Sentinel

Arterial and Venous Thrombotic Events in Patients with COVID-19 Compared to Influenza

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Background

- Case series of hospitalized COVID-19 patients have indicated many may develop arterial or venous thrombotic complications
- The incidence of arterial and venous thrombotic events in persons with COVID-19 is unclear
- It is unclear if these complications are more frequent for COVID-19 compared to other respiratory viral infections

https://www.sentinelinitiative.org/sites/default/files/documents/Coagulopathy_COVID19_Study_Synopsis_v2.0_0.pdf

Specific Aims

- Determine 90-day incidence of inpatient arterial and venous thrombotic events, separately, among those with COVID-19 and 2018-19 seasonal influenza
- Compare 90-day risk of inpatient arterial and venous thrombotic events, separately, between those with COVID-19 and influenza
    - Compare risk of death within 30 days of an event

Study Design & Data Source

- **Study design: Retrospective cohort study**
- **Data source: FDA's Rapid Sentinel Distributed Database**
  - 4 integrated health systems (electronic health records + claims)
  - 2 large national insurers (claims only)
  - COVID-19 and influenza identified via diagnosis codes and lab results (all care settings)
  - Inpatient thrombotic events identified via diagnosis codes
  - Lab data available: COVID-19, influenza, clinical labs
  - Measured pre-existing comorbidities and outpatient dispensed medications

Study Patients

Ensure influenza patients do not have COVID-19

	COVID-19 Cohort	Influenza Cohort
Inclusion Criteria	COVID-19 diagnosis code or positive NAAT All care settings April – Nov 2020	Influenza diagnosis code or positive NAAT All care settings Oct 2018 – April 2019
	≥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, so it was not an exclusion criterion

Primary Outcomes: Thromboembolic Events

Arterial Thrombosis

Acute myocardial infarction

Acute ischemic or embolic stroke

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 care setting, age, sex, baseline history 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 in persons with COVID-19 vs. influenza

Characteristics of Patients With COVID-19 and Influenza

Characteristic	COVID-19 Cohort (N=352,432) N (%)	Influenza Cohort (N=127,183) N (%)	Standardized Diff. After PS Adjustment
Age (years)	Mean 56 (SD 18) Median 44-71	Mean 52 (SD 17) Median 42-69	0.046
Male sex	160,490 (45.5)	51,610 (40.6)	-0.003
Comorbidities (days -365, 0)			
Asthma	32,566 (9.2)	15,160 (11.9)	-0.009
Atrial fibrillation/flutter	33,109 (9.4)	8,565 (6.7)	0.006
Chronic kidney disease	62,704 (17.8)	15,929 (12.5)	0.017
Diabetes mellitus	87,420 (24.8)	24,205 (19.0)	0.016
Heart failure	37,603 (10.7)	9,432 (7.4)	0.010
Hypertension	171,781 (48.7)	53,964 (41.6)	0.034
Prior CVD (days -365, -1)	87,945 (25.0)	24,112 (19.0)	0.004
Prior VTE (days -365, -1)	9,576 (2.7)	2,472 (1.9)	0.009
Outpatient meds (days -183, -3)			
ACE inhibitors	55,392 (15.7)	17,822 (14.0)	0.014
ARBs	46,951 (13.3)	14,249 (11.2)	0.008
Anticoagulants	29,036 (8.2)	8,004 (6.3)	0.005
Antiplatelets	18,217 (5.2)	5,355 (4.2)	0.008

Numbers of patients are prior to PS weighting and trimming.

90-Day Absolute Risk of Inpatient ATE and VTE for Patients With COVID-19 vs. Influenza

Outcome	COVID-19 Cohort			Influenza Cohort		
	No. Patients	No. Events	Absolute Risk	No. Patients	No. Events	Absolute Risk
ATE	352,432	9,421	**2.7%** (95% CI 2.6-2.7%)	127,183	1,726	**1.4%** (95% CI 1.3-1.4%)
VTE		6,040	**1.7%** (95% CI 1.7-1.8%)		660	**0.5%** (95% CI 0.5-0.6%)

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

Risk of Inpatient Arterial Thrombotic Events for COVID-19 vs. 2018-19 Influenza, by Index Care Setting

Cohort	No. Patients	No. Events	Site Adjusted Hazard Ratio (95% CI)	Site and PS Adjusted Hazard Ratio (95% CI)
Infection identified in all care settings (primary cohorts)				
COVID-19	352,432	9,421	1.89 (1.80-1.99)	1.10 (1.04-1.17)
Influenza	127,183	1,726		
Infection identified in ambulatory setting				
COVID-19	272,065	2,752	2.09 (1.90-2.29)	1.53 (1.38-1.69)
Influenza	118,618	535		
Infection identified in inpatient setting				
COVID-19	41,443	6,559	1.10 (1.04-1.18)	1.04 (0.97-1.11)
Influenza	8,269	1,190		

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

Risk of Death After Inpatient Arterial Thrombotic Events, COVID-19 vs. 2018-19 Influenza

Cohort	No. Patients with ATE	No. Deaths	Site Adjusted Hazard Ratio (95% CI)	Site and PS Adjusted Hazard Ratio (95% CI)
COVID-19	9,421	2,039	2.91 (2.45-3.45)	3.11 (2.56-3.78)
Influenza	1,726	140		

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

Risk of Inpatient Venous Thrombotic Events for COVID-19 vs. 2018-19 Influenza, by Index Care Setting

Cohort	No. Patients	No. Events	Site Adjusted Hazard Ratio (95% CI)	Site and PS Adjusted Hazard Ratio (95% CI)
Infection identified in all care settings (primary cohorts)				
COVID-19	352,432	6,040	3.19 (2.94-3.46)	1.95 (1.79-2.13)
Influenza	127,183	660		
Infection identified in ambulatory setting				
COVID-19	272,065	1,994	3.74 (3.25-4.30)	2.86 (2.46-3.32)
Influenza	118,618	219		
Infection identified in inpatient setting				
COVID-19	41,443	3,917	1.76 (1.60-1.94)	1.60 (1.43-1.79)
Influenza	8,269	440		

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

Risk of Death After Venous Thrombotic Events, COVID-19 vs. 2018-19 Influenza

Cohort	No. Patients with VTE	No. Deaths	Site Adjusted Hazard Ratio (95% CI)	Site and PS Adjusted Hazard Ratio (95% CI)
COVID-19	6,040	1,042	3.08 (2.24-4.24)	**3.06 (2.12-4.40)**
Influenza	660	39		

COVID-19 and influenza defined by a positive NAAT or diagnosis code in all care settings. Numbers of patients and events are prior to PS weighting and trimming.
Adjustment performed using propensity score stratum weighting to estimate an average treatment effect after trimming non-overlap.

Study Limitations & Considerations

Misclassification	• ICD-10 diagnoses for thromboembolic events not validated • Under-captured outcomes for COVID-19 (e.g., out-of-hospital death)
Selection bias	• Ambulatory cohorts
Generalizability	• Only included commercially insured individuals • One influenza season
Data availability	• SARS-CoV-2 and influenza labs primarily from outpatient settings • Vaccination: COVID cases identified prior to vaccine availability; influenza vaccination not identified • Incomplete race, Hispanic ethnicity data; not included in analyses

Conclusions

- Patients with COVID-19 in April-November 2020 had a higher risk of inpatient venous thrombotic events than patients with 2018-19 influenza

- There was some evidence of increased risk of arterial thrombotic events in patients with COVID-19 compared to influenza

- After an inpatient arterial or venous thrombotic event, the risk of death was more than 3 times higher for patients with COVID-19 versus influenza

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