First-Ever Ischemic Stroke In Covid-19: How Is It Different? – A Stroke Registry-Based Study From South India

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Abstract

Background and Aims: Stroke associated with COVID-19 has been characterised in several multicentre retrospective studies and meta-analyses. However, they did not distinguish first-ever ischemic strokes (F-AIS). Therefore, we aimed to study the incidence, clinical characteristics, and outcomes of a cohort of F-AIS associated with COVID-19 during the first wave of the pandemic and compare this cohort with those of F-AIS without COVID-19, COVID-19 without stroke. We also sought to compare the stroke admissions and mechanisms during the pandemic and immediate prepandemic periods.

Methods: This is an Institute Stroke Registry-based study and a retrospective review of prospectively collected data. We classified subjects into five groups: 1) COVID-19-associated ischemic stroke (n-17); 2) ischemic stroke not associated with COVID-19 in the pandemic (n-71); 3) COVID-19 without stroke in the pandemic (n-75), 4) ischemic stroke during the immediate pre-pandemic phase (n-88); 5) non-stroke and non-COVID-19 in pandemic (n-75). We collected demographics, risk factors, admission-NIHSS, time interval between COVID-19 and stroke, in-hospital stroke, mechanism, large artery occlusion (LAO), duration of hospitalisation and 90-day mRS in stroke subjects. We assessed long-term outcomes in COVID-19-associated F-AIS. We collected COVID-19 severity, inflammatory and coagulation parameters in COVID-19 subjects. Multiple logistic regression was performed to identify the independent risk factors for the occurrence of F-AIS and 90-day stroke mortality.

Results: Of 1369 COVID-19 patients admitted during the pandemic, 17 (1.24%) developed F-AIS. Patients with COVID-19-associated F-AIS showed significantly higher NIHSS, 90-day mortality, unfavourable outcome and notably cryptogenic with LAO than those without COVID-19. Majority of COVID-19 stroke survivors had a favourable long-term outcome. COVID-19-associated F-AIS showed a significantly higher proportion of hypertension, diabetes, and chronic kidney disease, severe COVID-19 and had higher interleukin-6 and D-dimer values than those without stroke. COVID-19 was found to be an independent risk factor for F-AIS (RR 0.35; P<0.01) and 90-day mortality in stroke (RR 4.81; P-0.03). The pandemic period showed a significantly higher proportion of cryptogenic strokes.

Conclusion: COVID-19 is an independent risk factor for F-AIS, and incidence was 1.24%. Most patients of COVID-19-associated F-AIS had vascular risk factors and severe COVID-19. They had

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higher stroke severity and largely cryptogenic with LAO. They had higher inflammatory marker and coagulation abnormalities. They are five times at increased risk of death than those without COVID-19. However, those who survived had good long-term outcomes.

Keywords: **First-ever ischemic stroke, Corona virus disease 19, Hypercoagulability, Cryptogenic stroke, Large artery occlusion.**

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INTRODUCTION

Coronavirus disease -19 (COVID-19) is caused by highly infectious severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). India reported the first case of COVID-19 on 30 January 2020, and the disease peaked first in early September 2020 and later in May 2021[1]. Acute ischemic stroke is one of the earliest described neurological complication associated with COVID-19[2]. Many multicentre retrospective studies and meta-analyses described the features of stroke associated with COVID-19[3-6]. However, first-ever ischemic strokes (F-AIS) were not analysed independently. Moreover, studies that determined long-term outcomes and the causal association of COVID-19 and F-AIS are scant[7].

AIMS

The aims of this study are 1) to determine the incidence of F-AIS among the patients with COVID-19 during the first wave of pandemic; 2) to compare the clinical and radiological features, and outcomes between F-AIS associated with and without COVID-19; 3) to compare the clinical and laboratory parameters between COVID-19 with and without F-AIS; 4) to determine the differences, if any, in the mechanism of F-AIS in the prepandemic and pandemic periods; and 5) to study the causal relationship between SARS-CoV2 infection and F-AIS.

METHODS

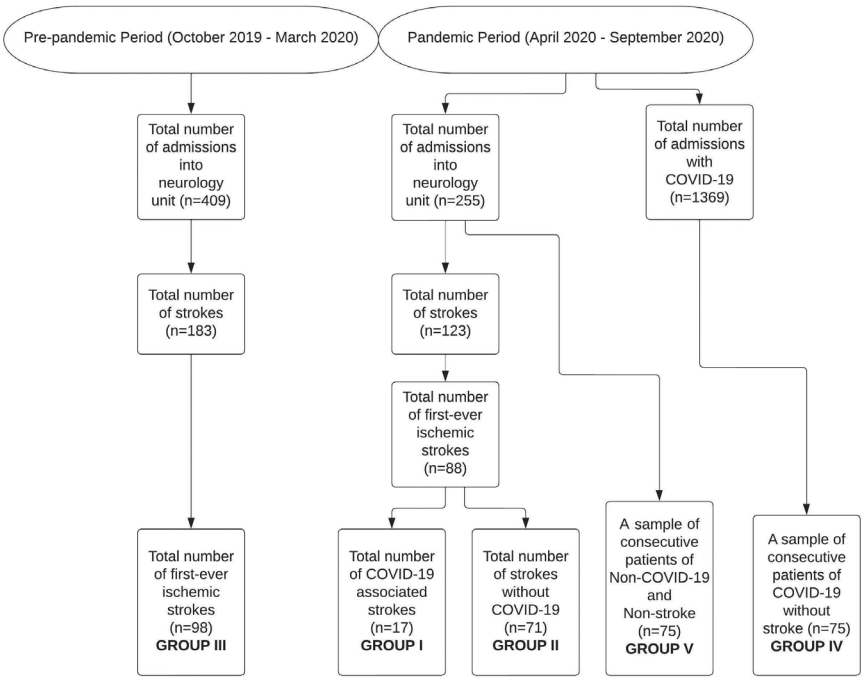
This study is an Institute Stroke Registry-based study and a retrospective review of prospectively collected data. The study period was between October 2019 and September 2020, and the Institutional Ethics Committee approved the study (Reference number - IEC/CARE/20837/2020/IIS). The study was conducted following the Declaration of Helsinki Ethical principles and Good Clinical Practices.

Working definitions

Time periods were defined as follows - 1) Pandemic period (first wave) April 2020 – September 2020; and 2) Pre-pandemic period October 2019 – March 2020. F-AIS was defined as focal cerebral infarction based on clinical and imaging evidence of ischemia in a defined vascular distribution occurring for the first time in life[8]. Patients were categorised into five groups (Supplementary figure 1) as per the following criteria - a) Group I: All consecutive patients with F-AIS admitted during the pandemic and tested reverse transcriptase-polymerase chain reaction (RT-PCR) positive for SARS-CoV2 b) Group II: All consecutive patients with F-AIS admitted during the pandemic and tested negative for SARS-CoV2 c) Group III: All consecutive patients with F-AIS admitted in pre-pandemic period d) Group IV: -Consecutive COVID-19 patients, without stroke admitted during the first wave of COVID-19; and e) Group V: Consecutive patients admitted for neurological diseases other than stroke and tested negative for SARS-CoV2, during the pandemic.

Data elements

In patients with F-AIS (Group I, II and III), we collected data pertaining to demographics, vascular risk factors, clinical features, National Institutes of Health Stroke Scale (NIHSS) at admission, NIHSS stroke severity, time interval between onset of COVID-19 and stroke (in group I), vascular territory, mechanism as per



Supplementary figure 1: Flow chart showing the cohorts of enrolled subjects.

Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification and duration of hospitalisation. Modified Rankin Scale (mRS) at 90 days and long-term outcomes were assessed by either video or physical consultation. In COVID-19 patients (groups I and IV), we collected details of disease severity, peak values of total leukocyte count (TLC), C-reactive protein (CRP), interleukin-6 (IL-6), procalcitonin (PCTQ), lactate dehydrogenase, serum ferritin, prothrombin time, and activated partial thromboplastin time, d-dimer and the lowest values of haemoglobin, absolute lymphocyte count and platelet count. In non-stroke cohorts (group IV and V), we collected details of demographics, vascular risk factors and comorbidities.

Statistical Analysis

We performed statistical analysis using SPSS version 21.0. (Armonk, NY: IBM Corp.). We used the unpaired student's t-test and Chi-square test as a test of significance for continuous and categorical data, respectively. We used the Mann-Whitney U test to compare differences between two groups when the dependent variable was not normally distributed. Adjustment for multiple comparisons was made using Bonferroni correction. A P-value ≤ 0.05 was considered significant. Multiple logistic regression (I and II) was done to identify the association between COVID-19 and 90-day mortality. Multiple logistic regression (I, II, IV and V) was done to identify the association between COVID-19 and the occurrence of F-AIS.

RESULTS

A total of 1369 patients were admitted to our hospital with COVID-19 during the first wave of pandemic. Of these, 25 (1.8%) developed acute stroke out of which 19 (1.38%) were ischemic and 6 (0.44%) were haemorrhagic strokes. 17 patients had (1.24%) had F-AIS and these were characterised and analysed further (Supplementary table 1 & Table 1). Mean age was 62.29 years (range 42-78), 13 (76.5%) were aged > 50 years and 11 (64.7%) males. Hypertension and diabetes was seen in 14 (82.4%) and 13 (76.5%), respectively. COVID-19 was severe in 11 (64.7%) and in 4 (23.5%) the infection was asymptomatic

at presentation. The median duration between the onset of COVID-19 and stroke was 9 days (range 1–45). Five (29.4%) developed stroke during in-hospital stay. The stroke was severe in 5 (29.4%). Admission-NIHSS was 12.59±8.33 (range 2-25). The stroke mechanism was undetermined (cryptogenic) in 10 (58.8%) and lacunar in one (5.9%). Stroke was due to large artery occlusion (LAO) in 10 (58.8%) subjects (Figure 1&2) with involvement of anterior circulation in 14 (82.4%) and multiple territories in 2 (11.8%).

Comparative analysis between the cohorts of F-AIS with and without COVID-19 is shown in Table 1. Comparative analysis of seventy-five consecutive COVID-19 patients without stroke (admitted in April and May 2020) with COVID-19-associated F-AIS patients is shown in Table 2. There was a significant drop of 40% in the total number of admissions into the neurology department during the pandemic compared to the immediate pre-pandemic period (Supplementary table 2). There were no differences in the proportion of stroke admission between the two periods (48.23% vs. 44.74%; p=0.38) [ischemic 36.86% vs. 30.56%; p=0.09; haemorrhagic 7.84% vs. 10.02%; p=0.34 and; F-AIS 23.9% vs. 27.9%; p=0.26]. When compared to prepandemic period, cryptogenic strokes were seen frequently in the pandemic (19.4% vs 33.8%; P=0.03).

Multiple logistic regression was performed to find independent risk factors of F-AIS using the following variables - age, male gender, hypertension, diabetes, coronary artery disease, chronic kidney disease and COVID-19. It showed that age > 50 years (RR, 0.36 [95% CI, 0.20–0.67]; P<0.01), diabetes (RR, 4.03 [95% CI, 2.1-7.5]; P<0.01) and COVID-19 (RR, 0.35 [95% CI, 0.18–0.68]; P<0.01) were the independent risk factors.

Among the patients with COVID-associated F-AIS, the mean duration of hospital stay was 13.6±11.7 (range 1-40) days. The 90-day mortality rate was 41.2%, and the median 90-day mRS in the remaining 10 (58.8%) patients was 2 (range 0-5). Multiple logistic regression showed that COVID-19 (RR, 4.81 [95% CI, 1.14–20.18] P=0.03) and admission-NIHSS (RR, 1.23 [95% CI, 1.06-1.42] P<0.01) were independently associated with 90-day mortality. There were significant differences in the outcome variables between COVID-19-associated and non-COVID-19 stroke groups: death rate (41.2% vs. 11.3%; p<0.01) and unfavourable outcome (64.7% vs. 31%; p=0.01). Of the remaining ten COVID-19-associated F-AIS subjects, one died due to urosepsis five months after the stroke. The mean long-term follow-up duration of the remaining nine patients was 20.00±1.00 (range 19-22) months, and seven of them showed good outcomes (mRS 0-2).

DISCUSSION

Acute ischemic stroke is infrequent in patients with COVID-19, and the exact incidence is unknown. Observational studies suggest that 1–6% of hospitalised COVID-19 patients develop stroke[3]. The most common type of stroke is ischemic stroke[6,9]. In our study, of 1.8% of COVID-19 patients developed acute stroke, out of which 17 (1.24%) had F-AIS.

Systematic reviews and meta-analyses suggest that COVID-19-associated ischemic stroke occurs more often in elderly males[6]. The reported mean time interval between the COVID-19 and stroke was eight days[4]. Similar were the observations in our study. COVID-19-associated ischemic strokes are more often severe. The reported median NIHSS was 15 (range 13-18)[6,10]. In our study, the mean admission-NIHSS was 12.59 (range 8-33). COVID-19-associated ischemic stroke usually occurs in the presence of cardiovascular risk factors. They are more likely to have hypertension, diabetes mellitus, and coronary artery disease[4,6,10]. Similar were our observations. Cryptogenic mechanism was observed in most case series[6]. Small vessel disease was infrequently reported[11]. Cryptogenic stroke accounted for 58.8% in our study. Of the 17 patients, 10 (58.8%) had LAO. Only one patient (5.9%) had lacunar stroke. The reported frequency of LAO in patients with COVID-19-associated ischemic stroke is higher[3-7,11].

We compared the clinical characteristics of COVID-19-associated F-AIS, and stroke without COVID-19. Admission-NIHSS and stroke severity was higher in COVID-19-associated stroke. Cryptogenic mechanism and LAO, longer hospital-stay and higher 90-day mortality were seen in COVID-19 F-AIS. We also compared features of COVID-19 subjects with and without stroke. Diabetes and hypertension were seen more frequently in the stroke. Severity of COVID-19 was more in stroke patients. Inflammatory and coagulation markers were

SUPPLEMENTARY TABLE 1: CHARACTERISTICS, AND OUTCOMES OF COVID-19-ASSOCIATED F-AIS

S.NO	Age (years)/ Sex	Risk Factors	Comorbidities	In-hospital Stroke	Clinical severity of COVID-19	Time(days) between Stroke and COVID-19	NIHSS at Onset	TOAST Category
1	78/M	DM, HTN, CAD, CKD, Tobacco	Hypothyroidism Pyelonephritis S/P stent)	No	Asymptomatic	Simultaneous Onset	4	5
2	62/M	DM, HTN, CAD	-	No	Severe	6	7	1
3	74/M	DM HTN Tobacco	Pulmonary tuberculosis (Past)	Yes	Severe	16	21	1
4	77/M	DM, HTN, Tobacco, Alcoholism, Atrial Fibrillation	-	No	Asymptomatic	Simultaneous Onset	14	3
5	42/M	DM; HTN; DLP	-	No	Non-severe	1	9	5
6	58/M	DM, HTN, CAD, Tobacco, Alcoholism	-	Yes	Severe	9	23	1
7	54/M	DM	-	Yes	Severe	10	24	5
8	67/F	HTN	Rheumatoid arthritis	No	Severe	6	10	2
9	48/F	None	-	No	Asymptomatic	Simultaneous Onset	4	1
10	62/F	DM, HTN, CKD	-	No	Severe	14	24	5
11	55/M	HTN, DLP, Alcoholism	-	No	Non-severe	6	7	5
12	76/F	DM, HTN	Obesity	No	Severe	5	19	5
13	47/M	Homocysteinemia, Tobacco, Alcoholism	-	No	Asymptomatic	Simultaneous Onset	4	5
14	50/M	DM, HTN	-	Yes	Severe	20	5	5
15	70/F	DM, HTN, CKD, DLP, Homocysteinemia	-	No	Severe	45	2	1
16	77/M	DM, HTN, DLP, Homocysteinemia	Femur fracture (Past)	No	Severe	7	12	5
17	62/F	DM, HTN, DLP	-	Yes	Severe	17	25	5

COVID-19- Corona virus disease -19, DM-Diabetes, HTN-Hypertension, CAD-Coronary artery disease, CKD-Chronic in Acute Stroke Treatment, AC- Anterior Circulation, PC -Posterior Circulation, LVO-Large vessel Occlusion, HRCT-ACS-Acute coronary syndrome, LVF-Left ventricular failure, DKA-Diabetic ketoacidosis, HAP-Hospital associated thrombosis and Pulmonary thromboembolism

Vascular territory/ number of territories	LVO	HRCT grade	MV	Stroke therapies	Duration of hospital stay (in days)	Complications	mRS at 90 days	Duration of follow up (in months)	mRS at last follow up
AC/2	--	5	No	Antiplatelet & Anticoagulants	7	None	0	20	1
AC/1	--	5	No	Antiplatelet & Anticoagulants	35	Bilateral Pyelonephritis; ACS with LVF; Sepsis	2	21	2
AC/1	--	5	Yes	Antiplatelet & Anticoagulants	40	DKA; HAP; Pyelonephritis; ARF and Sepsis	6	-	6
AC/1	++	3	Yes	Antiplatelet & Anticoagulants	11	HAP; Sepsis	6	-	6
AC/1	++	4	No	Antiplatelet	1	None	2	20	2
AC/1	--	5	No	Antiplatelet & Anticoagulants	12	DKA; HAP	6	-	6
AC/1	++	6	Yes	Antiplatelet & Anticoagulants	24	MI; Sepsis; HAP; UTI	4	22	4
AC/1	--	5	Yes	Antiplatelet & Anticoagulants	17	DKA; VAP; Sepsis	6	-	6
AC/1	--	1	No	Antiplatelet & Anticoagulants	3	None	0	19	0
AC/1	++	5	Yes	Antiplatelet &	6	Sepsis	6	-	6
AC/1	++	4	No	Antiplatelet & Anticoagulants	22	None	3	19	1
AC/1	++	5	Yes	Antiplatelet	15	HAP	5	-	6
PC/1	++	1	No	Antiplatelet & Anticoagulants	6	None	0	19	0
PC/3	--	6	No	Antiplatelet & Anticoagulants	22	Sepsis	4	20	4
PC/1	++	4	No	Antiplatelet	1	None	1	20	0
AC/1	++	5	Yes	rTPA	3	SICH	6	-	6
AC/1	++	5	Yes	Antiplatelet & Anticoagulants	9	MI; DVT & PTE; ARF	6	-	6

kidney disease, DLP-Dyslipidaemia, NIHSS - National Institute of Health Stroke Scale, TOAST - Trial of Org 10172 High resolution Computed Tomography, MV-Mechanical ventilation, rTPA-Recombinant Tissue plasminogen activator, Pneumonia, ARF-Acute renal failure, UTI-Urinary tract infection, SICH-Symptomatic ICH, DVT & PTE -Deep vein

TABLE 1: COMPARISON BETWEEN F-AIS COHORTS WITH AND WITHOUT COVID-19.

PARAMETER	COVID-19 STROKE	stroke without covid-19	P-VALUE
Total number of strokes n (%)	17 (100)	71 (100)	
Age and Gender			
Age (Mean±SD)	62.29±11.79	57.80±13.61	0.21
Age > 50 years n (%)	13 (76.5)	16 (22.5)	0.93
Male n (%)	11 (64.7)	54 (76.1)	0.34
Risk factors			
Diabetes n (%)	13 (76.5)	36 (50.7)	0.05
Hypertension n (%)	14 (82.4)	55 (77.5)	0.66
Coronary artery disease and Congestive heart failure n (%)	3 (17.6)	17 (23.9)	0.58
Atrial fibrillation and Pacemaker n (%)	1 (5.9)	2 (2.81)	0.53
Chronic kidney disease n (%)	3 (17.6)	5 (7.0)	0.17
Dyslipidemia n (%)	6 (35.3)	47 (66.2)	0.01
Hyperhomocysteinemia n (%)	3 (17.6)	16 (22.5)	0.66
Current tobacco consumption n (%)	5 (29.4)	17 (23.9)	0.64
Current alcohol consumption n (%)	4 (23.5)	10 (14.1)	0.34
In-hospital Strokes n (%)	5 (29.4)	1(1.4)	<0.01
Stroke severity			
Non severe (<20) n (%)	12 (70.6)	66 (93.0)	<0.01
Severe (>20) n (%)	5 (29.4)	5 (7.0)	
NIHSS at admission	12.59±8.33	8.41±6.66	0.03
Mechanism of Stroke (TOAST Categories)			
Large artery disease n (%)	5 (29.4)	25 (35.2)	0.65
Small artery disease n (%)	1 (5.9)	14 (19.7)	0.18
Cardio embolism n (%)	1 (5.9)	7 (9.9)	0.60
Other determined Etiology n (%)	0 (0.0)	1 (1.4)	0.62
Undetermined n (%)	10 (58.8)	24 (33.8)	0.05
Vascular involvement			
Anterior Circulation n (%)	14 (82.4)	46 (64.8)	0.65
Multiple vascular territories n (%)	2 (11.8)	13 (18.3)	0.83
LAO n (%)	10(58.8)	19 (26.8)	0.01
Non-LAO n (%)	7 (41.2)	52 (73.2)	
Outcome measures			
Duration of hospital stay (in days)	13.6±11.7	6.7±4.1	<0.01
Unfavorable Outcome at 90 days (mRS >2) n (%)	11 (64.7)	22 (31.0)	0.01
Death at 90 days n (%)	7 (41.2)	8 (11.3)	<0.01

COVID-19: Coronavirus disease 19; NIHSS: National Institute of Health Stroke Scale; LAO: Large artery occlusion; mRS: Modified Rankin Scale

significantly elevated in patients with COVID-19-associated stroke. We studied the differences between patients of non-COVID-19 F-AIS during the pandemic and those with F-AIS registered in the Institutional Stroke Register in the immediate six months before the pandemic. In-hospital stroke, cryptogenic mechanism and LAO stroke were higher in pandemic.

Published data suggest that patients with severe COVID-19 had an increased risk of acute ischemic stroke than patients with non-severe COVID-19[3,6]. In a study from Wuhan, stroke occurred in 5.7% of critically-ill patients compared to 0.8% with milder COVID-19[12].In

TABLE 2: COMPARISON BETWEEN COVID-19 COHORTS WITH AND WITHOUT F-AIS

PARAMETER	COVID-19 STROKE	COVID-19 without stroke	P-Value
Total number of subjects n (%)	17 (100)	75 (100)	--
Age (Mean±SD)	62.29±11.79	55.24±14.65	0.06
Age > 50 years n (%)	13 (76.5)	46 (61.3)	0.27
Male n (%)	11(64.7)	57 (76.0)	0.33
Risk factors			
Diabetes n (%)	13 (76.5)	26 (34.7)	<0.01
Hypertension n (%)	14 (82.4)	29 (38.7)	<0.01
Coronary artery disease n (%)	3 (17.6)	9 (12.0)	0.68
Chronic Kidney disease n (%)	3 (17.6)	2 (2.7)	0.04
COVID-19 Severity			
Non-severe n (%)	6 (35.3)	63 (84)	<0.01
Severe n (%)	11 (64.7)	12 (16)	
Inflammatory markers			
Total leukocyte count (x103/mL)	17.3±9.82	11.74±8.93	0.02
Absolute lymphocyte count (x103/mL)	11 (2.07-29.52)	12.46 (0-39.5)	0.33
Lactate dehydrogenase (U/L)	756.15±377.62	663.99±291.43	0.28
Interlukin-6 (pg/mL)	108.9 (7.07-494.87)	28.25 (6.4-1391.09)	0.01
C Reactive protein (mg/L)	2.3 (0.05-9.6)	1.2 (0.62-9.6)	0.12
Procalcitonin (ng/mL)	0.13 (0.05-69.94)	0.05 (0.05-29.2)	0.04
Serum ferritin (ng/mL)	242 (3.63-953)	182.7 (8.7-1500)	0.6
Markers of hypercoagulability			
Prothrombin time (sec)	15.55±3.43	12.9±1.34	<0.01
International normalized Ratio	1.29±0.31	0.88±0.40	<0.01
Activated partial thromboplastin time (sec)	52.54±36.29	34.82±6.12	<0.01
D-Dimer (ng/mL)	1200 (77-19102)	251 (49-69000)	<0.01
Others			
Hemoglobin (mg/dL)	10.46±2.33	12.41±2.40	<0.01

COVID-19: Coronavirus disease 19

our study, 64.7% of patients with COVID-19-associated stroke had severe COVID-19. Growing comparisons of COVID-19-positive and COVID-19-negative stroke cohorts support the association between COVID-19 and ischemic stroke[13]. Multivariate logistic regression analysis of our data suggests that COVID-19 is an independent risk factor for F-AIS, in addition to age (>50 years) and diabetes.

The exact mechanism by which COVID-19 increases the risk of ischemic stroke is unknown. Presumed hypothesis include coagulopathy, inflammation, platelet activation, and endotheliopathy[14-15]. COVID-19 is associated with the activation of coagulation and inflammatory pathways. Activation of the coagulation pathway with elevated D-dimer and fibrinogen is a common feature in severe COVID-19. A recent review found consistently elevated D-dimer in severe COVID-19[16]. 64.7% of COVID-19-associated stroke had severe infection in our study. D-Dimer was significantly higher in COVID-19-associated stroke. The other possible mechanism for initiating pathological thrombosis in COVID-19 is a hyper-inflammatory response with a resultant "cytokine storm"[17]. Patients with COVID-19 have elevated IL-6 and CRP[18]. In our study, patients

SUPPLEMENTARY TABLE 2: COMPARISON BETWEEN F-AIS COHORT OF PREPANDEMIC AND NON-COVID-19 STROKE OF THE PANDEMIC

PARAMETER	PREPANDEMIC time period	PANDEMIC time period	P-VALUE
Number of Admissions n (%)	409	255	---
Number of first ever ischemic strokes unrelated COVID-19 n (%)	98 (23.9)	71 (27.8)	0.26
Age (Mean±SD)	61.93±13.1	57.80±13.61	0.048
Age > 50 years n (%)	21 (21.4)	16 (22.5)	0.86
Male gender n (%)	69 (70.4)	54 (76.1)	0.41
In-hospital Strokes n (%)	0(0.0)	1 (1.4)	0.24
Stroke severity			
Non severe (<20) n (%)	93 (94.9)	66 (93.0)	0.60
Severe (>20) n (%)	5 (5.1)	5 (7.0)	
NIHSS at Onset (Mean±SD)	7.43±5.16	8.41±6.66	0.28
Mechanism of Stroke (TOAST Classification)			
Large artery disease n (%)	35 (35.7)	25 (35.2)	0.94
Small artery disease n (%)	18 (18.4)	14 (19.7)	0.83
Cardio embolism n (%)	23 (23.5)	7 (9.9)	0.02
Other determined Etiology n (%)	3 (3.1)	1 (1.4)	0.47
Undetermined n (%)	19 (19.4)	24 (33.8)	0.03
Large artery occlusion n (%)	23(23.5)	19 (26.8)	0.62
Outcome measures			
Duration of hospital stay (in days) (Mean±SD)	6.0±3.5	6.7±4.1	0.88
Unfavorable outcome at 90 days (mRS >2) n (%)	30 (30.6)	22 (31.0)	0.95
Deaths at 90 days n (%)	17 (17.3)	8 (11.3)	0.27

COVID-19: Coronavirus disease 19: NIHSS - National Institutes of Health Stroke Scale;
TOAST-Trial of ORG 10172 in Acute Stroke Treatment; mRS-Modified Rankin Scale

with COVID-19 had higher IL-6 levels than patients without stroke. The CRP titres had not reached statistical significance.

COVID-19-associated stroke is associated with high mortality. The reported pooled mortality rate was 31.7%, and the estimate is much higher in severely ill patients 84.8%[5,19]. Short-term mortality rate in patients with COVID-associated stroke was 41.2% in our study. Compared to individuals of stroke without COVID-19, patients with infection and stroke had a higher mortality[6]. COVID-19 was found to be an independent risk factor for 90-day mortality of stroke in present study.

In other studies, the cryptogenic stroke subtype was an independent predictor of mortality, and diabetes has been shown to increase the mortality and severity of COVID-19[20-21]. There was no difference in the mortality between patients with ischemic stroke who tested negative for COVID-19 during the pandemic and patients with ischemic stroke in the six months immediately before the pandemic in our study (17.0 vs 17.3, p=0.96). In our study, the mean in-hospital stay was longer (I3.6±11.7 vs 6.7±4.1, p<0.01) in COVID-19-associated stroke cohort than COVID-19 negative stroke cohort. Long-term functional outcome was favourable in most of the remaining nine patients (mRS 0-2 in 7; mRS 3-4 in 2). We followed up with the patients for a mean duration of 20.00±1.00 (range 19-22) months. Probably ours is the only study that studied the long-term functional outcome.

The present study is unique in many aspects. First, this is perhaps the first study to characterise the F-AIS associated with COVID-19. Second, we studied the long-term outcomes. Third, we showed COVID-19 to be an independent risk factor of ischemic stroke and mortality. Notwithstanding, there are a few limitations.

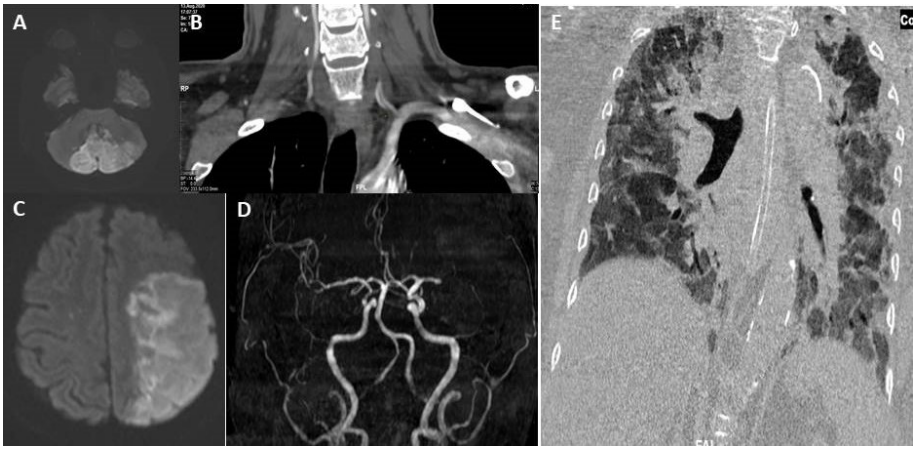


Fig. 1. MR brain diffusion-weighted axial image (A) showing cerebellar infarct due to acute thrombus in left subclavian artery extending into left vertebral as shown in CT angiogram coronal sections (B); MR brain diffusion-weighted axial image showing left MCA territory infarct (C) due to left distal M2 Middle cerebral artery thrombotic occlusion shown in 3D time-of-flight image (D). HRCT chest coronal image of the same patient showing extensive bilateral ground-glass opacities (E).

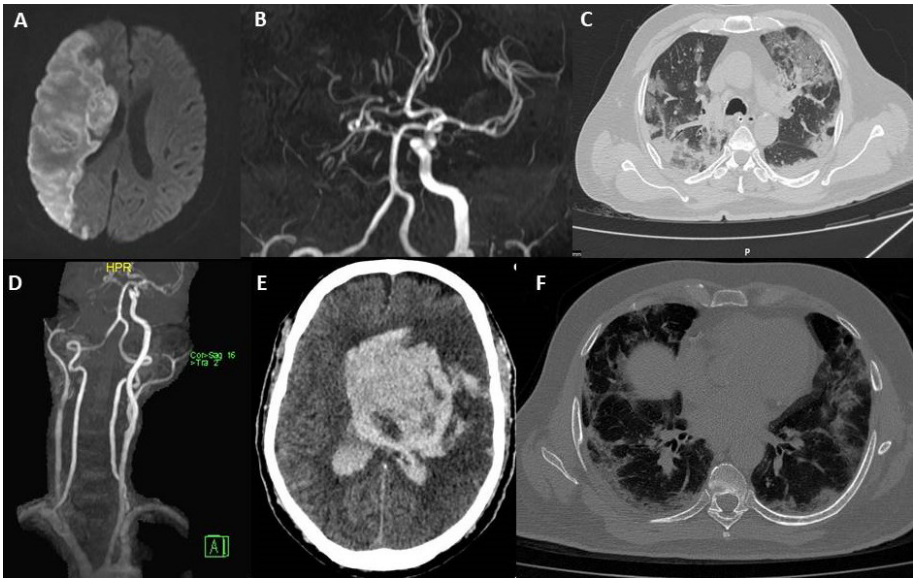


Fig. 2. MR brain diffusion-weighted axial image (A) showing right ICA infarct due to acute thrombotic occlusion of right ICA from the origin (B, D); HRCT chest axial image of the same patient showing extensive bilateral ground-glass opacities (C); CT brain axial image showing left MCA infarct with symptomatic intracerebral haemorrhage following intravenous thrombolysis (E); HRCT chest axial image of the same patient showing sub-pleural opacities (F).

First, this is a retrospective study. Second, inflammatory and coagulation markers were not available in all COVID-19 patients. However, this accounted only for small proportion. Third, data pertaining to dyslipidaemia, hyperhomocysteinemia, tobacco and alcohol consumption was lacking in COVID-19 patients without stroke. Fourth, COVID-19 patients without stroke who were recruited were predominantly non-severe. However, recruiting

consecutively admitted patients for analysis eliminated the bias. Fifth, the study is a single-centre study.

In conclusion, F-AIS accounted for 1.24%. Compared with stroke patients without COVID-19, those with COVID-19 had higher stroke severity and five-time higher risk of death. They are mainly cryptogenic and showed LAO. Compared with COVID-19 without stroke, those with stroke had a higher incidence of diabetes, hypertension and chronic kidney disease, severe infection and elevated inflammatory and coagulation parameters. SARS-CoV2 is an independent risk factor for F-AIS.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

All the primary data is submitted as research data files along with the manuscript.

REPORTING GUIDELINE

Reporting was done in accordance with STROBE guidelines.

REFERENCES

1. Mukherjee A, Kumar G, Sharma R, Menon G, Sahu D, Wig N, et al. Clinical profile of hospitalized COVID-19 patients in first & second wave of the pandemic: Insights from an Indian registry based observational study. Indian J Med Res. 2021;153(5): 619.
2. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, et al. Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. N Engl J Med. 2020 May 14;382(20):e60.
3. Stein LK, Mayman NA, Dhamoon MS, Fifi JT. The emerging association between COVID-19 and acute stroke. Trends in Neurosciences. 2021 Jul;44(7):527-37.
4. Yamakawa M, Kuno T, Mikami T, Takagi H, Gronseth G. Clinical Characteristics of Stroke with COVID-19: A Systematic Review and Meta-Analysis. Journal of Stroke and Cerebrovascular Diseases. 2020 Dec;29(12):105288.
5. Siow I, Lee KS, Zhang JJ, Saffari SE, Ng A, Young B. Stroke as a Neurological Complication of COVID-19: A Systematic Review and Meta-Analysis of Incidence, Outcomes and Predictors. Journal of Stroke and Cerebrovascular Diseases. 2021 Mar;30(3):105549.
6. Nannoni S, de Groot R, Bell S, Markus HS. Stroke in COVID-19: A systematic review and meta-analysis. International Journal of Stroke. 2021 Feb;16(2):137-49.
7. Qureshi AI, Baskett WI, Huang W, Shyu D, Myers D, Raju M, et al. Acute Ischemic Stroke and COVID-19. Stroke. 2021 Mar;52(3):905-12.
8. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors J(, Culebras A, et al. An Updated Definition of Stroke for the 21st Century. Stroke. 2013 Jul;44(7): 2064-89.
9. Zakeri A, Jadhav AP, Sullenger BA, Nimjee SM. Ischemic stroke in COVID-19-positive patients: an overview of SARS-CoV-2 and thrombotic mechanisms for the neurointerventionalist. J NeuroIntervent Surg. 2021 Mar;13(3):202-6.
10. Luo W, Liu X, Bao K, Huang C. Ischemic stroke associated with COVID-19: a systematic review and meta-analysis. J Neurol. 2022 Apr;269(4):1731-40.
11. Kihira S, Schefflein J, Mahmoudi K, Rigney B, N. Delman B, Mocco J, et al. Association of Coronavirus Disease (COVID-19) With Large Vessel Occlusion Strokes: A Case-Control Study. American Journal of Roentgenology. 2021 Jan;216(1):150-6.
12. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol. 2020 Jun 1;77(6):683.
13. Belani P, Schefflein J, Kihira S, Rigney B, Delman B, Mahmoudi K, et al. COVID-19 Is an Independent Risk Factor for Acute Ischemic Stroke. AJNR Am J Neuroradiol. 2020 Aug;41(8):1361-4.

14. Qiu F, Wu Y, Zhang A, Xie G, Cao H, Du M, et al. Changes of coagulation function and risk of stroke in patients with COVID-19. Brain Behav. 2021 Jun;11(6):e02185.
15. Esenwa C, Cheng NT, Luna J, Willey J, Boehme AK, Kirchoff-Torres K, et al. Biomarkers of Coagulation and Inflammation in COVID-19–Associated Ischemic Stroke. Stroke. 2021 Nov;52(11): e706-e709.
16. Violi F, Pastori D, Cangemi R, Pignatelli P, Loffredo L. Hypercoagulation and Antithrombotic Treatment in Coronavirus 2019: A New Challenge. Thromb Haemost. 2020 Jun;120(06):949-56.
17. McGonagle D, O'Donnell JS, Sharif K, Emery P, Bridgewood C. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. The Lancet Rheumatology. 2020 Jul;2(7):e437-e445.
18. Mackman N, Antoniak S, Wolberg AS, Kasthuri R, Key NS. Coagulation Abnormalities and Thrombosis in Patients Infected With SARS-CoV-2 and Other Pandemic Viruses. ATVB. 2020 Sep;40(9):2033-44.
19. Fridman S, Bres Bullrich M, Jimenez-Ruiz A, Costantini P, Shah P, Just C, et al. Stroke risk, phenotypes, and death in COVID-19. Neurology. 2020 Dec 15;95(24):e3373-e3385.
20. Renieri L. High mortality rate in COVID-19–associated stroke, analysis of risk factors. J Neurol Neurosurg Psychiatry. 2020 Dec;91(12):1249.
21. Siegler JE, Cardona P, Arenillas JF, Talavera B, Guillen AN, Chavarría-Miranda A, et al. Cerebrovascular events and outcomes in hospitalized patients with COVID-19: The SVIN COVID-19 Multinational Registry. International Journal of Stroke. 2021 Jun;16(4):437-47.