Stroke

CLINICAL AND POPULATION SCIENCES

Maintenance of Acute Stroke Care Service During the COVID-19 Pandemic Lockdown

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BACKGROUND AND PURPOSE: Timely reperfusion is an important goal in treatment of eligible patients with acute ischemic stroke. However, during the coronavirus disease 2019 (COVID-19) pandemic, prehospital and in-hospital emergency procedures faced unprecedented challenges, which might have caused a decline in the number of acute reperfusion therapy applied and led to a worsening of key quality measures for this treatment during lockdown.

METHODS: This prospective multicenter cohort study used data from the TRISP (Thrombolysis in Ischemic Stroke Patients) registry of patients with acute ischemic stroke treated with reperfusion therapies, that is, intravenous thrombolysis or endovascular therapy. We compared prehospital and in-hospital time-based performance measures (stroke-onset-to-admission, admission-to-treatment, admission-to-image, and image-to-treatment time) during the first 6 weeks after announcement of lockdown (lockdown period) with the same period in 2019 (reference period). Secondary outcomes included stroke severity (National Institutes of Health Stroke Scale) after 24 hours and occurrence of symptomatic intracranial hemorrhage (following the ECASS [European-Australasian Acute Stroke Study]-II criteria).

RESULTS: Across 20 stroke centers, 540 patients were treated with intravenous thrombolysis/endovascular therapy during lockdown period compared with 578 patients during reference period (−7% [95% CI, 5%–9%]). Performance measures did not change significantly during the lockdown period (2020/2019 minutes median: onset-to-admission 133/145; admission-to-treatment 51/48). Same was true for admission-to-image (20/19) and image-to-treatment (31/30) time in patients with available time of first image (n=871, 77.9%). Median National Institutes of Health Stroke Scale on admission (2020/2019: 11/11) and after 24 hours (2020/2019: 6/5) and percentage of symptomatic intracranial hemorrhage (2020/2019: 6.2/5.7) did not differ significantly between both periods.

CONCLUSIONS: The COVID-19 pandemic lockdown resulted in a mild decline in the number of patients with stroke treated with acute reperfusion therapies. More importantly, the solid stability of key quality performance measures between the 2020 and 2019 period may indicate resilience of acute stroke care service during the lockdown, at least in well-established European stroke centers.

GRAPHIC ABSTRACT: An online graphic abstract is available for this article.

Key Words: COVID-19 ■ intracranial hemorrhage ■ ischemic stroke ■ quality of care ■ reperfusion

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Nonstandard Abbreviations and Acronyms

COVID-19	coronavirus disease 2019
EVT	endovascular therapy
IVT	intravenous thrombolysis
NIHSS	National Institutes of Health Stroke Scale
sICH	symptomatic intracranial hemorrhage
TRISP	Thrombolysis in Ischemic Stroke Patients

Coronavirus disease 2019 (COVID-19), caused by infection of severe acute respiratory syndrome coronavirus 2, has emerged as a pandemic and public health crisis of global proportions with an effect on routine and specialized medical care. Most countries affected by the COVID-19 pandemic imposed a lockdown severely restricting public life to contain and mitigate the spread of COVID-19. Recently, it was reported that the overall number of acute stroke admissions to hospitals declined during the COVID-19 pandemic, especially after the announcement of lockdown.[1] Concurrently, adherence to the strict hygiene regulations in combination with adequate patient care posed a major challenge for prehospital and in-hospital emergency care and has led to altered stroke management pathways.[1–5] In line, the impact of COVID-19 on neurological services is considered to be profound.[6]

Timely reperfusion is an important goal in acute stroke treatment.[7,8] However, early initiation of reperfusion therapies is dependent on optimal prehospital and in-hospital chains, which might be altered during the COVID-19 pandemic. In 2 recent cohort studies, the number of patients treated with endovascular therapy (EVT) declined and treatment initiation was delayed during the early phase after the announcement of strict epidemic mitigation measures.[4,9]

We aimed to investigate, whether the number of patients receiving acute reperfusion therapies (EVT or intravenous thrombolysis [IVT]) decreased and whether time-based performance measures of acute stroke care and short-term outcomes were affected in patients with acute ischemic stroke admitted to 20 stroke centers across Europe during the COVID-19 lockdown period. Participating stroke centers have long-term experience in prospectively collecting detailed and high-quality data on acute stroke treatment.

METHODS

According to the American Heart Association Journals' implementation of the Transparency and Openness Promotion Guidelines, all data and materials can be accessed by request from the corresponding author (valerian.altersberger@usb.ch).

Study Design

For this cohort study, we used prospectively collected data from the TRISP (Thrombolysis in Ischemic Stroke Patients) registry, which has been previously described.[10] Twenty TRISP centers participated in this study. Data collection was done locally in each stroke center. Data from the local registries were pooled and retrospectively analyzed in an anonymized way at the stroke center in Basel. Data of patients treated at Swiss TRISP sites were in part extracted from the Swiss Stroke Registry or from local registries of participating centers. Parameters of interest for the present study were age, sex, National Institutes of Health Stroke Scale (NIHSS) score,[11] diagnosis of COVID-19, and the presence of wake-up stroke. The following dates and times were collected: stroke onset, hospital arrival, first image, and treatment initiation (IVT or EVT).

Outcomes

Primary outcomes were the following time-based performance parameters: onset-to-admission time (defined as time from stroke onset to hospital arrival) and admission-to-treatment time (defined as time of hospital arrival to time of treatment initiation). In wake-up strokes, time of stroke onset was defined as the time the patient was last known to be without the signs and symptoms of the current stroke (reported either by the patient self or by a third party). Treatment initiation was defined as the time of administration of intravenous alteplase in cases of IVT alone and bridging therapy or in case of EVT alone the time of groin puncture. For patients with an available time of first image, we performed a subgroup analysis of admission-to-image time (defined as time from hospital arrival to first image) and image-to-treatment time (defined as first image-to-treatment initiation). Secondary outcomes were the NIHSS score 24 hours after admission and the occurrence of symptomatic intracranial hemorrhage (sICH) defined by the Second European-Australasian Acute Stroke Study.[12]

Patients with acute ischemic stroke admitted within the first 6 weeks after the announcement of public life restrictions within the respective country were included (earliest period: February 27–April 9, latest period: March 17–April 28; Table I in the Data Supplement). Patients' data from the same period of each center in 2019 served as the reference group. All patients with missing data on admission-to-treatment time and all patients with in-hospital stroke were excluded.

The study was conducted in accordance with the Reporting of Studies Conducted Using Observational Routinely-Collected Data guidelines. A completed Reporting of Studies Conducted Using Observational Routinely-Collected Data checklist is presented in the Data Supplement (Methods in the Data Supplement).

Statistical Analysis

Statistical analyses were performed with SPSS Statistics version 25 (IBM).

We compared the time-based performance measures and baseline characteristics during the lockdown period with the reference period overall and on a weekly level using descriptive analyses. Post hoc, we added descriptive information on baseline characteristics, time-based performance measures, and secondary outcomes for the subgroup of patients with diagnosis of COVID-19. Categorical data were summarized as absolute counts and percentage, and continuous data were summarized as median and interquartile range. We used χ^2-test and Fisher exact test for categorical variables where appropriate and the Mann-Whitney *U* test for continuous variables.

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To assess variability between centers, time-based performance measures were analyzed on center-level separately. Adjustments for multiple testing were done using Bonferroni correction and false discovery rate.

Post hoc, we compared the time-based performance measures of centers in nations with mild versus those in nations with severe lockdown. The severity of lockdown was quantified by the Government Response Stringency Index (https://ourworldindata.org/policy-responses-covid) which used a composite measure based on nine response indicators, rescaled to a value from 0 to 100 (100=strictest). If policies vary at the subnational level, the response level of the strictest sub-region was used.[13] We calculated the mean index score of all days during the investigated period for each nation (Table II in the Data Supplement). A Government Response Stringency Index of 70 was chosen as the cutoff to differentiate between mild (≤70) and severe (>70) lockdown.

Role of the Funding Source/Ethics

The study's funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

The study was approved by the ethics committee in Basel, Switzerland, and written informed consent was waived. The requirement for additional local ethical approval differed between participating centers and was obtained if required. Anonymized data will be shared by request from any qualified investigator.

RESULTS

Data were eligible for analysis in 1118 (95.8%) of 1167 stroke patients treated with reperfusion therapies. Reasons for exclusion were missing data on admission-to-treatment time (n=26; 2.2%) and in-hospital stroke (n=23; 2.0%). A flow diagram is presented in the Data Supplement (Figure I in the Data Supplement).

Among all eligible patients, 540 received acute reperfusion therapy during the lockdown period and 578 during the reference period resulting in a difference of 38 patients or 6.6% (95% CI, 4.7%–8.9%). The proportion of patients treated with IVT alone (2020 versus 2019: 32.4% versus 38.1%), bridging (29.8% versus 27.7%), and EVT (37.5% versus 34.3%) did not differ significantly between both periods (Table 1). In one center (Brescia, Italy), the number of admitted patients increased considerably due to local reorganization of stroke care infrastructure and pathways (Table I in the Data Supplement). The number of missing data for each variable is presented in Table III in the Data Supplement. Figure 1 shows the number of patients admitted per day during the lockdown and reference period. Except for higher variability in the number of patients admitted within the first 2 weeks after lockdown, no clear trend was seen during the 6-week lockdown period.

Performance Measures and Short-Term Outcomes

Baseline characteristics are presented in Table 1. Patients admitted during the lockdown period were younger (median age 75 versus 77 years) and less likely transferred from another hospital (29.1% versus 34.9%. Proportion of patients with stroke with age <50 years, stroke severity on admission, rate of wake-up strokes, and gender were evenly distributed. Each time-based performance measure (onset-to-admission and admission-to-treatment time) did not differ significantly between both periods as well as the 2 in-hospital performance measures (admission-to-image and image-to-treatment time) which were available in a subgroup of patients (n=871, 77.9%) only. In addition, admission-to-IVT time and admission-to-EVT time did not differ significantly between both periods (Table 2, Figure 2). These results remained unchanged in analyses including patients transferred from other hospitals and patients primarily presenting at the stroke center separately (Table 2).

Analyses on center-level revealed that in 3 out of 20 centers the onset-to-admission time was significantly shorter and in 1 out of 20 significantly longer during the lockdown period compared with 2019. The admission-to-treatment time was significantly longer in 4/20 centers (Table IV in the Data Supplement). However, we did not identify any regional or national pattern among these centers. After adjustment for multiple testing using Bonferroni correction as well as false discovery rate, onset-to-admission time remained significantly shorter in one and longer in another center, whereas no significant change remained for admission-to-treatment time. Analysis of performance measures on a weekly level did not reveal a clear trend over time during the 6-week lockdown period (Figure 3, Table V in the Data Supplement).

Compared with the reference period, clinical outcome (NIHSS after 24 hours) and safety outcome (occurrence of sICH) did not differ significantly during both periods (Table 3).

Post Hoc Subgroup Analysis Comparing Centers in Nations With Mild and Severe Lockdown

Neither in centers with mild lockdown (n=192) nor in centers with severe lockdown (n=926) time-based performance measures (onset-to-admission time, admission-to-treatment time, admission-to-IVT time, and admission-to-EVT time) differed significantly between the lockdown period and the reference period. Although in centers with mild lockdown the number of patients treated with acute reperfusion therapy remained stable during the lockdown period, the number of treated patients in centers with severe lockdown measures

Table 1. Comparison of Baseline Characteristics Between the Lockdown Period (2020) and the Reference Period (2019)

	2020; n=540	2019; n=578	2020 vs 2019; *P* value	COVID-19 positive*; n=17
Age, y, median (IQR)	75 (64–82)	77 (67–84)	0.018	77 (60–82)
Age <50 y, n (%)	36 (6.7)	27 (4.7)	0.148	1 (5.9)
Men, n (%)	272 (50)	274 (47.4)	0.338	6 (35.3)
Stroke severity, NIHSS, median (IQR)	11 (5–17)	11 (5–18)	0.901	12 (7–18)
Wake-up stroke, n (%)	104 (19.3)	94 (16.5)	0.240	1 (5.9)
Transferred from other hospital, n (%)	157 (29.1)	202 (34.9)	0.040	5 (29.4)
Type of reperfusion therapy, n (%)				
Intravenous thrombolysis	175 (32.4)	220 (38.1)	0.140	6 (35.3)
Bridging	161 (29.8)	160 (27.7)		5 (29.4)
Endovascular therapy	204 (37.8)	198 (34.3)		6 (35.3)

COVID-19 indicates coronavirus disease 2019; IQR, interquartile range; and NIHSS, National Institutes of Health Stroke Scale.
*In patients admitted in 2020.

declined by 7.9% (95% CI, 5.6–10.7%; Table VI in the Data Supplement).

Descriptive Information on COVID-19–Positive Patients

Overall, 17 patients (3.1%) admitted during the lockdown period were COVID-19 positive. Compared with all other patients admitted during lockdown (n=523, 96.9%), stroke severity, age, percentage of wake-up stroke, and type of reperfusion therapy were similar, whereas the proportion of females was higher. Patients with COVID-19 had higher stroke severity after 24 hours (median NIHSS after 24 hours: 13 versus 6), but the risk of sICH was similar. Onset-to-admission time was shorter in COVID-19–positive patients, whereas in-hospital measures (admission-to-IVT time, admission-to-EVT time) were longer compared with the 2020 reference group (Tables 1 through 3).

DISCUSSION

This study shows the following key results: during the COVID-19 pandemic lockdown, the number of patients with acute ischemic stroke treated with acute reperfusion therapy was 7% lower compared with the reference

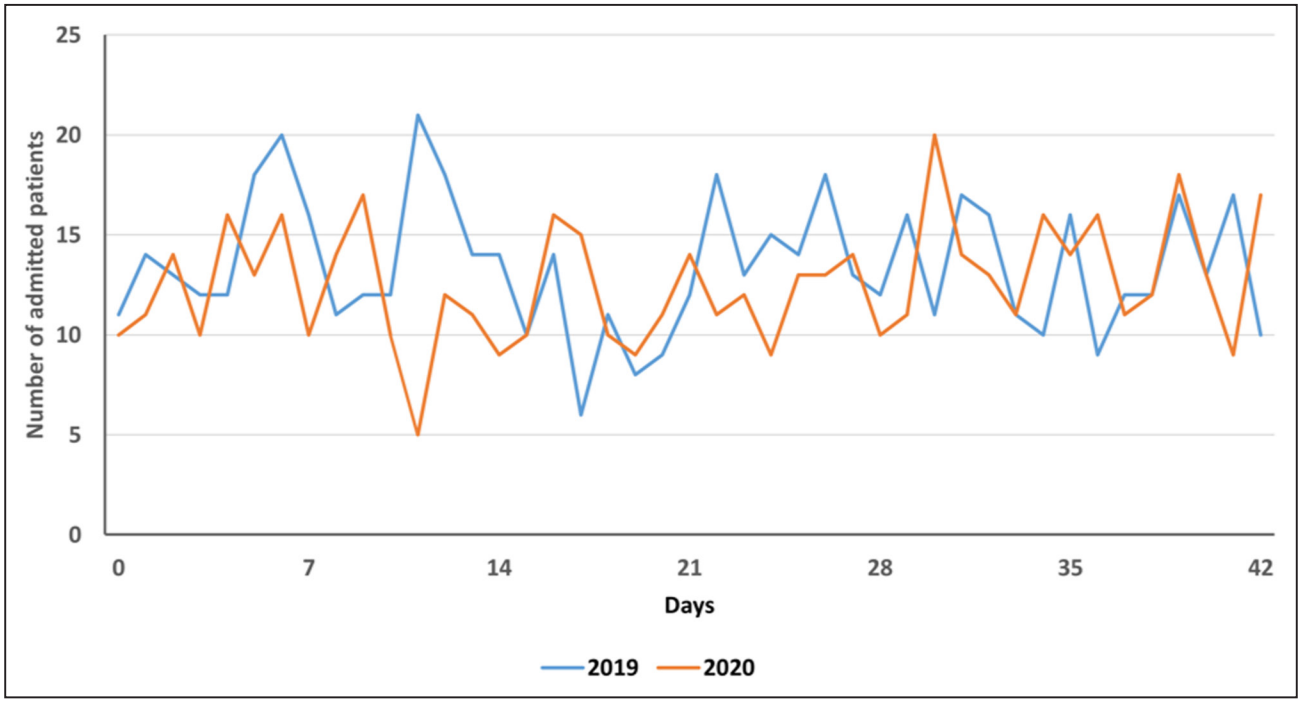

Figure 1. Number of admitted intravenous thrombolysis/endovascular therapy–treated patients each day after lockdown (2020) and during the reference period (2019).

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Table 2. Comparison of Time-Based Performance Measures Between the Lockdown Period (2020) and the Reference Period (2019)

Median performance measures in minutes (IQR)	2020	2019	2020 vs 2019; *P* value	COVID-19 positive*
Onset-to-admission	133 (74–279)	145 (76–246)	0.777	109 (71–190)
Admission-to-treatment	51 (28–77)	48 (29–78)	0.653	88 (55–141)
Admission-to-IVT	41 (26–61)	42 (25–60)	0.873	76 (30–136)
Admission-to-EVT	67 (43–101)	65 (40–98)	0.449	109 (70–218)
Admission-to-image	20 (12–32)	19 (12–30)	0.642	35 (26–92)
Admission-to-treatment for nontransferred patients	55 (31–88)	51 (29–83)	0.162	119 (70–193)
Admission-to-treatment for transferred patients	40 (22–60)	42 (28–66)	0.074	54 (39–90)
Admission-to-image	31 (16–57)	30 (16–53)	0.495	66 (25–102)

COVID-19 indicates coronavirus disease 2019; EVT, endovascular therapy; IQR, interquartile range; and IVT, intravenous thrombolysis.
*In patients admitted in 2020.

period in 2019. However, prehospital and in-hospital time-based performance measures, short-term clinical (NIHSS after 24 hours) and safety outcome (occurrence of sICH) did not change significantly during the lockdown period in all centers as a whole.

There is growing evidence that the COVID-19 pandemic affects acute stroke care globally. A single-center study from the United States and a multicenter study from Brazil suggested a decline in the number of admitted patients with acute ischemic stroke - in particular of those with transient ischemic attacks and mild strokes—during the COVID-19 pandemic.[14,15] A multicenter study from the United States found a decrease of 39% in the number of patients who received imaging evaluation for acute stroke between February 1, 2020, to February 29, 2020, and March 26, 2020 to April 8, 2020. Most of these patients with stroke were likely under consideration for EVT.[16] Our study included 20 stroke centers and most of our patients had mild to severe strokes, and all of them received acute reperfusion therapy. Unlike other studies, stroke severity on admission was not significantly higher during lockdown compared with the reference period in 2019 in our study.[15,17] Reason for the higher stroke severity in other studies was explained by lower number of admitted patients with mild strokes and transient ischemic attacks. However, in our study, only ischemic strokes with relevant clinical deficits qualifying for acute reperfusion therapies were included. In line with our findings, one study including only patients treated with EVT during the COVID-19 pandemic did not show a significant increase in stroke severity on admission compared with 2019.[9]

We found an overall decrease of 7% in the number of patients receiving acute reperfusion therapies during the first 6 weeks after lockdown compared with the same 6-week period in 2019. The decline was more

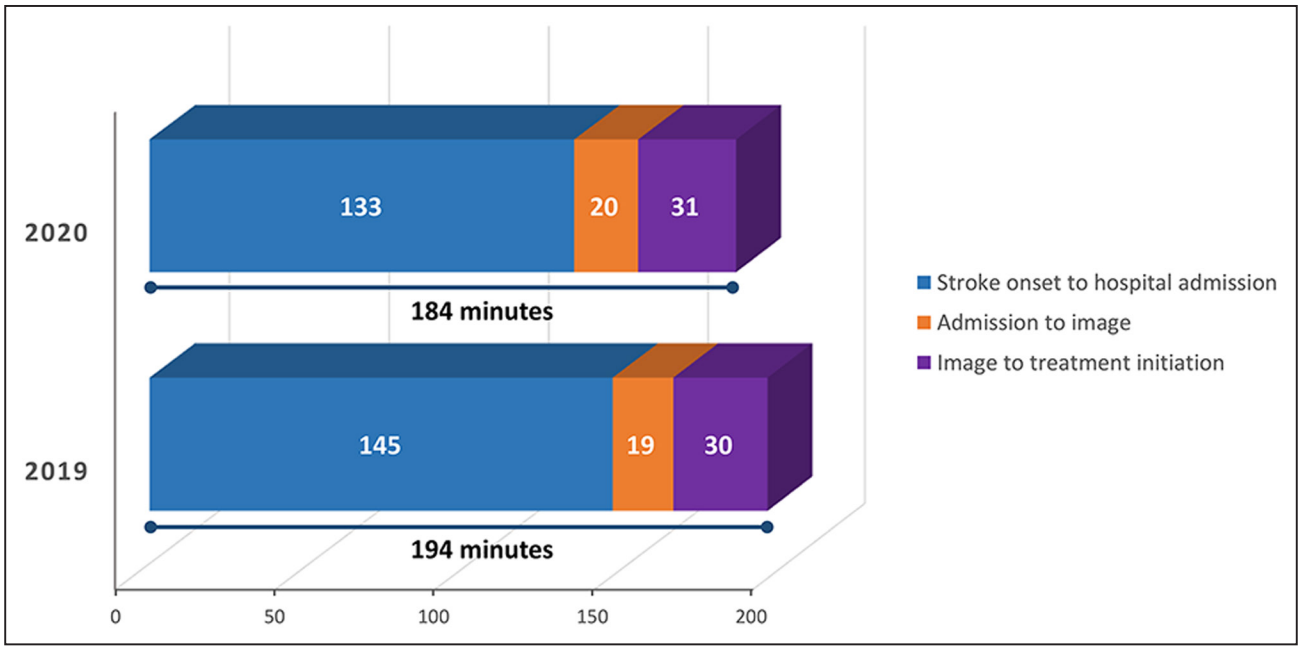

Figure 2. Median time intervals in minutes from stroke onset to reperfusion therapy after announcement of lockdown (2020) and during the reference period (2019).

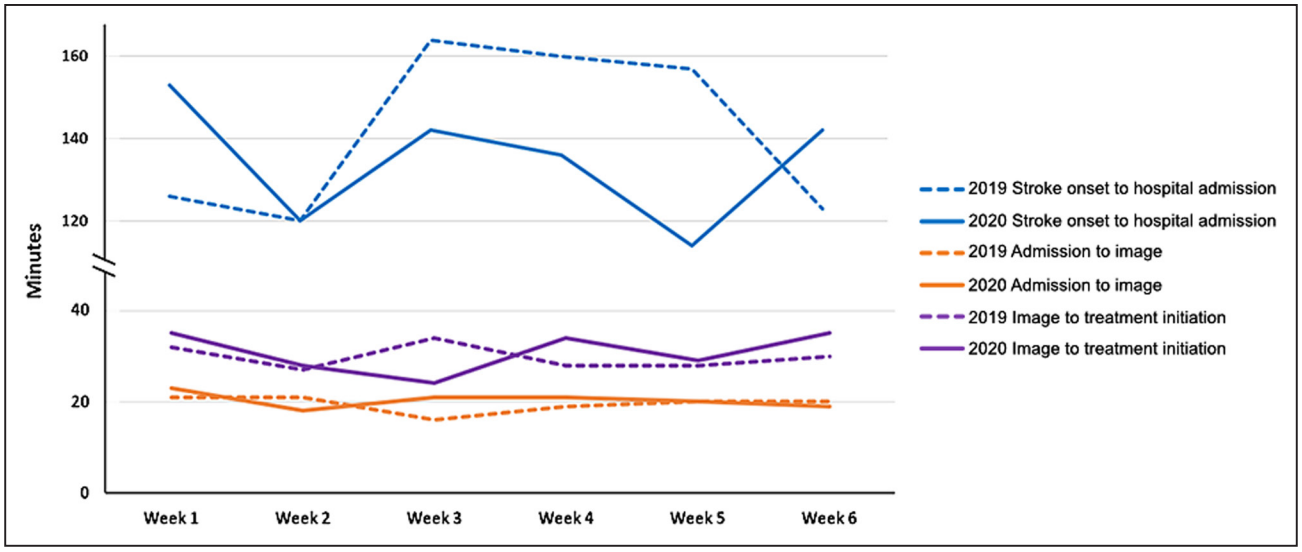

Figure 3. Median time intervals in minutes for different performance measures per wk after announcement of lockdown (2020) and during the reference period (2019).

pronounced in centers with severe lockdown (8%), whereas no decline was found in centers with mild lockdown. Therefore, it is likely that with increasing lockdown severity the number of hospital admissions of patients with acute stroke eligible for acute reperfusion therapies decreases. However, the decline in our study was lower than that in a nationwide study in France, which showed a decline of 21% in patients treated with EVT during the first stages of the pandemic (February 15–March 30) compared with the same period in 2019.[9] These differences (21% versus 7%) might partly be explained by different starting points of the investigated time period. When including patients admitted during the first 2 weeks after lockdown only, the decline in the number of patients admitted to hospital was similar (17%) in our study (Figure 1). Another study also showed a reduction in the mean number of EVTs (—32%) after COVID-19 confinement including 17 stroke centers from Europe, Canada, and the United States.[4] Data were collected up to April 15, 2020, and restriction measures were implicated later in Northern America (eg, in Ontario, Canada on March 23). Therefore, the lower reduction in acute reperfusion therapy in our study might be explained by our more extended observational timespan. In addition, a study from 280 stroke centers in China found a reduction in numbers of reperfusion therapies of 25% in February 2020 compared with February 2019.[5] In contrast, one study showed an increase in number of ischemic strokes caused by large vessel occlusion during the height of COVID-19 prevalence in New York.[18]

Studies for other diseases, like myocardial infarction, also showed a reduction of incidence of hospitalization and a decline in emergency department visits in general during the early stages of the COVID-19 pandemic.[19–21]

Our study was not designed to identify the cause of the decline in patients with stroke undergoing acute reperfusion therapies. It seems likely, however, that both behavioral and infrastructural changes related to the COVID-19 pandemic led to a reduction of timely admission of patients with acute ischemic stroke, especially during the initial phase of public lockdown. Considering reports of COVID-19 triggering or even causing stroke, it is unlikely that true incidence would have been declined.[22,23]

Besides lower numbers of patients receiving acute reperfusion therapies, 2 previous studies suggested that in-hospital workflows of acute stroke care might have been affected during the pandemic.[4,9] In stroke care, optimal prehospital and in-hospital workflows are crucial because any delay in treatment reduces the chance of better clinical outcome and increases the chance of treatment complications.[7,8] Therefore, time-based

Table 3. Comparison of Short-Term Clinical and Safety Outcome Between the Lockdown Period (2020) and the Reference Period (2019)

	2020	2019	2020 vs 2019; *P* value	COVID-19 positive*
NIHSS after 24 h, median (IQR)	6 (2–14)	5 (2–13)	0.674	13 (6–18)
Symptomatic intracranial hemorrhage (ECASS-2 criteria), n (%)	32 (6.2)	31 (5.7)	0.795	1 (5.9)

COVID-19 indicates coronavirus disease 2019; ECASS, European-Australasian Acute Stroke Study; IQR, interquartile range; and NIHSS, National Institutes of Health Stroke Scale.

*In patients admitted in 2020.

performance measures are strong indicators for the quality of acute stroke care. Quality of prehospital care is reflected by the onset-to-admission time and quality of in-hospital care by the admission-to-treatment, admission-to-image, and image-to-treatment time. Our data did not show significant differences in any of the time-based performance measures between the lockdown and the reference period. These results persisted in different subgroups, such as in patients transferred from another hospital, patients treated in centers with mild or severe lockdown, and treatment modality (IVT or EVT). This is in contrast to the results of 2 studies which found a significant increase in delays between the image-to-treatment time[9] and the onset-to-treatment time[4] in patients treated with EVT. However, in both of these studies information on performance measures were only available in 48.5%[4] and 57.1%,[9] respectively. Consistent with our results, a single-center study in Spain found no deterioration of performance measures of acute stroke care.[24] In our study, center-level analyses indicated that the COVID pandemic lockdown affected prehospital and in-hospital processes in some centers: whereas prehospital performance measures improved in 3 out of 20 centers and declined in 1 out of 20 centers after the lockdown, in-hospital performance measures declined in 4 out of 20 centers (Table IV in the Data Supplement). However, we could not identify any patterns in regions or nations. Furthermore, after adjusting for multiple testing the decline of the in-hospital performance measures did not remain significant. In contrast, the prehospital performance measures remained significantly improved in one and declined in another center. This might most likely be explained by local restructuring/reorganization of acute stroke care during lockdown.

In line with the absence of deterioration of quality of acute stroke care, we also found no differences in short-term clinical outcome and occurrence of sICH comparing the 2020 and 2019 period.

In our study, the number of patients with diagnosis of COVID-19 was very small (n=17) resulting in limited statistical validity. Thus, we performed descriptive analyses only. Except for a higher proportion of females in the COVID-positive cohort, other baseline characteristics were similar to patients without diagnosis of COVID-19. This is in contrast to 2 other studies including patients with stroke treated with acute reperfusion therapies, in which COVID-19–positive patients were predominately male.[25,26] We found COVID-19–positive patients to have worse clinical short-term outcome (median NIHSS after 24 hours: 13 versus 6) which is in line with 2 other studies, potentially reflecting multi-system complications of COVID-19.[25,26] The numerically longer time intervals from admission-to-treatment (IVT and EVT) might reflect delays due to hygiene regulations but also might result from variance across centers due to the small sample size. In a study with fewer COVID-19–positive patients (n=10) treatment times were similar or numerically even shorter for this patient cohort.[25]

Strengths of the present study are the high number of participating stroke centers resulting in a considerable sample size over this short period of time. We were also able to define specific time intervals for each center's lockdown period and to investigate performance measures reflecting prehospital and in-hospital quality of stroke care. Furthermore, the low number of missing data on the admission-to-treatment time (2.2%) and the onset-to-admission time (1.5%) reduced the risk of bias.

Our study has limitations: Apart from the general limitations of register-based studies, the extent of the lockdown of public life differed between regions and more importantly nations. In Sweden, for example, restriction measures were moderate in comparison to other countries. However, our data did not show evidence for regional trends although local variance was considerable. Also, TRISP centers have a long-term experience in treatment of acute stroke and may therefore not be representative of other regions and countries in Europe. In addition, as time-based performance measures—especially concerning EVT—improved over the last years in general, we were not able to investigate if a possible further improvement was hindered during the lockdown period. Lastly, our follow-up was limited to short-term outcomes.

CONCLUSIONS

In summary, our cohort study showed that the COVID-19 pandemic lockdown resulted in a mild decline in the number of patients with stroke treated with acute reperfusion therapies across Europe. However, the quality of acute stroke care service did not change relevantly between the 2020 and 2019 period. The solid stability of all key quality performance measures may indicate resilience of acute stroke care service during the lockdown, at least in well-established European stroke centers, and implies a quick and sufficient adaptation by these centers to the new situation. Our findings are important and reassuring regarding stroke care during the COVID-19 pandemic.

Future studies are needed to investigate the maintenance of stroke care quality in other parts of the world and to clarify whether long-term outcome and secondary stroke prevention are impaired.

ARTICLE INFORMATION

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Disclosures

Dr Heldner reports personal fees from Bayer and scientific advisory board honoraria from Amgen and a grant from Bangerter foundation, all outside the submitted work. Dr Zini reports personal fees from Stryker, personal fees from Medtronic, personal fees from Cerenovus, personal fees from Daiichi Sankyo, and personal fees from Boehringer Ingelheim outside the submitted work. Dr Nannoni reports grants from Swiss National Science Foundation (SNSF) outside the submitted work. Dr Gonçalves reports funding from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior—Brasil (CAPES) Finance Code 001. Dr Nolte reports research grants from German Ministry of Research and Education, German Center for Neurodegenerative Diseases, German Center for Cardiovascular Research, and speaker or consultation fees from Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer Pharma, Abbott, and W.L. Gore and Associates. 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Supplemental Materials

Expanded Methods
Online Tables I–VI
Online Figure I

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