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Thrombosis in hospitalized patients with viral respiratory infections versus COVID-19

Nathaniel R. Smilowitz, MD, MS, Varun Subashchandran, BS, Eugene Yuriditsky, MD, James M. Horowitz, MD, Harmony R. Reynolds, MD, Judith S. Hochman, MD, and Jeffrey S. Berger, MD, MS ***New York, NY***

We evaluated the incidence of thrombosis in patients hospitalized with non-COVID-19 acute viral respiratory illnesses nationwide from 2012 to 2014 and compared this to the incidence among patients hospitalized with COVID-19 at a large health system in New York. Non-COVID-19 viral respiratory illness was complicated by acute MI in 2.8% of hospitalizations, VTE in 1.6%, ischemic stroke in 0.7%, and other systemic embolism in 0.1%. The proportion of hospitalizations complicated by thrombosis was lower in patients with viral respiratory illness in 2002-2014 than in COVID-19 (5% vs 16%; $P< .001$).

Background Thrombosis is a prominent feature of the novel Coronavirus disease 2019 (COVID-19). The incidence of thrombosis during hospitalization for non-COVID-19 viral respiratory infections is uncertain. We evaluated the incidence of thrombosis in patients hospitalized with non-COVID-19 acute viral respiratory illnesses compared to COVID-19.

Methods Adults age >18 years hospitalized with a non-COVID-19 viral respiratory illness between 2002 and 2014 were identified. The primary study outcome was a composite of venous and arterial thrombotic events, including myocardial infarction (MI), acute ischemic stroke, and venous thromboembolism (VTE), as defined by ICD-9 codes. The incidence of thrombosis in non-COVID-19 viral respiratory illnesses was compared to the recently published incidence of thrombosis in COVID-19 from 3,334 patients hospitalized in New York in 2020.

Results Among 954,521 hospitalizations with viral pneumonia from 2002 to 2014 (mean age 62.3 years, 57.1% female), the combined incidence of arterial and venous thrombosis was 5.0%. Acute MI occurred in 2.8% of hospitalizations, VTE in 1.6%, ischemic stroke in 0.7%, and other systemic embolism in 0.1%. Patients with thrombosis had higher in-hospital mortality (14.9% vs 3.3%, $P< .001$) than those without thrombosis. The proportion of hospitalizations complicated by thrombosis was lower in patients with viral respiratory illness in 2002-2014 than in COVID-19 (median age 64; 39.6% female) in 2020 (5% vs 16%; $P< .001$)

Conclusion In a nationwide analysis of hospitalizations for viral pneumonias, thrombosis risk was lower than that observed in patients with COVID-19. Investigations into mechanisms of thrombosis and risk reduction strategies in COVID-19 and other viral respiratory infections are necessary. (Am Heart J 2021;231:93–95.)

Thrombosis is a prominent feature of the novel Coronavirus disease 2019 (COVID-19).[1] Nearly 1 in 6 adults hospitalized with COVID-19 will have arterial or venous thrombosis during hospital admission.[1] Non-COVID-19 viral respiratory infections, including viral influenza, confer excess thrombotic risk after hospital discharge, but the incidence of thrombosis during hospitalization is uncertain.[2] Previous estimates of in-hospital thrombotic risk are based on small series of patients with influenza.[3] Alveolar capillary microthrombi are 9 times as prevalent at autopsy in COVID-19 than in influenza, but there are limited data comparing rates of thrombosis in COVID-19 to non-COVID-19 respiratory viral illnesses.[4] We set out to evaluate the incidence of arterial and venous thrombosis in a cohort of patients hospitalized with non-COVID-19 acute viral respiratory illnesses compared to COVID-19.

Methods

Adults age >18 years hospitalized with a non-COVID-19 viral respiratory illness between 2002 and 2014 were identified from the United States Agency for Healthcare Research and Quality National Inpatient Sample (NIS) based on a primary or nonprimary *International Classification of Diseases, Ninth Revision Clinical*

From the and Leon H. Charney Division of Cardiology, Department of Medicine, New York University School of Medicine, New York, NY

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Reprint requests: Nathaniel R. Smilowitz, MD, MS, Leon H. Charney Division of Cardiology, Department of Medicine, New York University School of Medicine, 423 East 23rd Street, Room 12020-W, New York, NY 10010.

E-mail address: nathaniel.smilowitz@nyulangone.org.

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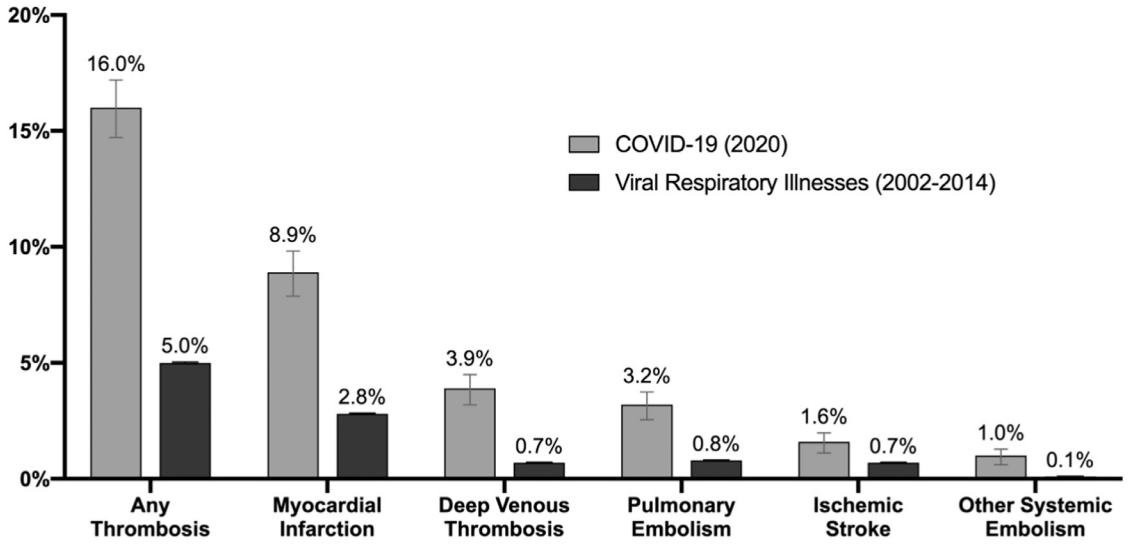
Figure 1



Thrombotic risks in COVID-19 versus previous viral respiratory illnesses. *$P < .01$ for all comparisons. Proportions are shown with 95% confidence intervals determined using the Wilson method with a correction for continuity. Some patients had >1 type of thrombotic event during hospitalization. ICD-9 diagnosis codes for myocardial infarction: 410.x1; pulmonary embolism: 415.1x; deep vein thrombosis: 451.11, 451.19, 451.81, 452, 453.2, 453.4x, 453.8x; acute ischemic stroke: 433.x, 434.x, 436, 437.1; other systemic embolism: 444.09, 444.1, 444.2x, 444.8x, 444.9, 445.01, 445.02.

Modification (ICD-9) diagnosis code for viral pneumonia as previously defined (480.x, 487.x, 488.x, 079.6, 484.1, 466.11).[5] The primary study outcome was a composite of venous and arterial thrombotic events, including myocardial infarction (MI), acute ischemic stroke, venous thromboembolism (VTE, including deep vein thrombosis or pulmonary embolism), or other arterial embolism, as defined by ICD-9 codes. In-hospital mortality was assessed in patients with and without thrombosis. Sensitivity analyses were performed in the cohort of patients with viral influenza. Sampling weights, clustering, and stratification were applied to all NIS analyses to determine national incidence estimates. The incidence of thrombosis in non-COVID-19 viral respiratory illnesses was compared to the recently published incidence of thrombosis in COVID-19 from 3,334 patients hospitalized in 4 NYU Langone Health system hospitals from March 1, to April 17, 2020.[1] No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Results and Discussion

Among 954,521 hospitalizations with viral pneumonia from 2002 to 2014 (mean age 62.3 [SEM 0.13], 57.1% female), the combined incidence of arterial and venous thrombosis was 5.0%. Acute MI occurred in 2.8% of hospitalizations, VTE in 1.6%, ischemic stroke in 0.7%, and other systemic embolism in 0.1%. Patients with thrombosis were older (68.5 vs 62.0 years, $P< .001$), more likely to be men (50.9% vs 42.4%, $P< .001$), and had higher in-hospital mortality (14.9% vs 3.3%, $P< .001$) than those without thrombosis. In a sensitivity analysis of 759,707 hospitalizations with viral influenza pneumonia (mean age 62.8 [SEM 0.14], 57.3% female), the combined incidence of arterial and venous thrombosis was 4.8%; MI occurred in 2.9%, VTE in 1.4%, and ischemic stroke in 0.7% of hospital admissions. The proportion of hospitalizations complicated by arterial and venous thrombosis was lower in patients with viral respiratory illness in 2002-2014 than in COVID-19 (median age 64 [IQR 51-75]; 39.6% female) in 2020 (5% vs 16%; Figure 1).

The present study provides important context for the risks of thrombosis observed in patients with COVID-19, which was 3-fold higher than the 5% risk of thrombosis in nearly 1 million hospitalizations for viral pneumonia.[1] The incidence of both arterial and venous thrombotic events was elevated in COVID-19 compared to non-COVID-19 respiratory illness, suggesting that mechanisms go beyond immobility associated with hospitalization. This is the largest series to evaluate risks of in-hospital thrombosis among patients with non-COVID-19 respiratory illnesses, a majority of which were due to viral influenza. Thrombotic risks associated with non-

COVID-19 viral pneumonias were similar to the 5.9% incidence previously reported in 119 patients with H1N1 Influenza A.[3] Our analyses is limited by the use of administrative data, which may be subject to reporting bias and coding errors. Antithrombotic and antimicrobial medications were not recorded in the NIS. The time sequence of diagnoses was not documented, and some patients could have been hospitalized for a primary thrombosis that was complicated by nosocomial viral pneumonia. Finally, differential methods of event ascertainment may limit the reliability of comparisons between thrombosis incidence from national administrative data and from our health system.

Conclusion

In this nationwide analysis of hospitalizations for viral pneumonias, thrombosis occurred in 5% of cases. Although substantial, this is significantly lower than thrombosis observed in patients hospitalized with COVID-19. Investigations into mechanisms of thrombosis and risk reduction strategies in COVID-19 and other viral respiratory infections are necessary.

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