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ABSTRACT

Objectives An increased risk of stroke has been reported among patients with COVID-19 caused by SARS-CoV-2. We aimed to investigate the nationwide prevalence of SARS-CoV-2 among patients with acute ischaemic stroke and to study the impact on stroke severity, quality of care and mortality on an individual patient level.

Design This was a nationwide register-based cohort study.

Setting We used data from several Danish registers which were linked at an individual patient level using the unique civil registration number assigned to all Danish citizens. Patients were identified from the Danish Stroke Registry and information on SARS-CoV-2 infection status was collected from the Danish National COVID-19 Registry. Concurrent SARS-CoV-2 infection was defined as a positive PCR test within 31 days prior to, and 1 day after, stroke admission. Information on comorbidity was collected from the Danish National Patient Registry and information on vital status was collected from the Danish Civil Registration System.

Participants A total of 11 502 patients admitted with acute ischaemic stroke from 10 March 2020 to 31 May 2021 were included in the study.

Results Among the included patients, the majority (84.6%) were tested for SARS-CoV-2, but only 68 had a positive test. These patients were more prone to have atrial fibrillation and were more often treated with reperfusion therapy. They had a significantly increased risk of severe stroke (adjusted relative risk (aRR) 1.93, 95% CI: 1.22 to 3.04) and a significantly increased 30-day mortality risk (aRR 2.29, 95% CI: 1.19 to 4.39). There was no difference in the proportion of patients fulfilling relevant performance measures on quality of care.

Conclusion In this nationwide study, only 0.6% of patients with acute ischaemic stroke were tested positive for a concurrent SARS-CoV-2 infection. The patients with SARS-CoV-2 presented with more severe strokes.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Nationwide study including all admitted patients with acute ischaemic stroke.
⇒ Comprehensive testing for SARS-CoV-2 in the study period.
⇒ High-quality register data linked at an individual patient level.
⇒ A low proportion of positive tests affects the statistical power in the analyses of impact of infection.
⇒ Information on stroke aetiology was not available.

INTRODUCTION

Severe COVID-19 has been associated with an increased risk of stroke,[1 2] and a higher risk of ischaemic stroke has been found in patients who have recovered from COVID-19.[3] COVID-19 has also been associated with higher rates of complications, more severe stroke, worse clinical outcomes and mortality, in patients with acute ischaemic stroke (AIS) undergoing revascularisation therapy.[4 5] These associations may be caused by a different stroke pathophysiology in COVID-19-related stroke.[2] COVID-19 may cause a systemic inflammatory response which increases the risk of venous thromboembolism and may increase the risk of thrombus generation in the left atrium in patients with atrial fibrillation.[6] Further, in large artery atherosclerotic disease, the inflammation may decrease the stability of atherosclerotic plaques and make them more vulnerable to rupture.[7] COVID-19 has also been seen to cause increased titres of lupus anticoagulant[8] which is associated with stroke risk.

A number of studies have described features of patients with COVID-19 and infection with SARS-CoV-2 and concomitant AIS[9–11]; however, in stroke cohorts, only a smaller proportion of patients have been tested for SARS-CoV-2 and/or the studies have not been population based and without controls. Hence, data from nationwide population-based cohorts of patients with AIS with routine SARS-CoV-2 testing are lacking.

Previously, data from Danish national registers have shown that the overall quality of acute stroke care remained high with only minor fluctuations during the COVID-19 pandemic.[12] At the same time, stroke admission rates remained largely unchanged.[13] In the present study, we aimed to investigate the prevalence of positive coronavirus tests among patients with AIS in Denmark and whether SARS-CoV-2 status had an impact on stroke severity, quality of care and mortality.

METHODS

This was a nationwide register-based study with data collected from several Danish registers and linked at an individual level using the unique 10-digit civil registration number assigned to all Danish citizens. We were hence able to track the individual disease course of patients with AIS and a positive SARS-CoV-2 test.

Registries

Patients were identified from the Danish Stroke Registry (DSR) where registration of patients admitted with stroke and transient ischaemic attack (TIA) is mandatory for all treating hospital departments.[14] The registry holds information on data regarding demography, risk factors and treatment, but also stroke care performance measures relating to the quality of diagnosis, workup, treatment, care and early rehabilitation. The estimated completeness of registration is >90% and there is a high validity of the acute stroke diagnoses in the registry.[15]

Information on COVID-19 infection status was collected from the Danish National COVID-19 Registry administered by the Danish Health Data Authority.[16] The registry contains information on all individuals in Denmark tested with reverse transcriptase PCR for SARS-CoV-2.

Finally, information was collected from the Danish National Patient Registry, which holds information on all discharge diagnoses from non-psychiatric hospitals,[17] and from the Danish Civil Registration System, which keeps electronic records on vital and emigration status for all Danish citizens.[18]

Study population

From the DSR, we included patients admitted with first-ever AIS in the period of 10 March 2020–31 May 2021, and who were Danish residents at least 1 year prior to and 2 years after admission. The study period was chosen, as it correlates with the time from the first national lockdown to the point where available data from DSR were accessible.

Patient and public involvement

No patients or members of the public were involved in the design or conduct of the study.

SARS-CoV-2 status

Concurrent SARS-CoV-2 infection was defined as a positive PCR test within 31 days prior to stroke admission and until 1 day after admission. From 24 May 2020, all Danes had access to free testing regardless of symptoms and without referral from a healthcare professional. According to instructions from the Danish health authorities set out on 21 April 2020, all patients admitted to a hospital for more than 24 hours were required to have a SARS-CoV-2 PCR test. Online supplemental figure 1 shows the daily COVID-19 tests per 1000 people in Denmark as compared with the UK, Italy and the USA in our study period.[19]

Stroke severity, quality of care and mortality

Information on stroke severity at the time of admission, as measured on the Scandinavian Stroke Scale (SSS), was obtained from the DSR.[20] The scale ranges from 0 to 58, where 58 corresponds to normal neurological function. Severe stroke was defined as an SSS score <30.[21] Information on 30-day mortality was obtained from the Danish Civil Registration System and information on quality of care was obtained from the DSR using the registered stroke care performance measures covering acute and prophylactic treatment, carotid vessel imaging and early rehabilitation. For each patient, we calculated an opportunity-based score defined as the number of fulfilled performance measures divided by the number of relevant performance measures as well as an all or no score, with a score of 1 if all relevant performance measures were met and a score of 0 if not all relevant measures were met.[12 22] Mortality was all-cause mortality with information on vital status obtained from the Danish Civil Registration System.

Comorbidity and risk factors

We calculated the Charlson Comorbidity Index score for each patient based on discharge diagnoses from the Danish National Patient Registry.[23] A score of 0 was defined as no comorbidity, a score of 1 was defined as moderate comorbidity and a score of ≥2 was defined as severe comorbidity (see online supplemental table 1). Information on vascular risk factors including known or newly diagnosed diabetes, hypertension, peripheral arterial disease, smoking and atrial fibrillation as well as information on living arrangements (living alone, living with someone or 'other') was obtained from the DSR.

Statistical analyses

We performed a compared analysis between patients with AIS with a concurrent SARS-CoV-2 infection and patients with AIS without a concurrent infection. Risk ratios for severe stroke and 30-day mortality were estimated using Poisson regression analyses with robust variance estimation[24] and mean differences in the opportunity-based scores were estimated using linear regression. Analyses were adjusted for age, sex, comorbidity, quality of care and immigrant status using stabilised inverse probability of treatment weights to estimate average treatment effects. The statistical analyses were carried out using STATA V.17 (StataCorp).

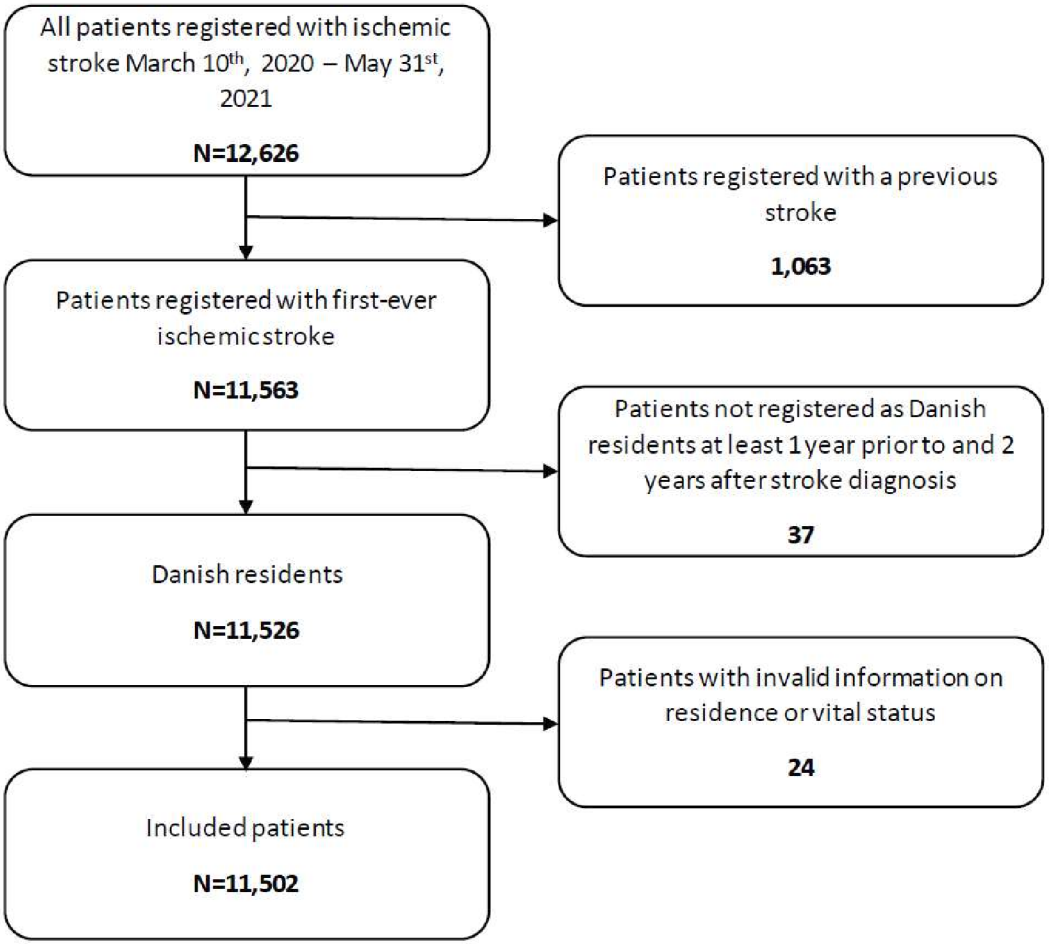

Figure 1 Patient inclusion flow chart.

RESULTS

In the study period, a total of 12 626 patients with AIS were admitted. After excluding patients with previous stroke, patients who were not Danish residents 1 year prior to stroke and 2 years after, and patients with invalid information on residence or vital status, a total of 11 502 patients were included in our analyses (figure 1).

Of the 11 502 included patients with AIS, 68 had a positive test for current SARS-CoV-2 infection. A total of 9735 patients (84.6%) were tested within 31 days prior to stroke admission and until 1 day after. A larger proportion of patients with SARS-CoV-2 were immigrants (14.7% vs 5.2%), had atrial fibrillation (25.0% vs 17.4%), were smokers (67.3% vs 62.2%), had a Charlson Comorbidity Index ≥2 (32.4% vs 27.4%) and presented with very severe stroke (13.2% vs 4.7%) (table 1).

For patients with a concurrent infection, there was a significantly increased mortality within 30 days after stroke admission with an adjusted relative risk (RR) of 2.29 (95% CI: 1.19 to 4.39) and a significantly increased risk of severe stroke with an adjusted RR of 1.93 (95% CI: 1.22 to 3.04). When further adjusting the mortality outcome for stroke severity, the increased mortality disappeared (adjusted RR of death 0.71 (95% CI: 0.31 to 1.60), p=0.62). There was no difference in quality of care between the patients with an adjusted mean difference in opportunity-based score of −0.1% (95% CI: −4.5% to 4.4%) (table 2).

Among the patients with SARS-CoV-2, more had reperfusion therapy with thrombolysis and thrombectomy. Fewer patients among those with SARS-CoV-2 were directly admitted to a stroke unit on the day of hospitalisation and fewer were assessed by an occupational or physiotherapist within 2 days of admission (table 3).

DISCUSSION

In this nationwide register-based study including 11 502 first-ever ischaemic stroke admissions from 10 March 2020 to 31 May 2021, we found a low prevalence of positive tests. Only 68 patients had a positive test corresponding to 0.6% of all patients admitted with AIS and 0.7% of the 9735 admitted patients registered with a PCR test result. Patients with a positive test were more often immigrants, more often had atrial fibrillation, were more often smokers and had more comorbidities in general. Further, patients with a positive SARS-CoV-2 test had more severe strokes, were more often treated with thrombolysis and thrombectomy, and had a higher risk of 30-day mortality.

Table 1 Characteristics of patients with AIS with concurrent SARS-CoV-2 infection as compared with patients with AIS without a concurrent infection or without a registered PCR test result

	Patients with no registered concurrent SARS-CoV-2 infection	Patients with concurrent SARS-CoV-2 infection
	N=11 434	N=68
Age, mean (SD)	74.2 (64.7–81.5)	74.7 (62.6–83.9)
Male, % (n)	56.6 (6477)	60.3 (41)
Immigrants, % (n)	5.2 (597)	14.7 (10)
Atrial fibrillation, % (n)	17.4 (1984)	25.0 (17)
Hypertension % (n)	58.7 (6677)	47.1 (32)
Diabetes, % (n)	16.7 (1906)	16.2 (11)
Charlson score, % (n)		
0	55.6 (6363)	54.4 (37)
1	17.0 (1941)	13.2 (9)
≥2	27.4 (3130)	32.4 (22)
Smoker, currently or in the past, % (n)	62.2 (6067)	67.3 (37)
Living arrangements, % (n)		
Living with someone	57.0 (6435)	59.7 (40)
Living alone	40.9 (4625)	*
Other	2.1 (237)	*
Prior acute myocardial infarction, % (n)	6.8 (771)	*
Peripheral arterial disease, % (n)	4.3 (477)	0.0 (0)
Stroke severity, % (n)		
Very severe	4.7 (532)	13.2 (9)
Severe	6.7 (768)	*
Moderate	18.2 (2078)	23.5 (16)
Mild	68.8 (7866)	50.0 (34)
Missing	1.7 (190)	*
Mortality, % (n)	5.9 (673)	11.8 (8)

*Omitted due to low numbers, N<5 (to avoid including personally identifiable data).
AIS, acute ischaemic stroke.

When adjusting the mortality outcome for stroke severity, there was no longer an increased risk of dying, indicating that stroke severity is a relatively strong mediator for the higher case fatality. There was no difference in the overall quality of care between patients with AIS with or without SARS-CoV-2.

Although the occurrence of AIS in patients with SARS-CoV-2 has been extensively studied, the prevalence of the infection among patients with AIS and its implications in a nationwide setting with routine testing independent of the presence of symptoms have not been investigated previously. In a nationwide

Table 2 Relative risk (RR) estimates and mean differences for outcomes among patients with AIS and concurrent SARS-CoV-2 infection as compared with patients with AIS without concurrent infection or without a registered PCR test result

	Estimates	Outcome counts	Adjusted estimates*
30-day mortality, RR (95% CI)	2.00 (1.04 to 3.85), p=0.10	681	2.29 (1.19 to 4.39), p=0.02
Severe stroke, RR (95% CI)	1.94 (1.24 to 3.04), p=0.01	1315	1.93 (1.22 to 3.04), p=0.01
Quality of care, opportunity-based score, MD, %	−2.4 (−7.3 to 2.5), p=0.25	–	−0.1 (−4.5 to 4.4), p=0.93

*30-day mortality and stroke severity were adjusted for age, sex and comorbidity. Quality of care was additionally adjusted for immigrant status.
AIS, acute ischaemic stroke; MD, mean difference.

Table 3 Proportions of patients with AIS and concurrent SARS-CoV-2 infection fulfilling the stroke care performance measures, as compared with patients with AIS and without a concurrent infection or without a registered PCR test result

	Proportion (%) and numbers (N) fulfilling the indicator	No concurrent infection N=11 434	Concurrent infection N=68
Opportunity-based score	% (±SD)	0.8 (±0.2)	0.8 (±0.2)
All or no score	% (N)	12.6 (1435)	17.6 (12)
Reperfusion therapy with EVT+IVT	% (N)	23.0 (2618)	27.9 (19)
Reperfusion therapy with EVT	% (N)	6.4 (725)	13.2 (9)
Reperfusion therapy with IVT	% (N)	21.6 (2457)	26.5 (18)
Door-to-needle <45 min (IVT)	% (N)	83.3 (1805)	*
Door-to-groin puncture <180 min (EVT)	% (N)	88.9 (638)	100.0 (9)
Admission to stroke unit on day of hospitalisation	% (N)	87.7 (10 010)	80.9 (55)
Platelet inhibitors (AIS without AFIB) ≤2 days after hospitalisation	% (N)	95.9 (8183)	*
Anticoagulation ≤14 days after hospitalisation (AIS/TIA with AFIB)	% (N)	94.1 (1509)	100.0 (13)
CT/MRI <6 hours from admission	% (N)	91.9 (9973)	*
Physiotherapy assessment ≤2 days after hospitalisation	% (N)	87.5 (7862)	68.8 (33)
Occupational therapy assessment ≤2 days after hospitalisation	% (N)	85.9 (7732)	72.0 (36)
Out-of-bed orders on day of admission	% (N)	87.0 (7893)	*
Nutritional screening ≤2 days after hospitalisation	% (N)	82.2 (8662)	87.9 (51)
Swallowing screen (indirect) on day of admission	% (N)	81.7 (7723)	83.7 (36)
Swallowing screen (direct) on day of admission	% (N)	79.4 (6884)	79.5 (31)
Carotid vessel imaging ≤2 days after hospitalisation	% (N)	95.5 (9319)	*

% indicates the proportion of patients fulfilling the indicator out of the number of patients for whom the indicator is relevant (eg, fulfilling the 'door-to-needle <45 min' indicator is only relevant for the patients receiving IVT).
*Omitted due to low numbers, N<5 (to avoid including personally identifiable data).
AFIB, atrial fibrillation; AIS, acute ischaemic stroke; EVT, endovascular treatment; IVT, intravenous thrombolysis; TIA, transient ischaemic attack.

study from Switzerland including 2341 patients with ischaemic stroke, 33% were tested for SARS-CoV-2 within 1 month before or after stroke onset. Among the included patients, 36 (1.5%) had had a positive test.[9] As a significant proportion of patients with SARS-CoV-2 infection may be asymptomatic, the impact of the infection in stroke is not necessarily sufficiently elucidated when only symptomatic COVID-19 patients are included. The strengths in our study include the large, nationwide dataset with the ability to link information on infection status to stroke outcome on an individual level and the fact that patients were tested independently of COVID-19 symptoms.

In our study period, the cumulative confirmed SARS-CoV-2 cases per million people were 47 929,[19] and the Danish population in the second quartile in 2021 was 5 843 347[25] which corresponds to a prevalence of positive SARS-CoV-2 cases in the general Danish population of 0.8%. The low prevalence of SARS-CoV-2 in this stroke cohort was somewhat unexpected given the previously described association between SARS-CoV-2 and an increased risk of AIS. One explanation for the low prevalence of positive SARS-CoV-2 tests in this stroke cohort could be a relatively high proportion of asymptomatic positive tests in the general population, compared with the routine testing of all admitted patients with AIS. Our data show that fewer patients with a positive SARS-CoV-2 test, as compared with patients with either a negative test or no registered test, were directly admitted to a stroke unit at the day of hospitalisation with stroke. It is not evident from our data, whether the patients with a positive test were admitted to a non-stroke unit due to symptoms of COVID-19 requiring treatment or whether the

information of a recent positive test at stroke symptom onset alone led to a primary admission at a non-stroke unit. It is also possible that patients with a positive test had an atypical stroke presentation, leading them to be admitted on a non-stroke department.

Knowledge on coronavirus infection status on a patient level did not influence care and the fulfilment of quality measures for patients with AIS admitted to a stroke unit. This is in line with previous results from a study on data from the DSR showing that the overall quality of care during the pandemic remained high.[12] Similar studies from other countries, including the USA and UK, also found that quality in stroke care was maintained and for some domains even improved.[26 27] This may, at least partly, be explained by lower admission rates. However, in Denmark, stroke admission rates remained unchanged during the pandemic.[13]

Given the low prevalence of patients with a positive SARS-CoV-2 test, we had low numbers in several of our outcomes, making censoring necessary. Data on COVID-19 vaccination were available, but due to the low numbers of patients with COVID-19, these data were omitted. We did not have information on stroke aetiology, but the findings that more patients with infection had thrombectomy and more had atrial fibrillation are in line with the systemic inflammatory response in COVID-19, potentially increasing the risk of thrombus formation in the left atrium and destabilising of atherosclerotic plaques.

Our study has limitations. Only patients hospitalised for their stroke were included which could have affected our results. In Denmark, patients with symptoms of stroke, also minor stroke, or TIA, are traditionally admitted to a hospital. Theoretically, patients with less prominent symptoms may have avoided hospitalisation during the pandemic, but a previous study using Danish national registers found that the stroke admission rates remained largely unchanged during the pandemic.[13] This reduces the risk of selection bias in the study. With 15.6% of the admitted patients not being registered with a PCR test result, it is possible that the prevalence of infection is underestimated. We report the results from the entire period, which must be seen in the light of the changing test strategies during the pandemic. Should there be patients with a SARS-CoV-2 infection among the patients who were not tested, it is likely that these patients would have been asymptomatic patients admitted before routine testing of all admitted patients. Another potential explanation is that the patients who were not tested had very short admissions or died before testing. In the case of the latter, infected but not tested patients would likely have drawn our results towards more conservative estimates. Further, even with an overall extensive testing, where 84.6% overall were tested, we found a low prevalence of SARS-CoV-2 among patients admitted with AIS. This would affect the statistical power; however, the statistically significant results support the observation of more severe stroke, higher mortality and higher reperfusion therapy rates among patients with a positive test. We have no information on the severity of the infection and cannot prove if symptomatic COVID-19 was associated with worse outcome. It is also possible that patients admitted with COVID-19 and subsequent devastating stroke were never transferred to a stroke unit and therefore not registered in the DSR. Finally, we do not have information on cause of death.

In conclusion, the prevalence of positive SARS-CoV-2 tests was very low among patients admitted with AIS in Denmark during the pandemic. Patients with a positive test had more comorbidities, more severe strokes, higher mortality and a higher reperfusion therapy rate but received the same quality of care when admitted to a stroke unit.

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Contributors JKM, RAB and CZS researched the literature and conceived the study. JNH oversaw the preparation of the statistical analysis plan and performed the data analyses. JKM, RAB, CZS, JNH, GA, CW and SPJ critically interpreted the data. JKM wrote the first draft of the manuscript. All authors critically interpreted the data. RAB, CZS, JNH, GA, CW and SPJ reviewed the manuscript and approved the final version of the manuscript. CZS acted as study guarantor.

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Competing interests None declared.

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Patient consent for publication Not applicable.

Ethics approval In Denmark, ethical approval and patient consent are not required for register-based research and neither was obtained for the present study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. The Danish Data Protection Agency can grant access to data to researchers from authorised institutions, through the Danish Health Authority. According to Danish data protection regulation, data cannot be shared publicly.

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