i.e., outpatient and ED) setting is less clear

Aims

Among those with COVID-19 or 2018-19 seasonal influenza initially diagnosed in the ambulatory setting:

- Calculate 90-day incidence of inpatient **arterial** and **venous** thrombotic events
- Compare 90-day risk of inpatient **arterial** and **venous** thrombotic events
- Compare risk of death within 30 days of an event

We examined these aims in the periods before and after COVID-19 vaccine availability.

Study Design & Data Source

- **Data source: FDA's Rapid Sentinel Distributed Database**
 - 4 integrated health systems (electronic health records + claims)
 - 2 large national insurers (claims only)
- **Study design: Retrospective cohort study**
 - Adults ≥ 18 years
 - COVID-19, influenza identified via diagnosis code or positive lab test (ambulatory setting)
 - Thrombotic events identified via diagnosis codes (inpatient setting)
 - Lab data: COVID-19, influenza, clinical labs (platelets, hemoglobin)
 - Identified pre-existing comorbidities, outpatient dispensed medications

Study Patients

To ensure influenza patients did not have COVID-19

	COVID-19 Cohort	Influenza Cohort
Inclusion Criteria	COVID-19 diagnosis code <u>or</u> positive NAAT Period 1: April 2020 – Nov 2020 Period 2: Dec 2020 – May 2021	Influenza diagnosis code <u>or</u> positive NAAT Oct 2018 – April 2019
	Ambulatory settings (outpatient, ED, institutional stay)	
	≥365 days of continuous enrollment at time of diagnosis	
Exclusion Criteria	Coinfection with another respiratory virus (RSV, adenovirus, parainfluenza, etc.)	

Prior **arterial** or **venous** thrombotic event increases risk for subsequent event; did not restrict to incident events

Primary Outcomes: Thromboembolic Events

Arterial thrombosis

Acute ischemic or embolic
stroke

Acute myocardial infarction



Venous thromboembolism

Acute upper/lower deep
venous thrombosis

Acute pulmonary embolism



Based on hospital discharge ICD-10 diagnosis (from any position)

- Mapped from ICD-9 diagnoses validated in Sentinel to ICD-10
- ICD-10 diagnoses underwent clinical review

Analysis

Absolute Risks

- Characteristics of COVID-19 and influenza cohorts
- Calculated **absolute risk of thromboembolic outcomes** within 90 days
 - Stratified by COVID-19 vaccine availability
- Calculated **absolute risk of death** within 30 days of a primary outcome

COVID-19 vs. Influenza

- Compared characteristics between COVID-19 and influenza cohorts
- Propensity score (PS) fine stratification
- **Weighted Cox regression**, accounting for PS, adjusted for Data Partner
 - Adjusted HRs (95% CIs) of outcomes for COVID-19 vs. influenza

Select Characteristics of Patients With COVID-19 or Influenza

Characteristic	COVID-19, Period 1 N = 272,065	Influenza N = 118,618	Standardized Diff. <u>After</u> PS Adjustment
Age in years [mean (SD)]	55.6 (17.5)	51.0 (16.5)	0.084
Female sex	55.5%	59.7%	0.005
Comorbidities (days -365, 0)			
Asthma	9.0%	11.3%	0.003
Atrial fibrillation/flutter	7.3%	4.8%	0.023
Chronic kidney disease	14.6%	10.2%	0.032
Diabetes mellitus	22.5%	17.1%	0.028
Heart failure	7.9%	4.9%	0.027
Hypertension	46.3%	38.6%	0.056
Hyperlipidemia	44.1%	37.2%	0.044
Obesity	24.3%	22.9%	0.019
Tobacco use	16.0%	15.7%	0.033
History (days -365, -1)			
Venous thromboembolism	2.2%	1.6%	0.012
Cardiovascular disease + outpatient anticoagulant	4.8%	3.2%	0.014
Positive NAAT at cohort entry	22.7%	1.8%	Not in PS model

Numbers of patients are prior to PS weighting and trimming.

COVID-19 period 1: April 2020-Nov 2020, prior to vaccine availability

Risk of Inpatient **Arterial** Thrombotic Events, COVID-19 vs. Influenza

Cohort	No. Patients	No. Events	Absolute Risk	Site Adjusted Hazard Ratio (95% CI)	Site and PS Adjusted Hazard Ratio (95% CI)
Influenza, 2018-2019	118,618	535	0.45% (0.41-0.49%)	ref	ref
COVID-19, period 1	272,065	2,752	1.01% (0.97-1.05%)	2.09 (1.90 to 2.29)	1.53 (1.38-1.69)
COVID-19, period 2	342,103	3,629	1.06% (1.03-1.10%)	2.22 (2.03 to 2.43)	1.69 (1.53-1.86)

Numbers of patients and events are prior to PS weighting and trimming.

COVID-19 Period 1: April 2020-Nov 2020, prior to vaccine availability; Period 2: Dec 2020-May 2021, vaccine available

Risk of Death After Inpatient **Arterial** Thrombotic Events, COVID-19 vs. Influenza

Cohort	No. Patients with ATE	No. Deaths	Site Adjusted Hazard Ratio (95% CI)	Site and PS Adjusted Hazard Ratio (95% CI)
Influenza, 2018-2019	535	46	ref	ref
COVID-19, period 1	2,752	534	2.43 (1.79 to 3.28)	2.65 (1.88-3.73)
COVID-19, period 2	3,629	703	2.42 (1.80 to 3.27)	2.53 (1.82-3.51)

Numbers of patients and events are prior to PS weighting and trimming.

COVID-19 Period 1: April 2020-Nov 2020, prior to vaccine availability; Period 2: Dec 2020-May 2021, vaccine available

Risk of Inpatient **Venous** Thrombotic Events, COVID-19 vs. Influenza

Cohort	No. Patients	No. Events	Absolute Risk	Site Adjusted Hazard Ratio (95% CI)	Site and PS Adjusted Hazard Ratio (95% CI)
Influenza, 2018-2019	118,618	219	0.18% (0.16-0.21%)	ref	ref
COVID-19, period 1	272,065	1,994	0.73% (0.70-0.77%)	3.74 (3.25 to 4.30)	2.86 (2.46-3.32)
COVID-19, period 2	342,103	2,994	0.88% (0.84-0.91%)	4.55 (3.96 to 5.22)	3.56 (3.08-4.12)

Numbers of patients and events are prior to PS weighting and trimming.

COVID-19 Period 1: April 2020-Nov 2020, prior to vaccine availability; Period 2: Dec 2020-May 2021, vaccine available

Risk of Death After Inpatient **Venous** Thrombotic Events, COVID-19 vs. Influenza

Cohort	No. Patients with VTE	No. Deaths	Site Adjusted Hazard Ratio (95% CI)	Site and PS Adjusted Hazard Ratio (95% CI)
Influenza, 2018-2019	219	15	ref	ref
COVID-19, period 1	1,994	316	2.34 (1.39 to 3.93)	2.36 (1.34-4.18)
COVID-19, period 2	2,994	527	2.68 (1.61 to 4.49)	2.58 (1.48-4.50)

Numbers of patients and events are prior to PS weighting and trimming.

COVID-19 Period 1: April 2020-Nov 2020, prior to vaccine availability; Period 2: Dec 2020-May 2021, vaccine available

Study Limitations & Considerations

Misclassification

- ICD-10 diagnoses for thromboembolic events not validated
- Clinicians may have been more likely to diagnose events in COVID-19
- Under-captured outcomes for COVID-19 (e.g., out-of-hospital death)

Generalizability

- Only included commercially insured individuals
- One influenza season
- Medically attended COVID-19 and influenza

Data Availability

- Small proportion of cohorts identified via positive laboratory test
- Vaccination status not identified due to incomplete capture
- Incomplete race, Hispanic ethnicity data; not included in analyses
- Inpatient medications unknown (e.g., prophylactic anticoagulation)

Conclusions

- Ambulatory patients diagnosed with COVID-19 both before and after vaccine availability had a higher risk of inpatient **arterial** and **venous** thrombotic events than patients with 2018-19 influenza
- After an inpatient **arterial** or **venous** thrombotic event, the risk of death was 2-3 times higher for patients with COVID-19 versus influenza

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