Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Intravenous tPA for Acute Ischemic Stroke in Patients with COVID-19

Thiago Carneiro, MD,* Jonathan Dashkoff, MD, PhD,* Lester Y. Leung, MD, MSc,† Christa O'Hana S. Nobleza, MD, MSCI,‡ Erika Marulanda-Londono, MD,§ Mausaminben Hathidara, MD,§ Sebastian Koch, MD,§ Nicole Sur, MD,§ Alexandra Boske, MD,¶ Barbara Voetsch, MD, PhD,# Hassan Aboul Nour, MD,‖ Daniel J Miller, MD,‖ Ali Daneshmand, MD, MPH,* Julie Shulman, MD,* Gioacchino Curiale, MD,* David M. Greer, MD, MA,* Jose Rafael Romero, MD,*** Pria Anand, MD,*[,1] and Anna M. Cervantes-Arslanian, MD*[,1]

Background/Purpose: Coronavirus disease 2019 (COVID-19) is associated with increased risk of acute ischemic stroke (AIS), however, there is a paucity of data regarding outcomes after administration of intravenous tissue plasminogen activator (IV tPA) for stroke in patients with COVID-19.

Methods: We present a multicenter case series from 9 centers in the United States of patients with acute neurological deficits consistent with AIS and COVID-19 who were treated with IV tPA.

Results: We identified 13 patients (mean age 62 (±9.8) years, 9 (69.2%) male). All received IV tPA and 3 cases also underwent mechanical thrombectomy. All patients had systemic symptoms consistent with COVID-19 at the time of admission: fever (5 patients), cough (7 patients), and dyspnea (8 patients). The median admission NIH stroke scale (NIHSS) score was 14.5 (range 3−26) and most patients (61.5%) improved at follow up (median NIHSS score 7.5, range 0−25). No systemic or symptomatic intracranial hemorrhages were seen. Stroke mechanisms included cardioembolic (3 patients), large artery atherosclerosis (2 patients), small vessel disease (1 patient), embolic stroke of undetermined source (3 patients), and cryptogenic with incomplete investigation (1 patient). Three patients were determined to have transient ischemic attacks or aborted strokes. Two out of 12 (16.6%) patients had elevated fibrinogen levels on admission (mean 262.2 ± 87.5 mg/dl), and 7 out of 11 (63.6%) patients had an elevated D-dimer level (mean 4284.6 ±3368.9 ng/ml).

Conclusions: IV tPA may be safe and efficacious in COVID-19, but larger studies are needed to validate these results.

Keywords: IV tPA—ischemic stroke—COVID-19—thrombolysis

From the *Department of Neurology, Boston University School of Medicine, 72 East Concord Street, Collamore C3 Neurology, Boston, MA 02118, United States; †Department of Neurology, Stroke and Cerebrovascular Diseases Division, Tufts Medical Center, Boston, MA, United States; ‡Department of Neurology, Neuroscience Critical Care Division, University of Mississippi Medical Center, Jackson, MS, United States; §Department of Neurology, University of Miami Miller School of Medicine, Miami, FL, United States; ¶Department of Neurology, Saint David's Round Rock Medical Center, Round Rock, TX, United States; #Department of Neurology, Lahey Hospital and Medical Center, Burlington, MA, United States; ‖Department of Neurology, Henry Ford Hospital, Wayne State University, Detroit, MI, United States; and **NHLBI's Framingham Heart Study, Framingham, MA, United States.

Received July 7, 2020; revision received July 20, 2020; accepted July 22, 2020.

Corresponding author. E-mail: pria2@bu.edu.

[1]These authors share senior authorship.

1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.105201

Introduction

Preliminary reports suggest that patients with Coronavirus Disease 2019 (COVID-19) are at high risk of hematologic complications, including disseminated intravascular coagulation (DIC).[1−3] Patients with COVID-19 may exhibit hemostatic abnormalities with the potential to precipitate both hemorrhagic and thromboembolic events, including mild thrombocytopenia, prolongation of both prothrombin time and international normalized ratio, and shortened activated partial thromboplastin time, and both ischemic stroke and intracerebral hemorrhage have been described in infected patients.[4−7] However, limited evidence exists in the literature for management of acute stroke in COVID-19 given the concomitant risk of hemorrhage, and recommendations are based on consensus only.[8]

The safety and efficacy of intravenous tissue plasminogen activator (IV tPA) for acute ischemic stroke in patients with COVID-19 remain unknown.[1] We present the outcomes of a multicenter series of patients with confirmed COVID-19 infection who were treated with IV tPA for suspected acute ischemic stroke.

Methods

All patients with COVID-19 who received IV tPA for acute neurological deficits between March 1, 2020 and July 1, 2020 were identified at the participating hospitals by the corresponding stroke provider at each institution. The study protocol was approved or given exemptions by local institutional review boards. All patients included were diagnosed with COVID-19 by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RT-PCR from a nasopharyngeal swab, presented with acute neurological deficits (< 24 h), received IV tPA per acute ischemic stroke American Heart Association guidelines, and underwent brain and intracranial vessel imaging.[9] Laboratory values were obtained within 24 hours of admission (Table 1). Stroke mechanism was primarily defined using the TOAST classification, with some strokes classified as embolic strokes of undetermined source (ESUS). [10,11]

Results

Patient characteristics

A total of 13 patients were identified at 9 centers. Mean age was 62 (±9.8) years, and 9 (69.2%) were male (Table 1). Median NIH stroke scale (NIHSS) score on admission was 14.5 (range 3−26). Eleven patients were treated within the standard window (4.5 h) with mean elapsed time between last known well and IV tPA administration of 155.4 (±24.2) min. One patient was treated with IV tPA in an extended window based on MRI/CT perfusion findings (600 min). One patient had IV tPA administered beyond the standard window based on clinical decision making with the patient (280 min).

CT angiography revealed large vessel occlusion (LVO) in 8 cases (61.5%) and MRI brain confirmed acute ischemic stroke in 4 cases (30.7%). Cerebral digital subtraction angiogram was performed in 4 (30.7%) patients. Three underwent thrombectomy, achieving thrombolysis in cerebral infarction (TICI) 3 reperfusion without complications, while one patient was found to have patent large vessels after IV tPA administration. The other four patients with LVO were not considered for thrombectomy due to unfavorable anatomy with proximal vessel stenosis or had intact collateral circulation with blood flow reconstitution distal to the occlusion site.

Stroke mechanisms included cardioembolic (3 patients), large artery atherosclerosis (2 patients), small vessel disease (1 patient), ESUS (3 patients) or cryptogenic with incomplete investigation (1 patient). Three patients were determined to have transient ischemic attacks (TIAs) or aborted strokes.

Systemic symptoms of COVID-19 were present in all patients, including fever (5 patients), cough (7 patients), and dyspnea (8 patients). Two out of 12 (16.6%) patients with fibrinogen levels tested had elevated fibrinogen levels on admission (mean 262.2 ± 87.5 mg/dl), and 7 out of 11 (63.6%) patients with D-dimer levels tested had an elevated D-dimer level (mean 4284.6 ±3368.9 ng/ml).

Safety and efficacy of IV tPA

No patients had symptomatic systemic or intracranial hemorrhage. One patient developed asymptomatic petechial hemorrhage in the area of infarction noted on routine follow-up imaging at 24 h. Median NIHSS score for patients with stroke at follow-up was 7.5 (range 0−25), and 8 (61.5%) patients had an improvement in their NIHSS score of 4 points or more. All patients survived to hospital discharge however one elderly patient was discharged to hospice because of severe respiratory symptoms.

Discussion

We describe a series of patients with COVID-19 who presented from the community and received IV tPA for acute ischemic stroke. In our series, intravenous thrombolysis was not associated with symptomatic complications, and the majority of patients had clinical improvement at follow-up.

Preliminary reports found a 1% incidence of stroke among hospitalized patients with COVID-19.[4,12] More recently, acute ischemic strokes have been noted in the early stages of illness, and LVO has been reported as the presenting symptom of COVID-19.[1,13,14] Patients with COVID-19 can also present with delirium, meningoencephalitis, and fever, which may be considered stroke mimics, posing a challenge in the evaluation for thrombolysis eligibility. [6,12] In 2 case series of LVO in patients with COVID-19, 45% of patients had encephalopathy at admission, suggesting that reduced level of consciousness could

Table 1. *Clinical characteristics of patients with acute neurological deficits and COVID-19*

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Age (years)	73	47	55	72	24	93	74	84	57	75
Sex	Male	Female	Male	Male	Male	Female	Male	Female	Male	Male
Medical history and stroke risk factors	Hypertension Dyslipidemia Smoking	Hypertension Diabetes	Hypertension Dyslipidemia	CAD	Diabetes Dyslipidemia Obesity Cocaine use	Atrial fibrillation CAD Hypertension	Stroke CAD Hypertension Cardiomyopathy	Stroke CAD Hypertension Dyslipidemia	CAD Hypertension Cocaine use	CAD Hypertension
Medications	None	Metformin	Olanzapine Valproic acid	None	None	Aspirin Clopidogrel Carvedilol	Aspirin Atorvastatin Lisinopril Metoprolol	Clopidogrel Hydrochlorothiazide Losartan Atenolol	None	Amlodipine Clonidine Metformin Metoprolol Simvastatin
NIHSS score at admission	7	8	17	26	18	16	21	13	10	24
NIHSS score at 24h	9	0	4	23	0	25 (intubated)	N/A	7	2	22
NIHSS score at last follow up	8 (day 11)	0 (day 3)	2 (day 12)	16 (day 2)	0 (day 1)	N/A (improvement noted)	0 (day 41)	7 (day 4)	0 (day 12)	19 (day 2)
Outcome status	Discharged to rehabilitation facility	Discharged home	Discharged to long term acute facility	Discharged home	Discharged home	Discharged to outpatient hospice.	Discharged home	Discharged home (baseline neurological exam)	Discharged to rehabilitation facility	N/A
Time to presentation	60 minutes	60 minutes	100 minutes	113 minutes	120 minutes	150 minutes	45 minutes	540 minutes	60 minutes	102 minutes
LKW to needle	160 minutes	100 minutes	150 minutes	184 minutes	165 minutes	180 minutes	120 minutes	600 minutes	115 minutes	225 minutes
Complications	None	None	None	Asymptomatic Petechial Hemorrhagic Transformation	None	None	None	None	None	None
Signs and symptoms of stroke	Right facial weakness Right hemiparesis Right sensory loss	Aphasia Right facial weakness Right hemiparesis Right hemisensory loss	Dysarthria Right hemiparesis, Altered mental status	Aphasia Right hemiparesis	Left hemiplegia Left hemisensory loss Left Homonymous Hemianopia Dysarthria	Left-sided weakness Dysarthria Neglect	Aphasia Right face weakness Right hemiplegia Right hemisensory loss	Right gaze deviation Right face weakness Right hemiparesis Right hemisensory loss	Vertigo Dysarthria Nausea Unsteady gait Left hemiparesis	Aphasia Right Hemiparesis Right hemianopia
Imaging	CT, CTA, MRI	CT, CTA, MRI, DSA	CT, CTA, MRI	CT, CTA	CT, CTA, CTP	CT, CTA, DSA	CT, CTA, DSA	CT, CTA CT Perfusion	CT, CTA, MRI	CT, CTA, MRI
Imaging Results	CTA: unremarkable MRI: Restricted diffusion in left internal capsule, left parietal and right frontal lobes	CTA: Left middle cerebral artery occlusion at M2 segment DSA: No evidence of LVO MRI: unremarkable	CTA: Left middle cerebral artery stenosis at M1 segment MRI: unremarkable	CTA: Left middle cerebral artery occlusion at distal M1 segment	CTA: Unremarkable	CT: Right frontotemporal hypodensity CTA: Right middle cerebral artery occlusion at distal M1 segment DSA: TICI III	CT: Old left frontal and right parietal hypodensities CTA: Left middle cerebral artery occlusion at M1 segment DSA: TICI III	CTA: Unremarkable MRI: Restricted diffusion in left ventral pons	CTA: Left vertebral occlusion /stenosis MRI: Restricted diffusion in both cerebellar hemispheres	CTA: Left middle cerebral artery occlusion at M2 segment L ICA thrombus MRI: Restricted diffusion in in left insula and left frontal and temporal lobes
Treatment for stroke	tPA	tPA	tPA	tPA	tPA	tPA and Thrombectomy TICI Score III	tPA and Thrombectomy TICI Score III	tPA	tPA	tPA
Covid-19 symptoms	Fever Cough Dyspnea	Cough	Fever Encephalopathy	Cough	Fever Dyspnea	Fever Dyspnea	Cough Dyspnea Malaise	Cough Dyspnea	Dyspnea	Cough
White cell count (1000/per mm3)	8.5	6.7	10.1	9.9	8.2	5.4	6.01	10.2	10.4	10.2
Absolute Lymphocyte count (1000/per mm3)	5.2	1.7	2.4	0.7	3.1	0.7	1.4	1.4	1.5	1.21
Platelet count (1000/per mm3)	213	291	209	186	142	214	173	402	207	280

(*Continued*)

Table 1 (*Continued*)

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Prothrombin time (sec)	13.3	15.8	11.2	13.5	14.1	10.8	14.8	12.6	13.1	10.5
Activated partial thromboplastin time (sec)	31	30	28	31.8	26	28.8	32.5	27.6	31.2	25.5
Fibrinogen (mg/dl)	463	101	206	266	217	N/A	613	154	56	410
D-dimer (ng/ml)	1892	266	895	5449	810	N/A	N/A	14831	341	5501
Ferritin (ng/ml)	123	118	36	336	2.207	552	N/A	674	177.5	229
Transthoracic echocardiogram	No LAE No RWA No cardiac shunt No cardiac thrombus	No LAE No intracardiac thrombus or vegetation. No RWA	N/A	N/A	No LAE No RWA No cardiac shunt No cardiac thrombus	LAE	N/A	N/A	No LAE No RWA No cardiac shunt No cardiac thrombus	No cardiac thrombus
Atrial Fibrillation	Not detected	Not detected	Not detected	Present	Not detected	Present	Not detected	Not detected	Not detected	Not detected
Stroke mechanism	ESUS	TIA/Aborted Stroke	TIA/Aborted Stroke	Cardioembolic (atrial fibrillation)	Cocaine Use TIA/ Aborted Stroke	Cardioembolic (atrial fibrillation)	Cryptogenic	SVD	Large artery atherosclerosis Cocaine use	Large artery atherosclerosis

be a common presenting symptom in patients with COVID-19-associated stroke.[1,13] In our series, 61.5% patients had large vessel occlusion, but only 7% developed encephalopathy. Of note, although the Wuhan findings suggested that stroke was more common among critically ill patients, the patients in our series presented from the community with mild viral illness.[4] Preliminary reports also suggest more severe illness in male patients with COVID-19, an observation that may be reflected in the male predominance of our cohort.

Growing evidence suggests SARS-CoV-2 infection is associated with a pro-thrombotic state. This process is mediated by an inflammatory cascade that leads to elevated D-dimer and fibrinogen levels, low anti-thrombin III levels and pulmonary congestion with microvascular thromboses, especially in critically ill patients.[2] A clot waveform analysis study in patients with COVID-19 demonstrated that hypercoagulability preceded or coincided with severe illness.[15] Anti-phospholipid antibodies have been detected in some COVID-19 patients with thromboembolic events, including those with LVOs and strokes.[13,16] Our study shows a wide distribution of stroke etiologies, suggesting that COVID-19 may increase the risk for stroke through a variety of mechanisms, including those seen in other viral disorders.[17] Further studies are required to elucidate stroke etiology and any causal relationship between SARS-CoV-2 infection and stroke.

IV tPA has been used anecdotally in COVID-19 to treat acute respiratory distress syndrome, but no published data exist specifically on the safety of IV tPA for acute ischemic stroke treatment.[2] COVID-19 may also increase the risk of systemic or cerebral hemorrhagic complications, and has also been reported in association with acute hemorrhagic necrotizing encephalopathy.[18] Our series suggests that symptomatic hemorrhagic complications with IV tPA in patients with COVID-19 are infrequent and lower than the rate of complications in the general population (between 2% and 3.3%), reiterating a pro-coagulable state rather than a bleeding disorder.[19,20] Larger studies correlating outcomes post-thrombolysis with hemostatic measures such as d-dimer, fibrinogen levels, and thromboelastography are needed to better understand which patients are most likely to safely benefit from IV tPA administration.

Post-mortem studies have found additional evidence of fibrin-rich thrombi in patients with COVID-19, raising concern that IV tPA may be of limited benefit in this patient population in the setting of prior studies demonstrating a lower efficacy of tPA thrombolysis in thrombi with high fibrin content compared with erythrocyte-rich emboli.[21,22] However, the majority of included patients had an NIHSS score improvement of 4 or more points and were discharged home, suggesting that IV tPA is efficacious in these patients. Given the small number of patients in our series, our observations should be taken with caution. The majority of patients in the study had moderate to severe

Table 1. *Continuation*

Variable	Patient 11	Patient 12	Patient 13
Age (years)	53	58	41
Sex	Female	Male	Male
Medical history and stroke risk factors	None	None	Hypertension Diabetes Heart Failure Morbid Obesity
Medications	None	None	Losartan Metformin Glipizide Furosemide
NIHSS score at admission	3	4	8
NIHSS score at 24h	1	3	21 (intubated)
NIHSS score at last follow up	0 (day 3)	3 (day 2)	19 (intubated day 24)
Outcome status	Home	Home	n/a
Time to presentation	133 minutes	122 minutes	85 minutes
LKW to needle	167 minutes	280 minutes	154 minutes
Complications	None	None	None
Signs and symptoms of stroke	Aphasia Right sensory loss	Aphasia Left Hemianopia	Dysarthria Right hemiparesis
Imaging	CT, CTA, CTP, DSA	CT, CTA	CT, CTA
Imaging Results	CTA: Left Middle Cerebral artery occlusion at M1 segment DSA: TICI III	CTA: Right middle cerebral artery occlusion at M2 segment	CT: Left temporoparietal and occipital hypodensities. Right parietal hypodensity. CTA: Unremarkable
Treatment for stroke	tPA Thrombectomy TICI III	tPA	tPA
Covid-19 symptoms	Fever Dyspnea	Cough Dyspnea	None
White cell count (1000/per mm3)	7.2	6.8	7.7
Absolute Lymphocyte count (1000/per mm3)	2.1	1.0	3.5
Platelet count (1000/per mm3)	210	464	223
Prothrombin time (sec)	12.8	13.5	14.2
Activated partial thromboplastin time (sec)	30	29	25pt
Fibrinogen (mg/dl)	265	132	266
D-dimer (ng/ml)	104	488	16.554
Ferritin (ng/ml)	65	446	740
Transthoracic echocardiogram	No LAE No cardiac thrombus	No LAE No cardiac thrombus	Cardiomyopathy EF 10% No cardiac thrombus
Atrial Fibrillation	Not detected	Not detected	Atrial tachycardias
Stroke mechanism	ESUS	ESUS	Cardioembolic

CT: computerized tomography
CTA: computed tomography angiography
CTP: CT perfusion
CAD: coronary artery disease
CMO: comfort measures only
DSA: Digital subtraction angiography
ESUS: Embolic stroke of undetermined source
LA: Left atrium
LAE: left atrial enlargement.
LKW: Last known well
LVO: Large vessel occlusion
N/A: Not available.
NIHSS: National Institutes of Health stroke scale
RWA: regional wall abnormality
SVD: Small vessel disease
TIA: Transient ischemic attack
TICI: Thrombolysis in cerebral infarction
Reference ranges:
White blood count: 4.500 to 11.000 per cubic millimeter
Absolute lymphocytes: 1.000 to 4.800 per cubic millimeter
Platelet count: 150.000 to 450.000 per cubic millimeter
Prothrombin time: 12.3 to 14.9 seconds
Activated partial-thromboplastin time: 25.4 to 34.9 seconds
Fibrinogen: 175 to 450 mg per deciliter;
D-dimer: 0 to 500 ng per milliliter
Ferritin: 30 to 400 ng per milliliter

strokes (median NIHSS 14.5) and presented from the community. Therefore, our results may not be generalizable to those with mild strokes or who are critically ill.

In spite of the uncertain hematologic effects of COVID-19, our findings suggest that IV tPA may be used safely in acute ischemic stroke patients with COVID-19 and is associated with improved outcomes. Larger studies are needed to better understand safety and efficacy in this patient population.

Author contributions

Dr. Carneiro contributed with writing and reviewing of the article.

Dr. Dashkoff contributed with writing and reviewing of the article.

Dr. Leung contributed with writing and reviewing of the article.

Dr. Nobleza contributed with writing and reviewing of the article.

Dr. Marulanda-Londono contributed with writing and reviewing of the article.

Dr. Hathidara contributed with writing and reviewing of the article.

Dr. Koch contributed with writing and reviewing of the article.

Dr. Sur contributed with writing and reviewing of the article.

Dr. Boske contributed with writing and reviewing of the article.

Dr. Voetsch contributed with writing and reviewing of the article.

Dr. Aboul Nour contributed with writing and reviewing of the article.

Dr. Miller contributed with writing and reviewing of the article.

Dr. Daneshmand contributed with writing and reviewing of the article.

Dr. Shulman contributed with writing and reviewing of the article.

Dr. Curiale contributed with writing and reviewing of the article.

Dr. Greer contributed with writing and reviewing of the article.

Dr. Romero contributed with writing and reviewing of the article.

Dr. Anand contributed with writing and reviewing of the article.

Dr. Cervantes-Arslanian contributed with writing and reviewing of the article.

Declaration of Competing Interest

None.

Acknowledgment: The authors have no acknowledgement.

References

1. Oxley T, Mocco J, Majiidi S, et al. Large-vessel stroke as a presenting feature of COVID-19 in the young. N Engl J Med 2020;382(20):e60.
2. Wang J, Hajizadeh N, Moore EE, et al. Tissue plasminogen activator (tPA) treatment for COVID-19 Associated Acute Respiratory Distress Syndrome (ARDS): a case series. J Thromb Haemost 2020. Available at http://doi.wiley.com/10.1111/jth.14828 Accessed April 16, 2020 .
3. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020;18:844-847.
4. Li Y, Wang M, Zhou Y, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. SSRN J 2020. Available at https://www.ssrn.com/abstract=3550025 Accessed April 16, 2020 .
5. Sharifi-Razavi A, Karimi N, Rouhani N. COVID-19 and intracerebral haemorrhage: causative or coincidental? New Microbes New Infect 2020;35:100669.
6. Olama M, Rahid A, Garozzo DCOVID-19-associated meningoencephalitis complicated with intracranial hemorrhage: a case report.
7. Oudkerk M, Büller HR, Kuijpers D, et al. Diagnosis, prevention, and treatment of thromboembolic complications in COVID-19: report of the National Institute for Public Health of the Netherlands [Published Online Ahead of Print, 2020]. Radiology. 2020;201629. https://doi.org/10.1148/radiol.2020201629.
8. Temporary Emergency Guidance to US Stroke Centers During the COVID-19 Pandemic. str. Epub2020.:STROKEAHA.120.030023.
9. Powers W, Rabinstein A, Ackerson T et al. Guidelines for the Early management of patients with acute ischemic stroke:2019Update to the 2018 Guidelines for the early Management of Acute Ischemic Stroke. Stroke. 2019 Dec;50(12):3331-3332.
10. Adams Jr HP, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24(1):35-41. https://doi.org/10.1161/01.str.24.1.35.
11. Hart RG, Diener HC, Coutts SB, et al. Embolic strokes of undetermined source: the case for a new clinical construct. Lancet Neurol 2014;13(4):429-438. https://doi.org/10.1016/S1474-4422(13)70310-7.
12. Mao L, Jin H, Wang M, et al. Neurological manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 2020. (published online).
13. Beyrouti R, Adams ME, Benjamin L, et al. Characteristics of ischaemic stroke associated with COVID-19. J Neurol Neurosurg Psychiatry 2020. jnnp-2020-323586.
14. Avula A, Nalleballe K, Narula N, et al. COVID-19 presenting as stroke. Brain Behav Immun 2020;S0889-1591(20)30685-1. https://doi.org/10.1016/j.bbi.2020.04.077.
15. Tan CW, Low JGH, Wong WH, Chua YY, Goh SL, Ng HJ. Critically ill COVID-19 infected patients exhibit increased clot waveform analysis parameters consistent with hypercoagulability. Am J Hematol 2020;95(7):e156-e158.
16. Zhang Y. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. N Engl J Med 2020;382:e38.
17. Grau AJ, Buggle F, Becher H, et al. Recent bacterial and viral infection is a risk factor for cerebrovascular ischemia: clinical and biochemical studies. Neurology 1998;50:196-203.

18. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19 – associated acute hemorrhagic necrotizing encephalopathy: CT and MRI features. Radiology 2020:201187.
19. Yaghi S, Boehme AK, Dibu J, et al. Treatment and outcome of thrombolysis-related hemorrhage: a multicenter retrospective study. JAMA Neurol 2015;72(12):1451-1457. https://doi.org/10.1001/jamaneurol.2015.2371.
20. Thomalla G, Simonsen CZ, Boutitie F, et al. MRI-guided thrombolysis for stroke with unknown time of onset. N Engl J Med 2018;379(7):611-622. https://doi.org/10.1056/NEJMoa1804355.
21. Carsana L, Sonzogni A, Nasr A, et al. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study [published online ahead of print. Lancet Infect Dis 2020; S1473-3099(20)30434-5. https://doi.org/10.1016/S1473-3099(20)30434-5.
22. Singh P, Kaur R, Kaur A. Clot composition and treatment approach to acute ischemic stroke: The road so far. Ann Indian Acad Neurol 2013;16(4):494-497. https://doi.org/10.4103/0972-2327.120433.