Original Article

Clinical Features and Outcome of Stroke with COVID-19. COVID-19 Stroke Study Group (CSSG), India

Rohit Bhatia, M. V. Padma Srivastava, P. N. Sylaja[2], Snigdha Komakula, Ashish Upadhyay[1], Vibhor Pardasani[3], Thomas Iype[4], Rajsrinivas Parthasarathy[5,12], Rajshekhar Reddy[6], Suman Kushwaha[7], Jayanta Roy[8], Satish P, Anjan Trikha[9], Naveet Wig[10], Lalit Dhar[11], Deepti Vibha, Venugopalan Y. Vishnu, Awadh Kishore Pandit, Anu Gupta, Elavarasi A, Ayush Agarwal, Vipul Gupta[12], Rakesh K. Singh[3], Harsh Oza[3], Hiral Halani[3], Dileep Ramachandran[4], Githin B. George[4], Praveen Panicker[4], Suresh MK[13], S Kumaravelu[14], Dheeraj Khurana[15], Srijithesh P. Rajendran[16], Vijaya Pamidimukkala[17], Salil Gupta[18], Jeyaraj D. Pandian[19], Debashish Chowdhury[20], Nirendra K. Rai[21], Arvind Sharma[22], Vivek K. Nambiar[23]

Departments of Neurology, [1]Biostatistics, [9]Anaesthesia, [10]Medicine and [11]Microbiology, All India Institute of Medical Sciences, New Delhi, [2]Department of Neurology, Sree Chitra Thirunal Institute for Medical Sciences and Technology, Thiruvananthapuram, Kerala, [3]Department of Neurology, Bombay Hospital and Medical Research Centre, Mumbai, Maharashtra, Departments of [4]Neurology and [13]Medicine, Government Medical College Thiruvananthapuram, Thiruvananthapuram, Kerala, Departments of [5]Neurology and [12]Neurointervention Surgery, Artemis Hospitals, Gurgaon, Haryana, [6]Department of Neurology, Max Super Speciality Hospital Saket, New Delhi, [7]Department of Neurology, Institute of Human Behaviour and Allied Sciences, Neurology, New Delhi, [8]Department of Neurology, Institute of Neurosciences, Kolkata, West Bengal, [14]Department of Neurology, Ramesh Hospitals Guntur, Andhra Pradesh, [15]Department of Neurology, Postgraduate Institute of Medical Education and Research, Chandigarh, [16]Department of Neurology, National Institute of Mental Health and Neuro Sciences, Bangalore, Karnataka, [17]Department of Neurology, Lalitha Super Specialty Hospital, Guntur, Andhra Pradesh, [18]Department of Neurology, Command Hospital Air Force Bangalore, Bangalore, Karnataka, [19]Department of Neurology, Christian Medical College, Ludhiana, Punjab, [20]Department of Neurology, Govind Ballabh Pant Institute of Postgraduate Medical Education and Research, New Delhi, Delhi, [21]Department of Neurology, All India Institute of Medical Sciences, Bhopal, Madhya Pradesh, [22]Department of Neurology, Zydus Hospital, Ahmedabad, Gujarat, [23]Department of Neurology, Amrita Institute of Medical Sciences, Cochin, Kerala

Abstract

Background and Purpose: Occurrence of stroke has been reported among patients with COVID-19. The present study compares clinical features and outcomes of stroke patients with and without COVID-19. **Methods:** The COVID-19 Stroke Study Group (CSSG) is a multicentric study in 18 sites across India to observe and compare the clinical characteristics of patients with stroke admitted during the current pandemic period and a similar epoch in 2019. The present study reports patients of stroke with and without COVID-19 (CoVS and non-CoVS, respectively) seen between February 2020 and July 2020. Demographic, clinical, treatment, and outcome details of patients were collected. **Results:** The mean age and gender were comparable between the two groups. CoVS patients had higher stroke severity and extent of cerebral involvement on imaging. In-hospital complications and death were higher among CoVS patients (53.06% vs. 17.51%; $P < 0.001$) and (42.31% vs. 7.6%; $P < 0.001$), respectively. At 3 months, higher mortality was observed among CoVS patients (67.65% vs. 13.43%; $P < 0.001$) and good outcome (modified Rankin score [mRS]: 0–2) was seen more often in non-CoVS patients (68.86% vs. 33.33%; $P < 0.001$). The presence of COVID-19 and baseline stroke severity were independent predictors of mortality. **Conclusions:** CoVS is associated with higher severity, poor outcome, and increased mortality. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and baseline stroke severity are independent predictors of mortality.

Keywords: COVID-19, ischemic stroke, SARS-CoV-2, stroke, thrombolysis

Introduction

The ongoing pandemic of COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, is no more a disease limited to the pulmonary system.

Observations over the past few months have suggested a multisystem involvement.[1] Stroke has been recognized and linked to COVID-19 infection relatively early in the pandemic.[2,3] Potential mechanisms for the occurrence of stroke include increased thrombotic milieu, endotheliopathy, inflammatory activity, worsening of preexisting risk factors, cardiac complications, etc. However, a direct causative association is yet to be established. Outcomes among COVID-19 patients with stroke are heterogeneous and could be influenced by many factors. A recent study from southern India described patients with COVID-19 and stroke and compared them against historical controls. The authors found increased mortality and morbidity among patients with stroke and coexisting COVID-19 infection.[4]

The present study aimed to evaluate and compare patients of stroke with and without COVID-19 and observe differences in demographics, stroke severity, risk factors, and outcomes.

Address for correspondence: Dr. Rohit Bhatia, Department of Neurology, All India Institute of Medical Sciences, New Delhi, India.
E-mail: rohitbhatia71@yahoo.com

Submitted: 11-Feb-2021 **Revised:** 07-Mar-2021 **Accepted:** 05-Jun-2021
Published: 30-Aug-2021

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DOI: 10.4103/aian.AIAN_122_21

Methods

The COVID-19 Stroke Study Group (CSSG) is a multicentric study conducted in 18 sites across India, to observe and compare the clinical characteristics of patients with stroke admitted during the current pandemic period and a similar epoch in 2019. Collaborative sites prospectively recruited patients with stroke seen during this period. The study was approved by the institutional ethics committee. The current paper compares patients with stroke and COVID-19 (CoVS) with patients with stroke and without COVID-19 (non-CoVS), seen between February 2020 and July 2020. Data were collected from sites where both CoVS and non-CoVS patients were seen in this period. Details of patient demographics, stroke risk factors (hypertension, diabetes mellitus, history of previous stroke, coronary artery disease, dyslipidemia, smoking, alcohol use, and renal dysfunction), type of stroke (ischemic, intracerebral hemorrhage [ICH], and cerebral venous thrombosis), time of onset, hospital arrival, and evaluation time taken [CT (computerised tomography time), thrombolysis treatment time, and endovascular treatment (EVT) details], imaging findings (Alberta Stroke Program Early CT Score [ASPECTS] and ICH volume), laboratory parameters wherever available (total leukocyte count [TLC], absolute lymphocyte count, erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], lactate dehydrogenase [LDH], Ferritin, D-dimer, blood sugar), evaluation details including Holter and echocardiography, ischemic stroke subtyping using trial of ORG 10172 in acute stroke treatment (TOAST) classification, medical treatment details, and surgical interventions performed (decompressive hemicraniectomy, hematoma evacuation, combination of hematoma evacuation and decompressive craniectomy, endarterectomy, and stenting), complications (pneumonia, deep venous thrombosis, urinary tract infection, bedsore, and cardiac) and outcomes (mortality at 1 and 3 months and modified Rankin score [mRS]) were collected. mRS ≤2 was taken as a good outcome.

Statistical analysis

Data were presented as mean (SD), median (IQR), and frequency (%). Continuous variables were compared using Student's *t*-test (following normal distributions) or Wilcoxon's sum-rank test (non-normal distribution). Qualitative variables were compared using Chi-square/Fisher's exact test. Univariate and multivariable analysis using a generalized linear model with family (binomial) and logit link (to account for the effect of different centers) was performed to observe the indepe T:\A-H\AIAN\AIAN_AOP\Output\PDF\1st Revises\AP Corrections\20210726 ndent effect of COVID-19 on mortality. A two-tailed *P* value of ≤0.05 was considered significant. Stata version 14 (StataCorp, Lakeway Drive College Station, Texas, USA) was used for analysis.

Results

A total of 665 stroke patients were seen between February 2020 and July 2020 at seven CSSG sites. These sites were chosen as both COVID-19 and non-COVID-19 stroke patients were managed at these sites. The mean age of patients was 60.17 ± 14.42 years; 69.47% (462) were males. In addition, 537 (80.87%) had an ischemic stroke, 118 (17.77%) had ICH, and 9 (1.36%) had cerebral venous thrombosis (CVT). Among these, 169 patients were suspected of having COVID-19. Suspicion was based on the history of fever ($n = 22$), respiratory symptoms ($n = 20$), and other reasons to suspect in the absence of symptoms of infection (place of stay, hot spot, history of contact; $n = 127$).

A total of 409 patients were tested for SARS-CoV-2 and 52 patients were found positive. The analysis is presented for patients who were tested for SARS-CoV-2. Among the 52 CoVS patients, 35 (67.30%) patients required ICU care, and 17 (32.69%) patients were managed in a non-ICU facility.

The details of CoVS ($n = 52$) and non-CoVS ($n = 357$) patients is described in Table 1. The mean age, gender, and risk factors were comparable between the two groups. Types of stroke were comparable in both groups. CoVS patients had a higher National Institutes of Health Stroke Scale (NIHSS) and lower Alberta Stroke Program Early CT Score (ASPECTS) scores at presentation. Among the available laboratory parameters, baseline TLC, ESR, and D-dimer were higher among CoVS patients. All major risk factors were equally distributed in the two groups. History of renal dysfunction was in higher proportion among CoVS patients. A higher number of non-CoVS patients underwent vascular imaging, echocardiography, Holter monitoring, and surgical interventions. In-hospital complications were higher among CoVS patients compared with non-CoVS. Twenty-two (42.31%) CoVS patients died during the hospital stay compared with 27 (7.6%) non-CoVS patients ($P \leq 0.00001$). The hospital stay was longer among CoVS patients ($P = 0.001$). Three months follow-up was completed for 45 CoVS patients and 335 non-CoVS patients. At three months, higher mortality was observed among CoVS patients (51.11%) versus 13.43%, $P < 0.001$) and good outcome was seen more often in non-CoVS patients (66.86% vs 33.33%, $P < 0.001$). We explored factors that could affect in-hospital and 3-months mortality in the two groups [Table 2]. Higher in-hospital complications were observed among CoVS patients who died during the hospital stay and at 3 months. Out of 22 CoVS patients who died in hospital, 19 (90.8%) patients developed in-hospital complications (14 [77.78%] had pneumonia, 3 [16.67%] had more than one complication, and 1 [5.56%] had bloodstream infection). A higher ferritin level was observed among CoVS patients who died at 3 months. Twenty-two patients in the CoVS group died compared with 30 patients who survived during the hospital stay [Table 3]. The patients who died were elder, had lower ASPECTS, higher NIHSS and ICH score, total leucocyte count, blood sugar, in-hospital complication rate, and presence of premorbid renal dysfunction. No difference among other risk factors, laboratory values, or treatment was observed. At three months, 23 (51.12%) patients died and 22 (32%) survived (data available for 45 patients only and includes patients who died during the hospital stay; Table 4). Higher age group, high

Table 1: Comparison of patients of stroke with and without COVID-19

	COVID-19 positive *n*=52	COVID-19 negative *n*=357	*P*
Age (years)	58.25±15.19	60.59±14.71	0.28
Gender (male/female)	35 (67.31%)	246 (68.91%)	0.81
	17 (32.69%)	111 (31.09%)	
Type of stroke			
IS	33 (64.71%)	274 (76.75%)	0.15
ICH	17 (33.33%)	76 (21.28%)	
CVT	1 (1.96%)	7 (0.28%)	
	N=51	N=357	
Systolic BP (mmHg)	150.65±32.04	149.45±27.70	0.76
Blood sugar (mg/dL)	155.62±60.22	141.88±56.70	0.11
	N=48	N=347	
Acute vascular imaging*	16 (48.48%)	219 (79.92%)	<0.005
	N=33	N=274	
TLC (thousand/mm^3)	12,020 (8600-13,975)	8700 (6800-11,000)	<0.0001
	N=48	N=347	
ALC (thousand/mm^3)	1900 (1400-2462)	1901.9 (1366.2-2460)	0.90
	N=45	N=344	
Ferritin (µg/L)	273 (90-616)	124.93 (64-265.1)	0.08
	N=21	N=17	
CRP (mg/L)	38 (5.5-220)	14.49 (5.6-118.6)	0.18
	N=36	N=84	
ESR (mm/h)	23 (11-34)	11 (6-30)	0.01
	N=30	N=235	
D-dimer (µg/mL)	179.5 (0.83-879.9)	1 (0.5-166)	0.04
	N=28	N=11	
LDH (µcat/L)	5.24 (3.74-8.78)	4.91 (3.75-6.16)	0.34
	N=17	N=22	
NIHSS	12 (6-16)	8 (4-13)	0.02
	N=49	N=332	
ASPECTS†	6.80±2.73	8.05±2.02	0.009
	N=31	N=249	
ICH volume (mL) †	24.5 (15-42)	21 (10-36.75)	0.34
	N=14	N=58	
Wake-up stroke	8 (15.38%)	45 (12.61%)	0.57
Door to CT time ‡	41.5 (19-80)	30 (15-39)	0.007
	N=44	N=337	
Intravenous thrombolysis §	4 (13.33%)	57 (20.8%)	
	N=30	N=274	0.46
EVT §	0 (0%)	9 (8.73%)	0.99
	N=9	N=103	
HT	36 (70.58%)	254 (71.14%)	0.93
	N=51	N=357	
DM	19 (37.25%)	169 (47.33%)	0.17
	N=51	N=357	
Previous stroke	11 (21.56%)	47 (13.16%)	0.10
	N=51	N=357	
Dyslipidemia	7 (14.58%)	59 (16.57%)	0.72
	N=48	N=356	
Smoking	12 (23.52%)	57 (15.96%)	0.65
	N=51	N=357	
Renal dysfunction	8 (15.68%)	23 (6.44%)	0.04
	N=51	N=357	
Echocardiography	22 (42.3%)	306 (85.71%)	<0.001
	N=52	N=357	

Contd..

Table 1: Contd..

	COVID-19 positive *n*=52	COVID-19 negative *n*=357	*P*
Holter	10 (19.61%)	246 (68.91%)	<0.001
	N=51	N=357	
Any vascular imaging	16 (31.37%)	258 (72.27%)	<0.001
	N=52	N=357	
TOAST etiology			
LAD-EC	2 (7.69%)	54 (19.85%)	0.08
LAD-IC	3 (11.54%)	63 (23.16%)	
Small vessel disease	4 (15.38%)	48 (17.65%)	
Cardioembolic	8 (30.77%)	43 (15.81%)	
Indeterminate	7 (26.72%)	58 (21.32%)	
Other determinate	2 (7.69%)	6 (2.21%)	
	N=26	N=272	
Surgical intervention (s)	2 (6.06%)	30 (22.39%)	0.03
	N=33	N=134	
Use of heparin			
Standard heparin	6 (15.38%)	0 (0.00)	<0.001
LMWH therapeutic	16 (41.03%)	18 (6.36%)	
LMWH prophylactic	7 (17.95%)	23 (8.13%)	
None	10 (25.64%)	242 (85.51%)	
In-hospital complications	26 (53.06%)	62 (17.51%)	<0.001
	N=49	N=354	
In-hospital mortality	22 (42.31%)	27 (7.6%)	<0.00001
	N=52	N=355	
mRS 0-2 at 3 months	15 (33.33%)	224 (66.86%)	<0.0001
	N=45	N=335	
3-months mortality	23 (51.11%)	45 (13.43%)	<0.001
	N=45	N=335	
Total hospital stay (days)	9 (4-16)	5 (2-9)	0.001
	N=52	N=352	

Data are in *n* (%) or median (IQR). IS: ischemic stroke; ICH: intracerebral hemorrhage; CVT: cerebral venous thrombosis; mRS: modified Rankin score; NIHSS: National Institute of Health Stroke Scale; EVT: endovascular thrombectomy; HT: hypertension; DM: diabetes mellitus; TLC: total leucocyte count; LDH: lactate dehydrogenase; ALC: absolute lymphocyte count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ASPECTS: Alberta Stroke Program Early CT score; TOAST: Trial of ORG in acute ischemic stroke; LAD-EC: large artery disease extracranial; LAD-IC: large artery disease intracranial; LMWH: low-molecular-weight heparin; *Vascular imaging at the time of presentation in patients with ischemic stroke; † numbers based on available data; ‡duration in minutes; § Among ischemic stroke patients when indicated

systolic BP, blood sugar level, NIHSS, total leucocyte count, and in-hospital complications were observed among patients with mortality at three months.

Twenty-one patients were symptomatic with either fever or respiratory symptoms and 31 patients had no clinically overt features of COVID-19. The presence of underlying coronary artery disease (CAD), diabetes, and higher total leukocyte count was observed among symptomatic patients [Table 5]. A total of 33 (63.46%) CoVS patients and 274 (76.75%) non-CoVS patients presented with ischemic stroke [Table 6]. The CoVS group had higher NIHSS and lower ASPECTS scores at presentation. The door to CT time, CT to needle time, and onset to needle time were comparable among both groups. None of the patients underwent EVT among the CoVS patients and only nine (8.73%) patients underwent EVT among the non-CoVS group. There was a trend toward a higher number of patients classified as cardioembolic and indeterminate among CoVS patients, ($P = 0.06$). Seventeen (32.69) patients had ICH among CoVS group and 74 (18.58%) among the non-CoVS group. The history of renal dysfunction was higher among patients with CoVS and the other risk factors were comparable in both groups [Table 7]. Higher mortality and a poor 3-month outcome were observed among CoVS patients for both ischemic and ICH stroke subtypes.

The factors found to be significantly associated with mortality in univariate analysis were adjusted in multivariate analysis to observe the independent effect of COVID-19 on mortality. Presence of COVID-19 (Odds ratio [OR] 6.61, 95% confidence interval [CI] 1.24–35, $P = 0.02$), age (OR 1.09, 95% CI 1.02–1.16, $P = 0.004$), higher NIHSS score (OR 1.21, 95% CI 1.08–1.36, $P = 0.001$), and leukocytosis (OR 1.00, 95% CI 1.00–1.00, $P = 0.02$) were independent predictors of mortality in the cohort.

Discussion

With time, the multifaceted nature of COVID-19 infection is emerging. Now believed to be a multisystem disease in its clinical behavior, cerebrovascular disease has emerged as a predominant comorbidity and a manifestation independent of pulmonary

Table 2: Mortality among COVID-19-positive versus COVID-19-negative patients

	COVID-19 positive *n*=52	COVID-19 negative *n*=357	*P*	COVID-19 positive *n*=52	COVID-19 negative *n*=357	*P*
	In-hospital mortality			3-months mortality		
Total patients died	22	27	-	23	45	-
Age (years)	63.63±10.85	62.59±11.01	0.74	63.69±10.70	64.26±12.25	0.85
Gender (male/female)	16 (72.73%) 6 (27.27%)	21 (77.78%) 6 (22.22%)	0.68	16 (69.57%) 7 (30.43%)	32 (71.11%) 13 (28.89%)	0.89
Type of stroke						
Ischemic	11 (50%)	18 (66.67%)	0.23	12 (52.17%)	31 (68.89%)	0.17
ICH	11 (50%)	9 (33.33%)		11 (47.83%)	14 (31.11%)	
CVT	0 (0.00)	0 (0.00)		0 (0.00)	0 (0.00)	
Systolic BP (mmHg)	158.36±27.06	159.66±26.35	0.86	158.17±26.45	153.97±25.91	0.52
Blood sugar (mg/dL)	177.36±78.84	163.57±63.37	0.51	176.65±76.07	158.38±57.00	0.29
TLC (thousand/mm^3)	13,000 (11,260-16,200) N=19	12,060 (10,200-14,400) N=25	0.49	13,000 (11,341-16,000) N=20	11,700 (9000-13,590) N=64	0.10
ALC (thousand/mm^3)	1845 (1423-2365) N=18	1664 (1029.6-2040) N=49	0.28	1624 (1344-2322) N=19	1536.8 (1100-2000) N=63	0.30
Ferritin (µg/L)	273 (190-472) N=9	216.95 (70-363.9) N=2	0.34	351 (190-990) N=10	70 (68-149) N=5	0.02
CRP (mg/L)	21 (8-183.5)	95.5 (57.5-168.87)	0.09	26 (8.5-146.6)	69.5 (11-120)	0.36
ESR (mm/h)	26 (15-36) N=11	26 (16-40) N=17	0.96	26 (15-34) N=13	26 (11-45) N=27	0.93
D-dimer (µg/mL)	2.5 (0.8-2200) N=11	260 (1-442) N=3	0.81	2.15 (0.81-572.5) N=12	260 (1-442) N=3	0.77
LDH (µcat/L)	5.09 (3.74-6.68) N=8	5.01 (5.01-5.01) N=1	0.48	5.09 (3.74-6.68) N=9	6.61 (5-10.06) N=3	0.35
NIHSS	16.5 (14-21) N=20	17 (12-22) N=24	0.80	16 (12-20)	13.5 (9-19)	0.35
Wake-up stroke	3 (13.64%)	7 (25.93%)	0.28	4 (17.39%)	11 (24.44%)	0.50
Door to CT time*	60 (15-83.5) N=20	32.5 (20-75) N=26	0.56	60 (16.5-83.5) N=20	30 (15-65) N=43	0.12
ASPECTS	5.4±3.37 6 (3-8)	6.72±2.88 7 (5-9)	0.32	5.72±3.25 6 (3-8)	7.33±2.64 8 (6-9)	0.11
Occlusion	3 (50%) N=6	7 (50%) N=14	0.99	4 (57.14%) N=7	14 (58.33%) N=24	0.64
Intravenous thrombolysis†	3 (27.27%) N=11	2 (11.11%) N=18	0.33	2 (16.66%) N=12	7 (22.58%) N=31	0.99
EVT†	None	None	-	0 N=4	1 (10%) N=10	0.99
CT to needle time*	15 (15-35) N=3	38 (38-38) N=1	-	32.5 (15-15) N=2	34 (23-40) N=6	-
Door to needle time*	35 (30-45) N=3	45 (45-45) N=1	-	32.5 (30-35) N=2	47.5 (45-52) N=6	-
Onset to needle time*	240 (90-255) N=3	487.5 (240-735) N=2	-	247.5 (240-255) N=2	210 (140-240) N=7	-
ICH volume (mL)	34 (18-50) N=29	37 (23-54) N=14	0.92	34 (18-50) N=9	30 (18.5-50) N=12	0.59
ICH score	3 (3-4) N=10	5 (3-5) N=9	0.73	3 (3-4) N=10	3 (2-4) N=9	0.55
HT	16 (76.19%) N=21	20 (74.07%) N=27	0.86	17 (77.27%) N=22	36 (80%) N=45	0.79
DM	7 (33.33%) N=21	18 (40.74%) N=27	0.59	8 (36.36%) N=22	19 (42.22%) N=45	0.64

Contd..

Table 2: Contd..

	COVID-19 positive *n*=52	COVID-19 negative *n*=357	*P*	COVID-19 positive *n*=52	COVID-19 negative *n*=357	*P*
	In-hospital mortality			3-months mortality		
Previous stroke	5 (23.81%) N=21	5 (18.52%) N=27	0.65	5 (22.73%) N=22	10 (22.22%) N=45	0.96
Dyslipidemia	4 (20%) N=20	4 (15.38%) N=26	0.68	3 (14.29%) N=21	8 (18.18%) N=44	0.69
Smoking	3 (14.29%) N=21	6 (22.22%) N=27	0.48	3 (13.64%) N=22	9 (20%) N=45	0.52
CAD	4 (19.05%) N=21	7 (25.93%) N=27	0.57	4 (18.18%) N=22	14 (31.11%) N=45	0.26
Alcohol use	5 (23.81%) N=21	2 (7.41%) N=27	0.11	5 (22.73%) N=22	3 (6.67%) N=45	0.07
Renal dysfunction	6 (28.57%) N=21	6 (22.22%) N=27	0.61	6 (27.27%) N=22	9 (20%) N=45	0.50
Echocardiography	5 (22.73%) N=22	17 (62.96%) N=27	0.005	7 (30.43%) N=23	33 (73.33%) N=45	0.001
Holter	2 (9.09%) N=22	4 (14.81%) N=27	0.61	3 (13.04%) N=23	12 (26.67%) N=45	0.14
Any vascular imaging	3 (13.64%) N=22	12 (44.44%) N=27	0.06	4 (28.57%) N=14	25 (73.52%) N=34	0.01
TOAST etiology						
LAD-EC	0 (0%)	1 (5.88%)	0.23	1 (14.9%)	2 (6.67%)	0.43
LAD-IC	1 (16.67%)	6 (35.29%		1 (14.29%)	10 (33.33%)	
SVD	1 (16.67%)	5 (29.49%)		1 (14.29%)	9 (30%)	
Cardioembolic	2 (33.33%)	3 (17.65%)		2 (28.57%)	5 (16.67%)	
Indeterminate	2 (33.33%)	2 (11.76%)		2 (28.57%)	4 (13.33%)	
Other determinate	- N=6	- N=17		- N=7	- N=30	
Surgical intervention (s)	1 (5.88%)	3 (16.67%)	0.31	1 (6.25%)	5 (20%)	0.22
In-hospital complications	19 (90.48%)	15 (55.56%)	0.008	20 (90.91%)	21 (46.67%)	<0.0001
Total hospital stay (days)	8.5 (3-16)	4 (2-13)	0.17	9 (3-20)	5 (3-13)	0.35
Aspirin	8 (42.11) N=19	13 (61.90%) N=21	0.14	10 (47.62) N=21	31 (69.70%) N=33	0.03
Clopidogrel	2 (10.53%) N=19	3 (14.29%) N=21	0.53	3 (14.29%) N=21	9 (27.27%) N=33	0.28
Statin	9 (47.37%) N=19	12 (57.14%) N=21	0.66	11 (52.38%) N=21	22 (66.67%) N=33	0.56

Data are in *n* (%) or median (IQR). IS: ischemic stroke; ICH: intracerebral hemorrhage; CVT: cerebral venous thrombosis; mRS: modified Rankin score; NIHSS: National Institute of Health Stroke Scale; EVT: endovascular thrombectomy; HT: hypertension; DM: diabetes mellitus; TLC: total leucocyte count; LDH: lactate dehydrogenase; ALC: absolute lymphocyte count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ASPECTS: Alberta Stroke Program Early CT score; LMWH: low-molecular-weight heparin; TOAST: Trial of ORG in acute ischemic stroke; LAD-EC: large artery disease extracranial; LAD-IC: large artery disease intracranial; SVD: small vessel disease; *duration in minutes; † when indicated in patients with acute ischemic stroke

symptomatology or severity.[2-5] A recent systematic review reported clinical behavior and outcome of patients with stroke and COVID-19.[6] Although it is still unclear if COVID-19 is incidental or causative in the stroke population, a recent study has suggested COVID-19 as an independent risk factor for stroke.[6]

In the present study, patients with stroke and COVID-19 had a more severe stroke and a greater extent of ischemic damage on imaging, suggesting a more aggressive disease behavior. Similar observations have also been reported previously.[7-11] We did not observe any major differences among known risk factors between the two groups of patients as well as the stroke subtypes apart from the history of renal dysfunction being higher among CoVS patients. In previous studies as well, no major differences among risk factors were observed among patients of stroke with or without COVID-19.[8,12] A recent

Table 3: In-hospital mortality in COVID-19-positive patients

	Died	Survived	*P*
Total patients	22	30	-
Age (years)	63.63±10.85	54.3±16.81	0.02
Gender (male/female)	16 (72.73%) 6 (27.27%)	19 (63.33%) 11 (36.67%)	0.55
Type of stroke			
Ischemic	11 (50%)	22 (75.86%)	0.03
ICH	11 (50%)	6 (33.33%)	
CVT	0 (0.00)	1 (3.45%)	
Total ICU stay (days)	19 (86.36%)	15 (50%)	0.01
Systolic BP (mmHg)	158.36±27.06	145±34.60	0.13
Blood sugar (mg/dL)	177.36±78.84 N=19	141.37±39.50 N=29	0.04
TLC (thousand/mm^3)	13,000 (11,260-16,200) N=19	10,600 (8160-12,480) N=29	0.008
ALC (thousand/mm^3)	1845 (1423-2365) N=19	1900 (1344-2500) N=27	0.92
Ferritin (µg/L)	273 (190-472) N=9	858.72 (51.8-616) N=12	0.43
CRP (mg/L)	21 (8-183.5) N=15	90 (5-410) N=21	0.45
ESR (mm/h)	26 (15-36) N=11	20 (11-34) N=19	0.45
D-dimer (µg/mL)	2.5 (0.8-2200) (0.6-9740) N=11	234 (0.93-833.8) (0.56-18,140) N=17	0.67
LDH (µcat/L)	5.09 (3.74-6.58) N=8	378 (6.31-8.78) N=18	0.36
NIHSS	16.5 (14-21) N=20	8 (3-12) N=11	0.001
Wake-up stroke	3 (13.5%)	5 (16.67%)	0.99
Door to CT time*	60 (15-83.5) N=20	31 (20-67.5) N=24	0.44
ASPECTS	5.4±3.37 6 (3-8) N=10	7.47±2.15 8 (6-9) N=21	0.04
Occlusion	3 (50%) N=6	5 (38.46%) N=13	0.99
Intravenous thrombolysis†	3 (27.27%) N=11	1 (5.26%) N=19	0.16
Type of thrombolytic agent			
rTPA	2 (9.09%)	1 (3.33%)	0.16
TNK	1 (4.35%)	0 (0.00%)	
EVT†	None	None	-
CT to needle time*	15 (15-35) N=3	38 (38-38) N=1	-
Door to needle time*	35 (30-45) N=3	44 (44-44) N=1	-
Onset to needle time*	240 (90-255) N=3	225 (225-225) N=1	-
ICH volume (mL)	34 (18-50) N=9	15 (14.5-23) N=5	0.07
ICH score	3 (3-4) N=10	1 (1-1) N=2	0.02

Contd..

Table 3: Contd..

	Died	Survived	*P*
HT	16 (76.19%) N=21	7 (66.67%) N=30	0.54
DM	7 (33.33%) N=21	12 (40.00%) N=30	0.77
Previous stroke	5 (23.81%) N=21	6 (20%) N=30	0.74
Dyslipidemia	4 (20%) N=20	3 (10.87%) N=28	0.42
Smoking	3 (14.29%) N=21	9 (30%) N=30	0.63
CAD	4 (19.05%) N=21	2 (6.67%) N=30	0.21
Alcohol use	5 (23.81%) N=21	6 (20.00%) N=30	0.74
Renal dysfunction	6 (28.57%) N=21	2 (6.67%) N=30	0.05
Echocardiography	5 (22.73%) N=22	17 (56.67%) N=30	0.02
Holter	2 (9.09%) N=22	8 (27.59%) N=29	0.12
Any vascular imaging	5 (13.64%)	11 (37.93%)	0.31
TOAST etiology			
LAD-EC	0 (0%)	2 (10%)	0.99
LAD-IC	1 (16.67%)	2 (10%)	
Small vessel disease	1 (16.67%)	3 (15%)	
Cardioembolic	2 (33.33%)	6 (30%)	
Indeterminate	2 (33.33%)	5 (25%)	
Other determinate	0 (0%) N=6	2 (10%) N=20	
Surgical intervention (s)	1 (5.88%) N=17	1 (6.25%%) N=16	0.99
Use of heparin	N=16	N=23	
Standard heparin	1 (6.25%)	5 (21.74%)	0.37
LMWH	7 (43.75%)	9 (39.13%)	
LMWH prophylactic	2 (12.50%)	5 (21.74%)	
None	6 (37.50%)	4 (17.39%)	
In-hospital complications	19 (90.48%) N=21	7 (25%) N=28	0.001
Total hospital stay (days)	8.5 (3-16) N=22	9 (6-16) N=30	0.76
Aspirin	8 (42.11%) N=19	16 (66.67%) N=24	0.09
Clopidogrel	2 (10.53%) N=19	5 (20.83%) N=24	0.60
Statin	9 (47.37%) N=19	16 (66.67%) N=24	0.43
HCQS	16 (80%) N=20	16 (59.26%) N=27	0.34
Doxycycline	4 (20%) N=20	6 (22.22%) N=27	0.66
Ivermectin	5 (25%) N=20	9 (33.33%) N=27	0.23
Methylprednisolone	8 (40%) N=20	3 (11.11%) N=27	0.05

Contd..

Table 3: Contd..

	Died	Survived	*P*
Dexamethasone	7 (35%)	5 (18.52%)	0.36
	N=20	N=27	

Data are in *n* (%) or median (IQR). IS: ischemic stroke; ICH: intracerebral hemorrhage; CVT: cerebral venous thrombosis; mRS: modified Rankin score; NIHSS: National Institute of Health Stroke Scale; TPA: recombinant tissue plasminogen activator or Alteplase; TNK: tenecteplase; EVT: endovascular thrombectomy; HT: hypertension; DM: diabetes mellitus; TLC: total leucocyte count; LDH: lactate dehydrogenase; ALC: absolute lymphocyte count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ASPECTS: Alberta Stroke Program Early CT score; TOAST: Trial of ORG in acute ischemic stroke; LAD-EC: large artery disease extracranial; LAD-IC: large artery disease intracranial; LMWH: low-molecular-weight heparin. *duration in minutes; †when indicated in patients with acute ischemic stroke

meta-analysis observed that the outcomes of patients with COVID-19 are influenced by a history of vascular events in the past and a prior history of cerebrovascular events has a 2.5-fold increase in COVID-19 disease severity.[13] The presence of underlying renal disease is also associated with poor outcomes among patients with and without dialysis dependence.[14]

We also compared the CoVS patients, who had clinical suspicion of having COVID-19 at the time of initial screening in the hospital (presence of fever and or respiratory symptoms), with the asymptomatic group. Although elevated leucocyte count in the symptomatic group could suggest an inflammatory activity, other potential inflammatory markers were comparable between the groups. However, patients symptomatic at presentation had higher CAD and diabetes suggesting that vascular risk factors could potentially increase the severity and manifestations of COVID-19 and occurrence of stroke.

Limited evaluation for stroke etiology in CoVS patients could either reflect a priority for COVID-19 management or feasibility issues of transferring stroke patients to non-COVID-19 designated areas or limited availability of resources and expertise within the COVID-19 care designated centers. A concern about the reduction in stroke admissions, optimum acute stroke care, and reduced acute interventions has been observed during the ongoing pandemic.[15-17] Guidelines and recommendations for stroke management during the pandemic have been suggested.[18] The initial difficulties with organizing systems of care have likely improved over time. A higher proportion of CoVS ischemic stroke patients were categorized into cardioembolism and indeterminate stroke etiology. Whether this is suggestive of an underlying cardiac involvement, a prothrombotic milieu or incomplete evaluation due to logistic reasons is unclear. In a recent study from New York, a significantly high number of patients with COVID-19 were placed in the cryptogenic category and embolic source of undetermined source (ESUS), potentially suggesting other mechanisms of stroke in these patients.[12]

Relatively few patients with COVID-19 underwent intravenous thrombolysis. Since the decision about thrombolysis depends upon many factors, it is likely that only the most eligible patients, and in areas where a protected code stroke triage[19] is available, were treated with thrombolysis. Higher door to CT time was observed among CoVS patients. Longer times to treatment have been reported during the ongoing pandemic.[20] None of the CoVS patients underwent endovascular therapy and the number of patients in the non CoVS group was also low. This may be related to many factors including no indication, patient's clinical status, availability, and logistics related to the provision of intervention facilities in the COVID-19-designated areas. Challenges related to EVT during COVID-19 have been previously outlined and methods to improve have been discussed.[21]

High in-hospital and 3 months mortality and a lower proportion of patients achieving a good outcome at 3 months were observed among CoVS patients. A higher stroke severity, systemic inflammatory effects of COVID-19, ARDS (acute respiratory distress syndrome) and sepsis, cardiac arrhythmias, systemic prothrombotic state, and thromboembolism could be contributing to a poorer outcome.[8,12,22-26] Higher mortality among CoVS patients has been observed in previous studies as well.[6] This is also suggested by the presence of increased inflammatory markers such as leukocyte counts, ferritin, LDH, and D-dimer levels among patients with COVID-19 with or without stroke.[7,25-31] However, in the present study, we could only observe higher leucocyte counts and ferritin among COVID-19-positive patients. No major difference was observed in other markers. This could be either due to the data being unavailable from all patients, dynamic nature of these values that could change with the severity of the disease or due to incidental occurrence of stroke in these patients where COVID-19 positivity may be a bystander and not a direct inciting agent. COVID-19 seems to be an independent risk factor for mortality in the present study. We could not, however, establish it as an independent risk factor for stroke occurrence as this was not a case-control study.

The strength of the study includes the multicentric, prospective follow-up data, unlike historical controls used in other studies. The study has limitations. This includes a low number of COVID-19-positive patients with stroke. Data from all stroke patients having COVID-19 could not be ascertained as patients were managed in designated locations and it was difficult to retrieve all data. EVT comparison could not be made as data were not available for COVID-19-positive patients. The study was underrepresented by female patients. Not all patients who presented with stroke were tested for SARS-CoV-2. Therefore, a higher number of patients with associated-asymptomatic COVID-19 may have been missed. Specific laboratory parameters were not available for all patients and 3 months outcome was missing in few patients, limiting the strength of the analysis.

Table 4: Three-month mortality in COVID-19-positive patients (data available for 45 patients)

	Died	Survived	*P*
Total patients	23	22	-
Age (years)	63.69 ±10.70	53.95 ±15.89	0.01
Gender (male/female)	16 (69.57%) 7 (30.43%)	14 (63.64%) 8 (36.36%)	0.75
Symptomatic	9 (39.13%)	9 (40.90%)	0.99
Asymptomatic	14 (60.89%)	13 (59.09%)	
Days symptomatic for COVID-19	0 (0-4)	0 (0-4)	0.94
Days between COVID-19 symptoms and stroke	0 (0-3)	0 (0-3)	0.98
Type of Stroke			
IS	12 (52.17%)	17 (77.27%)	0.05
ICH	11 (47.93%)	4 (18.18%)	
CVT	0 (0.00%)	1 (4.55%)	
ASPECTS	8 (3-8) N=11	7.5 (6-9) N=16	0.20
ICH volume (mL)	34 (18-50) N=9	27.5 (14.75-46) N=3	0.09
ICH score	3 (3-4) N=10	1 (1-1) N=1	0.12
Systolic BP (mmHg)	158.17±26.45	139.5±35.59	0.05
Blood sugar (mg/dL)	176.5±76.65	133.33±31.41	0.02
TLC (thousand/mm^3)	13,000 (11,341.5-16,000) N=20	9800 (8100-12,300) N=22	0.007
ALC (thousand/mm^3)	1624 (1344-2322) N=19	2229.7 (1423-2500) N=20	0.21
Ferritin (µg/L)	351 (190-990) N=10	188.6 (38-616) N=11	0.07
CRP (mg/L)	2.6 (0.8-14.66) N=16	9 (0.5-19) N=17	0.69
ESR (mm/h)	26 (15-34) N=13	17.5 (11-29) N=14	0.27
D-dimer (µg/mL)	2.15 (0.815-572.5) N=12	827 (166-3397) N=13	0.10
LDH (µcat/L)	305 (224-394) N=9	452 (231-615) N=8	0.56
NIHSS	16.5 (13-21) N=20	9 (2-15) N=21	0.004
Wake-up stroke	3 (13.64%)	1 (9.09%)	0.99
Door to CT time*	60 (16.5-83.5) N=20	25 (18-59) N=18	0.12
Intravenous thrombolysis†	2 (8.70%)	2 (9.09%)	0.90
CT to needle time*	15 (15-15)	36.5 (35-38)	0.09
Door to needle time*	32.5 (30-35)	44.5 (44-45)	0.12
Onset to needle time*	247.5 (240-255)	157.5 (90-225)	0.12
HT	17 (77.27%) N=22	15 (68.18%) N=22	0.73
DM	8 (36.36%) N=22	9 (40.91%) N=22	0.99
Previous stroke	5 (22.73%) N=22	5 (22.73%) N=22	0.99
Dyslipidemia	3 (14.28%) N=21	4 (19.04%) N=21	0.99
Smoking	3 (14.28%) N=21	6 (27.27%) N=22	0.45
CAD	4 (23.52%) N=17	1 (4.54%) N=22	0.99

Contd..

Table 4: Contd..

	Died	Survived	*P*
Alcohol use	5 (22.73%) N=22	15 (68.18%) N=22	0.99
Renal dysfunction	6 (27.27%) N=22	2 (9.09%) N=22	0.24
Echocardiography	7 (30.43%) N=23	14 (63.64%) N=22	0.03
Holter	3 (13.04%) N=23	7 (33.33%) N=21	0.11
Any vascular imaging	4 (17.39%) N=23	10 (45.45%) N=22	0.09
TOAST			
LAD-EC	1 (14.29%)	1 (6.67%)	0.99
LAD- C	1 (14.29%)	2 (13.33%)	
Small vessel disease	1 (14.29%)	2 (13.33%)	
Cardioembolic	2 (28.57%)	4 (26.67%)	
Indeterminate	2 (28.57%)	4 (26.67%)	
Other determinate	0 (0%) N=7	2 (13.33%) N=15	
Surgical intervention (s)	1 (6.25%) N=16	1 (8.33%) N=12	0.99
Use of heparin	N=17	N=16	
Standard heparin	1 (5.88%)	5 (31.25%)	0.11
LMWH	8 (47.06%)	5 (31.25%)	
LMWH prophylactic	2 (11.76%)	4 (25%)	
None	6 (35.29%)	2 (12.50%)	
In-hospital complications	20 (90.91%) N=22	5 (25%) N=20	0.001
Total hospital stay (days)	9 (3-20) N=23	8 (4-16) N=22	0.91

Data are in *n* (%) or median (IQR). IS: ischemic stroke; ICH: intracerebral hemorrhage; CVT: cerebral venous thrombosis; NIHSS: National Institute of Health Stroke Scale; mRS: modified Rankin score; EVT: endovascular thrombectomy; HT: hypertension; DM: diabetes mellitus; TLC: total leucocyte count; LDH: lactate dehydrogenase; ALC: absolute lymphocyte count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ASPECTS: Alberta Stroke Program Early CT score; TOAST: Trial of ORG in acute ischemic stroke; LAD-EC: large artery disease extracranial; LAD-IC: large artery disease intracranial; LMWH: low-molecular-weight heparin; *duration in minutes; †when indicated in patients with acute ischemic stroke

Table 5: Comparison of patients symptomatic and asymptomatic for COVID-19

	Symptomatic	Asymptomatic	*P*
Total patients (N=52)	21	31	-
Age (years)	61.04±14.28	56.35±15.73	0.27
Gender (male/female)	15 (71.43%)	20 (64.52%)	0.60
	6 (28.57%)	11 (35.48%)	
Type of stroke			
IS	14 (66.67)	19 (63.53%)	0.99
ICH	7 (33.33%)	10 (33.33%)	
CVT	0 (0.00%)	1 (3.33%)	
Systolic BP (mmHg)	156.47±25.82	146.70±35.5098	0.28
Blood sugar (mg/dL)	148.55±46.433	160.67±68.79	0.49
	N=20	N=28	
TLC (thousand/mm^3)	12,480 (12,040-15,800)	9700 (7900-13,000)	0.004
	N=19	N=29	
ALC (thousand/mm^3)	2003.07 (1476-4477)	1624 (1216-2365.2)	0.11
	N=18	N=27	
Ferritin (µg/L)	429 (312-616)	189.3 (51.8-782.3)	0.17
	N=9	N=12	
CRP (mg/L)	1.1 (5-5.4)	21 (8-170)	0.28
	N=17	N=19	
ESR (mm/h)	29 (15-38)	20 (11-26)	0.10
	N=13	N=17	
D-dimer (µg/mL)	381.5 (1-2200)	1.55 (0.82-827)	0.16
	(0.56-18,140)	(0.6-9740)	
	N=14	N=14	
LDH (µcat/L)	6.31 (3.59-10.64)	5.04 (3.74-7.58)	0.32
	N=7	N=10	
NIHSS	14 (8-18)	10.5 (3-16)	0.29
	N=19	N=30	
ICH volume (mL)	15 (14.5-23)	42 (32-53)	0.02
	N=7	N=7	
ICH score	5 (1-3)	7 (2-4)	
	N=5	N=7	
Wake-up stroke	2 (9.52%)	6 (19.35%)	0.44
Door to CT time*	60 (15-87)	25 (10-60)	0.16
	N=19	N=10	
ASPECTS score	6.76±2.86	6.83±2.72	0.95
	N=13	N=18	
Occlusion	4 (44.44%)	4 (40%)	0.99
Intravenous thrombolysis†			
	1 (4.76%)	3 (9.68%)	0.91
CT to needle time*	38 (38-38)	15 (15-35)	-
	N=1	N=3	
Door to needle time*	44 (44-44)	35 (30-45)	-
	N=1	N=3	
Onset to needle time *	225 (225-225)	240 (90-255)	-
	N=1	N=3	
HT	17 (85%)	19 (61.29%)	0.11
	N=20	N=31	

Contd..

Table 5: Contd...

	Symptomatic	Asymptomatic	*P*
DM	11 (55%) N=20	8 (25.81%) N=31	0.03
Previous stroke	3 (15%) N=20	8 (25.81%) N=31	0.43
Dyslipidemia	3 (15%) N=20	4 (14.29%) N=28	0.99
Smoking	7 (35%) N=20	5 (16.13%) N=31	0.17
CAD	5 (25%) N=20	1 (3.23%) N=31	0.02
Alcohol use	5 (25%) N=20	6 (19.35%) N=31	0.73
Renal dysfunction	2 (10%) N=20	6 (19.35% N=31	0.68
Echocardiography	12 (57.14%) N=21	10 (32.25%) N=31	0.07
Holter	8 (38.10%) N=21	2 (6.67%) N=30	0.006
Any vascular imaging	5 (23.81%)	9 (29.03%)	0.87
Surgical intervention (s)	0 (0.00%) N=14	2 (10.53%) N=19	0.49
Use of heparin	N=17	N=22	
Standard heparin	3 (17.65%)	3 (13.64%)	0.22
LMWH	7 (41.18%)	9 (40.91%)	
LMWH prophylactic	5 (29.41%)	2 (9.09%)	
None	2 (11.76%)	8 (36.36%)	
HCQS	10 (52.63%) N=19	22 (78.57%) N=28	0.12
Remdesivir	1 (5.26%) N=19	0 (0.00) N=28	0.11
Doxycycline	4 (21.05%) N=19	6 (21.43%) N=28	0.23
Ivermecttin	8 (42.11%) N=19	6 (21.43%) N=28	0.06
Methylprednisolone	4 (21.05%) N=19	7 (25%) N=28	0.21
Dexamethasone	6 (31.58%) N=19	6 (21.43%) N=28	0.06
In-hospital complications	12 (60%) N=20	14 (48.28%) N=29	0.56
Total hospital stay (days)	12 (7-20) N=21	7 (3-11) N=31	0.41
In-hospital mortality	8 (38.10%) N=21	14 (45.16%) N=31	0.77
3-months mortality	9 (50%) N=18	14 (51.85%) N=27	0.90
mRS 0-2 at 3 months	4 (22.22%) N=18	11 (40.74%) N=27	0.33

Data are in *n* (%) or median (IQR). IS: ischemic stroke; ICH: intracerebral hemorrhage; CVT: cerebral venous thrombosis; mRS: modified Rankin score; NIHSS: National Institute of Health Stroke Scale; EVT: endovascular thrombectomy; HT: hypertension; DM: diabetes mellitus; CAD: coronary artery disease; TLC: total leucocyte count; LDH: lactate dehydrogenase; ALC: absolute lymphocyte count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ASPECTS: Alberta stroke program early CT score; LMWH: low-molecular-weight heparin; HCQS: hydroxychloroquine; mRS: modified Rankin score; *duration in minutes; †when indicated in patients with acute ischemic stroke

Table 6: Comparison of patients of ischemic stroke with and without COVID-19

	COVID-19 positive	COVID-19 negative	*P*
Total patients	33	274	-
Age (years)	57.39±15.32	62.35±14.51	0.06
Gender (male/female)	19 (57.58%) 14 (42.42%)	189 (68.98%) 85 (31.02%)	0.18
Systolic BP (mmHg)	146.51±21.27 N=33	148.18±23.90 N=272	0.70
Blood sugar (mg/dL)	164.25±69.34 N=32	144.15±60.81 N=269	0.08
Acute vascular imaging*	15 (45.45%)	219 (79.92%)	<0.0001
Occlusion	8 (44.44%) N=18	106 (46.29%) N=229	0.88
TLC (thousand/mm^3)	10,600 (8160-13,000) N=29	8600 (6450-10,500) N=297	0.002
ALC (thousand/mm^3)	2010 (1400-2500) N=29	1904 (1436.2-2436) N=265	0.62
Ferritin (µg/L)	321 (90-616) N=13	101.78 (61-256) N=14	0.18
CRP (mg/L)	102.2 (11-540) N=23	12.29 (5-71) N=63	0.004
ESR (mm/h)	22 (11-34) N=21	10 (6-27) N=189	0.03
D-dimer (µg/mL)	234 (0.84-833.8) N=19	1.5 (0.5-166) N=10	0.06
LDH (µcat/L)	6.45 (2.66-9.34) N=8	4.91 (4.05-6.36) N=16	0.56
NIHSS	12 (7-15.5) N=32	8 (4-13) N=274	0.01
ASPECTS	6.80±2.73 N=31	8.05±2.02 N=249	0.009
Wake-up stroke	4 (12.12%)	36 (13.14%)	0.87
Door to CT time†	30 (15-87) N=27	30 (15-37) N=491	0.15
Intravenous Thrombolysis ‡	4 (13.79%) N=29	56 (20.51%) N=273	0.53
CT to needle time†	25 (15-36.5) N=4	30 (20-40) N=63	0.41
Door to needle time†	38.5±7.23 N=4	57.75±27.34 N=62	0.08
Onset to needle time†	202.5±75.99 N=4	205.93±108.68 N=64	0.54
EVT ‡	0 (0.00) N=8	9 (8.73%) N=103	0.99
HT	22 (68.75%) N=32	185 (67.51%) N=274	0.88
DM	13 (40.63%) N=32	142 (51.82%) N=274	0.23

Contd..

Table 6: Contd..

	COVID-19 positive	COVID-19 negative	*P*
Previous stroke	8 (25%)	38 (13.87%)	0.09
	N=32	N=274	
Dyslipidemia	6 (12.5%)	53 (19.41%)	0.86
	N=48	N=273	
Smoking	8 (25%)	45 (16.42%)	0.22
	N=32	N=274	
CAD	4 (12.50%)	51 (18.61%)	0.39
	N=32	N=274	
Echocardiography	17 (51.52%)	251 (91.61%)	<0.0001
	N=33	N=274	
Holter	7 (21.88%)	217 (79.20%)	<0.0001
	N=32	N=274	
Any vascular imaging	14 (42.42%)	242 (88.32%)	<0.0001
	N=33	N=274	
TOAST etiology			
LAD-EC	2 (7.69%)	54 (20.00%)	0.06
LAD-IC	3 (11.54%)	63 (23.33%)	
Small vessel disease	4 (15.38%)	47 (17.41%)	
Cardioembolic	8 (30.77%)	43 (15.93%)	
Indeterminate	7 (26.92%)	58 (21.48%)	
Other determinate	2 (7.69%)	5 (1.85%)	
	N=26	N=270	
Surgical intervention (s)	1 (6.25%)	12 (15.58%)	0.32
	N=16	N=77	
Use of heparin	N=27	N=334	
Standard heparin	6 (22.22%)	0 (0.00)	<0.0001
LMWH	10 (37.04%)	18 (7.79%)	
LMWH Prophylactic	5 (18.52%)	13 (5.63%)	
None	6 (22.22%)	200 (85.58%)	
In-hospital complications	16 (50%)	27 (15.81%)	<0.0001
	32	N=272	
In-hospital mortality	11 (33.33%)	18 (6.59%)	<0.0001
	N=33	N=273	
Cause of death			
Vascular	1 (3.03%)	4 (22.22%)	0.10
Nonvascular	10 (30.30%)	6 (3.33%)	
Unknown	2 (6.06%)	6 (33.33%)	
Both vascular and nonvascular	0 (0.00)	2 (11.11%)	
	N=13	N=18	
mRS 0-2 at 3 months	12 (41.34%)	178 (69.26%)	<0.0001
	N=29	N=257	
3-months mortality	12 (41.38%)	31 (12.06%)	<0.0001
	N=29	N=257	
Total hospital stay (days)	9 (4-18)	4 (2-8)	0.001
	N=33	N=271	

Data are in *n* (%) or median (IQR). NIHSS: National Institute of Health Stroke Scale; mRS: modified Rankin score; EVT: endovascular thrombectomy; HT: hypertension; DM: diabetes mellitus; TLC: total leucocyte count; LDH: lactate dehydrogenase; ALC: absolute lymphocyte count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ASPECTS: Alberta Stroke Program Early CT score; TOAST: Trial of ORG in acute ischemic stroke; LAD-EC: large artery disease extracranial; LAD-IC: large artery disease intracranial; ; LMWH: low-molecular-weight heparin; *Vascular imaging at the time of presentation in patients with ischemic stroke; †duration in minutes; ‡when indicated in patients with acute ischemic stroke

Table 7: Comparison of patients of hemorrhagic stroke with and without COVID-19

	COVID-19 positive	COVID-19 negative	*P*
Total patients	17	76	-
Age (years)	60.29±14.46	56.59±12.59	0.28
Gender (male/female)	15 (88.24%) 2 (11.76%)	54 (71.05%) 22 (28.95%)	0.14
Systolic BP (mmHg)	161.64±46.08	156.05±30.51	0.53
Blood sugar (mg/dL)	141±31.44 N=14	135.19±39.77 N=72	0.60
TLC (thousand/mm^3)	12,900 (11,800-15,000) N=17	8955 (7760-12,160) N=72	0.0001
ALC (thousand/mm^3)	1713.6 (1560-2322) N=14	1747 (1135.5-2628.25) N=72	0.67
Ferritin (µg/L)	243.3 (134-544) N=8	265.1 (64-377.6) N=3	0.54
CRP (mg/L)	8.5 (2.9-77.5) N=12	93.24 (93-190.15) N=20	0.07
ESR (mm/h)	22 (15-28) N=8	14 (8-37.5) N=40	0.36
D-dimer (µg/mL)	97.15 (0.8-4106.5) N=8	0.6 (0.6-0.6) N=1	0.11
LDH (µcat/L)	5.08 (4.73-7.56) N=9	4.66 (3.3-6.16) N=6	0.31
NIHSS	14 (6-20) N=15	11 (6-18) N=53	0.83
ICH volume (mL)	24.5 (15-42) N=14	21 (9.6-35) N=56	0.33
ICH score	3 (2-4) N=12	2 (1-3) N=44	0.11
Wake-up stroke	4 (23.53%)	8 (10.53%)	0.14
Door to CT time*	59.5 (29-75) N=16	28 (17-40) N=71	0.02
HT	13 (76.47%) N=17	68 (89.47%) N=76	0.14
DM	6 (35.29%) N=17	25 (32.89%) N=76	0.85
Previous stroke	3 (17.65%) N=17	8 (10.53%) N=76	0.41
Dyslipidemia	1 (5.88%) N=17	6 (7.89%) N=76	0.77
Smoking	3 (17.65%) N=17	11 (14.47%) N=76	0.74
CAD	2 (11.76%) N=17	9 (11.84%) N=76	0.99
Alcohol use	5 (29.41%) N=17	10 (13.16%) N=76	0.10
Renal dysfunction	4 (23.53%) N=17	3 (3.95%) N=76	0.006
Echocardiography	5 (29.41%) N=17	50 (65.79%) N=76	0.006
Surgical intervention (s)	1 (6.67%) N=15	18 (31.58%) N=57	0.05
Use of heparin	N=10	N=48	
LMWH therapeutic	5 (50.00%)	0 (0.00)	<0.0001
LMWH prophylactic	1 (10.00%)	10 (20.83%)	
None	4 (40.00%)	38 (79.17%)	

Contd..

Table 7: Contd..

	COVID-19 positive	COVID-19 negative	*P*
In-hospital complications	10 (66.67%) N=15	19 (25.33%) N=75	0.002
In-hospital mortality	11 (64.71%) N=17	9 (12%) N=75	<0.0001
Cause of death			
Vascular	2 (11.76%)	4 (36.36%)	0.41
Nonvascular	6 (35.29%)	3 (27.27%)	
Unknown	2 (11.76%)	3 (27.27%)	
Both vascular and nonvascular	0 (0.00) N=10	1 (9.09%) N=11	
mRS 0-2 at 3 months	2 (13.34%) N=15	39 (54.92%) N=71	0.003
3-months mortality	11 (73.33%) N=15	14 (19.72%) N=71	<0.0001
Total hospital stay (days)	9 (5-12) N=17	7 (3-16) N=74	0.001

Data are in *n* (%) or median (IQR). ICH: intracerebral hemorrhage; NIHSS: National Institute of Health Stroke Scale; mRS: modified Rankin score. HT: hypertension; DM: diabetes mellitus; TLC: total leucocyte count; LDH: lactate dehydrogenase; ALC: absolute lymphocyte count; CRP: C-reactive protein; LMWH: low-molecular-weight heparin. ESR: erythrocyte sedimentation rate; *duration in minutes

Conclusions

Stroke associated with COVID-19 is associated with higher stroke severity, morbidity, and mortality. The presence of COVID-19 and baseline stroke severity are independent risk factors for mortality. Multidisciplinary care and advances in understanding these comorbidities will help in improving outcomes among patients.

Acknowledgments

Ayush Mohan, Sudhir Pachipala, Biswamohan Misra, Yogesh PM, Manish Shalunke, Pranjal Gupta, Archana Sharma, Deepak Yadav, Mohit Anand, Rahul Singhal, Rahul Onam, Prashant Bhatale, Seetha Lakshmi, Saranya Gomathy, Priyanka Sehrawat, Kamlesh Tayade, Ankit Goyal, Akhil Sahib, Govinda Siripurapu, Srujana Billa, Saman Fatima, Satish Barki, Pedapati Radhakrishna.

We thank all the faculty, residents, and nursing staff who were involved in the management of stroke patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, *et al*. Extrapulmonary manifestations of COVID-19. Nat Med 2020;26:1017–32.
2. Bhatia R, Srivastava MVP. COVID-19 and stroke: Incidental, triggered or causative. Ann Indian Acad Neurol 2020;23:318-24.
3. Ahmad I, Rathore FA. Neurological manifestations and complications of COVID-19: A literature review. J Clin Neurosci 2020;77:8-12.
4. Mathew T, John SK, Sarma G, Nadig R, Kumar RS, Murgod U. COVID-19-related strokes are associated with increased mortality and morbidity: A multicenter comparative study from Bengaluru, South India. Int J Stroke 2020;16:429-436.
5. Trejo-Gabriel-Galán JM. Stroke as a complication and prognostic factor of COVID-19. Neurologia (Engl Ed) 2020;35:318-22.
6. Belani P, Schefflein J, Kihira S, Rigney B, Delman BN, Mahmoudi K, *et al*. COVID-19 is an independent risk factor for acute ischemic stroke. AJNR Am J Neuroradiol 2020;41:1361-4.
7. Bhatia R, Pedapati R, Komakula S, Srivastava MVP, Vishnubhatla S, Khurana D. Stroke in coronavirus disease 2019: A systematic review. J Stroke 2020;22:324–35.
8. Benussi A, Pilotto A, Premi E, Libri I, Giunta M, Agosti C, *et al*. Clinical characteristics and outcomes of inpatients with neurologic disease and COVID-19 in Brescia, Lombardy, Italy. Neurology 2020;95:e910-20. doi: 10.1212/WNL.0000000000009848.
9. Mehrpour M, Shuaib A, Farahani M, Hatamabadi HR, Fatehi Z, Ghaffari M, *et al*. Coronavirus disease 2019 and stroke in Iran: A case series and effects on stroke admissions. Jun 26:1747493020937397. doi: 10.1177/1747493020937397. Epub ahead of print.
10. 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. Int J Stroke. 2021;16:437-447.
11. Agarwal A, Vishnu VY, Vibha D, Bhatia R, Gupta A, Das A, *et al*. Intracerebral hemorrhage and SARS-CoV-2: Association or causation. Ann Indian Acad Neurol 2020;23:261-4.
12. Yaghi S, Ishida K, Torres J, Brian MG, Eytan R, Kelley H, *et al*. SARS2-CoV-2 and stroke in a New York healthcare system. Stroke 2020;51:2002–11.
13. Aggarwal G, Lippi G, Michael Henry B. Cerebrovascular disease is associated with an increased disease severity in patients with coronavirus disease 2019 (COVID-19): A pooled analysis of published literature. Int J Stroke 2020;15:385-9.
14. Yang D, Xiao Y, Chen J, Chen Y, Luo P, Liu Q, *et al*. COVID-19 and chronic renal disease: Clinical characteristics and prognosis. QJM 2020;113:799-805.
15. Diegoli H, Magalhães PSC, Martins SCO, Morro CHC, Franca PHC, Safanelli J, *et al*. Decrease in hospital admissions for transient ischemic attack, mild, and moderate stroke during the COVID-19 era. Stroke 2020;51:2315-21.
16. Hoyer C, Ebert A, Huttner HB, Puetz V, Kallmünzer B, Barlinn K, *et al*.

Acute stroke in times of the COVID-19 pandemic: A multicenter study. Stroke 2020;51:2224-7.
17. Sylaja PN, Srivastava MVP, Shah S, Bhatia R, Khurana D, Sharma A, *et al*. The SARS-CoV-2/COVID-19 pandemic and challenges in stroke care in India. Ann N Y Acad Sci 2020;1473:3-10.
18. Bhatia R, Sylaja PN, Srivastava MVP, Khurana D, Pandian JD, Suri V, *et al*. Consensus statement-Suggested recommendations for acute stroke management during the COVID-19 pandemic: Expert Group on Behalf of the Indian Stroke Association. Ann Indian Acad Neurol 2020;23(Suppl 1):S15-23.
19. Khosravani H, Rajendram P, Notario L, Chapman MG, Menon BK. Protected code stroke: Hyperacute stroke management during the coronavirus disease 2019 (COVID-19) pandemic. Stroke 2020;51:1891-5.
20. Schirmer CM, Ringer AJ, Arthur AS, Binning MJ, Fox WC, James RF, *et al*. Delayed presentation of acute ischemic strokes during the COVID-19 crisis. J Neurointerv Surg 2021;2:639-42.
21. Chowdhury T, Rizk AA, Daniels AH, Al Azazi E, Sharma D, Venkatraghavan L. Management of acute ischemic stroke in the interventional neuroradiology suite during the COVID-19 pandemic: A global survey. J Neurosurg Anesthesiol 2021;33:44-50.
22. Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, *et al*. COVID-19 and Thrombotic or thromboembolic disease: Implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. J Am Coll Cardiol 2020;75:2950-73.
23. Bikdeli B, Madhavan MV, Gupta A, Jimenez D, Burton JR, Der Nigoghossian C, *et al*. Pharmacological agents targeting thromboinflammation in COVID-19: Review and implications for future research. Thromb Haemost 2020;120:1004-24.
24. Hernández-Fernández F, Sandoval Valencia H, Barbella-Aponte RA, Collado-Jiménez R, Ayo-Martín Ó, Barrena C, *et al*. Cerebrovascular disease in patients with COVID-19: Neuroimaging, histological and clinical description. Brain 2020;143:3089-103.
25. Castro RA, Frishman WH. Thrombotic complications of COVID-19 infection: A review. Cardiol Rev 2021;29:43-7.
26. Zeng F, Huang Y, Guo Y, Yin M, Chen X, Xiao L, *et al*. Association of inflammatory markers with the severity of COVID-19: A meta-analysis. Int J Infect Dis 2020;96:467-74.
27. Pérez CA. Looking ahead: The risk of neurologic complications due to COVID-19. Neurol Clin Pract 2020;10:371-4.
28. Tan YK, Goh C, Leow AST, Tambyah PA, Ang A, Yap ES, *et al*. COVID-19 and ischemic stroke: A systematic review and meta-summary of the literature. J Thromb Thrombolysis 2020;50:587-95.
29. Ntaios G, Michel P, Georgiopoulos G, Guo Y, Li W, Xiong J, *et al*. Characteristics and outcomes in patients with COVID-19 and acute ischemic stroke: The global COVID-19 stroke registry. Stroke 2020;51:e254-8.
30. Huang G, Kovalic AJ, Graber CJ. Prognostic value of leukocytosis and lymphopenia for coronavirus disease severity. Emerg Infect Dis 2020;26:1839–41.
31. Yamada T, Wakabayashi M, Yamaji T, Chopra N, Mikami T, Miyashita H, *et al*. Value of leukocytosis and elevated C-reactive protein in predicting severe coronavirus 2019 (COVID-19): A systematic review and meta-analysis. Clin Chim Acta 2020;509:235–43.