Stroke

CLINICAL AND POPULATION SCIENCES

Increased COVID-19 Mortality in People With Previous Cerebrovascular Disease: A Population-Based Cohort Study

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BACKGROUND: The aim of the study was to determine the association between previous stroke and mortality after coronavirus disease 2019 (COVID-19) according to sex, age groups, and stroke subtypes.

METHODS: Prospective population-based cohort study including all COVID-19 positive cases between February 1 and July 31, 2020. Comorbidities and mortality were extracted using linked health administration databases. Previous stroke included transient ischemic attack, ischemic stroke, hemorrhagic stroke, spontaneous subarachnoid hemorrhage, and combined stroke for cases with more than one category. Other comorbidities were obesity, diabetes, hypertension, ischemic heart disease, atrial fibrillation, heart failure, chronic obstructive pulmonary disease, chronic kidney disease, cirrhosis, dementia, individual socioeconomic index, and deprivation index. Cases were followed up until December 31, 2020. Primary outcome was mortality of any cause after COVID-19 positivity. Cox proportional regression analysis adjusted for comorbidities was used. Stratified analyses were performed for sex and age (<60, 60–79, and ≥80 years).

RESULTS: There were 91 629 COVID-19 cases. Previous strokes were 5752 (6.27%), of which 3887 (67.57%) were ischemic, 1237 (21.50%) transient ischemic attack, 255 (4.43%) combined, 203 (3.53%) hemorrhagic, and 170 (2.96%) subarachnoid hemorrhage. There were 9512 deaths (10.38%). Mortality was associated with previous stroke (hazard ratio [HR]=1.12 [95% CI, 1.06–1.18]; $P<0.001$), in both sexes separately (men=1.13 [1.05–1.22]; $P=0.001$; women=1.09 [1.01–1.18]; $P=0.023$), in people <60 years (HR=2.97 [1.97–4.48]; $P<0.001$) and 60 to 79 years (HR=1.32 [1.19–1.48]; $P<0.001$) but not in people ≥80 years (HR=1.02 [0.96–1.09]; $P=0.437$). Ischemic (HR=1.11 [1.05–1.18]; $P=0.001$), hemorrhagic (HR=1.53 [1.20–1.96]; $P=0.001$) and combined (HR=1.31 [1.05–1.63]; $P=0.016$) strokes were associated but not transient ischemic attack. Subarachnoid hemorrhage was associated only in people <60 years (HR=5.73 [1.82–18.06]; $P=0.003$).

CONCLUSIONS: Previous stroke was associated with a higher mortality in people younger than 80 years. The association occurred for both ischemic and hemorrhagic stroke but not for transient ischemic attack. These data might help healthcare authorities to establish prioritization strategies for COVID-19 vaccination.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: COVID-19 ■ hemorrhagic stroke ■ ischemic stroke ■ mortality ■ transient ischemic attack ■ subarachnoid hemorrhage

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Nonstandard Abbreviations and Acronyms

COVID-19	coronavirus disease 2019
HR	hazard ratio
ICD-10	*International Classification of Diseases, Tenth Revision*
SAH	subarachnoid hemorrhage
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
TIA	transient ischemic attack

Coronavirus disease 2019 (COVID-19) is a new disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that has provoked a worldwide pandemic with >3 million deaths after 1 year.[1] A large part of the biomedical research has focused on identifying risk factors associated with greater severity or mortality to improve preventive and therapeutic strategies. Demographic factors, such as age, male sex, ethnicity, and socioeconomic status, as well as comorbidities, such as diabetes, hypertension, and cardiovascular disease, are repeatedly associated with greater mortality in almost every study.[2–4] However, the vast majority of studies are retrospective hospital cohorts, and there are very few prospective population-based studies. Thus, it is possible that some of the previous findings cannot be extrapolated to the general population.

Regarding the association between previous stroke and mortality due to COVID-19 results have been diverse. Some studies have found a positive association,[2,5] whereas others have not.[6] The main problem lies in the fact that previous studies have considered the history of stroke either encompassed by cardiovascular disease or associated with dementia, which makes it hard to unmask the specific degree of independent association.[3,7] Furthermore, previous studies have not distinguished between stroke subtypes (ischemic or hemorrhagic), the evolution of which may be different due to their diverse pathophysiology.[8–10]

Since age and sex are 2 crucial risk factors for COVID-19 mortality, and both are associated with stroke prevalence, in the present study we aimed to determine if a previous stroke is an independent risk factor for mortality after COVID-19. In addition, we aimed to determine if this association is maintained within the different sexes, age groups, and stroke subtypes, which include transient ischemic attack (TIA), ischemic stroke, hemorrhagic stroke, and spontaneous nontraumatic subarachnoid hemorrhage (SAH).

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Registry Features and Data Acquisition

Catalonia is a region of Spain that has universal public health care coverage, including primary and hospital health care, as well as drug prescription. Public coverage includes around 98% of the population. Moreover, one-fourth of the population has additional private health insurance and uses both systems.[11] A Catalan central registry of insured people allows the linking of individual information from all health administration databases. This information includes individual sociodemographic data and aggregated primary care service areas data. An individual's health care identification code allows Catalan residents to be tracked across several health administration databases, including acute and emergency hospitals (conjunt mínim bàsic de dades d'hospitalitzats d'aguts) and emergency discharge datasets (conjunt mínim bàsic de dades d'urgències hospitalàries); pharmacy invoicing database; episode diagnosis database for primary care (conjunt mínim de dades d'atenció primària), which records information on comorbidity and date of diagnosis; laboratory database, including data of SARS-CoV-2 nucleic acid amplification test results; and specific epidemiological mandatory registry for SARS-CoV-2 infection. All CMBD databases register the information using the *Tenth Revision of the International Classification of Diseases* codes (*ICD-10*).[12] The registries have an automated data validation system to check data consistency and identify potential errors, and external audits are performed periodically to ensure the quality and reliability of data.

Study Design and Participants

We conducted a population-based, prospective cohort study using linked health administration databases in Catalonia, Spain. The first case of the COVID-19 outbreak in Catalonia was registered during the third week of February, so we included cases from February 1, 2020, to July 31, 2020.

We included all cases registered in the Catalan Service of Epidemiological Surveillance (regional epidemiological surveillance registry for SARS-CoV-2 infection in Catalonia) which had tested positive for COVID-19 within the aforementioned period using all types of tests (polymerase chain reaction, antibody test, ELISA, and epidemiological confirmation by chest imaging information). The study included all positive cases within the population of Catalonia (symptomatic and asymptomatic) and with any severity degree (ambulatory and hospitalized).

Comorbidity information was obtained from conjunt mínim de dades d'atenció primària using a selection of *ICD* codes. Previous stroke was defined as any of the following cerebrovascular diseases registered up to the date of the first positive COVID-19 test: TIA (*ICD-10* code group G45 except G45.4 transient global amnesia), ischemic stroke (*ICD-10* code group I63), hemorrhagic stroke (*ICD-10* code group I61), and spontaneous SAH (*ICD-10* code I60). A further category called combined stroke was created for cases with both ischemic and hemorrhagic subtypes. Cases with TIA and ischemic stroke were classified as ischemic stroke and cases with hemorrhagic stroke and SAH were classified as SAH.

We included all comorbidities that had previously been associated with COVID-19 mortality. Age was categorized into 3 groups (<60, 60–79, and ≥80 years), according to changes in mortality risk observed in previous studies.[13] Obesity was defined as a body mass index value equal to

or higher than 30 or as a previous diagnosis extracted from primary care database. Smoking status was grouped into current, former, and never smokers. Previous cancer was considered if diagnosis had been made within the previous 5 years. All comorbidities and *ICD-10* codes used are summarized in Table I in the Supplemental Material.

Information regarding socioeconomic status was also retrieved from the Catalan central registry of insured people for every subject, using 2 levels (individual and primary care service area). Individual socioeconomic level was derived from the individual yearly income range information used to calculate pharmacy copayment. Copayment ranges are derived from tax declarations and social security benefits received as follows: exempted (nonworking population or people receiving noncontributory pension), income per year <18 000 € (20 468 USD); income per year from 18 000 € (20 468 USD) to 100 000 € (113 710 USD); and income per year >100 000 € (113 710 USD). The socioeconomic status of the primary care area of influence is defined by the index of deprivation that ranges from 0 (less deprived) to 100 (more deprived).

Observation Period and Outcome

Included cases were observed until December 31, 2020. The primary outcome was mortality after COVID-19 defined as any death (including hospital and nonhospital deaths) occurring after the infection during the study period. Mortality data were extracted from regional epidemiological surveillance registry for SARS-CoV-2 infection in Catalonia (Specific registry for SARS-CoV-2 infection deaths notified by the mortuary companies), which is based on death certificate data that include *ICD-10* code U071: COVID-19 virus confirmed, and U072: COVID-19 virus not confirmed.[14] Since regional epidemiological surveillance registry for SARS-CoV-2 infection in Catalonia only registers deaths directly attributed to COVID-19, we also extracted all deaths from the Central Registry of Insurance (CRA) to incorporate mortality due to COVID-19 complications. However, final cause of death was not available. Cases were censored at the first of either death date or study end date.

The STROBE guidelines were used to ensure the reporting of this observational study.[15]

Statistical Analysis

We used descriptive statistics to report demographics and comorbidity information. Continuous variables are provided as means with SD if normally distributed, or as medians and interquartile ranges if not normally distributed. Bivariate analysis between cases with and without previous stroke was done to detect nonadjusted differences.

For the time to event analyses regarding the main outcome (mortality after COVID-19), cumulative incidence of event curves was estimated for each group (previous stroke versus no previous stroke). They were considered separately by using the Kaplan-Meier method and were compared statistically by using the log-rank test. We fitted an a priori multivariable Cox proportional regression model adjusted for all comorbidities and individual socioeconomic status to determine which variables were associated with an increased risk of mortality. All cardiac comorbidities (atrial fibrillation, ischemic heart disease, and heart failure) were categorized into a single variable (heart disease). Deprivation index was categorized into quintiles. There were 4 cases with missing sex information and 1884 cases with missing data about their deprivation indexes which were not imputed. Hazard ratios (HR) with 95% CI were calculated for the variable previous stroke and for each subtype (TIA, ischemic stroke, hemorrhagic stroke, SAH, and combined stroke). Stratified analyses were performed for each sex category and for each age group category. We used the variance inflation factor to assess multicollinearity between the variables included in the models. Deprivation index was not included in the stratified analysis since it was not associated in the full-adjusted model. Finally, to analyze specifically the relationship between time of previous stroke and mortality, we have categorized previous strokes into recent stroke (30 days or less before positivity for SARS-COV-2) and late stroke (>30 days before positivity) in a separate multivariate analysis.

All analyses were performed using R statistical software, version R-4.0.0.

Ethical

Cases were not formally involved in the study design or the outcome measures. Data from different health administration databases were linked and deidentified by a team not involved in the study analysis; only a full deanonymized database was available to the study investigators (U. Lazcano and E. Cuadrado-Godia). The study protocol was approved by the Ethical Review Board of Parc Salut Mar (Code 2020/9604) Barcelona, Spain.

RESULTS

Participants

There were 91 629 COVID-19 cases from February 1, 2020, to July 31, 2020. Of them 19 266 (21.1%) were hospitalized and 1656 (1.8%) were admitted to the intensive care unit. Four cases were excluded because of incomplete information. The cohort's mean age was 55 years and 58.5% were women. Cases with previous stroke were 5752 (6.2%); most of them were ischemic strokes (3887 [67.6%]), followed by TIA (1237 [21.5%]), combined strokes (255 [4.43%]), hemorrhagic strokes (203 [3.53%]), and SAH (170 [2.96%]).

Baseline characteristics and bivariate analysis between cases with and without previous stroke are summarized in Table 1. In general terms, previous stroke cases were older and had a higher prevalence of all vascular risk factors and comorbidities. Individual and primary care socioeconomic levels were lower in cases with previous stroke.

Mortality After COVID-19

During the observation period, there were 9512 deaths (10.3%). No cases were lost during follow-up. Mean time (SD) of death was 25.57 (40.9) days and 8627 cases (90.7%) died within the first 3 months. Thirty percent of the cases with previous stroke died against 9% of the cases without previous stroke. Mean time (SD) from stroke onset to death was 2932 (2660) days.

Table 1. Baseline Characteristics and Bivariate Comparison Between Cases With and Without Previous Stroke

	Total cohort, N=91 629	No previous stroke, N=85 877	Previous stroke, N=5752	*P* value
Age, mean (SD)	57.1 (21.4)	55.5 (21.0)	80.7 (12.2)	<0.0001
Age in categories, n (%)				<0.0001
<60 y	52 387 (57.2%)	51 994 (60.5%)	393 (6.83%)	
60–79 y	20 345 (22.2%)	18 620 (21.7%)	1725 (30.0%)	
≥80 y	18 897 (20.6%)	15 263 (17.8%)	3634 (63.2%)	
Sex, n (%)				<0.001
Female	53 579 (58.5%)	50 406 (58.7%)	3173 (55.2%)	
Male	38 046 (41.5%)	35 467 (41.3%)	2579 (44.8%)	
Tobacco smoking status, n (%)				<0.001
Never smoker	70 258 (76.7%)	66 221 (77.1%)	4037 (70.2%)	
Former smoker	11 172 (12.2%)	10 026 (11.7%)	1146 (19.9%)	
Current smoker	10 199 (11.1%)	9630 (11.2%)	569 (9.89%)	
Obesity, n (%)	14 429 (15.7%)	12 747 (14.8%)	1682 (29.2%)	<0.001
Diabetes, n (%)	11 468 (12.5%)	9597 (11.2%)	1871 (32.5%)	<0.0001
Hypertension, n (%)	29 720 (32.4%)	25 203 (29.3%)	4517 (78.5%)	<0.0001
COPD, n (%)	2794 (3.05%)	2275 (2.65%)	519 (9.02%)	<0.001
Ischemic heart disease, n (%)	2933 (3.20%)	2338 (2.72%)	595 (10.3%)	<0.001
Heart failure, n (%)	2675 (2.92%)	2014 (2.35%)	661 (11.5%)	<0.0001
Atrial fibrillation, n (%)	3600 (3.93%)	2629 (3.06%)	971 (16.9%)	<0.0001
Chronic kidney disease, n (%)	5235 (5.71%)	4183 (4.87%)	1052 (18.3%)	<0.0001
Liver cirrhosis, n (%)	525 (0.57%)	447 (0.52%)	78 (1.36%)	<0.001
Cancer, n (%)	15 660 (17.1%)	13 790 (16.1%)	1870 (32.5%)	<0.001
Dementia, n (%)	3067 (3.35%)	2326 (2.71%)	741 (12.9%)	<0.0001
ISL, n (%)				<0.001
Exempts	3113 (3.40%)	2888 (3.36%)	225 (3.91%)	
<18 000 €	57 750 (63.0%)	53 498 (62.3%)	4252 (73.9%)	
18 000–100 000 €	29 898 (32.6%)	28 640 (33.4%)	1258 (21.9%)	
>100 000 €	864 (0.94%)	847 (0.99%)	17 (0.30%)	
Deprivation index, n (%)				<0.001
1	18 226 (20.3%)	16 976 (20.2%)	1250 (22.1%)	
2	17 753 (19.8%)	16 546 (19.7%)	1207 (21.3%)	
3	17 871 (19.9%)	16 704 (19.9%)	1167 (20.6%)	
4	17 988 (20.0%)	16 959 (20.2%)	1029 (18.2%)	
5	17 895 (19.9%)	16 888 (20.1%)	1007 (17.8%)	
Death, n (%)	9512 (10.4%)	7736 (9.01%)	1776 (30.9%)	<0.0001

COPD indicates chronic obstructive pulmonary disease; and ISL, individual socioeconomic level.

In a bivariate analysis, age, male sex, and all comorbidities, including previous stroke and socioeconomic status, were associated with a higher mortality (Table II in the Supplemental Material).

The cumulative incidence of mortality was higher in cases with previous stroke, both globally and for each subgroup (log-rank test <0.001), with a higher mortality incidence in ischemic, hemorrhagic, and combined groups (Figure 1).

Fully adjusted multivariate survival Cox analysis showed that previous stroke is associated with an increased mortality after COVID-19 (HR=1.12 [95% CI, 1.06–1.18]; *P*<0.001). Other independent factors associated with an increased risk of death were age, male sex, obesity, diabetes, hypertension, heart disease, chronic kidney disease, chronic obstructive pulmonary disease, liver cirrhosis, cancer, dementia, and individual socioeconomic status (Figure 2).

Within the different stroke subtypes, ischemic stroke (HR=1.11 [1.05–1.18]; *P*=0.001), hemorrhagic stroke (HR=1.53 [1.20–1.96]; *P*=0.001), and combined stroke (HR=1.31 [1.05–1.63]; *P*=0.016) were

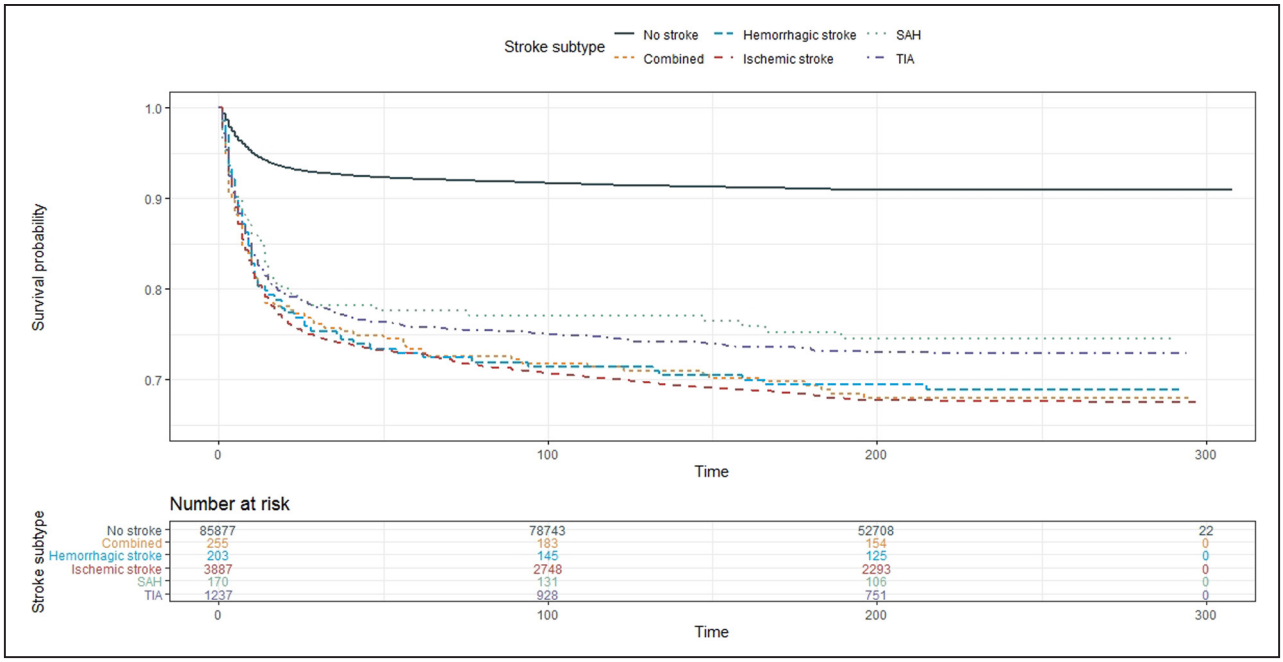

Figure 1. Kaplan-Meier survival plot stratified for stroke subtypes.
SAH indicates subarachnoid hemorrhage; and TIA, transient ischemic attack.

associated with mortality, whereas previous TIA (HR=1.02 [0.91–1.14]; *P*=0.759) and SAH (HR=1.27 [0.94–1.72]; *P*=0.123) were not associated.

Stratified Analyses According to Age and Sex

Stratified analyses regarding sex showed that previous stroke was associated with an increased risk of mortality in both men (HR=1.13 [1.05–1.22]; *P*=0.001) and women (HR=1.09 [1.01–1.18]; *P*=0.023). Both ischemic (HR=1.13 [1.04–1.23]; *P*=0.004) and hemorrhagic stroke (HR=1.43 [1.03–1.99]; *P*=0.032) were associated with mortality in men, whereas in women only hemorrhagic (HR=1.67 [1.14–2.43]; *P*=0.008) and combined stroke (HR=1.50 [1.10–2.05]; *P*=0.011) were associated.

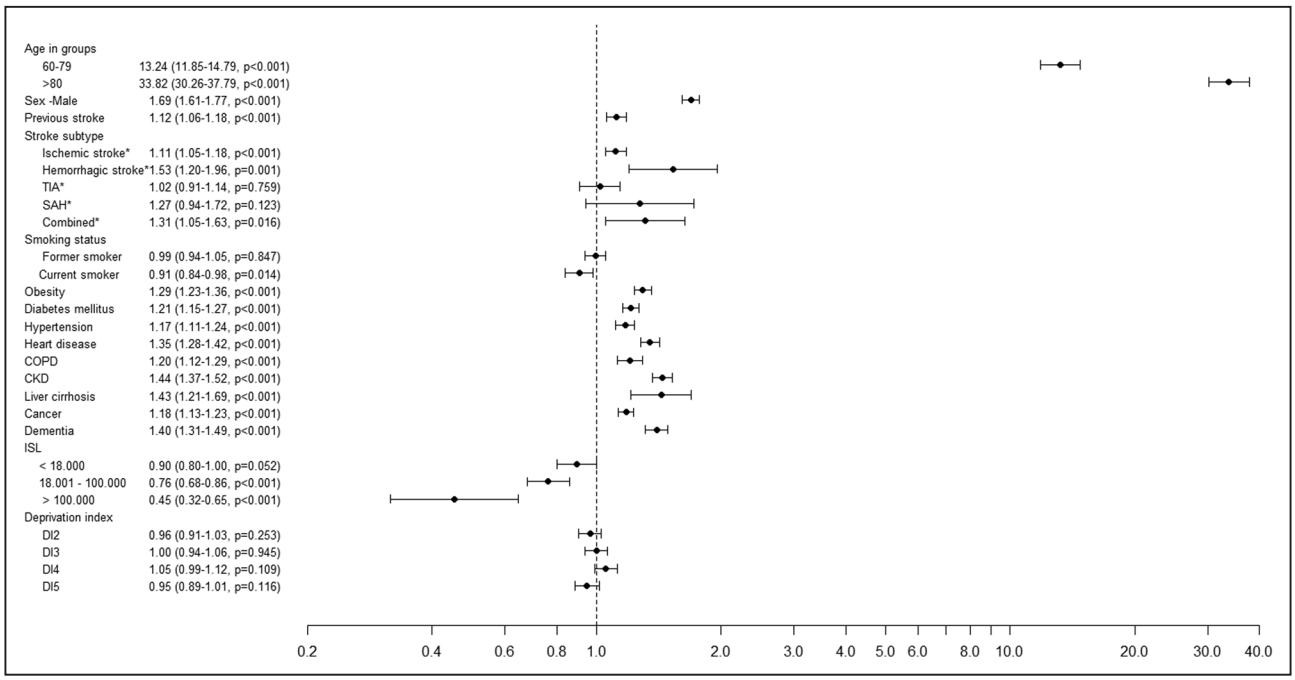

Figure 2. Forest plot showing adjusted hazard ratios for mortality in coronavirus disease 2019 (COVID-19) population.
COPD indicates chronic obstructive pulmonary disease; ISL, individual socioeconomic level; SAH, subarachnoid hemorrhage; and TIA, transient ischemic attack. *Stroke subtypes have been analyzed in a separated model.

Regarding age, it showed a clear influence in the association of previous stroke with mortality after COVID-19. Previous stroke was associated with a higher mortality in younger people (HR for <60 years: 2.97 [1.97–4.48]; *P*<0.001; HR for 60–79 years: 1.32 [1.19–1.48]; *P*<0.001) but not in the elderly group (HR for ≥80 years: 1.02 [0.96–1.09]; *P*=0.437). Ischemic stroke (HR=3.46 [2.13–5.61]; *P*<0.001), hemorrhagic stroke (HR=5.11 [1.62–16.16]; *P*<0.003), and SAH (HR=5.73 [1.82–18.06]; *P*=0.003) were associated in the <60 years group, whereas ischemic stroke (HR=1.31 [1.16–1.49]; *P*<0.001) was the only subtype associated in the 60 to 79 years group. Complete Cox survival analyses for each age and sex group are depicted in Table 2. Finally, to analyze the effect of stroke recency on the risk of mortality, a new fully adjusted analysis was performed. Recent strokes had a higher risk of mortality (HR=1.97 [1.70–2.29]; *P*<0.001) than late strokes (HR=1.06 [1.00–1.12]; *P*=0.005), and once again, the effect was different regarding age but not sex (Table III in the Supplemental Material). Recent stroke was associated with higher mortality in both sexes and all age groups, whereas late stroke was only associated in <60 and 60 to 79 years groups.

DISCUSSION

This analysis of data covering 98% of the population in Catalonia shows that previous stroke increases the risk of mortality after COVID-19, independently of any other existing cardiovascular diseases or dementia. There are no differences according to sex, whereas age shows a strong modifying effect. The risk of death with a previous stroke is tripled in people younger than 60 years. But in elderly people, only recent stroke raises mortality after COVID-19. Including all the population, mortality risk is increased in people with previous ischemic, hemorrhagic, or combined stroke but not in people with previous TIA or SAH.

The association of cerebrovascular diseases with COVID-19 mortality has been previously described in several studies but not in all of them.[2,6,7] Our investigation differs from previous works because most of them have used retrospective hospital cohorts.[16] There are very few population studies, and none of them has covered the entire population of a health region.[6,7] Moreover, previous studies have analyzed cerebrovascular diseases as a whole and have not evaluated the influence of each stroke subtype. Finally, the effect of age and sex had not been assessed.

In our study, age is the most important risk factor for mortality after COVID-19. However, we wanted to ascertain if the association between previous stroke and mortality could be different regarding age. We found that previous stroke was associated with mortality only in age group <60 years (HR=2.97 [1.97–4.48]; *P*<0.001) and age group 60 to 79 years (HR=1.32 [1.19–1.48]; *P*<0.001) but not in age group ≥80 years (HR=1.02 [0.96–1.09]; *P*=0.437). Since the prevalence of all comorbidities, such as heart disease, chronic kidney disease, and cancer, rises with age, and all of them were associated with an increased risk of mortality after COVID-19, there could be a lesser influence of previous stroke in this group of age due to a higher impact of the other diseases. In general, the magnitude of association of all mortality risk factors was attenuated in age ≥80 years, suggesting that the risk might be distributed within each comorbidity. A previous meta-analysis did not find any influence of age on the association between previous cerebrovascular disease and COVID-19 mortality.[16] However, most studies included were retrospective and with small sample sizes.

Male sex is another well-known independent risk factor for COVID-19 mortality.[3,4,7] In our study, male sex was associated with mortality in bivariate and multivariate analyses, as well as in all age groups, independently of other risk factors. In addition, we wanted to assess if the association of previous stroke with mortality was similar in both sexes. We found that previous stroke was a risk factor for mortality in both men and women without relevant differences. Hence, sex seems to have no influence on the increased risk of mortality after COVID-19 in people with previous strokes.

Current smoking was associated with a lower risk of death in the fully adjusted model. This association has been previously described and is partially driven by adjustment for chronic obstructive pulmonary disease, which is caused mainly by tobacco smoking. Therefore, it does not prove any protective effect of nicotine smoking.[7,17]

Previous dementia was also associated with a higher risk of mortality independently of age and having a previous stroke. A previous population study performed in the UK analyzed dementia and stroke together.[16] Although patients with stroke have a higher risk of vascular dementia, the first cause of dementia in our population is Alzheimer disease.[18] Therefore, studying both pathologies together prevented from concluding the origin of the association. In our analysis, we have proved that people with previous stroke have a higher risk of mortality after COVID-19, independently of having dementia.

In our COVID-19 population, individual socioeconomic level was associated with mortality, whereas deprivation index was not. Previous studies have found that both indicators of worse socioeconomic status are predictive of higher mortality, probably because of poorer baseline health statuses. However, universal health care system in our population might have contributed to balance access to health care, as it has been found in previous studies.[19]

Compared with other vascular diseases, stroke is a heterogenous disease. It might be studied as a whole, but it entails several different pathophysiological processes

Table 2. Multivariate Cox Regression Analysis for COVID-19 Mortality Stratified by Sex and Age Groups

	Age<60	Age 60–79	Age≥80	Sex male	Sex female
Age 60–79				11.82 (10.28–13.59, *P*<0.001)	15.25 (12.77–18.21, *P*<0.001)
Age <80				28.81 (25.00–33.20, *P*<0.001)	41.71 (35.00–49.71, *P*<0.001)
Sex, male	2.08 (1.68–2.56, *P*<0.001)	1.73 (1.58–1.88, *P*<0.001)	1.68 (1.59–1.78, *P*<0.001)		
Previous stroke	2.97 (1.97–4.48, *P*<0.001)	1.32 (1.19–1.48, *P*<0.001)	1.02 (0.96–1.09, *P*=0.437)	1.13 (1.05–1.22, *P*=0.001)	1.09 (1.01–1.18, *P*=0.023)
Ischemic stroke	3.46 (2.13–5.61, *P*<0.001)	1.31 (1.16–1.49, *P*<0.001)	1.02 (0.95–1.10, *P*=0.527)	1.13 (1.04–1.23, *P*=0.004)	1.09 (1.00–1.19, *P*=0.061)
Hemorrhagic stroke	5.11 (1.62–16.16, *P*=0.005)	1.83 (1.18–2.84, *P*=0.007)	1.32 (0.96–1.80, *P*=0.084)	1.43 (1.03–1.99, *P*=0.032)	1.67 (1.14–2.43, *P*=0.008)
TIA	0.41 (0.06–2.96, *P*=0.378)	1.12 (0.86–1.47, *P*=0.401)	0.98 (0.87–1.11, *P*=0.785)	1.05 (0.89–1.24, *P*=0.556)	0.98 (0.85–1.14, *P*=0.797)
SAH	5.73 (1.82–18.06, *P*=0.003)	1.54 (0.82–2.86, *P*=0.176)	1.05 (0.73–1.50, *P*=0.790)	1.28 (0.84–1.95, *P*=0.252)	1.24 (0.81–1.91, *P*=0.320)
Combined	3.20 (0.79–12.97, *P*=0.103)	1.59 (1.12–2.27, *P*=0.010)	1.11 (0.83–1.47, *P*=0.487)	1.17 (0.86–1.59, *P*=0.326)	1.50 (1.10–2.05, *P*=0.011)
Former smoker	1.24 (0.93–1.64, *P*=0.141)	0.96 (0.87–1.05, *P*=0.352)	0.97 (0.90–1.05, *P*=0.438)	1.03 (0.96–1.10, *P*=0.383)	0.94 (0.83–1.07, *P*=0.362)
Current smoker	1.22 (0.94–1.59, *P*=0.138)	0.88 (0.78–0.99, *P*=0.037)	0.84 (0.75–0.94, *P*=0.002)	0.92 (0.85–1.01, *P*=0.072)	0.92 (0.77–1.09, *P*=0.332)
Obesity	2.72 (2.15–3.45, *P*<0.001)	1.44 (1.32–1.57, *P*<0.001)	1.16 (1.10–1.23, *P*<0.001)	1.27 (1.19–1.36, *P*<0.001)	1.31 (1.23–1.40, *P*<0.001)
Diabetes	1.95 (1.46–2.59, *P*<0.001)	1.23 (1.13–1.34, *P*<0.001)	1.12 (1.06–1.19, *P*<0.001)	1.17 (1.10–1.24, *P*<0.001)	1.24 (1.17–1.33, *P*<0.001)
Hypertension	1.59 (1.22–2.06, *P*=0.001)	1.25 (1.15–1.37, *P*<0.001)	0.98 (0.92–1.05, *P*=0.637)	1.12 (1.04–1.21, *P*=0.003)	1.21 (1.12–1.30, *P*<0.001)
Heart disease	1.86 (1.23–2.82, *P*=0.004)	1.49 (1.35–1.65, *P*<0.001)	1.34 (1.26–1.42, *P*<0.001)	1.41 (1.32–1.52, *P*<0.001)	1.28 (1.18–1.37, *P*<0.001)
COPD	1.46 (0.77–2.75, *P*=0.249)	1.47 (1.30–1.66, *P*<0.001)	1.12 (1.03–1.22, *P*=0.008)	1.21 (1.12–1.31, *P*<0.001)	1.20 (1.06–1.36, *P*=0.005)
CKD	2.39 (1.44–3.95, *P*=0.001)	1.84 (1.66–2.06, *P*<0.001)	1.41 (1.33–1.50, *P*<0.001)	1.46 (1.35–1.57, *P*<0.001)	1.46 (1.36–1.57, *P*<0.001)
Liver cirrhosis	1.74 (0.91–3.33, *P*=0.096)	1.28 (1.03–1.59, *P*=0.023)	1.16 (0.86–1.54, *P*=0.328)	1.40 (1.15–1.71, *P*=0.001)	1.53 (1.14–2.05, *P*=0.005)
Cancer	3.71 (2.96–4.64, *P*<0.001)	1.47 (1.36–1.60, *P*<0.001)	0.99 (0.94–1.04, *P*=0.711)	1.16 (1.09–1.23, *P*<0.001)	1.20 (1.13–1.28, *P*<0.001)
Dementia	5.41 (3.03–9.66, *P*<0.001)	1.99 (1.70–2.33, *P*<0.001)	1.34 (1.25–1.43, *P*<0.001)	1.51 (1.37–1.66, *P*<0.001)	1.32 (1.22–1.43, *P*<0.001)
ISL<18 000 €	0.41 (0.30–0.55, *P*<0.001)	0.93 (0.79–1.10, *P*=0.411)	1.20 (1.02–1.43, *P*=0.032)	0.84 (0.71–0.98, *P*=0.032)	0.95 (0.82–1.09, *P*=0.461)
ISL 18 000–100 000 €	0.28 (0.20–0.39, *P*<0.001)	0.71 (0.60–0.85, *P*<0.001)	1.17 (0.98–1.40, *P*=0.087)	0.73 (0.62–0.86, *P*<0.001)	0.79 (0.67–0.93, *P*=0.004)
ISL>100 000 €	0.12 (0.02–0.89, *P*=0.037)	0.31 (0.18–0.54, *P*<0.001)	1.34 (0.83–2.17, *P*=0.228)	0.34 (0.22–0.53, *P*<0.001)	0.79 (0.44–1.42, *P*=0.427)

CKD indicates chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; ISL, individual socioeconomic level; SAH, subarachnoid hemorrhage; and TIA, transient ischemic attack.

with different risk factors and prognoses.[8–10] Our study is the first one to analyze the influence of each stroke subtype in the whole COVID-19 population. The association of previous stroke with mortality after COVID-19 was different regarding the previous stroke subtypes. The risk increased in previous ischemic, hemorrhagic, and combined strokes, but it did not rise in people with previous TIA. In relation to SAH, the risk was associated with mortality only in the <60 years group. This might be due to the fact that mean age of SAH cases is lower than that of other stroke subtypes, and most SAH cases were in this age group.[20]

As individuals with cerebrovascular disease might carry a higher risk of mortality due to a previous impaired functional status, this could explain the difference found in TIA.[16] Other sequelae such as dysphagia could explain

a higher risk of complications and death, as suggested in a recent study of COVID-19 mortality in individuals with intellectual disability.[21] Moreover, previous strokes could be associated with a high risk of cardiovascular events that can be precipitated by the setting of infection and hypercoagulability related to COVID-19. However, our study did not include any measure of previous disability or dysphagia to prove these hypotheses, and information regarding vascular events during follow-up was not analyzed. Future studies should address these issues.

Finally, we analyzed the effect of recency of previous cerebrovascular disease on mortality. As expected, recent stroke had a higher risk of mortality than late stroke. This result is in agreement with a multicentric study that found a higher risk of mortality in strokes happening in people with COVID-19.[22] This association might be explained by a higher disability and an increased vascular risk in the recent stroke group.

The results of our study might have important public health implications. COVID-19 vaccination programs for people younger than 80 years could prioritize people with previous stroke and other comorbidities, due to their negative influence in COVID-19 mortality. In our country, people with previous stroke are not prioritized for vaccination.

Our study has some strengths. Since public health coverage is almost universal in Catalonia, it provides comprehensive data on demographics, comorbidities, and socioeconomic status of almost all COVID-19 cases. All these data, including mortality information, are registered in a centralized program that is constantly reviewed and updated by the Public Data Analysis for Health Research and Innovation Program. This program has allowed to perform previous population studies with a similar methodology.[23]

Nevertheless, our study has some limitations. Our analysis derives from the first pandemic wave in Catalonia, when COVID-19 tests were performed mainly in symptomatic cases. The magnitude of association of all comorbidities could have changed if asymptomatic cases would have been included, but we think that it would not have switched the direction of the association. We are aware of the fact that ethnicity information was not incorporated, and non-White ethnicity has been found to be a risk factor for COVID-19 mortality in other population studies.[5,7] In addition, the association between stroke and stroke subtypes with mortality might be different in other populations. Spain is a country with a high prevalence of cerebrovascular diseases and a previous meta-analysis has shown that the prevalence of comorbidities is associated with geographic differences in COVID-19 severity and mortality.[2,24] Finally, the final cause of death was not captured, which would have helped clarify if the increased risk of mortality in people with previous strokes was due to the severity of COVID-19 or to a new vascular event or another complication. Although unrelated deaths could have been included, 90% of cases died within the first 3 months after the infection, suggesting a likely relationship between COVID-19 and death. Information regarding ischemic stroke subtypes that carry different risk of subsequent vascular events and prognoses was neither available.[25]

In spite of all this, we think that our study gives solid insights into the prognostic role of previous cerebrovascular diseases in COVID-19 mortality. Further studies, including other geographic areas, asymptomatic cases, stroke cause, and final cause of death, might expand knowledge to this important issue.

CONCLUSIONS

In the COVID-19 population of Catalonia, previous stroke was associated with a higher mortality in people younger than 80 years. The association is maintained for ischemic and hemorrhagic stroke but not for previous TIA. Previous SAH is associated with COVID-19 mortality only in people younger than 60 years. Using data from population studies might help health care authorities deal with risk stratification and implement prioritization strategies for COVID-19 vaccination.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Materials

Expanded Materials and Methods
Expanded Results
Supplemental Tables I–III
Supplemental Figure I
STROBE checklist

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