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.

Recombinant tissue plasminogen activator (rTPA) management for first onset acute ischemic stroke with covid -19 and non-covid -19 patients

Eman M Khedr,[a] Ahmed Abdelwarith,[b] Gehad Moussa,[b] and Mostafa Saber,[b]

Objectives: Cerebrovascular stroke (CVS) is one of the well-known complications of coronavirus-2019 (Covid-19), but less is known about the outcome and safety of thrombolytic therapy in these patients. In this study we compare the efficacy and safety of Tissue plasminogen activator (rTPA) in acute ischemic stroke (AIS) patients with or without Covid-19 infection. *Materials and methods:* A comparative prospective study in which all patients who presented with AIS and eligible for rTPA were recruited from the emergency department and classified into 2 groups (AIS with Covid-19 infection and AIS without Covid-19 as controls). Demographic data, symptoms of Covid-19, clinical examination, neuroimaging, and laboratory investigations were obtained in each patient. National Institute of Health Stroke Scale (NIHSS) and the Modified Rankin Scale (mRS) were assessed before, immediately after rTPA, and 3 months later. *Results:* There were 22 patients in the COVID-19 group and 25 control patients. Those with COVID-19 were more likely to have a history of smoking and Diabetes Mellitus than controls. On admission, motor symptoms were more severe in patients with COVID-19. COVID-19 patients were more likely to have symptomatic intra-cerebral hemorrhage and radiological hemorrhagic transformation than controls. Onset to door time (ODT) and onset to successful reperfusion time were significantly longer in Covid-19 patients than controls. Clinical improvement and frequency of re-occlusion and recurrent ischemic stroke at 3 months follow-up did not differ between groups, although there was higher number of deaths (27.3%) in the Covid-19 group than controls (16%). *Conclusions:* Using rTPA is safe and effective in patients with AIS with or without COVID-19 infection despite the high frequency of hemorrhagic transformation and high number of deaths.

Keywords: Covid-19—Recombinant tissue plasminogen activator—Acute ischemic stroke—Outcomes

Abbreviation: AIS, acute ischemic stroke; CVS, cerebrovascular stroke; rTPA, tissue plasminogen activator; Covid-19, coronavirus-2019; ODT, onset to door time; IV, intravenous; PCR, polymerase chain reaction; NIHSS score, National Institute of Health Stroke Scale; ASPECTS, Alberta stroke programme early CT score; ECASS II, European Cooperative Acute Stroke Study II; GIT, Gastrointestinal tract; GCS, Glasgow coma scale; MRS, Modified Rankin Scale; NAChR, nicotinic acetylcholine receptor; ECASII, radiological hemorrhagic transformation; LVO, large vessel occlusion

From the [a]Department of Neurology and Psychiatry, Faculty of Medicine, Assiut University, Assiut, Egypt; and [b]Department of Neuropsychiatry, Aswan University, Aswan, Egypt.

Received October 22, 2022; revision received January 19, 2023; accepted January 20, 2023.

Corresponding author. E-mails: emankhedr99@aun.edu.eg, emankhedr99@yahoo.com.

1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2023.107031

Introduction

Acute ischemic stroke (AIS) is one of the prominent causes of morbidity and mortality globally and is time sensitive medical emergency. The only medication now known to be successful for treatment of AIS is intravenous (IV) recombinant tissue plasminogen activator (rTPA) with potential complement drugs now under study.[1] Because of its thrombolytic activity, rTPA can restore brain circulation.[2] However, delayed rTPA delivery is associated with increased intracerebral hemorrhage, hemorrhagic transformation and death.[3]

Acute cerebrovascular stroke (CVS), particularly ischemic, is a common critical complication of COVID-19,[4] with a tendency for major vessel occlusion, multi-territory stroke, and involvement of otherwise rarely afflicted arteries. The pathophysiology and effective management of ischemic stroke caused by COVID-19 are as yet unknown, although increasing data indicates that cytokine storm-induced coagulopathy and endotheliopathy are potential targetable pathways.[5]

A recent study in the United States looked at the impact of IV rTPA on 13 patients who had acute ischemic stroke with systemic symptoms associated with covid-19. At follow-up, 61.5% of patients had improved, with no systemic or symptomatic intracranial hemorrhages. Thus, IV rTPA may be safe and effective in COVID-19, but larger studies are needed to confirm these findings.[6]

Aim of this work was to compare the clinical presentation, the outcome and safety, of rTPA for first onset AIS with covid-19 versus non covid-19 patients.

Material and methods

Patients with AIS and were eligible for rTPA were recruited from the emergency Department of Neurology at Aswan University Hospital immediately after admission, during the period from 1st of February 2022 to the end of September 2022.

Inclusion criteria: Both sexes, aged between 18 years and 80 years old, clinically diagnosed as AIS with an NIHSS score between 5 and 22.[7]

Exclusion criteria: conditions associated with acute bleeding diathesis, systolic blood pressure >185 and/or diastolic >110 mmHg, active internal bleeding, and cerebral hemorrhage or extensive regions of apparent hypodensity on a CT scan of the brain indicate irreversible damage. Also, platelet count less than 100.000/mm^3, current anticoagulant with INR more than 1.7, prothrombin time longer than 15 s or prothrombin time more than 40 s, and therapeutic dosages of low molecular weight heparin received in 24 h (not include the prophylactic doses) are all hematologic exclusion criteria.

Out of 215 patients with AIS that were recruited during this period, only 47 patients were eligible for rTPA (see Fig. 1 flowchart). On admission a complete history was taken including demographic data, clinical manifestations of covid-19 infection, time of symptom onset, previous medications, body mass index (BMI) and known or newly diagnosed risk factors (atrial fibrillation, heart failure, coronary artery disease (using ECG and Echo-cardiography), hypertension (blood pressure of >160/90 mmHg or already under treatment with antihypertensive drugs),

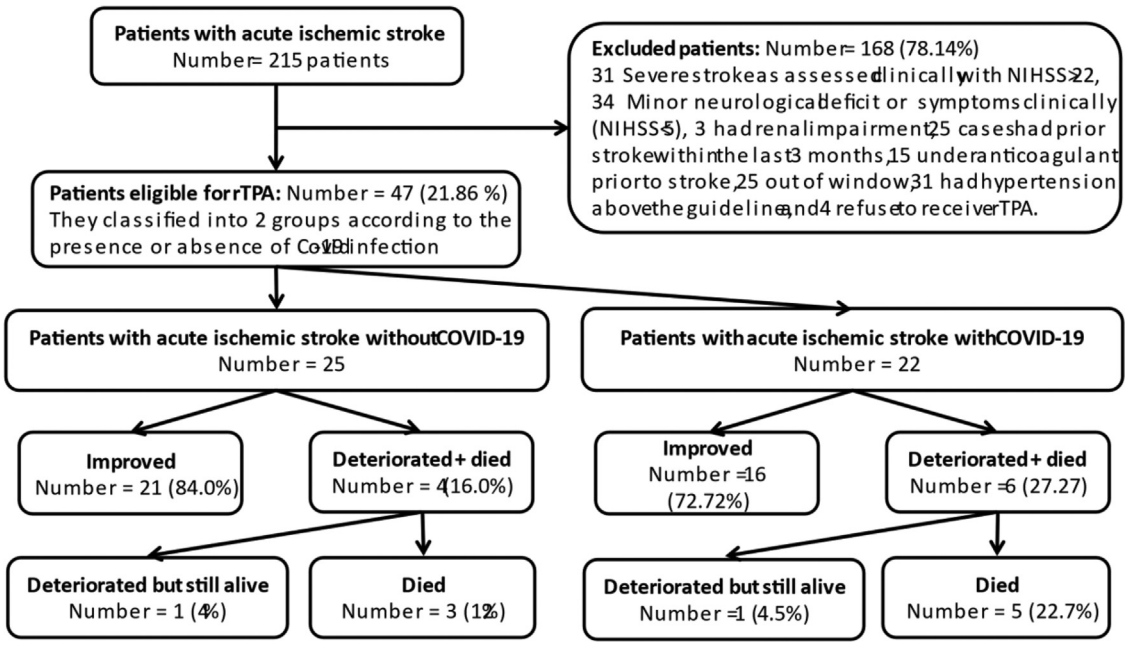

Fig. 1. *Flow chart of patients with acute ischemic stroke.*

diabetes mellitus, smoking. Complete blood picture (CBC) (Hemoglobin; 12-16, WBC; 3.5-10[10]), blood glucose (glucose levels >140 mg/dL preprandial, glucose level >200 mg/dL postprandial, lipid profile; hyperlipidemia (cholesterol concentration of >200 mg/dL and/or triglyceride concentration >140 mg/dL, LDL: 85-125 and HDL: 40-80 mg/dL), INR (0.8-1.1and PTT), and renal function (creatinine; 0.8-1.3, Blood urea; 16-40mg/dL) were performed. Abnormal classification ranges were based on in-house data averages.

A neurological examination was performed including assessments of National Institute of Health Stroke Scale (NIHSS score)[8] and the Alberta Stroke Programme Early CT score (ASPECTS).[9] This is a 10-point quantitative score used to assess early ischemic changes on non-contrast CT. A score of ≤7 points (most ischemic change) is used to characterize patients with the worst functional outcome of intravascular treatment.[9,10] A CT brain and CT angiogram were obtained as well as carotid Doppler ultrasound. Hemorrhage was defined according to the European Cooperative Acute Stroke Study II (ECASS II) [2] and classified as hemorrhagic infarction HI 1 and HI 2 or parenchymal infarction PH 1 and PH 2.

A neurologist assigned stroke subtypes on the basis of the Trial of ORG 10172 in Acute Stroke Treatment-criteria (TOAST): atherosclerotic (large artery disease), cardioembolic, lacunar (small artery disease), other determined etiologies and undetermined etiology.[11]

The diagnosis of COVID-19 was confirmed using the WHO definition: a combination of clinical history with confirmatory tests including reverse transcriptase polymerase chain reaction (PCR) to detect the presence of SARS-CoV-2 ribonucleic acid on a nasopharyngeal swab that was collected immediately at admission, lung computerized tomography (CT) scan findings with ground glass appearance.[12] All patients underwent PCR at admission even in the absence of Covid-19 symptoms. Twenty-five patients (13 males, 12 females) had negative PCR and were considered as a control group and 22 (14 males, 8 females) had positive PCR and formed the COVID-19 infection group.

On admission at the emergency department, 2 cannulas, a nasogastric tube (for Ryle feeding) and a urinary catheter were inserted, and an ECG performed. rTPA 0.9 mg /kg not exceeding 90 mg total), with 10% of total treatment dose given as an initial bolus over the first minute, and the remaining dose infused over 60 min. Follow-up blood pressure, NIHSS and Glasgow coma scale (GCS) were taken every 30 min. CT brain and NIHSS were performed 24 h later if deterioration was observed.

Follow up: The patients were followed up 3 months later. Outcome was evaluated using the NIHSS and Modified Rankin scale (mRS).[13] A favorable outcome was defined as a reduction in the NIHSS by ≥ 4 points at 3-month assessment compared with baseline assessment.[14]

The modified Rankin scale (mRS) measures the degree of functional neurological disability after stroke with a range from no symptoms to slight disability (0-2), moderately severe disability (3-4), and severe/death (5-6).[15]

Three-month mortality was a secondary goal.

Ethical consideration: The study was approved by the local ethical committee of Aswan university and the Institutional Review Board (IRB) (ID: 536/6/21). Written informed consent was obtained from each patient or a close relative and confidentiality was guaranteed. Registry at clinicaltrials.gov ID: NCT05258565.

Statistical analysis

Data was analyzed using IBM-SPSS 21.0 (IBMSPSS Inc., Chicago, IL, USA). Descriptive statistics: means, standard deviations, and percentages. Tests of significance: the chi-square test was used to compare the difference frequency distributions between the groups. Independent t-tests were used to compare the means of dichotomous data. A significant p-value was considered to be <0.05.

Results

Demographic data (Table 1)

Out of 215 ischemic stroke patients, forty-seven were eligible for rTPA and wer enrolled in this study. Their ages ranged from 40 to77 years with a mean of 60.38 ± 9.42 (SD). 27 patients were males (57.4%) and 20 were females (42.5%). Patients were classified according to age (age 35-54 and ≥ 55years). Patients with COVID-19 were significantly more common in the younger age group than controls (p value < 0.05).

Risk factors and etiologies

There were no significant differences between groups in pre-existing risk factors except for a history of smoking, which was significantly more common in covid-19 patients ($P = 0.04$) (Table 1) and mean blood glucose level at admission, which was significantly higher in the Covid-19 patients than controls (185.77 ± 95.83 vs 136.32 ± 31.5), ($P = 0.019$). There were no statistically significant differences (P=> 0.05) between the 2 groups as regards stroke etiology and previous treatment before occurrence of stroke among studied groups (Table 2). Interestingly there were 3 patients in the Covid-19 group who had no risk factors or comorbidities for stroke, but none in the control group.

Presenting symptoms of the 22 patients with positive PCR (Covid-19 infection group) symptoms (Table 3)

According to the guideline criteria of the use of rTPA, as well as WHO criteria of symptomatic COVID-19; the symptoms of Covid-19 in the present study ranging from

Table 1. *Demographic and associated risk factor of acute ischemic with or without COVID-19.*

Variables	Total population (N=47)	Acute ischemic stroke without COVID-19 Control group (N=25)	Acute ischemic stroke with Covid-19 infection (N=22)	T value or X^2	P value
Age (Years) mean±SD	60.38± 9.417	62.32± 6.453	58.18± 11.709	2.32	0.13
Age 35-54 y	12(25.5%)	3(12%)	9(40.9%)	5.144	0.042
Age 55->70 y	35(74.5%)	22(88%)	13(59.1%)		
Gender - Number of cases (%)					
Male	27(57.4%)	13(52%)	14(63.6%)	0.68	0.55
Female	20(42.5%)	12(48%)	8(36.4%)		
Occupational state					
Working	19(40.4%)	8(32%)	11(50%)	1.574	0.246
Not working	28(59.6%)	17(68%)	11(50%)		
Past history of risk factors - Number of cases (%)					
Atrial fibrillation (AF)	5(10.6%)	3(12%)	2(9.1%)	0.104	0.564
Ischemic heart disease/ coronary artery disease	5(10.6%)	5(20%)	0(0%)	4.92	0.05
Hypertension	23(48.9%)	15(60%)	8(36.4%)	2.61	0.14
Diabetes mellitus	15(31.9%)	6(24%)	9(40.9%)	1.54	0.34
Smoking or stop from less than 2 years	12(25.5%)	3(12%)	9(40.9%)	5.14	0.04*
Previous transient ischemic attack (TIA)	6(12.8%)	3(12%)	3(13.6%)	0.028	0.6
Body mass Index					
Normal (18.5:24.9)	24(51.1)	14(56%)	10(45.5)	0.521	0.564
Overweight and obese(25:≥30)	23(48.9%)	11(44%)	12(54.5%)		
Risk factors at admission					
Blood pressure as a risk factor at admission					
Hypertension number (%)	34(72.4%)	18(72%)	16(72.8%)		1.0
Blood glucose level at admission mean±SD	159.47 ± 73.039	136.32 ± 31.5	185.77 ± 95.83	5.94	0.019*
Diabetic number (%)	18(38.3%)	6(24%)	12(54.5%)		0.04*
Laboratory investigations at admission number (%)					
Dyslipidaemia	24(51%)	13(52%)	11(50%)	0.019	0.56
HB (abnormal)	7(14.9%)	4(16%)	3(13.6%)	0.052	0.57
WBC (abnormal)	6(12.8%)	3(12%)	3(13.6%)	0.028	0.6
Increase renal chemistry	3(6.4%)	1(4%)	2(9.1%)	0.50	0.45
Platelets count mean±SD	304.08 ± 68.95	292.48 ± 59.37	317.61 ± 78.24	1.29	0.26
INR mean±SD	1.09 ± 0.19	1.09 ± 0.16	1.09 ± 0.22	0.003	0.95
Na level mean±SD	139.44 ± 2.97	139.83 ± 2.79	139 ± 3.19	0.75	0.39
K level mean±SD	4.1123 ± .48942				
4.1276 ± .53488	4.0944 ± .44520	0.012			0.836

mild to moderate with no patients with severe symptoms as organ failure or coma.

Out of 22 patients with positive PCR, 11 (50%) had symptoms of Covid-19 infection, while the remainder were non-symptomatic. 9 patients (40.9%) had symptoms of Covid-19 infection at home with an onset ranging from 2 to 9 days before the onset of stroke. The other two patients developed symptoms immediately after admission at emergency department. Only 2 (9.1%) cases had a positive PCR test before admission.

Manifestations of Covid-19 infection were fever, headache, respiratory and/or GIT symptoms. None of the control group had covid-19 symptoms.

Table 4 summarizes clinical and neurological findings at admission. Complete hemiplegia was more common among patients with Covid-19 whereas hemiparesis was the commonest presentation among controls, suggesting that motor symptoms were worse in Covid-19 patients (P=0.013). There were no other significant differences between groups.

Radiological findings (Table 5)

There were no significant differences between groups as regards to type and size of artery occlusion, CT angiogram, ASPECT score at admission (CT) and symptomatic hemorrhagic transformation. Symptomatic intracerebral hemorrhage (in which the NIHSS increased by 4 or more points) was observed only in COVID-19 patients while no cases were recorded in the controls (9.1 versus 0%), but this difference was not significant ($P = 0.21$).

Radiological hemorrhagic transformation (ECASII) occurred more frequently in Covid-19 patients ($P = 0.04$). The first of these patients was admitted with an NIHSS

Table 2. *Stroke etiology, previous treatment before occurrence of stroke among studied groups.*

Variables	Total population (N=47)	Acute ischemic stroke without COVID-19 Control group ($N = 25$)	Acute ischemic stroke with Covid-19 infection ($N = 22$)	T value or X^2	P value
Stroke aetiology					
Atherosclerosis	36(76.6%)	19(76%)	17(77.3%)	0.01	0.59
Cardio embolism	4(8.5%)	2(8%)	2(9.1%)	0.018	0.64
Lacunar	3(6.4%)	3(12%)	0(0%)	2.82	0.23
Other (Post-covid-19 vaccine)[#]	2(4.3%)	2(8%)	0(0%)	1.83	0.49
Undetermined (Cryptogenic)	3(6.4%)	0(0%)	3(13.6%)	3.64	0.09
Pre stroke treatment with Oral anticoagulants drugs					
No	45(95.7%)	24(96%)	21(95.5%)	2.01	0.36
Yes	1(2.1%)	1(4%)	0(0%)		
Unknown	1(2.1%)	0(0%)	1(4.5%)		
Pre stroke treatment with Antiplatelet drugs					
No	37(78.7%)	21(84%)	16(72.7%)	1.60	0.44
Yes	9(19.1%)	4(16%)	5(22.7%)		
Unknown	1(2.1%)	0(0%)	1(4.5%)		
Pre stroke treatment with Statins drugs					
No	40(85.1%)	23(92%)	17(77.3%)	2.002	0.22
Yes	7(14.9%)	2(8%)	5(22.7%)		

[#]post- Astrazenca vaccine

score of 20 which had risen to 24 after rTPA (parenchymal hematoma type1). The second patient had an NIHSS score of 16 on admission which rose to 25 after 3 h rTPA (parenchymal hematoma type 2 with substantial mass effect attributable to the hematoma). The third patient developed asymptomatic petechial hemorrhages around the infarction margins (hemorrhagic infarction type1).

The frequency of re-occlusion (transient improvement in the first 24 h), and recurrent ischemic stroke at 3 months did not differ between groups.

Onset to door time (ODT) was significantly longer in Covid-19 patients than controls (90.00 ± 58.77 vs 124.32 ± 57.5 $P = 0.04$). The time window (onset to successful reperfusion time) was significantly longer in Covid-19 patients than controls (153.27 ± 56.14 vs 118.67 ± 59.22 $P = 0.04$).

Table 3. *Clinical data of COVID-19 infection group (22 cases).*

Time of covid-19 diagnosis	
Diagnosed 2-5 days before stroke onset (before admission)	2(9.1%)
Diagnosed at Emergency department after the onset of stroke onset	20 (72.9%)
Covid-19 symptoms at stroke onset	
Asymptomatic at home	11(50%)
Symptomatic at home before onset of stroke	9(40.9%)
Symptomatic at emergency department	2(9.1%)
Systemic manifestations of COVID-19	
Dyspnoea and Desaturation	4(18.2%)
Fever, headache, fatigue	5(22%)
Respiratory tract infection and cough	6(27.3%)
GIT manifestation (diarrhoea and/or vomiting)	6(27.3%)

Outcome (Table 6)

There was no significant difference in stroke severity between groups at baseline and no difference in outcomes at 3 months. 92% of control patients (non-COVID) and 81.8% of those with Covid-19 showed an improvement in NIHSS scores after rTPA (> 4 points reduction compared with baseline assessment). Similar results were seen using the mRS, with a favorable outcome (0-2) in 14 cases (63.6%) with Covid-19 infection versus 19 (76%) in controls. There was also a higher number of deaths in the COVID group than the controls although the differences were not significant ($P = 0.29$). A two−way repeated measure ANOVA analysis of the NIHSS data indicated no significant difference in overall recovery rates between groups (Time (baseline assessment of NIHSS, post-rTPA, and 3 months later) X group (AIS with versus without COVID-19) interaction showed no significant interaction: $P = 0.740.$, F=0.199, DF= 1.40(51)).

Discussion

A major consequence of covid-19 infection is development of acute ischemic stroke.[5] The primary form of treatment for AIS is intravenous thrombolysis (rTPA), and early treatment is crucial for successful reperfusion.[7] As the result, eligible patients should start IV rTPA as soon as possible after stroke, even if mechanical thrombectomy is being considered. Here we compared the clinical presentation, outcome and safety of IV-rTPA in patients with

Table 4. *Clinical and neurological findings at admission.*

Variables	Total population ($N = 47$)	Acute ischemic stroke without COVID-19 Control group ($N = 25$)	Acute ischemic stroke with associated Covid-19 ($N = 22$)	T value or X^2	P value
Glasgow Coma Scale					
Moderate (9-12)	1(2.1%)	0(0%)	1(4.5%)	1.16	0.468
Mild (13-15)	46(97.9)	25(100%)	21(95.5%)		
Affected side of the body					
Right side	22(46.8%)	13(52%)	9(40.9%)	0.57	0.56
Left side	25(53.2%)	12(48%)	13(59.1%)		
Motor affection					
Mono paresis/plegia	2(4.3%)	1(4%)	1(4.5%)	8.67	0.013*
Hemiparesis	19(40.4%)	15(60%)	4(18.2%)		
Dense Hemiplegia	26(55.3%)	9(36%)	17(77.3%)		
Aphasia	5(10.6%)	2(8%)	3(13.6%)	0.39	0.65
Gaze deviation	7(14.9%)	3(12%)	4(18.2%)	0.35	0.69

Table 5. *Radiological Criteria of occluded vessel among studied groups.*

Variables	Total population (N=47)	Control Acute ischemic stroke without COVID-19 (Control group) ($N = 25$)	Acute ischemic stroke with Covid-19 infection ($N = 22$)	T value or X^2	P value
Type of artery occlusion					
Anterior circulation	44(93.6%)	24(96%)	20(90.9%)	0.50	0.59
Posterior circulation	3(6.4%)	1(4%)	2(9.1%)		
Size of occluded vessel					
Large vessels	23(48.9%)	11(44%)	12(54.5%)	0.52	0.56
Middle and small vessels	24(51.1%)	14(56%)	10(45.5%)		
CT angiography					
Internal carotid artery (ICA)	1(2.1%)	0(0%)	1(4.5%)	6.11	0.52
Middle cerebral artery −M1 segment	20(42.6%)	9(36%)	11(50%)		
M2 segment	8(17%)	6(24%)	2(9.1%)		
M3 segment	2(4.3%)	1(4%)	1(4.5%)		
M4 segment	13(27.7%)	7(28%)	6(27.3%)		
Anterior cerebral artery (ACA)	1(2.1%)	1(4%)	0(0%)		
Posterior circulation	2(4.3%)	1(4%) vertebra-basilar	1(4.5%) Pontine		
Symptomatic intracerebral hemorrhage (increase NIHSS >4 points					
No	45(95.7%)	25(100%)	20(90.9%)	2.37	0.21
Yes	2(4.3%)	0(0%)	2(9.1%)		
Radiological hemorrhagic transformation according to ECASII					
No	44(93.6%)	25(100%)	19(86.4%)	4.2	0.04*
Yes	3(6.4%)	0(0%)	3(13.6%)		
Transient improvement and subsequent recurrence of the presenting neurological deficits(during the first 24 h of onset)					
No	41(87.2%)	23(92%)	18(81.8%)	1.08	0.39
Yes	6(12.8%)	2(8%)	4(18.2%)		
Recurrent ischemic stroke at 3 months follows up3 month					
No	41(87.2%)	22(88%)	19(86.4%)	0.028	0.6
Yes	6(12.8%)	3(12%)	3(13.6%)		
ASPECT score at admission (CT)					
Predict good function outcome (>7points)	39(83%)	23(92%)	16(72.7%)	3.07	0.12
Predict worse function outcome (≤**7 points)**	8(17%)	2(8%)	6(27.3%)		
Pre-Hospital Delay					
Onset to door time (ODT)/min	100.06 ± 60.09	90.00 ± 58.77	124.32 ± 57.51	4.19	0.04*
Time window (Onset to successful reperfusion time)	134.91 ± 59.76	118.76 ± 59.22	153.27 ± 56.14	4.17	0.04*

Table 6. *Outcome of acute ischemic stroke in the studied groups after thrombolytic therapy.*

Variables	Total population (N=47)	Acute ischemic stroke without COVID-19 Control group ($N = 25$)	Acute ischemic stroke with Covid-19 infection ($N = 22$)	T value or X^2	P value
NIHSS1(PRE-thrombolytic)					
Stroke Severity at admission according to NIHSS					
Moderate number (%)	40 (85.1%)	23(92%)	17(77.3%)	2.002	0.22
Moderate to severe number (%)	7(14.9%)	2(8%)	5(22.7%)		
NIHSS2 (POST-thrombolytic)					
Improvement number (%)	41(87.2%)	23(92%)	18(81.8%)	1.08	0.58
No changes number (%)	3(6.4%)	1(4.8%)	2(9.1%)		
Deterioration but still alive number (%)	3(6.4%)	1(4.8%)	2(9.1%)		
NIHSS3 (after 3 MONTH)					
Improvement (>4 points) number (%)	37(78.7%)	21(84%)	16(72.7%)	2.46	0.29
Deterioration and/or died number (%)	10(21.3%)	4(16%)	6 (27.3%)		
Modified Rankin Scale (After 3 months)					
No symptoms to slight disability (0-2) number (%)	33(70.2%)	19(76%)	14(63.6%)	1.07	0.58
Moderately severe disability (3-4) number (%)	6(12.8%)	3(12%)	3(13.6%)		
Severe and died (5-6) number (%)	8(17%)	3(12%)	5(22.7%)		
Discharge status (Outcome)					
Discharge at home	34(72.3%)	20(80%)	14(63.6%)	1.692	0.429
Discharge to destination other than home	11(23.4%)	4(16%)	7(31.8%)		
In hospital death	2(4.2%)	1(4%)	1(4.5%)		

and without COVID-19. The main findings were: First, the proportion of patients with AIS with or without Covid-19 who received rTPA was nearly equal at a relatively low rate of 21%. Second, most of the COVID-19 patients had preexisting risk factors (except 3 cases) similar to controls. Third, there was some non-significant evidence that the severity of neurological deficits was greater in the Covid-19 group than the controls. Fourth, onset to door time (ODT) and onset to successful reperfusion time were significantly longer in Covid-19 patients than controls. Fifth, symptomatic intra-cerebral hemorrhage and radiological hemorrhagic transformation were more common in COVID-19 patients despite the fact that there was no significant difference in outcome at 3 months between groups.

In the present study the mean age of AIS patient with Covid-19 infection was similar to controls and there were no differences in sex distribution. A similar result was noted by Qureshi et al 2021 in their analysis of 27 676 patients who found that the mean age of AIS with COVID-19 was similar compared with those without COVID-19.[16]

However, when our patients was classified according to age group (Age 35-54 and ≥ 55years) we found that patients with COVID-19 was significantly more common in the younger age group than controls (p value < 0.05). Sasanejad et al 2021 (multicenter study included 9 centers with 545 stroke patients) found that at baseline, there were no significant differences in age, sex, and vascular risk factors between cases with and without COVID-19.[17] Majidi et al 2020 noted that COVID-19 patients with strokes vs. non-COVID-19 patients with strokes were more likely to be younger, male, and white.[18]

Several other case series suggested that patients with COVID-19 who developed AIS were younger than those who were not infected.[19–21]

Our findings suggest that most of the COVID-19 patients who develop AIS had preexisting risk factors similar to AIS without COVID-19 (except 3 cases that had no apparent risk factor). The same result was recorded by Qureshi et al 2021 in their analysis of a large number of different studies.[16] Ramos Araque, et al, 2021[22] also reported a high prevalence (42%) of cryptogenic strokes in COVID-19 patients, as did Yaghi et al 2020.[21] This may be due to a hypercoagulable state brought about by inflammation[23,24] since severe acute respiratory Syndrome Coronavirus 2 directly infects endothelial cells, causing diffuse endothelial inflammation.[25]

There was a slightly increased incidence of coronary artery disease/ischemic heart disease in the COVID-19 patients (20 vs 0% $P = 0.05$), which is consistent with a report of Ganatra S, et al, 2020.[26] Mean blood glucose level at admission was also significantly higher among Covid-19 patients than in controls ($P = 0.019$). Hyperglycemia could be attributed to the stress response in reaction to ischemic stroke itself and this could potentially have been exacerbated by acute infection with Covid-19. Alternatively, COVID-19 might predispose infected individuals to hyperglycemia through effects on glucose homeostasis, inflammation, altered immune status and possibly through

activation of the renin−angiotensin−aldosterone system.[27] Lou M, et al.2021 found that high blood glucose enhances blood viscosity, platelet adhesion and aggregation, and blood flow status, raising the likelihood of thrombosis.[28] Norris T, et al, 2022 observed a linear relationship between either stroke or cardiac ischemia and higher blood glucose at admission, but no linear relationship with other cardiovascular complications.[29] Qureshi et al 2021 found that the percentage of AIS patients with different risk factors (hypertension, diabetes, hyperlipidemia, AF, myocardial infarction, and congestive heart failure) was similar in patients with and without COVID-19.[16]

Interestingly, three Covid-19 patients had no risk factors for cerebrovascular illness or comorbidities, suggesting that COVID-19 mechanisms may be responsible. Direct viral infiltration of blood vessel walls may cause endothelitis.[30]

In the present study there was some evidence that the severity of AIS was greater in Covid than controls ($P = 0.013$) but there was no difference between the rates of the use of rTPA among AIS with COVID-19 compared with those without COVID-19 that was consistent with Benussi et al 2020.[31] This may be related to stroke severity, the infection itself, a tendency to large vessel occlusion, and the clinical progression due to the longer ODT compared with controls. Fàbregas et al 2021 also found that patients with ischemic stroke and concomitant COVID-19 infection had a more severe neurological deficit at admission.[32]

In the present study large vessel occlusion (LVO) was more common in COVID-19 patients than non-COVID-19 patients (54.5 vs 44%) but the difference was not significant which may be attributed partially to the small sample size. This result was consistent with previous study[33] in which Khedr and their colleagues found a higher rate of major vascular occlusion in AIS with Covid than non-COVID-19 patients ($P = < 0.001$).

There was transient improvement with subsequent recurrence of neurological deficits occurred more frequently in the Covid-19 group than controls during the 1st 24 h after receiving IV tPA. This may have resulted from recanalization but may also be explained by improvement in collateral blood flow. Carneiro T, et al, 2021 reported similar findings in four patients with large vessel occlusion.[34]

COVID-19 patients were treated within the typical time window (4.5 h) between last-known well and IV tPA administration, although controls were treated faster. (153.27 ± 56.14 vs 118.76 ± 59.22 with $P = 0.04$). Similarly, onset to door time (ODT) was significantly longer in COVID-19 patients. The additional delay may result from differences in the processing time of Covid patients in the prehospital setting.

Teo KC, et al 2020 reported a similar result of up to 60 min additional delay in 73 patients with COVID_19 compared with 89 non-covid patients.[35] Topcuoglu MA, et al, 2021 found that the delay between symptom onset and hospital admission was significant longer in Covid-19 patients (approximately 1000 min later).[36]

There was no significant difference in hospital time delay between groups as every incoming stroke patient was treated as potentially infected with COVID-19. A slight but not significant increase in hospital time delay may be related to the initial screening of respiratory and gastrointestinal symptoms in the emergency room.

Safety and outcomes

Radiological hemorrhagic transformation was observed only in patients with Covid-19 and may be related to endothelial damage accompanying COVID-19, the large size of infarction, stroke severity (high NIHSS), hyperglycemia on admission, as well as multiple other comorbidities.

Tan YK, et al, 2020 also observed hemorrhagic transformation in 3 out of 29 cases (10.3%)[37] and Khedr et al (2021b) reported that COVID-19 patients exhibited a greater rate of hemorrhagic transformation (14.3%) than non-COVID-19 patients (1.6%) ($P < 0.001$).[33]

La Barbera, et al, 2020 suggested that ischemic stroke patients with Covid-19 who received IV tPA may be at greater risk for symptomatic hemorrhage due to the presence of disseminated intravascular coagulation (DIC), micro-hemorrhage, or other vasculopathy associated with the virus. They also found significant hemorrhagic transformation with cerebral edema in imaging in the hours following IV tPA administration.[33,38] Alwahdy, A.S., et al., 2022 observed that COVID-19 patients have high inflammatory and hypercoagulability markers, which have been linked to death, disability, and post-thrombolytic cerebral hemorrhage.[39] Sasanejad et al., 2021 found that, after adjustment for confounding variables, discharge mRS score ≤ 2 in-hospital mortality, and hemorrhagic transformation were similar in COVID-19 and non-COVID-19 patients.[17] They observed that the incidence of all types of hemorrhagic transformation (symptomatic or asymptomatic) was increased, but not significantly, in COVID-19 patients.[40] Carneiro T, et al., 2020 observed that symptomatic hemorrhagic consequences with IV rTPA in COVID-19 patients were rare and lower than the overall population (2 and 3.2%).[6] They suggested that IV rTPA may be used safely in patients with COVID-19 infection. However, most of these previous studies did not directly compare patients with and without Covid-19 infection. Here we directly compared two groups who were recruited over the same period and in the same hospital. Katz JM, et al,2020 reported that patients with severe manifestations of COVID-19 had significantly more ischemic strokes with complications such as hemorrhagic transformation than those with milder or no COVID-19 symptoms.[41] Qureshi et al 2021 found that AIS was associated with discharge to a destination other than home or death after adjusting for potential confounders.[16]

In the present study, 92% of control patients and 81.8% of those in the Covid-19 group had improved NIHSS scores after rTPA. A similar result was seen in the mRS scores with a more favorable outcome among controls than AIS with Covid-19 infection. This means that the improvement was less pronounced, with a higher number of deaths in Covid-19 group than non-Covid-19 infection although the differences were not significant (P=0.29). Martí-Fàbregas et al. 2021 observed that COVID-19 patients had a 39.3% mortality rate three months after beginning, compared to 16.1% for non-COVID-19 patients, a risk ratio of 2.44.[32]

Limitations of the study

The main limitation is the small sample size. A multicenter study is recommended with increased recruitment.

Strengths of the study

This study's greatest strengths are its prospective design and direct comparison between a group with COVID-19 and a group without COVID-infection who were treated throughout the same time period.

Conclusion

Stroke is an important complication of COVID-19 due to severity and the impact on prognosis, it is relatively rare (~2% of hospitalized patients). rTPA remains the cornerstone for management of AIS, with or without COVID-19 infection despite the high incidence of hemorrhagic transformation.

Funding

None.

Declaration of Competing Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Acknowledgments: Thank you to Professor John C. Rothwell for his revision of the language, Sobell Department of Motor Neuroscience and Movement Disorders, National Hospital for Neurology and Neurosurgery, Queen Square, London, UK.

References

1. Gottula AL, Barreto AD, Adeoye O. Alteplase and adjuvant therapies for acute ischemic stroke. Semin Neurol 2021;41:16-27. https://doi.org/10.1055/s-0040-1722720.
2. Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. Lancet 1998;352:1245-1251. https://doi.org/10.1016/s0140-6736(98)08020-9.
3. Kim JS. tPA helpers in the treatment of acute ischemic stroke: are they ready for clinical use? J Stroke 2019;21:160-174. https://doi.org/10.5853/jos.2019.00584.
4. Khedr EM, Soliman RK, Abo-Elfetof N, et al. Clinical and radiological characteristics of acute cerebrovascular diseases among egyptian patients with COVID-19 in upper Egypt. Front Neurol 2021;12. 635856.10.3389/fneur.2021.635856.
5. Vogrig A, Gigli GL, Bnà C, et al. Stroke in patients with COVID-19: clinical and neuroimaging characteristics. Neurosci Lett 2021;743. 135564.10.1016/j.neulet.2020.135564.
6. Carneiro T, Dashkoff J, Leung LY, et al. Intravenous tPA for acute ischemic stroke in patients with COVID-19. J Stroke Cerebrovasc Dis 2020;29. 105201.10.1016/j.jstrokecerebrovasdis.2020.105201.
7. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995;333:1581-1587. https://doi.org/10.1056/NEJM199512143332401.
8. Brott T, Adams Jr. HP, Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke 1989;20:864-870. https://doi.org/10.1161/01.str.20.7.864.
9. Barber PA, Demchuk AM, Zhang J, et al. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. Lancet 2000;355:1670-1674. https://doi.org/10.1016/s0140-6736(00)02237-6.
10. Dzialowski I, Hill MD, Coutts SB, et al. Extent of early ischemic changes on computed tomography (CT) before thrombolysis: prognostic value of the Alberta Stroke Program Early CT Score in ECASS II. Stroke 2006;37:973-978. https://doi.org/10.1161/01.STR.0000206215.62441.56.
11. 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;24:35-41. https://doi.org/10.1161/01.str.24.1.35.
12. World Health Organization W. COVID-19 case definition. 2021.
13. Rankin J. Cerebral vascular accidents in patients over the age of 60. II. Prognosis. Scott Med J 1957;2:200-215. https://doi.org/10.1177/003693305700200504.
14. Delgado MG, Michel P, Naves M, et al. Early profiles of clinical evolution after intravenous thrombolysis in an unselected stroke population. J Neurol Neurosurg Psychiatry 2010;81:282-285. https://doi.org/10.1136/jnnp.2009.185363.
15. van Swieten JC, Koudstaal PJ, Visser MC, et al. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19:604-607. https://doi.org/10.1161/01.str.19.5.604.
16. Qureshi AI, Baskett WI, Huang W, et al. Acute ischemic stroke and COVID-19: an analysis of 27 676 patients. Stroke 2021;52:905-912. https://doi.org/10.1161/STROKEAHA.120.031786.
17. Sasanejad P, Afshar Hezarkhani L, Arsang-Jang S, et al. Safety and outcomes of intravenous thrombolytic therapy in ischemic stroke patients with COVID-19: CASCADE initiative. J Stroke Cerebrovasc Dis 2021;30. 106121-106121.
18. Majidi S, Fifi JT, Ladner TR, et al. Emergent large vessel occlusion stroke during New York City's COVID-19 outbreak: clinical characteristics and paraclinical findings. Stroke 2020;51:2656-2663. https://doi.org/10.1161/STROKEAHA.120.030397.

19. Oxley TJ, Mocco J, Majidi S, et al. Large-vessel stroke as a presenting feature of Covid-19 in the young. N Engl J Med 2020;382:e60. https://doi.org/10.1056/NEJMc2009787.
20. Sweid A, Hammoud B, Bekelis K, et al. Cerebral ischemic and hemorrhagic complications of coronavirus disease 2019. Int J Stroke 2020;15:733-742. https://doi.org/10.1177/1747493020937189.
21. Yaghi S, Ishida K, Torres J, et al. SARS-CoV-2 and stroke in a New York healthcare system. Stroke 2020;51:2002-2011. https://doi.org/10.1161/STROKEAHA.120.030335.
22. Ramos-Araque ME, Siegler JE, Ribo M, et al. Stroke etiologies in patients with COVID-19: the SVIN COVID-19 multinational registry. BMC Neurol 2021;21. 43.10.1186/s12883-021-02075-1.
23. Divani AA, Andalib S, Di Napoli M, et al. Coronavirus disease 2019 and stroke: clinical manifestations and pathophysiological insights. J Stroke Cerebrovasc Dis 2020;29:104941. https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.104941.
24. Li Y, Li M, Wang M, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. Stroke Vasc Neurol 2020;5:279-284. https://doi.org/10.1136/svn-2020-000431.
25. Pranata R, Huang I, Lim MA, et al. Impact of cerebrovascular and cardiovascular diseases on mortality and severity of COVID-19-systematic review, meta-analysis, and meta-regression. J Stroke Cerebrovasc Dis 2020;29:104949. https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.104949.
26. Ganatra S, Dani SS, Shah S, et al. Management of cardiovascular disease during coronavirus disease (COVID-19) pandemic. Trends Cardiovasc Med 2020;30:315-325. https://doi.org/10.1016/j.tcm.2020.05.004.
27. Lim S, Bae JH, Kwon HS, et al. COVID-19 and diabetes mellitus: from pathophysiology to clinical management. Nat Rev Endocrinol 2021;17. 11-30.10.1038/s41574-020-00435-4.
28. Lou M, Yuan D, Liao S, et al. Potential mechanisms of cerebrovascular diseases in COVID-19 patients. J Neurovirol 2021;27:35-51. https://doi.org/10.1007/s13365-021-00948-2.
29. Norris T, Razieh C, Yates T, et al. Admission blood glucose level and its association with cardiovascular and renal complications in patients hospitalized with COVID-19. Diabetes Care 2022;45:1132-1140. https://doi.org/10.2337/dc21-1709.
30. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020;395:1417-1418. https://doi.org/10.1016/s0140-6736(20)30937-5.
31. Benussi A, Pilotto A, Premi E, et al. Clinical characteristics and outcomes of inpatients with neurologic disease and COVID-19 in Brescia, Lombardy, Italy. Neurology 2020;95:e910-e920. https://doi.org/10.1212/WNL.0000000000009848.
32. Martí-Fàbregas J, Guisado-Alonso D, Delgado-Mederos R, et al. Impact of COVID-19 infection on the outcome of patients with ischemic stroke. Stroke 2021;52:3908-3917. 10.1161/strokeaha.121.034883.
33. Khedr EM, Abo-Elfetoh N, Deaf E, et al. Surveillance study of acute neurological manifestations among 439 Egyptian patients with COVID-19 in Assiut and Aswan University Hospitals. Neuroepidemiology 2021;55:109-118. https://doi.org/10.1159/000513647.
34. Carneiro T, Dashkoff J, Leung L, et al. Response to the letter to the editor: consideration needed for early anticoagulation following intravenous tPA in patients with COVID-19. J Stroke Cerebrovasc Dis 2021;30. 105789.10.1016/j.jstrokecerebrovasdis.2021.105789.
35. Teo KC, Leung WCY, Wong YK, et al. Delays in stroke onset to hospital arrival time during COVID-19. Stroke 2020;51:2228-2231. https://doi.org/10.1161/strokeaha.120.030105.
36. Topcuoglu MA, Pektezel MY, Oge DD, et al. Stroke mechanism in COVID-19 infection: a prospective case-control study. J Stroke Cerebrovasc Dis 2021;30. 105919.10.1016/j.jstrokecerebrovasdis.2021.105919.
37. Tan YK, Goh C, Leow AST, et al. COVID-19 and ischemic stroke: a systematic review and meta-summary of the literature. J Thromb Thrombolysis 2020;50:587-595. https://doi.org/10.1007/s11239-020-02228-y.
38. LaBarbera VA, Azher A, Jayaraman MV, et al. Partial recanalization of a large vessel acute ischemic stroke with intravenous tissue plasminogen activator, followed by systemic anticoagulation, in the setting of COVID-19-induced hypercoagulability: a case report. Neurohospitalist 2021;11:246-250. https://doi.org/10.1177/1941874420977308.
39. Alwahdy AS, Margaretha IY, Pramesti KS, et al. Case series of intravenous thrombolysis for acute ischemic stroke in confirmed COVID-19 patients: single-centre experience. Egypt J Neurol Psychiatr Neurosurg 2022;58. 5.10.1186/s41983-021-00434-w.
40. Sasanejad P, Afshar Hezarkhani L, Arsang-Jang S, et al. Safety and outcomes of intravenous thrombolytic therapy in ischemic stroke patients with COVID-19: CASCADE initiative. J Stroke Cerebrovasc Dis 2021;30. 106121.10.1016/j.jstrokecerebrovasdis.2021.106121.
41. Katz JM, Libman RB, Wang JJ, et al. COVID-19 severity and stroke: correlation of imaging and laboratory markers. AJNR Am J Neuroradiol 2021;42:257-261. 10.3174/ajnr.A6920.