An increased risk for ischemic stroke in the short-term period following COVID-19 infection: A nationwide population-based study

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Introduction

COVID-19 infection was found to be associated with an increased risk for ischemic stroke. Yet, the overall incidence, the strength of the association and the risk periods, which were not consistent between studies, need further investigation.

Methods and Materials

We linked between two national databases: the national COVID-19 database and the Israeli National Stroke Registry.

The self-controlled case series method was used to estimate the association between COVID-19 infection and a first ischemic stroke. In this method, only cases are sampled, thus all fixed confounders are controlled for.

The study population included all Israeli residents who had both a first ischemic stroke event and a first COVID-19 diagnosis during 2020. The date of the PCR test served to define the day of exposure (day 0), and the 28 days following this date were categorized into three risk periods: days 1-7, 8-14, and 15-28.

Since the policy during the start of the pandemic was to perform a PCR test upon hospitalization, a spike of events on day zero may reflect a reversed causality bias. To avoid bias, we analyzed the data with the risk period starting a day after the PCR test performance (i.e., on day 1).

An incidence rate ratio (IRR) with a 95% confidence interval (95% CI) was calculated based on the incidence rate of events in a post-exposure period (i.e., the risk period), compared to the incidence rate in the absence of an exposure (i.e., the control period).

Results

From January 1, 2020 to December 31, 2020, 308,015 Israelis aged 18+ were diagnosed with COVID-19 and 9,535 were diagnosed with a first ischemic stroke. Linking the national COVID-19 database and the Israeli National Stroke Registry, 555 persons had both diagnoses during 2020.

Results

The mean age of the study population was 71.5±13.7, 55.1% were males, 77.8% had hypertension, 73.7% had hyperlipidemia, 51.9% had diabetes, 28.5% had ischemic heart disease and 25.6% had atrial fibrillation. Comparing between the risk period and the control period, we found a very similar distribution of the cardiovascular risk factors. The peak of events occurred on day zero (n=30), following by day 1 (n=21) (Figure).

Figure. Days from COVID-19 exposure to event
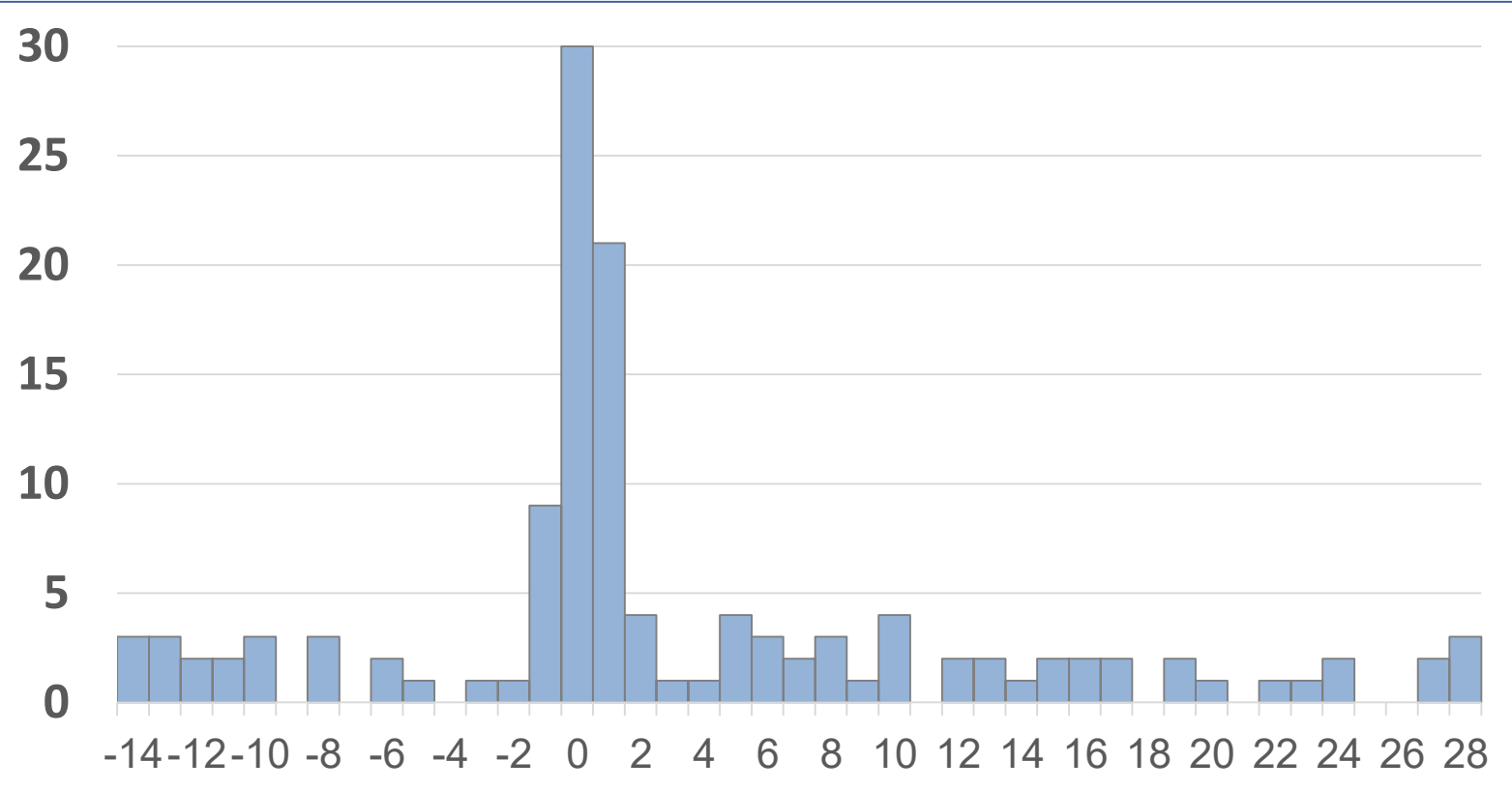
The risk for an acute ischemic stroke was 3.3-fold higher in the first week following COVID-19 diagnosis, compared with a control period (IRR =3.3; 95% CI 2.3-4.6) (Table). The IRR among males (IRR =4.5; 95% CI 2.9-6.8) was 2.2-fold higher compared to females.

Table. The IRR for a first ischemic stroke, with day zero excluded from the risk period

Risk period (days)	Number of events	IRR (95% CI)	P-value
Buffer period: days -4 to -14	19	**1.03** (0.65-1.64)	0.90
Pre-diagnosis risk period: days -3 to 0	41	**7.03** (5.06-9.76)	<0.001
Post-exposure risk period: days 1 to 7	36	**3.26** (2.30-4.62)	<0.001
Post-exposure risk period: days 8 to 14	13	**1.44** (0.82-2.51)	0.19
Post-exposure risk period: days 15 to 28	18	**1.13** (0.70-1.83)	0.59
Control period	428	**1** (ref)	

Conclusions

Physicians should be aware of the elevated risk for ischemic stroke among patients experiencing COVID-19, particularly among men with high burden of cardiovascular risk factors.

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