

COVID-19 and Risk of Acute Ischemic Stroke Among Medicare Beneficiaries Aged 65 Years or Older

Self-Controlled Case Series Study

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Abstract

Background and Objectives

Findings of association between coronavirus disease 2019 (COVID-19) and stroke remain inconsistent, ranging from significant association to absence of association to less than expected ischemic stroke among hospitalized patients with COVID-19. The current study examined the association between COVID-19 and risk of acute ischemic stroke (AIS).

Methods

We included 37,379 Medicare fee-for-service (FFS) beneficiaries aged ≥ 65 years diagnosed with COVID-19 from April 1, 2020, through February 28, 2021, and AIS hospitalization from January 1, 2019, through February 28, 2021. We used a self-controlled case series design to examine the association between COVID-19 and AIS and estimated the incidence rate ratios (IRRs) by comparing incidence of AIS in risk periods (0–3, 4–7, 8–14, 15–28 days after diagnosis of COVID-19) vs control periods.

Results

Among 37,379 Medicare FFS beneficiaries with COVID-19 and AIS, the median age at diagnosis of COVID-19 was 80.4 (interquartile range 73.5–87.1) years and 56.7% were women. When AIS at day of exposure (day = 0) was included in the risk periods, IRRs at 0–3, 4–7, 8–14, and 15–28 days following COVID-19 diagnosis were 10.3 (95% confidence interval 9.86–10.8), 1.61 (1.44–1.80), 1.44 (1.32–1.57), and 1.09 (1.02–1.18); when AIS at day 0 was excluded in the risk periods, the corresponding IRRs were 1.77 (1.57–2.01) (day 1–3), 1.60 (1.43–1.79), 1.43 (1.31–1.56), and 1.09 (1.01–1.17), respectively. The association appeared to be stronger among younger beneficiaries and among beneficiaries without prior history of stroke but largely consistent across sex and race/ethnicities.

Discussion

Risk of AIS among Medicare FFS beneficiaries was 10 times (day 0 cases in the risk period) as high during the first 3 days after diagnosis of COVID-19 as during the control period and the risk associated with COVID-19 appeared to be stronger among those aged 65–74 years and those without prior history of stroke.

Classification of Evidence

This study provides Class IV evidence that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is associated with increased risk of AIS in the first 3 days after diagnosis in Medicare FFS beneficiaries ≥ 65 years of age.

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Glossary

AIS = acute ischemic stroke; **CDC** = Centers for Disease Control and Prevention; **CI** = confidence interval; **COVID-19** = coronavirus disease 2019; **FFS** = fee-for-service; **GV** = geographic variation; **ICD-10-CM** = International Classification of Diseases, 10th revision, Clinical Modification; **IQR** = interquartile range; **IRR** = incidence rate ratio; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2.

Several studies have suggested that infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19), has been associated with an increased risk of cerebrovascular events including acute ischemic stroke (AIS).¹⁻⁶ However, the findings of association between COVID-19 and stroke were not consistent, as studies reported the rates of stroke among patients with COVID-19 ranging from 0.4% to 8.0% with an average of 1.4%.² Two studies using similar study design suggested that risk of ischemic stroke increased significantly following diagnosis of COVID-19.^{3,6} One study suggested that the rates of stroke were similar between hospitalized patients with and without COVID-19,⁷ and another study showed that ischemic stroke occurred less often than expected among hospitalized patients with COVID-19.⁸ Differences in study designs, countries, inclusion criteria of patients and comparison groups, sample size, and controlling for confounders may contribute to the inconsistent findings. Few studies focused on the older population, where most stroke occurred.⁹

The objective of the current study is to examine the association between COVID-19 and risk of AIS among Medicare fee-for-service (FFS) beneficiaries aged 65 years or older. We used a self-controlled case series study design that is based on within-person comparisons and implicitly controls for all fixed confounding effects. Our study included more than 37,000 Medicare FFS beneficiaries who were diagnosed with COVID-19 during April 1, 2020–February 28, 2021 and AIS hospitalizations during January 1, 2019–February 28, 2021.

The primary research question of the present study is to determine the association between SARS-CoV-2 infection and risk of AIS among Medicare FFS beneficiaries ≥65 years.

Methods

Study Population

We used the real-time Medicare geographic variation (GV) files to identify the beneficiaries for this study. First, we identified all Medicare beneficiaries who had been diagnosed with COVID-19 from January 1, 2020, through February 28, 2021 from Part A (inpatient claims) and Part B (physician's office claims). We used ICD-10-CM code U07.1 to identify Medicare beneficiaries diagnosed with COVID-19. If the beneficiaries had more than one date for a COVID-19 diagnosis, the first diagnosed date was chosen. Second, we used the primary diagnosis code for AIS (ICD-10-CM code I63) to

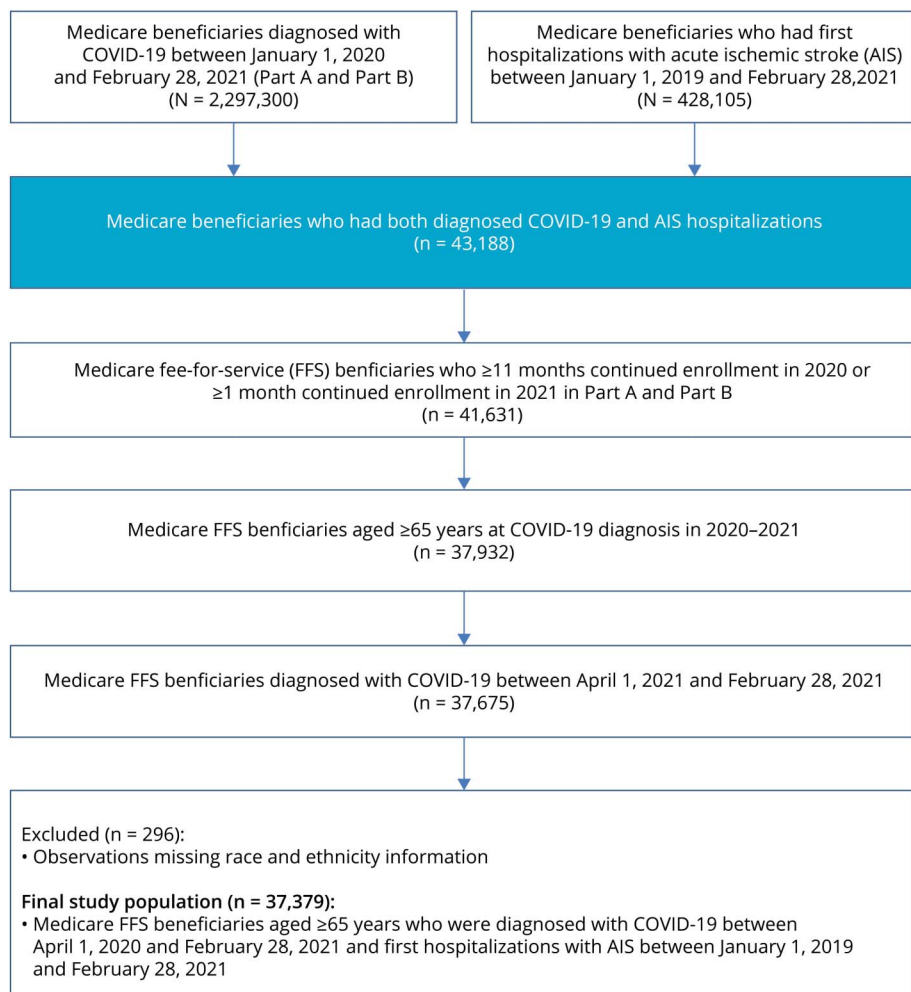
identify the beneficiaries with AIS hospitalizations from January 1, 2019, through February 28, 2021. The diagnosis of ischemic stroke in the administrative datasets is valid and the concordance between ICD-10-CM codes in administrative datasets and the clinical diagnosed stroke was shown to be generally high.^{10,11} If the beneficiaries had more than one date of AIS hospitalization during the study period, the first hospitalization date was chosen. Third, we merged the above 2 datasets using the beneficiaries' IDs to create the dataset including all Medicare beneficiaries diagnosed with COVID-19 from January 1, 2020, through February 28, 2021, and incident AIS from January 1, 2019, through February 28, 2021. Fourth, we further identified all Medicare FFS beneficiaries with at least 11 months continuous enrollment in Medicare Parts A (hospitalization) and B (office-based care) in 2020 or at least 1 month enrollment in 2021, and those who were diagnosed with COVID-19 from April 1, 2020, through February 28, 2021. For the beneficiaries who died before March 1, 2021, they must have had continuous enrollment in Medicare Parts A and B before death.

From January 1, 2019, through February 28, 2021, there were 2,297,300 beneficiaries diagnosed with COVID-19, and during January 1, 2019, through February 28, 2021, there were 428,105 beneficiaries hospitalized with incident or recurrent AIS. In the merged dataset, there were 43,188 beneficiaries diagnosed with COVID-19 and incident AIS, among which 41,631 met FFS criteria (≥11 months enrollment in both Part A and B in 2020, or ≥1 month enrollment in both Part A and B in 2021) and of these, 37,932 beneficiaries were aged ≥65 years. Of those Medicare FFS beneficiaries aged ≥65 years, 37,675 were diagnosed with COVID-19 from April 1, 2020, to February 28, 2021. After excluding the beneficiaries with missing information on race/ethnicities, the final analytical cohort had 37,379 Medicare FFS beneficiaries diagnosed with COVID-19 and AIS (Figure 1).

Exposure and Outcome

The exposure variable was COVID-19, and the index date of COVID-19 diagnosis for each FFS beneficiary was identified through Medicare real-time GV Part A and Part B claims data for the period between April 1, 2020, and February 28, 2021. The outcome was AIS, and the index date of AIS was identified using primary diagnosis codes in Part A from January 1, 2019, through February 28, 2021. For Medicare FFS beneficiaries with more than one date of being diagnosed with COVID-19 or AIS during the study period, the first occurrence of events was chosen as the index date. If the Medicare

Figure 1 Flowchart of US Medicare FFS Beneficiaries With Diagnosed COVID-19 and Acute Ischemic Stroke, 2019–2021



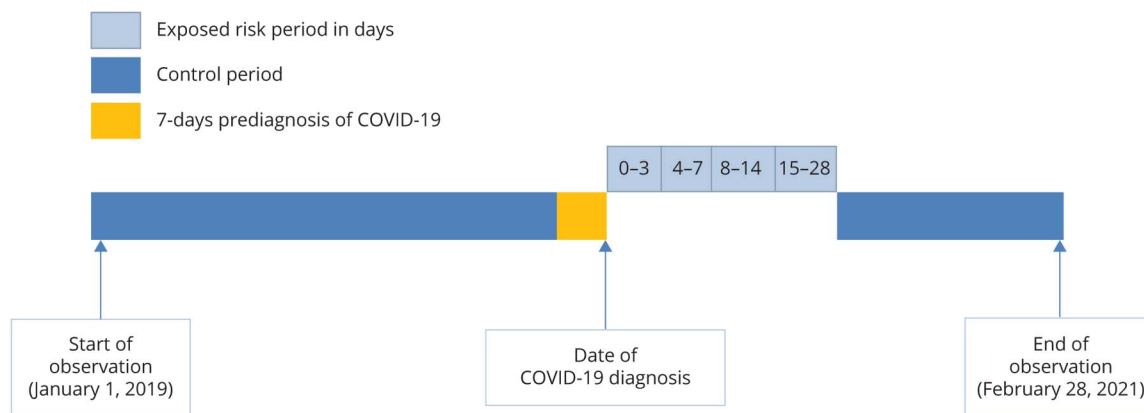
FFS beneficiaries had a diagnosis of stroke (any type and including transient ischemic attack) based on the Chronic Conditions Warehouse definition used by Centers for Medicare and Medicaid Services¹² that occurred before January 1, 2019, they were classified as having a prior history of stroke.

Statistical Analysis

We calculated the median age and interquartile range (IQR) and the distribution of age group, sex, race/ethnicities, AIS with and without prior history of stroke, and death before end of follow-up for all Medicare FFS beneficiaries. We used self-controlled case series study design to estimate incidence rate ratio (IRR) and 95% confidence interval (CI) for risk of AIS between 0 and 28 days following a diagnosis of COVID-19. As shown in Figure 2, the self-controlled case series design is based on within-person comparisons (self-matched) after exposure during an observation period subdivided into risk and control periods, and this method implicitly controls for all fixed confounders during the period of study.¹³ The null hypothesis, IRR = 1.0, implies that AIS event rates remained

constant during the entire observation period and were not affected by having COVID-19. An IRR >1.0 or <1.0 implies an increased or reduced risk of AIS following diagnosis of COVID-19. The study observation period started on January 1, 2019, and ended on February 28, 2021, or the date of death for those who died before the end of follow-up. We categorized the risk periods after diagnosis of COVID-19 into 0–3, 4–7, 8–14, and 15–28 days and the remaining periods served as control periods.¹⁴ However, we observed a higher number of AIS at day 0 of COVID-19 (n = 1,924) and more than expected number of AIS cases that occurred 7 days before the COVID-19 index date. We could not determine whether these AIS cases may have occurred after SARS-CoV-2 infection since the incubation period for COVID-19 may extend up to 14 days.¹⁵ Therefore, we conducted 2 analyses: one analysis had a preexposure period from day –7 to day –1, and the risk periods of 0–3, 4–7, 8–14, and 15–28 days (day 0 cases in the risk periods) and another analysis with a preexposure period from day –7 to day 0, and the risk periods of 1–3, 4–7, 8–14, and 15–28 days (day 0 cases not in the risk periods) for total AIS analysis.^{6,16} Other studies observed

Figure 2 Graphic Representation of Self-Controlled Case Series Study Design



similar pattern of cases distribution around the COVID-19 index date^{3,6} and suggested that most patients with the same date of ischemic stroke and COVID-19 were indeed infected with SARS-CoV-2 before stroke event.⁶ Therefore, we presented results of the risk periods including day 0 cases for the stratified and sensitivity analyses.

There are 2 key assumptions of the self-controlled case series design: (1) events do not influence subsequent exposures; (2) events do not influence the length of observation periods.¹⁷ Among FFS beneficiaries with AIS, 28.5% of them ($n = 10,663$) died before March 1, 2021, and the assumption of event being independent of observation period was violated (due to increased mortality after AIS hospitalization), therefore we used the modified self-controlled case series method that takes into account the event-dependent observation period of time.^{17,18} The IRRs were adjusted for age at diagnosis of COVID-19 from 65 to 90 years of age by 2-year age groups.

We conducted stratified analyses by age groups (65–74 years, 75–84 years, and ≥ 85 years), sex, race/ethnicities (non-Hispanic White, non-Hispanic Black, Hispanic, and all other race/ethnicities), and status of history of prior stroke (first vs recurrent stroke). We tested for interaction to examine whether the IRRs for risk of AIS changed significantly across the subgroups in the stratified analyses based on the likelihood ratio tests and presented adjusted p values by using the Holm method for multiple comparisons.^{13,17,19}

We conducted several sensitivity analyses: (1) we restricted the starting time to January 1, 2020, to reduce the potential temporal changes in AIS before and after the COVID-19 pandemic ($n = 21,756$); (2) we excluded Medicare beneficiaries with I63.8 and I63.9 (less specific codes for AIS, $n = 17,251$ after exclusion); (3) we excluded all beneficiaries who died before the end of observation period ($n = 26,716$ after exclusion) and used the standard self-controlled case series analysis; (4) studies suggested that pneumococcal vaccination was not associated with stroke.²⁰ We examined the association

between pneumococcal vaccination and risk of AIS as a negative control to identify potential biases in using self-controlled case series design in Medicare claims data (first date of pneumococcal vaccination and AIS hospitalization, $n = 23,651$). We changed the starting time to the date of pneumococcal vaccination because patients with heart disease or stroke are advised to get vaccinated against pneumonia,²¹ which may affect the probability of pneumococcal vaccination.²² We used the standard self-controlled case series analysis among stroke survivors. SAS, version 9.4 (SAS Institute), was used for analysis, and R package SCCS was used for self-controlled case series analyses.¹⁷

This activity was reviewed by the Centers for Disease Control and Prevention (CDC) and was conducted consistent with applicable federal law and CDC policy (see for example 45 CFR part 46, 21 CFR part 56; 42 USC §241(d); 5 USC §552a; 44 USC §3,501 et seq.).

Standard Protocol Approvals, Registrations, and Patient Consents

The CDC Human Subjects Coordinator determined that this study did not require review for human subjects protections because the data did not contain personal identifiers and were not originally collected specifically for this study. Therefore, the requirement of informed consent was waived.

Data Availability

Medicare data are available from Centers for Medicare & Medicaid Services, Department of Health and Human Services, for any qualified investigator.

Results

Among 37,379 Medicare FFS beneficiaries diagnosed with COVID-19 and AIS, the median age was 80.4 years (IQR 73.5–87.1 years), 56.7% (95% CI 56.2%–57.2%) were women, and 75.9% (75.4%–76.3%) were non-Hispanic White. Among the beneficiaries, 34.0% (33.5%–34.5%) had

prior history of stroke and 28.5% (28.1%–29.0%) died before the end of the observation period (Table 1).

When AIS at day of exposure (day 0) was included in the risk period, IRRs at 0–3, 4–7, 8–14, and 15–28 days following COVID-19 diagnosis were 10.3 (9.86–10.8), 1.61 (1.44–1.80), 1.44 (1.32–1.57), and 1.09 (1.02–1.18); when AIS at day 0 was excluded in the risk period, the corresponding IRRs were 1.77 (1.57–2.01) (day 1–3), 1.60 (1.43–1.79), 1.43 (1.31–1.56), and 1.09 (1.01–1.17), respectively (Table 2).

The association appeared to be stronger among younger (ages 65–74 years) beneficiaries and among beneficiaries without prior history of stroke. The age-adjusted IRRs at 0–3, 4–7, 8–14, and 15–28 days following the diagnosis of COVID-19 were 14.7 (13.6–15.8), 2.45 (2.02–2.92), 1.70 (1.46–1.98), and 1.06 (0.92–1.22) among those aged 65–74 years compared to 7.04 (6.46–7.66), 1.10 (0.89–1.35), 1.15 (0.98–1.34), and 1.05 (0.93–1.19) among those aged ≥85 years ($p < 0.001$); the corresponding comparisons for beneficiaries with and without prior history of stroke were 7.92 (7.26–8.63), 1.00 (0.78–1.27), 1.22 (1.03–1.43), and 1.10 (0.96–1.25) vs 14.6 (13.9–15.4), 2.41 (2.13–2.73), 1.88 (1.70–2.08), and 1.24 (1.14–1.36) ($p < 0.001$). The pattern of association between COVID-19 and risk for AIS were largely consistent across sex and race/ethnicities (Table 3) and for the sensitivity analyses (Table 4). The IRRs between pneumococcal vaccination and AIS were approximately 1.0 across the exposure period, suggesting the validity of using self-controlled case series design in Medicare claims data (Table 4).

This study provides Class IV evidence that SARS-CoV-2 infection, the virus that causes COVID-19, is associated with increased risk of AIS in the first 3 days after diagnosis in Medicare FFS beneficiaries ≥65 years of age.

Discussion

We found that the incidence of AIS hospitalizations was 10 times (day 0 cases in the risk periods) as high during the first 3 days after diagnosis of COVID-19 as during the control period among Medicare FFS beneficiaries aged ≥65 years. There was a graded stronger association from older to younger beneficiaries. The association appeared to be stronger among the beneficiaries without prior history of stroke. We observed a higher number of AIS ($n = 1,924$) at day 0 of COVID-19 index date. A Swedish study using self-controlled case series design also found higher number of ischemic stroke and COVID-19 at day 0. The IRR for ischemic stroke was 6.18 (4.06–9.42) for the first week following diagnosis of COVID-19 (including day 0 cases in the risk periods) and IRR of 2.97 (1.71–5.15) excluding day 0 cases.⁶ With the mean incubation period for COVID-19 of 5.1 days (97.5% of patients developing symptoms within 12.5 days), the Swedish study

suggested that the patients at day 0 were highly likely to be infected with SARS-CoV-2 before their stroke event. Most hospitals screen all patients for COVID-19 on hospital admission in the United States, and some patients with AIS may have had SARS-CoV-2 infection before hospitalizations and continue to have positive testing results after the initial infection. Those patients were likely to have the same date of AIS hospitalizations and COVID-19 diagnosis in the Medicare claims but also to have an AIS precipitated by SARS-CoV-2 infection.

Our results of increased risk for AIS following diagnosis of COVID-19 were consistent with other studies.^{1,3,5,6} Modin et al.³ used Danish nationwide register data and self-controlled case series design to examine the association between COVID-19 and ischemic stroke and reported an IRR of 12.9 (7.1–23.5) during the first 14 days following diagnosis of COVID-19. However, using data extracted from the

Table 1 Characteristics of US Medicare Fee-for-Service Beneficiaries With Diagnosed COVID-19 and Acute Ischemic Stroke, Medicare 2019–2021

Characteristics	Medicare FFS beneficiaries, n	Median or % (95% CI)
Age, y, median (IQR)	37,379	80.4 (73.5–87.1)
Age group, y		
65–74	11,305	30.2 (29.8–30.7)
75–84	13,873	37.1 (36.6–37.6)
≥85	12,201	32.6 (32.2–33.1)
Sex		
Men	16,199	43.3 (42.8–43.8)
Women	21,180	56.7 (56.2–57.2)
Race/ethnicities		
Non-Hispanic White	28,361	75.9 (75.4–76.3)
Non-Hispanic Black	5,030	13.5 (13.1–13.8)
Hispanic	2,560	6.9 (6.6–7.1)
All other race/ethnicities	1,428	3.8 (3.6–4.0)
History of stroke^a		
Yes	12,715	34.0 (33.5–34.5)
No	24,664	66.0 (65.5–66.5)
Death before end of follow-up		
Yes	10,663	28.5 (28.1–29.0)
No	26,716	71.5 (71.0–71.9)

Abbreviations: CI = confidence interval; COVID-19 = coronavirus disease 2019; FFS = fee-for-service; IQR = interquartile range.

^a Medicare FFS beneficiaries who had stroke before January 1, 2019.

Table 2 Acute Ischemic Stroke Among US Medicare Fee-for-Service Beneficiaries Diagnosed With COVID-19, 2019–2021

Risk period	Events, n	Crude IRR (95% CI)	Age-adjusted IRR (95% CI) ^a
Day 0 cases in the risk period, d			
–7 to –1	789	1.82 (1.69–1.95)	1.91 (1.78–2.05)
0–3	2,173	9.82 (9.40–10.3)	10.3 (9.86–10.8)
4–7	322	1.53 (1.37–1.71)	1.61 (1.44–1.80)
8–14	523	1.37 (1.25–1.49)	1.44 (1.32–1.57)
15–28	735	1.04 (0.96–1.12)	1.09 (1.02–1.18)
Baseline ^b	32,837	1.0	1.0
Day 0 cases not in the risk period, d			
–7 to 0	2,713	5.34 (5.13–5.55)	5.60 (5.37–5.83)
1–3	249	1.69 (1.49–1.91)	1.77 (1.57–2.01)
4–7	322	1.52 (1.36–1.70)	1.60 (1.43–1.79)
8–14	523	1.36 (1.25–1.49)	1.43 (1.31–1.56)
15–28 d	735	1.04 (0.96–1.12)	1.09 (1.01–1.17)
Baseline ^b	32,837	1.0	1.0

Abbreviations: CI = confidence interval; COVID-19 = coronavirus disease 2019; IRR = incidence rate ratio.

^a Adjusted by age at diagnosis of COVID-19 of 65–90 years of age by 2-year age group.

^b All time from observation start on January 1, 2019, to 7 days before date of COVID-19 diagnosis and after 28 days of diagnosis of COVID-19.

electronic medical records of 54 health care facilities in the United States, Qureshi et al.⁷ documented similar rates of AIS among patients hospitalized with and without COVID-19 (1.3% vs 1.0%). Another retrospective cohort study of hospitalized patients with COVID-19 within a major health system in the New York City metropolitan area reported lower prevalence of imaging-confirmed AIS compared to the contemporary controls (patients without COVID-19) and historical controls (patients in 2019), but suggested that the rate of AIS may be underestimated due to the challenge of diagnosing stroke among critically ill patients with COVID-19.²³ A cross-sectional study of the hospital discharge data from a health care system in New York state with data collected from January to April 2020 found that the prevalence of AIS was significantly less frequent among patients with diagnosed COVID-19 compared to those without COVID-19 (adjusted odds ratio 0.29 [0.18–0.48]).⁸ Residual confounding and uncertainties in coding of COVID-19 during the early phase of the pandemic may contribute to this observed association. The findings of our study support those of previous studies of a significant association between COVID-19 and stroke and provide further evidence of the association from a large Medicare cohort of beneficiaries 65 years or older.

Our results suggest that the risk of AIS following diagnosis of COVID-19 was higher among beneficiaries aged 65–74 years compared to those aged ≥85 years (IRR in 0–3 days 14.7 [13.6–15.8] vs 7.04 [6.46–7.66], $p < 0.001$). We are not aware of any study that provided age-stratified analysis of risk of

COVID-19–associated AIS. The reasons for stronger association among younger Medicare beneficiaries are not clear. Studies have reported increased incidence of large vessel stroke among younger patients with COVID-19.^{4,24} Other studies observed that patients with COVID-19 and stroke were significantly younger than patients with stroke without COVID-19,^{23,25–27} with a pooled age difference of 6 years.² In the general population, the incidence of stroke increases rapidly with age.^{9,28} If COVID-19 disproportionately affects younger patients with respect to risk of stroke, it might partly explain the stronger association between COVID-19 and AIS among younger Medicare beneficiaries because of relatively lower baseline risk among younger beneficiaries. On the other hand, the higher risk among younger beneficiaries might be due to inclusion bias because older beneficiaries with severe COVID-19 might have not survived to get tested for COVID-19 or evaluated for stroke. Further studies are needed to examine the incidence of stroke subtypes by age group.

The risk of AIS following diagnosis of COVID-19 appeared to be higher among beneficiaries without a history of stroke compared to those with a history of stroke (IRR in 0–3 days 14.6 [13.9–15.4] vs 7.92 [7.26–8.63], $p < 0.001$). The reasons for the stronger association among the beneficiaries without history of stroke are not clear. Medicare beneficiaries with history of stroke may be more likely to be on medications for secondary prevention of stroke.^{29,30} The beneficiaries who had a history of stroke were older than the beneficiaries without a history of stroke (median age 82.1 years vs 79.2

Table 3 Acute Ischemic Stroke Among US Medicare Fee-for-Service Beneficiaries With Diagnosed COVID-19 by Selected Characteristics, 2019–2021

Characteristics	Events, n	Crude IRR (95% CI)	Age adjusted IRR (95% CI) ^a	P value ^b
Age group, y				
65–74				
–7 to –1 d	228	2.06 (1.80–2.35)	2.14 (1.88–2.45)	
0–3 d	794	14.1 (13.1–15.1)	14.7 (13.6–15.8)	
4–7 d	128	2.35 (1.97–2.79)	2.45 (2.05–2.92)	
8–14 d	168	1.63 (1.40–1.90)	1.70 (1.46–1.98)	
15–28 d	204	1.02 (0.89–1.17)	1.06 (0.92–1.22)	
Baseline ^c	9,783	1.0	1.0	
75–84				
–7 to –1 d	277	1.80 (1.60–2.03)	1.87 (1.66–2.11)	
0–3 d	790	10.1 (9.41–10.9)	10.5 (9.78–11.4)	
4–7 d	107	1.44 (1.19–1.74)	1.50 (1.24–1.81)	
8–14 d	196	1.43 (1.24–1.65)	1.49 (1.30–1.72)	
15–28 d	277	1.09 (0.96–1.23)	1.13 (1.00–1.28)	
Baseline ^c	12,226	1.0	1.0	
≥85				
–7 to –1 d	284	1.71 (1.52–1.93)	1.79 (1.59–2.02)	
0–3 d	589	6.72 (6.18–7.31)	7.04 (6.46–7.66)	
4–7 d	87	1.05 (0.85–1.29)	1.10 (0.89–1.35)	
8–14 d	159	1.09 (0.94–1.28)	1.15 (0.98–1.34)	
15–28 d	254	1.00 (0.88–1.14)	1.05 (0.93–1.19)	
Baseline ^c	10,828	1.0	1.0	<0.0011
Sex				
Men				
–7 to –1 d	369	1.96 (1.77–2.18)	2.10 (1.89–2.33)	
0–3 d	990	10.4 (9.78–11.1)	11.2 (10.5–11.9)	
4–7 d	147	1.64 (1.39–1.93)	1.75 (1.49–2.07)	
8–14 d	259	1.59 (1.40–1.80)	1.70 (1.50–1.93)	
15–28 d	285	0.95 (0.84–1.07)	1.02 (0.91–1.15)	
Baseline ^c	14,149	1.0	1.0	
Women				
–7 to –1 d	420	1.77 (1.61–1.95)	1.83 (1.66–2.02)	
0–3 d	1,183	9.57 (9.01–10.2)	9.87 (9.29–10.5)	
4–7 d	175	1.47 (1.26–1.70)	1.52 (1.31–1.76)	
8–14 d	264	1.21 (1.07–1.37)	1.25 (1.11–1.41)	
15–28 d	450	1.11 (1.01–1.22)	1.15 (1.04–1.26)	
Baseline ^c	18,688	1.0	1.0	0.011

Continued

Table 3 Acute Ischemic Stroke Among US Medicare Fee-for-Service Beneficiaries With Diagnosed COVID-19 by Selected Characteristics, 2019–2021 (continued)

Characteristics	Events, n	Crude IRR (95% CI)	Age adjusted IRR (95% CI) ^a	P value ^b
Race/ethnicities				
Non-Hispanic White				
–7 to –1 d	601	1.82 (1.68–1.97)	1.90 (1.76–2.07)	
0–3 d	1,613	9.51 (9.04–10.0)	9.97 (9.46–10.5)	
4–7 d	239	1.48 (1.30–1.68)	1.55 (1.37–1.76)	
8–14 d	398	1.36 (1.23–1.50)	1.43 (1.29–1.58)	
15–28 d	560	1.04 (0.96–1.13)	1.09 (1.00–1.19)	
Baseline ^c	24,950	1.0	1.0	
Non-Hispanic Black				
–7 to –1 day	99	2.01 (1.65–2.46)	2.11 (1.72–2.57)	
0–3 d	268	11.0 (9.76–12.5)	11.6 (10.2–13.1)	
4–7 d	39	1.68 (1.23–2.30)	1.76 (1.28–2.41)	
8–14 d	62	1.42 (1.11–1.83)	1.49 (1.16–1.91)	
15–28 d	100	1.16 (0.95–1.42)	1.22 (1.00–1.49)	
Baseline ^c	4,462	1.0	1.0	
Hispanic				
–7 to –1 d	59	2.11 (1.63–2.74)	2.20 (1.70–2.86)	
0–3 d	190	13.1 (11.2–15.2)	13.6 (11.7–15.9)	
4–7 d	30	2.12 (1.48–3.04)	2.22 (1.54–3.19)	
8–14 d	36	1.38 (0.99–1.93)	1.45 (1.04–2.02)	
15–28 d	56	1.16 (0.89–1.51)	1.21 (0.93–1.59)	
Baseline ^c	2,189	1.0	1.0	
All other race/ethnicities				
–7 to –1 d	30	1.74 (1.21–2.51)	1.86 (1.29–2.69)	
0–3 d	102	11.9 (9.71–14.6)	12.8 (10.4–15.8)	
4–7 d	14	1.74 (1.03–2.96)	1.87 (1.10–3.18)	
8–14 d	27	1.83 (1.25–2.69)	1.96 (1.34–2.89)	
15–28 d	19	0.71 (0.45–1.12)	0.76 (0.48–1.20)	
Baseline ^c	1,236	1.0	1.0	0.010
History of stroke				
Yes				
–7 to –1 d	238	1.52 (1.34–1.73)	1.69 (1.48–1.92)	
0–3 d	566	7.13 (6.55–7.76)	7.92 (7.26–8.63)	
4–7 d	67	0.90 (0.70–1.14)	1.00 (0.78–1.27)	
8–14 d	147	1.09 (0.93–1.28)	1.22 (1.03–1.43)	
15–28 d	243	0.98 (0.86–1.12)	1.10 (0.96–1.25)	
Baseline ^c	11,454	1.0	1.0	

Continued

Table 3 Acute Ischemic Stroke Among US Medicare Fee-for-Service Beneficiaries With Diagnosed COVID-19 by Selected Characteristics, 2019–2021 (continued)

Characteristics	Events, n	Crude IRR (95% CI)	Age adjusted IRR (95% CI) ^a	P value ^b
No				
–7 to –1 d	551	2.45 (2.25–2.66)	2.48 (2.28–2.70)	
0–3 d	1,607	14.4 (13.7–15.2)	14.6 (13.9–15.4)	
4–7 d	255	2.38 (2.10–2.69)	2.41 (2.13–2.73)	
8–14 d	376	1.85 (1.67–2.05)	1.88 (1.70–2.08)	
15–28 d	492	1.23 (1.12–1.34)	1.24 (1.14–1.36)	
Baseline ^c	21,383	1.0	1.0	<0.001

Abbreviations: CI = confidence interval; COVID-19 = coronavirus disease 2019; IRR = incidence rate ratio.

^a Adjusted by age at diagnosis of COVID-19 of 65–90 years by 2-year age group.

^b P Value for interaction was calculated using likelihood ratio test and adjusted for multiple comparison based on Holm methods.

^c All times from observation start on January 1, 2019, to 7 days before date of COVID-19 diagnoses and after 28 days of diagnosis of COVID-19.

years, $p < 0.05$) and this might partly contribute to the stronger association because of the stronger association between COVID-19 and AIS among younger Medicare beneficiaries. The association between COVID-19 and AIS appeared to be stronger among men compared to women ($p = 0.011$). The detailed analysis suggested that the difference was mainly driven by the IRRs 8–14 days after diagnosis of COVID-19 (1.70 (1.50–1.93) among men vs 1.25 (1.11–1.41) among women. The association between COVID-19 and AIS appeared to be different across race/ethnic group ($p = 0.010$). There is no difference between non-Hispanic White and non-Hispanic Black ($p = 0.293$) and between Mexican American and Other ($p = 0.268$) but the risk appeared to be stronger among Mexican American and Other compared to non-Hispanic White and non-Hispanic Black. However, the pattern of association remained largely consistent across race/ethnic group, and these statistically significant differences by sex and race/ethnicities may not be clinically significant. Further study is warranted to determine the sex and race/ethnic-specific association between COVID-19 and AIS.

Many studies provided evidence showing the presence of systemic infection, such as influenza, systemic respiratory tract infection, and herpes zoster, as a trigger of stroke.^{31–36} The mechanisms underlying the association between COVID-19 and risk of stroke are not yet fully understood but are considered complex and may involve multiple pathways. The key proposed mechanisms suggested that SARS-CoV-2 binds to the angiotensin-converting enzyme 2 receptors of epithelial and endothelial cells where the immunologic activation occurs that can lead to development of cytokine storm and hypercoagulability, and an increased tendency of blood clots formation, leading to increased risk of AIS.^{2,37} SARS-CoV-2 infection may also have direct viral injury causing viral-induced endotheliitis, potentially leading to angiopathic thrombosis.³⁸ The analysis of endothelial cells from the human brain suggested that SARS-CoV-2 can directly affect the

brain endothelial cells, triggering a unique gene expression profile in brain endothelia, and increase the risk of stroke.³⁹

Studies suggested that COVID-19–associated ischemic strokes are more severe, with worse functional outcomes and significantly higher mortality, than non-COVID-19–associated ischemic strokes.^{2,27,40,41} Although the overall incidence of COVID-19–associated AIS is not clear, emerging evidence suggests that the incidence of large vessel stroke may increase in patients with COVID-19 who might not have the typical risk factors for stroke.^{2,4,24} Timely diagnosis of COVID-19–associated stroke and providing recommended treatment might play important roles in reducing the morbidity and mortality in patients with temporally COVID-19–associated stroke during the pandemic. Further studies are warranted to examine the long-term effects of COVID-19–associated stroke.

The main strength of this study is the use of the self-controlled case series study design. This study design is based on within-person comparisons and implicitly controls for all fixed confounders.⁴² Also, the self-controlled case series is more efficient than other observational study designs and provides more precise estimates of the exposure effects on risk of outcomes.¹³

Our study had several limitations. First, we used Medicare real-time GV preliminary data that are updated on a monthly basis. We might have missed some beneficiaries with diagnosed COVID-19 and AIS or have misclassified some beneficiaries who died before end of follow-up as alive because of delayed reporting. However, Centers for Medicare & Medicaid Services indicated that more than 95% of Medicare FFS in-hospital claims were received within 3 months.⁴³ Second, Medicare beneficiaries with COVID-19 were identified through the administrative claims data and might be subject to misclassification. However, one study suggested

Table 4 Sensitivity Analyses of Acute Ischemic Stroke Among US Medicare Fee-for-Service Beneficiaries, Medicare 2019–2021

Risk period	Number of events	Crude IRR (95% CI)	Age-adjusted IRR (95% CI) ^a
Restricted the starting time of the study period to January 1, 2020^c			
–7 to –1 d	789	1.90 (1.77–2.05)	1.93 (1.80–2.08)
0–3 d	2,173	10.2 (9.76–10.7)	10.4 (9.92–10.9)
4–7 d	322	1.58 (1.42–1.77)	1.61 (1.44–1.80)
8–14 d	523	1.40 (1.28–1.52)	1.42 (1.30–1.55)
15–28 d	735	1.05 (0.97–1.13)	1.07 (0.99–1.15)
Baseline ^b	17,214	1.0	1.0
Excluding AIS with I63.8 and I63.9 diagnosis codes^d			
–7 to –1 d	403	1.95 (1.76–2.15)	2.00 (1.81–2.21)
0–3 d	1,108	10.3 (9.63–10.9)	10.5 (9.89–11.2)
4–7 d	186	1.81 (1.57–2.09)	1.86 (1.61–2.16)
8–14 d	299	1.61 (1.44–1.81)	1.66 (1.48–1.86)
15–28 d	392	1.15 (1.04–1.27)	1.18 (1.07–1.31)
Baseline ^b	14,863	1.0	1.0
Deleted Medicare FFS beneficiaries who died before the end of observation period^e			
–7 to –1 d	505	2.26 (2.17–2.34)	2.25 (2.16–2.34)
0–3 d	1,487	11.7 (11.6–11.7)	11.6 (11.6–11.7)
4–7 d	204	1.61 (1.47–1.75)	1.61 (1.47–1.75)
8–14 d	353	1.61 (1.51–1.72)	1.61 (1.50–1.71)
15–28 d	459	1.07 (0.98–1.17)	1.07 (0.98–1.17)
Baseline ^b	23,708	1.0	1.0
Medicare FFS beneficiaries who had pneumococcal vaccination and AIS from January 1, 2019, to February 28, 2021^f			
0–3 d	256	1.13 (0.99–1.25)	1.13 (0.99–1.28)
4–7 d	254	1.12 (0.99–1.25)	1.12 (0.98–1.27)
8–14 d	447	1.13 (1.03–1.23)	1.13 (1.03–1.23)
15–28 d	841	1.07 (0.99–1.14)	1.07 (0.99–1.14)
Baseline ^b	21,853	1.0	1.0

Abbreviations: AIS = acute ischemic stroke; CI = confidence interval; COVID-19 = coronavirus disease 2019; FFS = fee-for-service; IRR = incidence rate ratio.
^a Adjusted by age at diagnosis of COVID-19 of <65–90 years by 2-year age group.

^b All time from observation start on January 1, 2019, to 7 days before date of COVID-19 diagnoses and after 28 days of diagnosis of COVID-19.

^c The starting time of the observation period was January 1, 2020, and ended on February 28, 2021 (n = 21,756).

^d Excluded AIS cases that had I63.8 and I63.9 ICD-10 diagnosis codes (n = 17,251).

^e Medicare FFS beneficiaries who died before the end of follow-up were excluded (n = 26,716).

^f Included Medicare FFS beneficiaries who had pneumococcal vaccination and AIS from January 1, 2019, to February 28, 2021. If the Medicare beneficiaries had more than one pneumococcal vaccination or AIS hospitalizations, the first date was chosen for the analysis. The date of pneumococcal vaccination was the starting time of the study period and ended on February 28, 2021. Standard self-controlled case series was used among stroke survivors (n = 23,651).

that the physicians and hospitals were likely to follow the recommendations and guidelines regarding COVID-19 diagnosis because of the seriousness of the COVID-19 pandemic.⁴⁴ Third, the dates of diagnosed COVID-19 and AIS in

Medicare data might be subject to error. Diagnostic testing for COVID-19 in outpatient settings, especially during the early phase of the pandemic, was limited and types of tests used to confirm COVID-19 and turnaround time from the onset of

symptoms to return a positive test varied. In addition, the beneficiaries without COVID-19 symptoms were unlikely to get tested in the outpatient settings. We observed higher number of AIS and COVID-19 at day 0 and more than the expected AIS hospitalizations within 7 days before the index date of diagnosed COVID-19. Screening all patients for COVID-19 on hospital admission including some patients who may continue to have positive testing results after the initial infection might contribute to the higher number of AIS and COVID-19 at day 0. These factors may affect the accurate timing of exposure to SARS-CoV-2 among Medicare beneficiaries. Fourth, the self-controlled case series methods assume that the other confounders affecting the outcome remain largely unchanged during the study period. However, the COVID-19 pandemic affected all hospitals and health care systems, including changes in emergency department visits and hospitalizations for stroke or stroke-like symptoms, care of acute stroke, and access to preventive care.^{5,27,45-47} These changes may affect the assumption of unchanged confounders during the study period. In the sensitivity analyses, we restricted the starting time of the study to January 1, 2020, and pattern of association remained largely consistent. Fifth, we restricted our study to Medicare FFS beneficiaries, which included about 60% of Medicare beneficiaries, thus our findings are not generalizable to non-FFS beneficiaries.

Incidence of AIS hospitalizations was 10 times (including day 0 cases in the risk periods) as high during the 3 days after diagnosis of COVID-19 as during the control periods and risk associated with COVID-19 appeared to be stronger among younger Medicare FFS beneficiaries and among beneficiaries without history of stroke.

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Mary G. George, MD, MSPH	Division for Heart Disease and Stroke Prevention, Centers for Disease Control and Prevention, Atlanta, GA	Interpreted the data; revised the manuscript for intellectual content
Anping Chang, MPH	Division for Heart Disease and Stroke Prevention, Centers for Disease Control and Prevention, Atlanta, GA	Generated the analytical datasets
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