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ORIGINAL ARTICLE

Stroke admissions and revascularization treatments in Denmark during COVID-19

Nicolas Drenck[1] | Josefine Grundtvig[1] | Thomas Christensen[2,6] | Helle Klingenberg Iversen[3,6] | Christina Kruuse[4,6] | Thomas Truelsen[3,6] | Troels Wienecke[5,6] | Hanne Christensen[1,6]

[1]Department of Neurology, Copenhagen University Hospital–Bispebjerg and Frederiksberg, Copenhagen, Denmark

[2]Department of Neurology, Copenhagen University Hospital–Nordsjællands Hospital, Hillerød, Denmark

[3]Department of Neurology, Copenhagen University Hospital–Rigshospitalet, Copenhagen, Denmark

[4]Department of Neurology, Copenhagen University Hospital–Herlev Gentofte, Copenhagen, Denmark

[5]Department of Neurology, Zealand University Hospital, Roskilde, Denmark

[6]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Correspondence
Nicolas Drenck, Department of Neurology, Copenhagen University Hospital–Bispebjerg and Frederiksberg, Copenhagen, Denmark.
Email: ndrenck@gmail.com

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Abstract

Objective: The aim of this study was to assess the number of stroke-related admissions and acute treatments during the first two waves of COVID-19 and lockdowns in the Capital Region of Denmark and the Region of Zealand.

Materials & Methods: The weekly numbers of admitted patients with stroke were retrieved from electronic patient records from January 2019 to February 2021 and analysed to reveal potential fluctuations in patient volumes during the pandemic.

Results: A total of 23,688 patients were included, of whom 2049 patients were treated with tissue-type plasminogen activators (tPA) and 552 underwent endovascular thrombectomy (EVT). We found a transient decrease in the number of weekly admitted patients (pts/week) with all strokes (−9.8 pts/week, 95% CI: −19.4; −0.2, $p = .046$) and stroke mimics (−30.1 pts/week, 95% CI: −39.9; −20.3, $p < .001$) during the first lockdown compared to pre-COVID-19. The number of subarachnoid haemorrhage, intracerebral haemorrhage, and ischaemic stroke admissions showed insignificant declines. Analysing all COVID-19 periods collectively revealed increased volumes of ischaemic stroke (+6.2 pts/week, 95% CI: +1.6; +10.7, $p = .009$) compared to pre-COVID levels, while numbers of stroke mimics remained lower than pre-COVID. Weekly tPA and EVT treatments remained constant throughout the study period.

Conclusions: Our results are comparable with other studies in finding reductions in stroke-related admissions early in the pandemic. This is the first study to report increased stroke volumes following the first wave of the pandemic. The mechanisms behind the observed drop and subsequent rise in strokes are unclear and warrant further investigation.

KEYWORDS
COVID-19, ischaemic stroke, pandemic, stroke, thrombectomy, thrombolysis

1 | INTRODUCTION

In early 2020, an outbreak of the novel disease known as COVID-19 spread across the world, causing the World Health Organisation to characterise the outbreak as a pandemic on 11 March 2020.[1] Almost all countries have been affected by the pandemic, and in many places daily life was subject to strict restrictions. On Wednesday, 11 March 2020, the Danish government introduced

what would become the first national lockdown effective from Friday, 13 March 2020.[2]

From early on in the pandemic, reports of a distinct decline in the number of stroke-related admissions, ranging from 10% to 90%, emerged coming from the World Stroke Organization (WSO), with similar reports coming from the Danish Stroke Society.[3–6]

Stroke risk is largely determined by modifiable factors such as hypertension, physical inactivity, smoking, diet, and diabetes. No clear causal association between COVID-19 and the suspected drop in stroke-related admissions has been established.

The objective of this study was to analyse the number of stroke-related admissions to hospital and the number of patients treated with tissue-type plasminogen activators (tPA) and endovascular thrombectomy (EVT) before and during the first two waves of the COVID-19 pandemic, by analysing data gathered from electronic patient records. We hypothesised that our data would remain consistent with the reported findings from around the world, showing a reduced number of stroke-related admissions and tPA and EVT treatments coinciding with the beginning of the pandemic.

2 | MATERIALS & METHODS

Data for the study were retrieved with the SlicerDicer tool in the electronic patient records system, Epic Sundhedsplatformen (Epic Systems Corporation, Verona, WI, United States of America, version November 2020), which is used by all public hospitals involved in the study.

2.1 | Study population

The study included data from the Capital Region of Denmark and the Region of Zealand, which cover an area with a population of 2.70 million.[7] All patients presenting with signs of stroke or TIA are evaluated to determine if further examination at a stroke centre is needed. At the stroke centre, targeted diagnostic work-up, including neuroimaging, is used to assess the patient's eligibility for intravenous tPA treatment and/or EVT, both of which are considered key treatment options to improve outcome after ischaemic stroke.[8] No alterations were made in existing stroke treatment pathways during the study period.

For this study, we identified patients based on the following criteria: (1) aged 18 years or older; (2) admission to departments involved in the study (Capital Region of Denmark; four departments of neurology, one department of neurosurgery and Region of Zealand; one department of neurology and one department of geriatrics); (3) Diagnosis-Related Group (DRG) codes for subarachnoid haemorrhage (SAH/DI60), intracerebral haemorrhage (ICH/DI61), ischaemic stroke (IS/DI63), TIA (DG459) or unspecified neurological symptoms (stroke mimics/DR298A). The stroke mimic code (DR298A) is used when no distinct cause of the symptoms or diagnosis is found. Thus, cases in which symptoms are found to arise from, for example, Todd's paralysis, tumours, migraine, and metabolic causes, are not covered by this DRG code.

All departments involved in the study have designated stroke units, which are an integral part of stroke treatment according to both Danish and international guidelines.[9,10] Furthermore, two departments perform tPA treatment in the Capital Region of Denmark, while one department performs all tPA treatment in the Region of Zealand. A single department in the Capital Region of Denmark carries out EVT treatment in cases of large vessel occlusion for both regions. Reports have shown that >90% of stroke patients are admitted to a stroke unit on the day of stroke onset. All departments treating patients with acute stroke are required by law to prospectively report data to the Danish Stroke Registry (DSR),[11] and the latest yearly report from The Danish Clinical Quality Program–National Clinical Registries–showed a very high level of agreement between and DSR and The National Patient Registry (LPR) from which SlicerDicer draws its data.

2.2 | Study period

The study period covered 1 January 2019–28 February 2021. We divided the study period into four parts. 'Pre-COVID' data covered the date interval from 1 January 2019–12 March 2020 and provided a baseline for patient numbers. The widespread government mandated shutdown of society, effective from Friday, 13 March, marked the start of the pandemic and the first lockdown period in Denmark, 'Lockdown 1', which covered 13 March 2020–17 May 2020.[2] On 18 May 2020, society had reopened to such an extent that we defined it as the end of the first lockdown and the beginning of an intermission period, 'Intermission', which covered 18 May 2020–10 December 2020. The intermission period ended with reinstatement of restrictions and the transition into a second lockdown effective from 11 December 2020, 'Lockdown 2', which lasted the remainder of the study period and covered 11 December 2020–28 February 2021.

2.3 | Search queries

A series of eight search queries were developed to obtain the number of admitted patients from the departments involved in the study from SlicerDicer. Separate queries were made for the five prespecified DRG codes (DI60, DI61, DI63, DG459, and DR298) as well as one query containing both the intracerebral haemorrhage (DI61) and ischaemic stroke (DI63) codes, returning the number of 'all strokes'. Two queries contained both the code for ischaemic stroke (DI63) and an added criterion denoting either tPA (BOHA1) or EVT (KAAL11) respectively.

In addition to the overall number of patients, the number of male and female patients was recorded separately, as well as the mean age of patients using the subgroups tool in SlicerDicer. Search results were returned for either 7 days intervals (DI61, DI63, all strokes (DI61 + DI63), DG459, DR298A, and tPA) or

1 month intervals (DI60 and EVT). In some cases, the date intervals were adjusted to accommodate the beginning and end of the study periods. All search criteria were linked to the same event (hospitalisation) and the diagnosis criterion was linked to the unique time point of diagnosis in order to minimise the risk of duplicates due to patient transfers between hospitals. The search query outline is illustrated in Figure 1.

To accommodate potential registration delays for the procedures, the final data extraction was performed at least 1 month after the last day of the study period.

In Denmark, there is a national consensus among stroke physicians that patients with ischaemic stroke (DI63), who experience complete resolution of symptoms following tPA or EVT, should maintain their diagnosis, opposed to having it changed to TIA (DG459), as this is an expression of successful revascularization treatment and not a misdiagnosis. Therefore, the search queries for tPA and EVT patients were coupled only to the ischaemic stroke (DI63) DRG code. At all tPA and EVT capable centres included in this study, great efforts are made to ensure correct DRG coding.

2.4 | Analysis of data

To analyse changes in patient numbers during the study period, the weekly mean number of admitted patients was calculated for each of the DRG codes in each of the time periods. Normality of data was

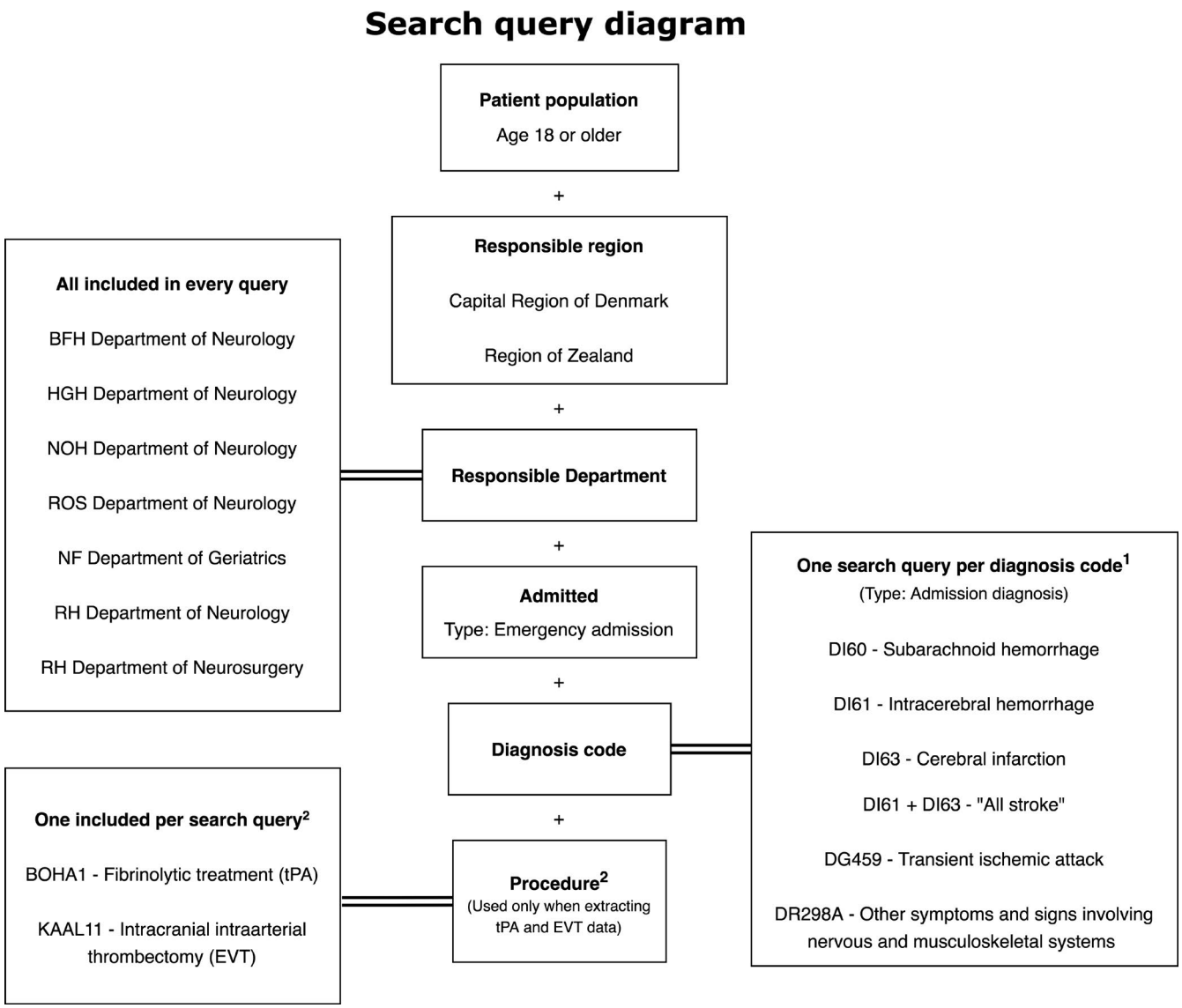

FIGURE 1 A diagram depicting the search query used for data collection in SlicerDicer. [1]Separate search queries were constructed for each individual diagnosis code (DI60, DI61, DI63, DG459, and DR298), as well as one containing both DRG codes DI61 and DI63. [2]The criterion 'Procedure' was added only in conjunction with diagnosis code DI63 and only when extracting tPA and EVT data. Abbreviations: BFH, Copenhagen University Hospital–Bispebjerg and Frederiksberg; EVT, Endovascular thrombectomy; HGH, Copenhagen University Hospital–Herlev Gentofte; NF, Nykøbing Falster Hospital; NOH, Copenhagen University Hospital–Nordsjællands Hospital; RH, Copenhagen University Hospital–Rigshospitalet; ROS, Zealand University Hospital; tPA, Tissue-type plasminogen activators

TABLE 1 Total number of patients, number and percentage of male patients and mean age of patients for each diagnosis and procedure

		Pre-COVID	Lockdown 1	Intermission	Lockdown 2
SAH (DI60)	N total	249	26	96	48
	N male (%)	102 (41.0%)	15 (57.7%)	35 (36.5%)	25 (52.1%)
	Mean age (SD)	60.9 (2.5)	62.0 (5.2)	60.9 (5.1)	62.0 (2.0)
ICH (DI61)	N total	956	115	462	175
	N male (%)	516 (54.0%)	67 (58.3%)	237 (51.3%)	94 (53.7%)
	Mean age (SD)	71.9 (4.2)	67.8 (4.6)	71.8 (3.2)	72.1 (2.7)
IS (DI63)	N total	5534	777	2913	1105
	N male (%)	3133 (56.6%)	414 (53.3%)	1633 (56.1%)	642 (58.1%)
	Mean age (SD)	72.5 (1.6)	71.3 (1.6)	72.3 (1.5)	72.8 (1.3)
All strokes (DI61 + DI63)	N total	6490	892	3375	1280
	N male (%)	3649 (56.2%)	481 (53.9%)	1870 (55.4%)	736 (57.5%)
	Mean age (SD)	72.2 (2.3)	70.5 (1.7)	72.3 (2.1)	73.1 (2.7)
TIA (DG459)	N total	2157	320	1108	433
	N male (%)	1149 (53.3%)	185 (57.8%)	603 (54.4%)	230 (53.1%)
	Mean age (SD)	71.7 (2.3)	71.4 (1.5)	71.5 (1.8)	73.6 (1.3)
Stroke mimics (DR298A)	N total	4703	439	1577	495
	N male (%)	2056 (43.7%)	178 (40.5%)	675 (42.8%)	249 (50.3%)
	Mean age (SD)	57.1 (1.9)	58.9 (2.8)	55.6 (3.3)	56.8 (2.7)
tPA	N total	1132	178	530	209
	N male (%)	647 (57.2%)	97 (54.5%)	315 (59.4%)	133 (63.6%)
	Mean age (SD)	71.1 (4.1)	71.0 (2.5)	70.9 (3.6)	71.3 (2.5)
EVT	N total	298	46	152	56
	N male (%)	162 (54.4%)	25 (54.3%)	79 (52.0%)	27 (48.2%)
	Mean age (SD)	70.7 (3.0)	72.7 (3.2)	70.0 (4.2)	72.3 (3.2)

Abbreviations: EVT, Endovascular thrombectomy; ICH, Intracerebral haemorrhage; IS, Ischaemic stroke; SAH, Subarachnoid haemorrhage; SD, Standard deviation; TIA, Transient ischaemic attack; tPA, Tissue-type plasminogen activators.

evaluated using Shapiro–Wilk's tests and two-sample Student's *t*-tests and Mann–Whitney *U*-tests were employed to compare patient numbers between different time periods where appropriate. Three separate analyses were performed: (1) comparing pre-COVID data to the first lockdown period (Pre-COVID vs. Lockdown 1); (2) comparing the intermission period to the second lockdown (Intermission vs. Lockdown 2); (3) comparing pre-COVID data to data from all 'COVID time periods' (Pre-COVID vs. Lockdown 1 + Intermission +Lockdown 2). Likewise, weekly mean numbers of admitted male and female patients as well as the mean age of all patients were compared between different time periods for each DRG code as described above.

Results are presented as patient numbers (N), percentages (%) as well as mean ages and weekly mean patient numbers with standard deviations (SD). Differences in weekly means as well as a 95% confidence intervals (95% CI) are also listed. For each DRG code and procedure, the number of patients is plotted in bar charts in monthly (DI60 and EVT) or 7 days (DI61, DI63, all stroke (DI61 + DI63), DG459, DR298A, and tPA) intervals. Statistical significance was reached when the *p*-value was below .05 ($p < .05$).

Statistical analysis was performed using the R statistical software package (version 4.0.2) and the RStudio development environment (version 1.3.1056).

2.5 | Ethics

The Ethics Committee of the Capital Region of Denmark waives approval for registry-based studies on aggregated anonymised data (Section 14.2 of the Committee Act. 2; http://www.en.nvk.dk/).

3 | RESULTS

Our search queries returned a combined total of 23,688 patients across the five DRG codes. Of the total number of patients, 12,238 were male, corresponding to 51.7%. Of the total number of patients, 2049 patients were treated with tPA of whom 1192 (58.2%) were male, and 552 patients were treated with EVT of whom 293 (53.1%) were male. Results are presented in more detail in Tables 1 and 2.

TABLE 2 Mean number of weekly admitted patients and standard deviation (SD) for each part of the study period, including a combined 'All COVID' comprising data from the three COVID periods (Lockdown 1, Intermission and Lockdown 2)

Mean number of weekly admitted patients, N (SD)						
		Pre-COVID	Lockdown 1	Intermission	Lockdown 2	All COVID
SAH (DI60)	All	4.0 (1.1)	2.8 (0.5)	3.2 (1.0)	4.1 (1.0)	3.3 (1.0)
	Male	1.6 (0.7)	1.7 (0.5)	1.1 (0.8)	2.2 (0.1)	1.5 (0.8)
	Female	2.4 (1.0)	1.1 (0.3)	2.1 (0.7)	1.9 (0.9)	1.9 (0.7)
ICH (DI61)	All	15.3 (4.3)	12.8 (4.3)	15.6 (3.6)	15.7 (3.5)	15.1 (3.8)
	Male	8.3 (2.5)	7.0 (0.9)	7.9 (2.7)	8.1 (2.8)	7.8 (2.5)
	Female	7.0 (3.2)	5.8 (4.4)	7.7 (2.6)	7.6 (2.7)	7.3 (3.0)
IS (DI63)	All	88.6 (11.0)	81.4 (12.1)	98.1 (11.1)	96.0 (12.8)	94.8 (13.0)
	Male	50.2 (7.7)	42.8 (6.8)	55.2 (7.6)	56.4 (6.2)	53.3 (8.6)
	Female	38.5 (5.9)	38.6 (10.8)	42.9 (7.1)	39.6 (8.2)	41.5 (8.1)
All strokes (DI61 + DI63)	All	103.9 (12.9)	94.1 (12.8)	113.7 (11.6)	111.7 (14.9)	110.0 (14.2)
	Male	58.5 (8.5)	49.8 (6.6)	63.1 (9.1)	64.5 (7.0)	61.1 (9.7)
	Female	45.5 (7.2)	44.4 (11.3)	50.6 (6.2)	47.2 (9.9)	48.8 (8.3)
TIA (DG459)	All	34.6 (7.5)	34.1 (8.9)	37.4 (6.8)	37.5 (5.3)	36.9 (6.9)
	Male	18.4 (5.2)	19.8 (4.5)	20.4 (4.5)	20.0 (3.7)	20.2 (4.2)
	Female	16.1 (4.7)	15.6 (4.4)	17.0 (4.8)	17.5 (4.6)	16.9 (4.6)
Stroke mimics (DR298A)	All	75.4 (13.7)	45.3 (6.8)	53.2 (11.1)	42.6 (5.7)	49.6 (10.5)
	Male	33.1 (7.1)	18.6 (3.9)	22.9 (5.2)	21.3 (4.8)	21.9 (5.1)
	Female	42.3 (9.0)	26.6 (5.2)	29.9 (7.8)	21.3 (3.5)	27.5 (7.4)
tPA	All	18.2 (4.9)	18.5 (2.0)	17.8 (4.1)	18.2 (5.2)	18.0 (4.0)
	Male	10.4 (3.2)	10.0 (1.9)	10.8 (2.9)	11.4 (2.9)	10.8 (2.7)
	Female	7.8 (3.0)	8.5 (2.3)	7.1 (3.0)	6.8 (3.3)	7.3 (3.0)
EVT	All	4.9 (1.5)	4.8 (1.3)	4.8 (1.5)	4.7 (1.8)	4.8 (1.4)
	Male	2.7 (1.0)	2.5 (1.1)	2.7 (0.8)	2.3 (0.6)	2.5 (0.8)
	Female	2.2 (0.7)	2.2 (0.3)	2.2 (1.1)	2.4 (1.2)	2.2 (1.0)

Abbreviations: EVT, Endovascular thrombectomy; ICH, Intracerebral haemorrhage; IS, Ischaemic stroke; SAH, Subarachnoid haemorrhage; SD, Standard deviation; TIA, Transient ischaemic attack; tPA, Tissue-type plasminogen activators.

The patient numbers for each of the diagnose codes during the study period are plotted as bar charts in Figure 2 A-H.

3.1 | Analysis 1: Pre-COVID versus lockdown 1

When analysing patient numbers, we found that mean weekly patient numbers (pts/week) for all stroke (DI61 + DI63) were significantly lower during Lockdown 1 than pre-COVID (−9.8 pts/week, 95% CI: −19.4; −0.2, $p = .046$). Similarly, numbers of patients with stroke mimics (DR298A) were significantly lower during Lockdown 1 than pre-COVID (−30.1 pts/week, 95% CI: −39.9; −20.3, $p < .001$). Our results also indicated lower patient numbers during Lockdown 1 for SAH (DI60), intracerebral haemorrhage (DI61), and ischaemic stroke (DI63); however, in all three cases, the differences failed to reach statistical significance (See Table 3).

For male patients, a similar pattern emerged, showing significantly lower patient numbers for all stroke (DI61 + DI63) and stroke mimics (DR298A), as well as significantly fewer patients with ischaemic stroke (DI63). For female patients, SAH (DI60) and stroke mimics (DR298A) showed significantly lower patient numbers. Results are presented in more detail in Table 3.

3.2 | Analysis 2: Intermission versus lockdown 2

The comparison of the Intermission period with Lockdown 2 showed a significantly lower total number of patients with stroke mimics (DR298A) (−10.6 pts/week, 95% CI: −18.1; −3.1, $p = .007$) as well as of female patients (−8.6 pts/week, 95% CI: −12.0; −3.0, $p = .001$) during Lockdown 2 compared to the Intermission. Furthermore, the number of male patients with SAH (DI60) was found to be higher during Lockdown 2 than that of the Intermission (+1.1 pts/week, 95% CI: +0.0; +2.1, $p = .0495$), and the total number of SAHs (DI60) was higher (+0.8 pts/week, 95% CI: −0.7; +2.4, $p = .256$) but did not reach significance. Results are presented in more detail in Table 3.

3.3 | Analysis 3: Pre-COVID versus All COVID (lockdown 1 + intermission +lockdown 2)

The analysis of all pre-COVID versus All COVID data showed significantly fewer patients with stroke mimics (DR298A) in the COVID period for all patients (−25.8 pts/week, 95% CI: −31.0; −22.0, $p < .001$), for male patients (−11.2 pts/week, 95% CI: −13.7; −8.8, $p < .001$), and for female patients (−14.8 pts/week, 95% CI: −18.0; −12.0, $p < .001$).

Despite the findings of lower patient numbers with all stroke (DI61 + DI63) during Lockdown 1, a significantly higher number of patients with all stroke (DI61 + DI63) was found in the collective 'all COVID' period for total patients (+6.0 pts/week, 95% CI: +0.9; +11.2, $p = .023$) and female patients (+3.3 pts/week, 95% CI: +0.4; +6.3, $p = .026$), while the difference in male patients did not reach significance (+2.7 pts/week, 95% CI: −0.8; +6.2, $p = .129$). Similarly, ischaemic stroke (DI63) showed a significant increase in the number of patients for total patients (+6.2 pts/week, 95% CI: +1.6; +10.7, $p = .009$), for male patients (+3.2 pts/week, 95% CI: +0.1; +6.3, $p = .045$), and for female patients (+3.0 pts/week, 95% CI: +0.3; +5.6, $p = .028$). Results are presented in more detail in Table 3.

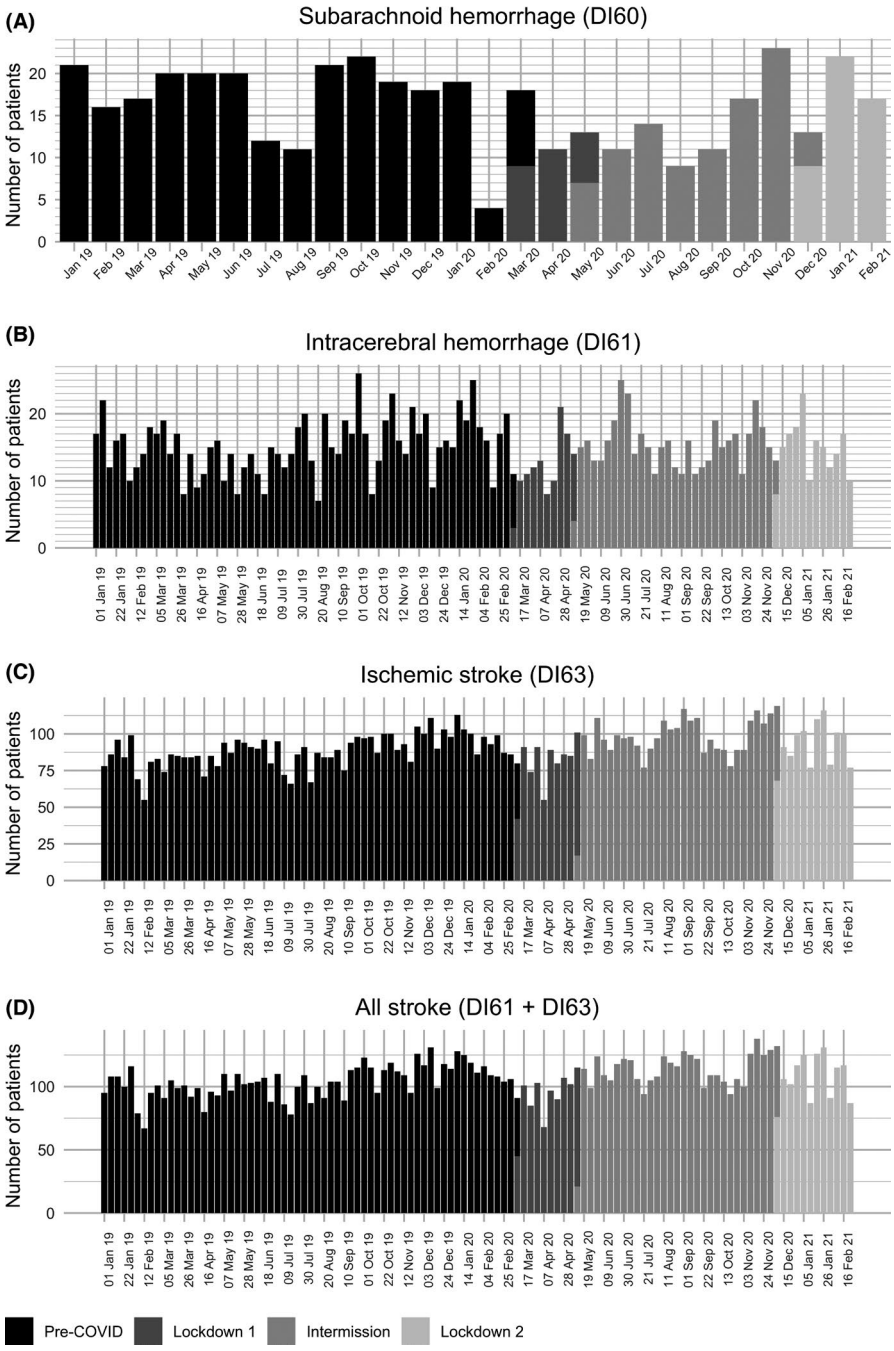

FIGURE 2 A–D Weekly and monthly patient volumes for each diagnosis. E–H Weekly and monthly patient volumes for each diagnosis

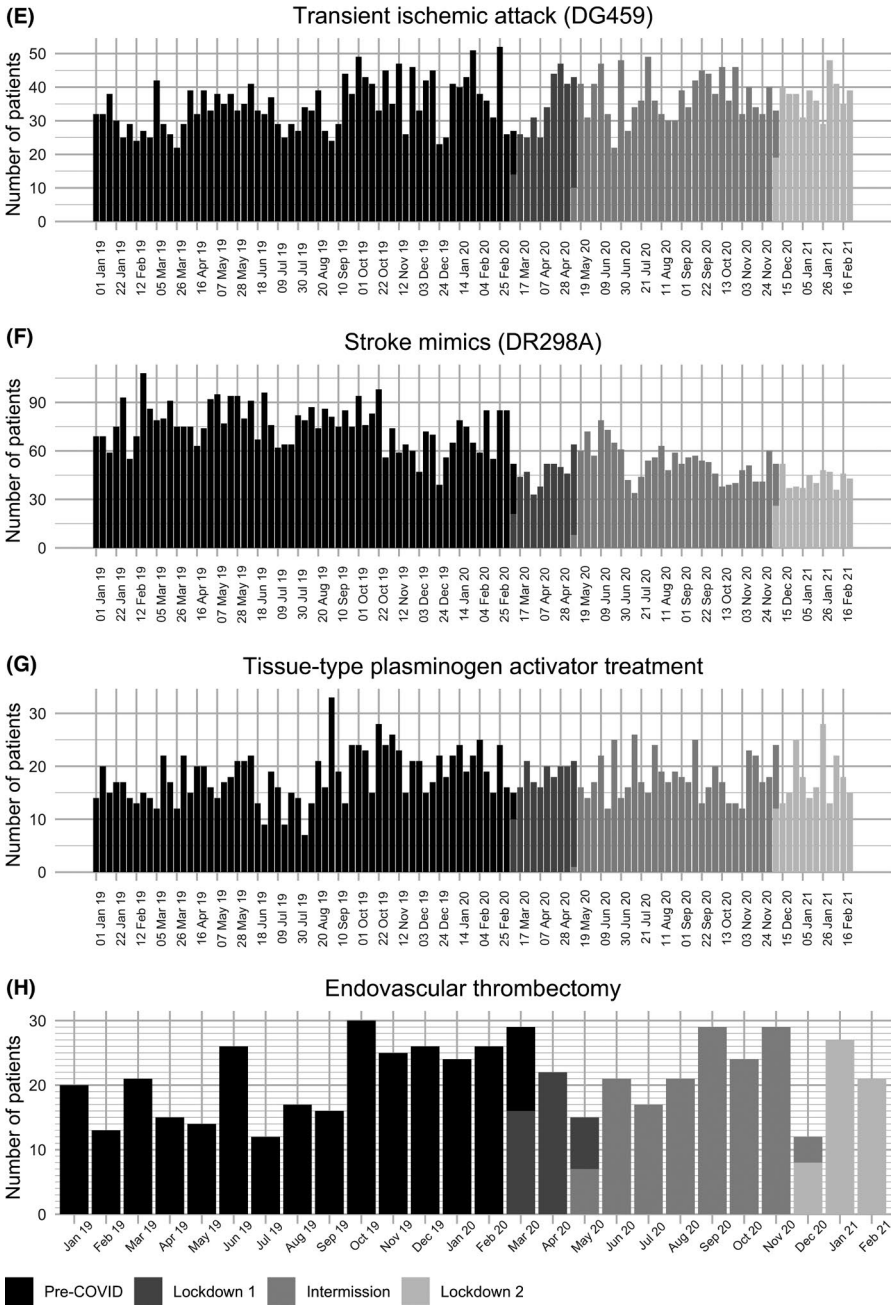

FIGURE 2 (Continued)

3.4 | Variation in mean age of patients

Analysis of patient mean age for each of the diagnoses and the procedures showed slight but significant differences in mean age with patients being slightly younger during Lockdown 1 compared to pre-COVID for ischaemic stroke (DI63) (71.5 vs. 72.5, $p = .038$) and slightly older for stroke mimics (DR298A) (58.9 vs. 57.1, $p = .022$). Likewise, patients with TIA (DG459) were slightly older during Lockdown 2 than during Intermission (73.6 vs. 71.5, $p = .002$) (see Table 1 and Appendix 1, Table S1).

4 | DISCUSSION

This study found that weekly mean patient numbers for all stroke (DI61 + DI63) and stroke mimics (DR298A) were lower during Lockdown 1 than pre-COVID, with the difference in all stroke being caused mainly by a decrease in male patients. The results show lower numbers of female patients with SAH (DI60) and lower numbers of male patients with ischaemic stroke (DI63) during Lockdown 1. The data suggest a drop in the number of intracerebral haemorrhage (DI61); however, this failed to reach statistical significance.

TABLE 3 Results of the three analyses comparing different parts of the study period

		Analysis 1 Pre-COVID vs. Lockdown 1		Analysis 2 Intermission vs. Lockdown 2		Analysis 3 Pre-COVID vs. All COVID	
		Difference in mean [95% CI]	*p*	Difference in mean [95% CI]	*p*	Difference in mean [95% CI]	*p*
SAH (DI60)	All	−1.2 [−2.33; 0.08]	.058	0.8 [−0.7; 2.4]	.256	−0.7 [−1.5; 0.1]	.082
	Male	0.0 [−0.9; 1.0]	.941	1.1 [0.0; 2.1]	.0495	−0.2 [−0.9; 0.4]	.631
	Female	−1.3 [−2.5; −0.1]	.039	−0.2 [−1.3; 0.9]	.661	−0.5 [−1.2; 0.1]	.110
ICH (DI61)	All	−2.5 [−5.8; 0.7]	.123	0.1 [−2.0; 3.0]	.859	−0.1 [−1.7; 1.4]	.859
	Male	−1.3 [−3.1; 0.5]	.148	0.2 [−2.0; 3.0]	871	−0.5 [−1.5; 0.5]	288
	Female	−1.2 [−3.8; 1.3]	.334	−0.1 [−2.0; 1.9]	.926	0.4 [−1.0; 2.0]	.451
IS (DI63)	All	−7.3 [−15.6; 1.1]	.087	−2.1 [−10.7; 6.5]	.623	6.2 [1.6; 10.7]	.009
	Male	−7.4 [−13.1; −1.7]	.012	1.2 [−4.2; 6.6]	659	3.2 [0.1; 6.3]	.045
	Female	0.1 [−4.8; 5.1]	.955	−3.3 [−8.8; 2.2]	.232	3.0 [0.3; 5.6]	.028
All strokes (DI61 + DI63)	All	−9.8 [−19.4; −0.2]	.046	−2.0 [−11.3; 7.2]	.660	6.0 [0.9; 11.2]	.023
	Male	−8.7 [−15.0; −2.4]	.007	1.4 [−5.0; 7.8]	.669	2.7 [−0.8; 6.2]	.129
	Female	−1.1 [−6.9; 4.7]	.707	−3.4 [−8.8; 2.0]	.214	3.3 [0.4; 6.3]	.026
TIA (DG459)	All	−0.5 [−7.0; 6.0]	.846	0.1 [−4.7; 4.9]	.960	2.3 [−0.5; 5.1]	.108
	Male	1.3 [−2.5; 5.2]	.497	−0.4 [−3.6; 2.8]	812	1.8 [−0.1; 3.6]	.062
	Female	−0.5 [−4.0; 3.0]	.769	0.5 [−3.0; 4.0]	.776	0.7 [−1.1; 2.5]	.425
Stroke mimics (DR298A)	All	−30.1 [−39.9; −20.3]	<.001	−10.6 [−18.1; −3.1]	.007	−25.8 [−31.0; −22.0]	<.001
	Male	−14.5 [−19.6; −9.3]	<.001	−1.6 [−5.4; 2.2]	.389	−11.2 [−13.7; −8.8]	<.001
	Female	−15.6 [−22.2; −9.1]	<.001	−8.6 [−12.0; −3.0]	.001	−14.8 [−18.0; −12.0]	<.001
tPA	All	0.3 [−3.2; 3.8]	.855	0.4 [−2.9; 3.6]	1.000	−0.2 [−1.9; 1.6]	.859
	Male	−0.4 [−2.7; 1.9]	.733	0.6 [−1.5; 2.8]	.547	0.4 [−1.0; 2.0]	.450
	Female	0.7 [−1.5; 3.0]	.519	−0.3 [−3.0; 2.0]	.733	−0.5 [−2.0; 1.0]	.367
EVT	All	−0.1 [−2.1; 1.9]	.907	−0.2 [−2.5; 2.2]	.873	−0.1 [−1.2; 1.0]	.861
	Male	−0.1 [−1.5; 1.2]	.844	−0.4 [−1.5; 0.8]	.485	−0.1 [−0.8; 0.6]	.752
	Female	−0.0 [−0.9; 0.9]	.974	0.2 [−1.6; 2.0]	.814	0.0 [−0.6; 0.7]	.976

Note: The table contains differences in mean number of weekly admitted patients as well as a 95% confidence interval (CI) for each analysis. Results of Student's *t*-tests/Mann–Whitney *U*-tests are listed as *p*-values.

Abbreviations: 95% CI, 95% Confidence interval; EVT, Endovascular thrombectomy; ICH, Intracerebral haemorrhage; IS, Ischaemic stroke; SAH, Subarachnoid haemorrhage; TIA, Transient ischaemic attack; tPA, Tissue-type plasminogen activators.

No differences were found in numbers of TIA (DG459) or patients treated with tPA or EVT during Lockdown 1 compared to pre-COVID data.

These findings are consistent with the earliest reports of declining numbers of stroke and TIA-related admissions, and other more recent studies have also reported a decrease in the number of patients presenting with ischaemic stroke during COVID-19. Furthermore, a number of studies, which did not distinguish between stroke subtypes, report a reduced number of total stroke admissions.[3,5,6,12–16]

Decreases in overall patient numbers with ischaemic stroke (DI63) and all stroke (DI61 + DI63) were in this study found to be caused by lower numbers of male patients, which was not previously identified in the other studies.

Despite the results showing slight variations in patients' mean age between time periods for some of the DRG codes, the magnitude of the differences is likely clinically insignificant and also does not seem to suggest a consistent trend of either older or younger patients during COVID-19.

When comparing the Intermission period to Lockdown 2, we found a lower weekly number of patients with stroke mimics (DR298A) during Lockdown 2, and while our results suggested a higher number of SAHs (DI60) during Lockdown 2, this difference only barely reached significance for male patients. Results for the other DRG codes showed no differences.

When pre-COVID data were compared to all COVID data (Lockdown 1 +Intermission +Lockdown 2), we found the number of patients with all stroke (DI61 + DI63) to be significantly higher

during the COVID-19 periods. The results show this to be caused by an increase in ischaemic stroke (DI63) numbers while ICH (DI61) remained unchanged. Numbers of stroke mimics (DR298A) remained lower throughout the COVID-19 periods. The remaining DRG codes showed no differences between pre-COVID and COVID-19 periods. Likewise, the number of patients treated with tPA or EVT remained unchanged.

The unexpected finding of increased patient numbers with all stroke (DI61 + DI63) caused by a rise in numbers of ischaemic stroke (DI63) in the collective COVID-19 periods suggests that patient volumes did not only return to pre-COVID levels but also increased further following Lockdown 1. This is evident in Table 2, which shows markedly higher intakes of ischaemic stroke (DI63) patients during the Intermission and Lockdown 2 periods as compared to pre-COVID and Lockdown 1. Few studies examining the period following the first wave of the pandemic have been published, and none have included as long a post-lockdown period as the one in this study. The previous studies found stroke volumes to remain low or return to pre-COVID levels within the first 2 months.[17,18] This study is currently the most extensive in terms of study period, and also the first to report increased volumes of ischaemic stroke (DI63) and all stroke (DI61 + DI63) following the first wave of the pandemic.

The scope of this study did not include data on stroke severity. Consequently, we cannot draw final conclusions as to whether the observed transient decline during Lockdown 1 and subsequent rise in stroke admissions comprise mild and severe stroke presentations equally.

A large American study reported a decrease in the total volume of stroke patients during the pandemic with an increased proportion of more severe strokes, indicating that the decrease in total volume was brought on mainly by a decrease in mild stroke presentations.[19] In contrast, other studies have not identified differences in stroke severity during the pandemic.[14,20] Since tPA and EVT rates were not found to fluctuate in this study, it may be hypothesized that the changes in stroke volumes were due to mild stroke presentations. However, the size of the study population may have also limited our analyses' ability to detect differences in revascularization treatments, and it is possible that an analysis based on a larger cohort would have been able to detect smaller fluctuations in tPA and EVT volumes if present.

The finding of constant tPA and EVT rates is similar to that of some studies,[15,16] while others report reductions in patients receiving tPA and/or EVT.[12,14,20] The ability to maintain treatment activity might in part have been determined by the regional severity of the pandemic and availability of resources for COVID-19 management. Reports from Italy and France have described how the most severely affected regions have had to drastically reorganize stroke treatment pathways. In the Italian region of Lombardy, a large number of stroke centres were converted into COVID-19 centres to cope with COVID patient loads early on in the pandemic.[21,22] In contrast, Denmark has been affected relatively mildly by the COVID pandemic resulting in relatively few alterations in existing stroke treatment pathways. We might therefore find tPA and EVT to remain stable because the stroke centres in our study have had adequate resources to uphold their usual treatment activity.

The cause of the reduced stroke volumes reported globally remains unknown. Similar reductions have been reported for patients presenting with acute myocardial infarction, extremely premature birth rates, and overall emergency department visits, suggesting that the phenomenon is not unique to stroke.[23–25]

There is no reason to assume that COVID-19 itself reduces the risk of thromboembolic diseases such as ischaemic stroke or TIA. On the contrary, studies have found increased stroke risk related to respiratory infections,[26–28] and one study found higher rates of cerebrovascular events in patients with increasing severity of COVID-19 infection.[29] Social distancing practices may have led to people spending more time alone, drastically increasing the risk of stroke symptoms going unnoticed by others. Thus, patients may not present with their symptoms, simply because they are never recognised. Another plausible factor is fear of contracting the infection when visiting a general practitioner or a hospital emergency department. This has been suggested in multiple studies investigating stroke in the COVID-19 era,[15,16,30] and the theory is corroborated by a Gallup Panel survey in which 83% of respondents expressed that they were moderately to very concerned about COVID-19 exposure at a general practitioner or emergency department.[31] Patient interviews regarding hospital usage revealed a similar aversion to hospitals, as they were seen as 'infectious reservoirs'.[25] As society and patients have adjusted to life with COVID-19, the 'shock-effect' and fear of infection may have partly worn off, leading to less apprehension towards seeking medical help. This could in part help explain the return to normal stroke patient numbers after Lockdown 1; however, it offers no explanation for the increase to even higher levels observed. It is well established that the risk of recurrent stroke is highest in the days immediately following the initial event.[32] If the transient decrease in stroke-related presentations during Lockdown 1 represented unrecognised (and, thus, untreated) strokes/TIAs, it could present a higher risk of recurrent strokes caused by the lack of preventive measures taken following the initial event. This phenomenon could contribute to the observed increase in ischaemic stroke (DI63) and all stroke (DI61 + DI63) volumes following Lockdown 1, although this hypothesis remains purely theoretical and would require further investigation to establish a causal association.

4.1 | Strengths and limitations

We retrieved data from the electronic patient records system, EPIC Sundhedsplatformen, used universally in the Capital Region of Denmark and the Region of Zealand. By doing so, we were able to obtain data from all patients treated at public hospitals during the study period. This, combined with the fact that all acute stroke treatment in Denmark is carried out by the public hospital system, means that our data effectively cover all acute stroke admissions. The use of the DR298A DRG code for stroke mimics may lead to exclusion of other conditions initially mimicking stroke, such as Todd's

paralysis, tumours, migraine, and metabolic causes, which are coded with other DRG codes. Consequently, a systematic underestimation of the number of patients with stroke mimics is to be expected with this approach. However, we have no reason to suspect changes in coding practices or in the distribution of conditions mimicking stroke (DR298A and others) during the study period. The extent of underestimation should, therefore, be equal throughout the study period allowing the decrease in DR298A to be indicative of a decrease in all stroke mimics. This assumption is, however, subject to uncertainty, which poses a limitation to the analysis.

In this study, several hypotheses were generated leading to multiple statistical comparisons, thus increasing the risk of type I errors. Given the study's broad and exploratory nature, this risk was deemed acceptable; however, it is important to bear this limitation in mind when interpreting the results. The results highlight important trends; yet, they are not suited to draw definitive conclusions as to causality.

Having a continuous study period could potentially make our analysis sensitive to seasonal variations in stroke numbers. The role of seasonal variations in stroke has been investigated, and while some studies failed to show significant variations,[33] others have found stroke numbers to peak in winter and spring, and be low during summer, which was supported by a meta-analysis that found evidence of numbers peaking in winter and decreasing during the summer.[34–36] However, in this study, a pre-COVID baseline level of patient numbers was used that covered all seasons, thereby minimising the risk of confounding by seasonal variations.

5 | CONCLUSIONS

In this study, a transient reduction in weekly patient numbers was found with all stroke (DI61 + DI63) and stroke mimics (DR298A) during the first lockdown. The results indicate that the same might be the case for SAH (DI60), intracerebral haemorrhage (DI61), and ischaemic stroke (DI63). The cause of this decline remains unknown but might be founded in apprehension to seek medical assistance due to fear of exposure to the virus in the hospital, or failure to recognize stroke symptoms amid social distancing practices. In contrast, the number of TIAs (DG459) and patients treated with tPA and EVT remained constant throughout the entire study period.

This study also found increased numbers of patients with ischaemic stroke (DI63) and all stroke (DI61 + DI63) in the time following the first lockdown (i.e., the first wave of the pandemic). Such an increase has not previously been reported and no studies have so far included data from such a long time period following the first lockdown. The causality between COVID-19 and the post-lockdown increase in stroke is unknown but may relate to an under-detection of strokes and subsequent lack of preventive measures during the first lockdown. This study underlines the need for a robust organization of stroke care facilitating access to care also when the healthcare system is under pressure.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data from SlicerDicer used in this study are available from the corresponding author upon reasonable request.

ORCID

Nicolas Drenck https://orcid.org/0000-0001-7652-5311

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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