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COVID-19 Impact on Stroke Admissions during France's First Epidemic Peak: An Exhaustive, Nationwide, Observational Study

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Keywords
Stroke · Coronavirus disease 2019 · Severe acute respiratory syndrome coronavirus 2 · Non-COVID diseases

Abstract
Introduction: The coronavirus disease 2019 (COVID-19) pandemic continues to have great impacts on the care of non-COVID-19 patients. This was especially true during the first epidemic peak in France, which coincided with the national lockdown. The aim of this study was to identify whether a decrease in stroke admissions occurred in spring 2020, by analyzing the evolution of all stroke admissions in France from January 2019 to June 2020. ***Methods:*** We conducted a nationwide cohort study using the French national database of hospital admissions (Information Systems Medicalization Program) to extract exhaustive data on all hospitalizations in France with at least one stroke diagnosis between January 1, 2019, and June 30, 2020. The primary endpoint was the difference in the slope gradients of stroke hospitalizations between pre-epidemic, epidemic peak, and post-epidemic peak phases. Modeling was carried out using Bayesian techniques. ***Results:*** Stroke hospitalizations dropped from March 10, 2020 (slope gradient: −11.70), and began to rise again from March 22 (slope gradient: 2.090) to May 7. In total, there were 23,873 stroke admissions during the period March–April 2020, compared to 29,263 at the same period in 2019, representing a decrease of 18.42%. The percentage change was −15.63%, −25.19%, −18.62% for ischemic strokes, transient ischemic attacks, and hemorrhagic strokes, respectively. ***Discussion/Conclusion:*** Stroke hospitalizations in France experienced a decline during the first lockdown period, which cannot be explained by a sudden change in stroke incidence. This decline is therefore likely to be a direct, or indirect, result of the COVID-19 pandemic.

Introduction

Because of the coronavirus disease 2019 (COVID-19) pandemic, healthcare providers have been forced to mobilize their resources in order to cope. The care of non-COVID patients has certainly been impacted [1–4]. France faced a shortage of medical resources during the first epidemic peak, in spring 2020, despite undertaking a national lockdown (March 17–May 10, 2020) [5, 6]. On the final day of this lockdown, 16,820 COVID-19 related hospital deaths were recorded [7]. The pressure experienced by the healthcare system may have resulted in collateral damage with regard to other patients, particularly for those with serious or urgent diseases [1, 8]. Moreover,

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many patients have been hesitant to seek healthcare, a phenomenon described in the literature regarding the severe acute respiratory syndrome (SARS) epidemics [9, 10]. To date, several works have described the decrease in hospital admissions for non-COVID-19 diseases, but rarely on a national level [11, 12]. The aim of this study was to determine whether the number of hospital admissions for stroke in France decreased during the COVID-19 epidemic peak and lockdown period, by analyzing the evolution in the number of all stroke hospitalizations from January 2019 to June 2020. The secondary objectives were to observe the evolution of different types of stroke; to compare selected hospitalization characteristics between the epidemic peak period March–April 2020 and March–April 2019; to study the correlation between the incidence of hospital admission for COVID-19 and the evolution in stroke admissions between March–April 2020 and March–April 2019 by French administrative department.

Materials and Methods

Study Design and Setting

Anonymized data were extracted from the French national "Information Systems Medicalization Program" (PMSI) database, which includes all public and private hospitalization data in France. Diagnoses are coded using the International Classification of Diseases, 10th Revision. A stroke diagnosis is defined by the French national agency for hospitalization data as follows: subarachnoid hemorrhage (I60.-), intracerebral hemorrhage (I61.-), other nontraumatic intracranial hemorrhage (I62.-), cerebral infarction (I63.-), stroke not specified as hemorrhage or infarction (I64.-), transient cerebral ischemic attacks and related syndromes (G45.-). We defined three categories of stroke: "haemorrhagic" (I60, I61, I62), "ischaemic" (I63), and "transient" (G45). The procedures performed during hospitalization are coded according to the Common French Classification of Medical Acts. The database request, made on October 13, 2020, included all hospital admissions, pediatric ages included, between January 1, 2019, and June 30, 2020, with at least one main diagnosis of stroke among the different medical units. While IV thrombolysis data were not available, thrombectomy data were available in this database and were identified by one of the following Common French Classification of Medical Acts codes: EAFA001, EAJF341, EANF002. In order to avoid counting the same episode twice, only one admission was counted if two admissions for the same patient were separated by 1 day or less. The study size was therefore defined by the relevant entries extracted from the database. The location of hospital stay was determined at initial admission.

The primary endpoint is the difference in slopes of stroke hospitalizations between the different periods (pre-epidemic, epidemic peak, post-epidemic peak) estimated by the model. The same model estimates the 3 knots (the number of knots being arbitrarily defined), the 4 segments, and the slopes. The secondary endpoints were the difference in the number of stroke admissions between March–April 2019 and March–April 2020: number of strokes, number of each stroke subtype, the proportion of men, the proportion of deaths.

Statistical Methods

We considered the change in the number of stroke admissions as centered 7-day rolling means. We modeled the evolution of stroke hospitalizations in four segments of lines (stability, fall, rise, return to baseline) joined by three estimated knots. Disregarding possible seasonality effects, we assumed relative stability of hospitalizations, including during the summer of 2019, before a sudden change in 2020. Modeling was carried out using Bayesian techniques with a 95% credibility interval. Probability of superiority is rounded at both extremities to <0.0001 and >0.9999. The prior distributions are assumed to be very uninformative except for the position of each of the 3 knots, which is assumed to be uniformly distributed over the time interval between February 15, 2020, and June 30, 2020.

A spatial correlation study was carried out by graphically representing, by French administrative department, the incidence rates of COVID-19 hospitalizations in March–April 2020, and the ratio between the number of stroke admissions in March–April 2020 and those in March–April 2019. The incidence rates of COVID-19 hospitalizations were standardized by age and sex, using the official data estimates of French administrative department populations by quinquennial ages and gender in 2020 [13]; if two COVID-19 stays for the same patient were separated by 1 day or less, only one was counted. An ecological normal regression was fitted to data from metropolitan France between the ratio of stroke hospitalizations and standardized incidence of COVID-19 hospitalizations, and a quadratic spatial trend was established in order to adjust for spatial effects. We used SAS Enterprise Guide 8.3 for selecting the database, and R 4.0.2, R Core Team (2020) for the analyses.

Results

From January 1, 2019, to June 30, 2020, there were 249,013 hospitalizations for stroke in France. There were 29,263 cases over the period March–April 2019, compared to 23,873 in March–April 2020. With the exception of a slight decrease in the summer of 2019, the number of strokes remains constant over the study period until a drop in March 2020 (shown in Fig. 1).

The posterior medians for three knots were estimated on: March 10, 2020, March 22, 2020, and May 7, 2020 (K3), with small credibility intervals (Table 1). After March 10, 2020, the slope of the second "fall" segment was negative (−11.70). At K3, i.e., after the "rise" period, the mean number of hospital admissions is still −37.26 per day compared to the number calculated if the slopes of all segments had remained the same as that of the first segment. After K3, the slope of the fourth segment remains higher than that of the first segment (posterior median

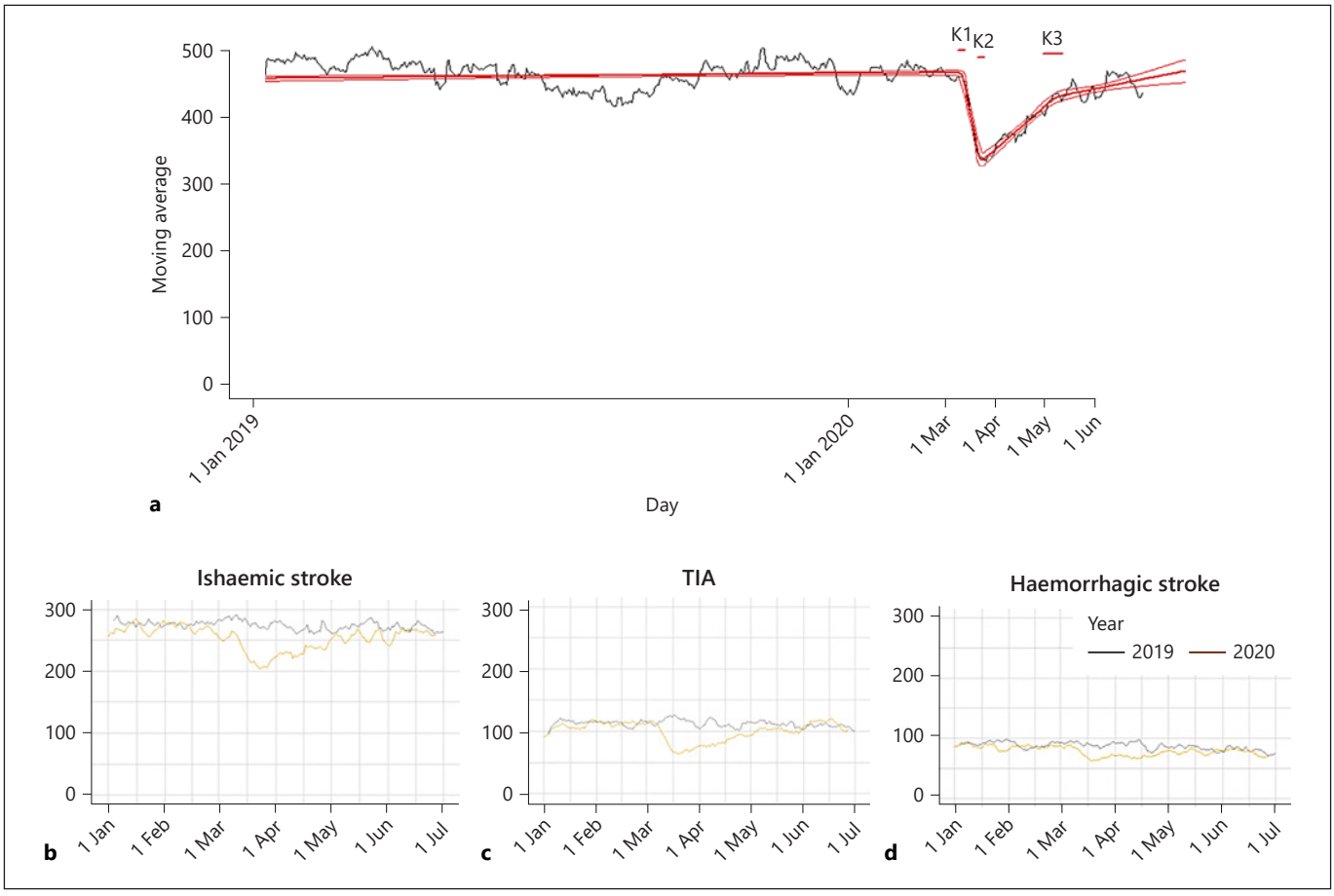

Fig. 1. Evolution of the number of hospital admissions for stroke in France. Data are centered by 7-day rolling means. **a** Evolution from January 1, 2019, to June 30, 2020, with modeling of the posterior median represented in red with its 95% credibility interval. Horizontal short lines represent the 95% credibility interval of the knots K1 (March 10, 2020), K2 (March 22, 2020), and K3 (May 7, 2020). Evolution of the number of hospital admissions in France from January to June for ischemic stroke (**b**), TIA (**c**), and hemorrhagic stroke (**d**), with data represented in yellow for the year 2020 and in gray for 2019.

0.4663), resulting in an upward slope compared to the "stability" period, albeit lower than that of the third "rise" period (2.090).

The decrease in hospital admissions concerns all three types of stroke during the period March–April 2020 (shown in Fig. 1b–d). Decrease in hospitalizations is common to all subtypes of hemorrhagic stroke. Stroke hospitalizations with at least one thrombectomy procedure decreased by 18.69% between March–April 2019 and March–April 2020 (Table 2).

Hospital stays were shorter in March–April 2020 than in March–April 2019, while the age and the proportion of men were comparable (Table 2). The death rate was slightly higher in 2020. In March–April 2020, 2.26% of hospitalizations for stroke were associated with a COVID-19 diagnosis.

As shown in Figure 2a, the number of stroke admissions decreased between March–April 2019 and March–April 2020 for 89 out of 96 administrative departments in metropolitan France. The greatest decrease is observed in the region of Paris, the northeast and the southeast, whereas standardized incidence rates of COVID-19 hospitalization by administrative department are higher in the northeast and the Parisian region (shown in Fig. 2b). Spatial models showed that the incidence of COVID-19 hospitalizations explains the ratio of stroke admissions (as the zero line is outside of the credible interval of the smoothed effect), whether the spatial trend is included in the model or not (shown in Fig. 2c, d).

Table 1. Quantitative results were obtained by modeling the evolution of hospital admission numbers for stroke

	Posterior median	95% credible interval	Probability of superiority
Slope segment 1	0.02012	[0.004876; 0.03655]	0.9953
Slope segment 2	−11.70	[−16.25; −8.552]	<0.0001
Slope segment 3	2.090	[1.772; 2.470]	>0.9999
Slope segment 4	0.4863	[0.1883; 0.7784]	0.9991
Difference between slopes 4 and 1	0.4663	[0.16594; 0.7585]	0.9984
Difference between slopes 3 and 4	−1.611	[−2.132; −1.105]	<0.0001
Knot 1*	429.9	[427.4; 431.7]	
Knot 2*	441.2	[439.4; 443.3]	
Knot 3*	487.8	[479.7; 491.5]	
Delay between knot 2 and knot 1, days	11.34	[8.253; 15.28]	>0.9999
Delay between knot 3 and knot 2, days	46.64	[38.30; 49.84]	>0.9999
Difference in mean number of hospitalizations at knot 3	−37.26	[-51.09; −26.78]	<0.0001

* K1, K2, K3: in days since January 4, 2021.

Table 2. Characteristics of stroke hospital admissions

	March–April 2019	March–April 2020	Evolution 2020/2019, %
Age, years			
Median (Q1, Q3)	75 (64, 85)	75 (64, 85)	0
Mean (SD)	72.77 (15.52)	72.77 (15.33)	0
Duration of hospital stay, days			
Median (Q1, Q3)	7 (3, 13)	6 (3, 11)	−14.29
Mean (SD)	10.24 (13.07)	9.090 (10.50)	−11.23
Proportion of men			
Men, *n* (% of total)	15,059 (51.46)	12,355 (51.75)	0.56
Admissions ending in death			
Deaths, *n* (% of total)	3,032 (10.36)	2,661 (11.15)	7.63
Admissions by stroke subtype, *n*			
All	29,263	23,873	−18.42
Ischemic	16,776	14,154	−15.63
TIA	6,978	5,220	−25.19
Hemorrhagic	5,509	4,483	−18.62
Stroke not specified as hemorrhage or infarction	1,050	773	−26.38
Hemorrhagic strokes by subtype, *n*			
Subarachnoid hemorrhage	1,148	942	−17.94
Intracerebral hemorrhage	3,472	2,847	−18.00
Other nontraumatic intracranial hemorrhages	1,145	918	−19.83
Mechanical thrombectomy, *n*			
Patients undergoing thrombectomy	1,118	909	−18.69

SD, standard deviation; Q1, lower quartile; Q3, upper quartile.

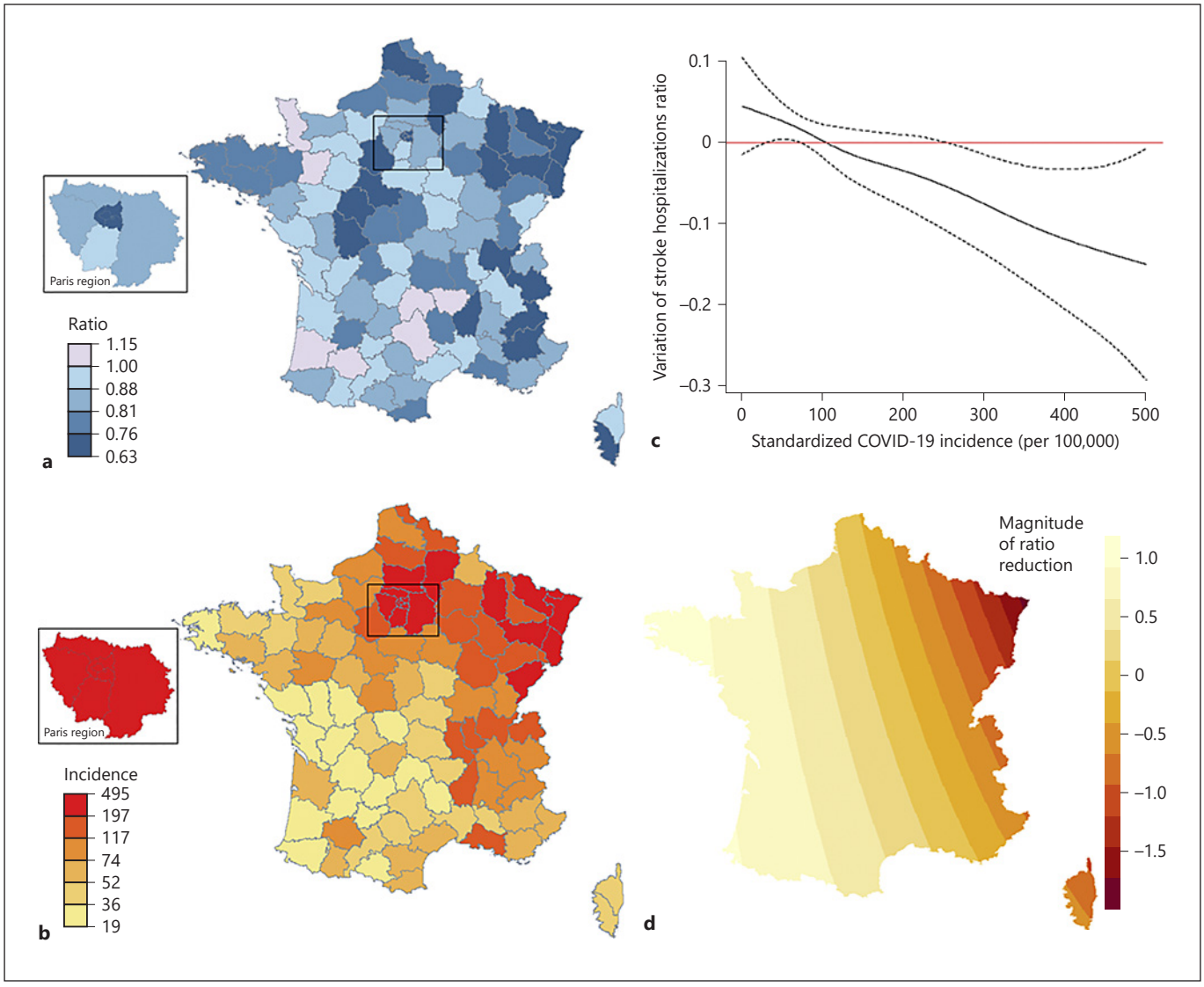

Fig. 2. Effect of the incidence of COVID-19 hospital admissions on the stroke hospitalization ratio (March–April 2020: March–April 2019) and estimated spatial quadratic trend to adjust for a potential spatial effect. **a** On the map of France by administrative department, the stroke hospitalization ratio is represented by varying shades of color (March–April 2020: March–April 2019): pink if 1 or above; blue if lower than 1. The ratios lower than 1 have been classed into quartiles. **b** Age and sex standardized incidence of COVID-19 admissions (per 100,000 inhabitants). The classes are automatically computed: nclass = $1 + 3.3 \times \log_{10}(N)$, where nclass is the number of classes and N is the variable length. **c** Plot of the variation of stroke hospitalization ratio according to standardized COVID-19 incidence (per 100,000 inhabitants). The smoothed effect line is shown in black, and the credible interval is shown as black dashed lines. **d** Map of estimated spatial quadratic trend in metropolitan France: the magnitude of the reduction increases from yellow to red. Because of the different spatial scales between aggregated data for French administrative departments and the continuous quadratic trend, the unit in the map is an estimation of ratio reduction.

Discussion/Conclusion

The number of admissions for stroke decreased significantly in France during the first COVID-19 epidemic peak, and this decrease is seen across all stroke subtypes. Proportions between the sexes did not change. Differences in the duration of hospital stay and the mortality rate are difficult to interpret because some long-term hospital stays in 2020 may have ended after data extraction, and/or relevant data may have been updated at a later date.

This sudden decrease of hospitalizations cannot be explained by seasonality, nor by a change of hospital facility, because our study is national. The comparable spatial distribution of COVID-19 and decreased stroke admissions seems to reflect causality because the link between them persists when a spatial trend is modeled.

This phenomenon was described in the literature for emergency department visits during the 2003 SARS outbreak in Taipei [10] and Toronto [14]. More recently, the authors described the impact of lockdown on emergency department visits in Lebanon [15]. Equally, in a tertiary pediatric emergency department in Cincinnati, USA, the volume of patients decreased at a daily rate of −19.4% after the launch of public health interventions against COVID-19 [16]. Few works focused on the decrease in stroke admissions during the pandemic, concentrating mainly on emergency departments, or on limited geographical areas [11, 12]. In 2021, Daniel et al. [17] showed a nationwide decrease of strokes in Germany, and a worldwide study by Nogueira et al. [18] on 457 stroke centers found an 11.5% decline in stroke admissions during the pandemic [17, 18]. Siegler et al. [11] hypothesize that this decrease is a consequence of patients presenting milder symptoms, therefore less likely to seek healthcare. The lack of interaction and communication during lockdown could also have increased under-recognition of stroke signs and limited encouragement by relatives to seek care [19–21]. Due to this crisis situation, the quality of care and patient follow-up may have deteriorated as COVID-19 activity increased, with a higher probability of caregivers underdiagnosing stroke. It may also have resulted from healthcare providers redirecting a higher proportion of patients out of hospital. In support of these hypotheses, our study found a greater decline in stroke admissions in several administrative departments experiencing a higher incidence of COVID-19 hospitalization. It is also possible that the epidemic context and the lockdown measures could have influenced stroke risk factors on the short term, although this is not our main hypothesis.

In the literature, the incidence of neurological symptoms in COVID-19 patients is between 1.6% and 2.5% [22–26]. A bicenter study in New York City found a higher probability of stroke with SARS coronavirus 2 infections than with influenza (OR 7.6), after adjustment for age, sex, and race [26]. It appears that COVID-19 is likely to increase the incidence of stroke, probably because of its pathophysiology, involving inflammation and hypercoagulability [24, 26–28]. Although COVID-19 may be responsible for neurological symptoms, it may also have been a concurrent cause of death [27].

Our study also pointed to a decrease in thrombectomy procedures, which indicates a global decrease in stroke therapies, as suggested in the literature [21]. However, we were unable to assess the evolution in the number of thrombolysis, as this information is unavailable in the PMSI database.

To our knowledge, this is the first nationwide study in France, a country with a relatively high incidence rate of stroke, to describe the evolution of stroke admissions during the first COVID-19 epidemic peak. We have been able to highlight the decline in stroke admissions while taking into account its evolution over the entire year. These results alert us to the need for ensuring appropriate care for non-COVID-19 patients during the epidemic. The impact of the epidemic on cerebrovascular diseases may be seen in the months and years to come.

A first limitation of using the PMSI national database is the possible delay between patient discharge and coding. However, the extent of this bias is limited, because diagnoses made during hospitalization have to be sent to the national database during the month following discharge. Second, this database has been designed for funding allocation, and not for epidemiological purposes. Therefore, there may be a variation in the quality of the medical information, according to the relation between coding and funding. However, homogeneity of coding is provided by strict, national rules with regular checks carried out by the funding body, thus limiting misclassification bias.

This study has determined a nationwide decrease in stroke hospital admissions at the time of the first COVID-19 wave in France. The drastic lockdown measures and unprecedented epidemic context have most likely impacted the probability of patients seeking hospital assistance in France, particularly in those regions most affected by COVID-19. In light of these findings, the care provided for stroke should be reconsidered in order to prevent underdiagnosis, to improve outpatient medical care, and to facilitate health provider decision-making during the crisis.

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Statement of Ethics

This study adheres to French legislation regarding the reuse of anonymized data (MR-005 of Commission Nationale de l'Informatique et des Libertés) and is registered at Strasbourg University Hospital under the reference 21-2019. Relevant data files

aredepositedontheHealthDataHub(reference:F20200813210442). Participants' informed consent is not required. The Strasbourg University Hospital Ethics Committee has approved this study (reference: CE-2021-14).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

C.R., V.W., and E.-A.S. designed the study; P.T.B.L. and C.R. extracted the data; C.R., P.T.B.L., E.-A.S., V.W., F.B.-F., H.L., and C.S. analyzed the data; E.-A.S., C.R., T.F., and P.T.B.L. performed the statistical analysis; C.R. wrote the manuscript; all authors reviewed, revised, and approved the final report. Manuscript edition was provided by Dr. Kate Dunning (Strasbourg University Hospital).

Data Availability Statement

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

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