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Stroke Mechanism in COVID-19 Infection: A Prospective Case-Control Study

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Background: The characteristics and pathophysiological mechanisms involved in acute ischemic stroke in patients with COVID-19 infection have not been fully clarified. We prospectively studied the phenotypic and etiological features of acute stroke occurring in COVID-19 infection. Patients & methods: Within nine months starting from April-2020, the presence of COVID-19 infection was determined by thoracic CT and SARS-CoV-2 PCR in all acute stroke cases managed in a single tertiary center. Consecutive and prospective data on vascular risk factors/comorbidities, in-hospital quality metrics, discharge outcomes, etiological subclassification and blood markers of thrombosis / inflammation were compared in 44 COVID-19 positive cases (37 acute ischemic stroke, 5 TIA, 2 intracerebral hematoma) and 509 COVID-19 negative patients (355 ischemic, 105 TIA, 44 hematoma and 5 stroke mimic). Results: COVID-19 positive patients had more severe strokes, delayed hospital admission, longer hospital stay, higher mortality rates, but had similar vascular risk factors/comorbidities frequency, thrombolysis/thrombectomy utilization rates, metrics, and stroke etiological subtype. They had significantly higher CRP, fibrinogen, ferritin, leukocyte count and lower lymphocyte count. No difference was detected in aPTT, INR, D-dimer, platelet, hemoglobin, homocysteine levels and ANA, anti-dsDNA antibody and ENA panel positivity rates. Anti-phospholipid antibodies have been studied in 70% of COVID-19 positive and all cryptogenic patients, but were never found positive. Tests for coagulation factor levels and hereditary thrombophilia did not show major thrombophilia in any of the stroke patients with COVID-19. Conclusion: We documented that there is no significant difference in etiological spectrum in acute stroke patients with COVID-19 infection. In addition, cryptogenic stroke and antiphospholipid antibody positivity rates did not increase.

Key Words: COVID-19—Viral pneumonia—Anticoagulation—Stroke—Intracerebral hemorrhage—Transient ischemic attack

Introduction

Many critical differences have been observed in the epidemiology and management of collateral diseases such as acute stroke during the “coronavirus disease 2019” (COVID-19) pandemic that has deeply affected our daily lives for more than a year. The increase in stroke rate associated with COVID-19 infection reported in the first wave was not supported in most of the subsequent studies. Differences, if any, in phenotype, underlying mechanisms and treatment responses of acute stroke in “Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)” positive patients remained scarcely clarified until now. In addition, the role of SARS-CoV-2 induced coagulopathy and thromboinflammation in the stroke mechanism is still a matter of debate.
In this study, we report the phenotypic characteristics along with inflammatory and coagulation profile of acute stroke occurring in the setting of COVID-19 disease in a relatively large and homogenous cases series.

**Patients and methods**

A total 554 consecutive acute stroke patients hospitalized at Hacettepe University hospitals between 16.4.2020 and 14.1.2021 were prospectively included in this study. The study protocol was approved by the non-interventional ethics committee of Hacettepe University, and the relevant committee of the Turkish Ministry of Health; database registration consent [for details see reference #3] was obtained from all patients or their representatives.

As part of the hospital inpatient admission policy, real time reverse transcriptase polymerase chain reaction (RT PCR) for the SARS-CoV-2 virus was tested on the first day of presentation to the hospital and then when needed. WHO clinical progression scale was determined for each PCR positive patient. Low-dose thorax computed tomography (CT) were obtained in all acute patients on emergency basis as per hospital policy and the Turkish expert opinion.

The clinical severity of stroke was quantified by National Institutes of Health Stroke Scale (NIHSS) at admission, 24 hours, and at discharge. Pre-morbid and discharge functional status was assessed using the modified Rankin scale (mRS). A mRS less than 3 was defined as “good or favorable clinical outcome”, and “0 or 1” as an “no/minimal disability”. The Causative Classification of Stroke algorithm was used for etiological classification of stroke.

Admission erythrocyte sedimentation rate, complete blood count (platelet x10⁹/µL, normal range, 156–373), hemoglobin (g/dL, normal range, 13.6–17.2), leukocyte (x10³/µL, normal range, 4.3–10.3), lymphocyte (x10³/µL, normal range, 1.3–3.5), C reactive protein (CRP, mg/dL, normal range, 0-0.8), activated partial thromboplastin time (aPTT, normal range, 22.5–32 s), prothrombin time (PT, normal range, 10.4–12.6 s) and International Normalized Ratio (INR, normal range, 0.8–1.2), procalcitonin (ng/mL, normal range, 0–0.1), D-dimer (mg/L, normal range, 0–0.55), fibrinogen (mg/dL, normal range, 180–350), homocysteine (µmol/L, normal range <15), ferritin (µmol/L, normal ranges 11–336) were studied in all patients. Antinuclear antibody (ANA), anti-double stranded DNA (anti-dsDNA), extractable nuclear antigen (ENA) panel, antiphospholipid antibodies including lupus anticoagulant (30–38 s, with dRVVT-Dilute Russell’s viper venom time), anticardiolipin antibodies (IgG, normal range, 0–12 GPL/mL and IgM, normal range, 0–12 MPL/mL) and beta 2 glycoprotein-I (IgG and IgM, RU/mL, normal range <20), Factor VIII / V / X / XIII levels (as percent), genetic analyses for common hereditary thrombophilias (Factor V Leiden, Prothrombin G20210A, Methylenetetrahydrofolate reductase (MTHFR) A1298C and C677T polymorphism, Plasminogen activator inhibitor-1 (PAI-1) polymorphism) were studied in selected cases.

**Statistics**

Comparisons between groups such as COVID-19 positive and negative acute stroke cases, were performed using Pearson’s Chi Square, Fisher’s Exact and its Freeman-Halton extension tests, and Kruskal-Wallis test for categorical variables, and Student’s t, Mann-Whitney U and ANOVA for continuous variables. Distribution normality was tested by Kolmogorov-Smirnov or Shapiro-Wilk tests as appropriate. Multivariable logistic regression models were constructed to search the association between COVID-19 infection and different stroke characteristics including outcomes. Logistic regression models were adjusted for variables with p < 0.1 in univariate analyses. All statistical analyses were performed using SPSS version 22. P < 0.05 was set as the threshold for statistical significance.

**Results**

**Characteristics of COVID-19 positive cases**

Seventeen of 44 cases diagnosed with COVID-19 infection were PCR and thorax CT positive, 8 cases were PCR positive and thorax CT negative, and 19 cases were PCR negative but thorax CT positive. In 6 patients in the latter group, the antibody test performed later was found to be positive in four cases. 40 (91%) of these patients were hospitalized for two or more days. Thirty-three (75%) patients had a “mild” degree of COVID-19, and 19 of them required oxygen by mask or nasal prongs at the time of stroke occurrence. While non-invasive mechanical ventilation (NIVM) or high flow oxygen therapy (HFOT) was applied in six of the 11 (25%) patients in the severe category, 5 patients were intubated and invasive mechanical ventilation (IMV) was applied.

**Ischemic stroke**

There were a total of 355 COVID-19 negative and 37 COVID-19 positive ischemic stroke patients. Of these, 276 (78%) PCR negative and 34 (92%) PCR positive cases were hospitalized in our center, and the remaining were either transferred to other centers or managed at home (Supplementary Fig. 1).

While male and active smoker ratio was lower in COVID-19 positive strokes, no significant difference was found in terms of the frequency of vascular risk factors. In COVID-19 positive cases, the clinical severity of stroke (NIHSS) was significantly higher, and symptom onset to hospital admission interval was significantly longer (approximately 1000 minutes later, Table 1).
Table 1. Clinical characteristics of patients with acute ischemic stroke.

|                                | COVID-19 (+) | COVID-19 (-) | p     |
|--------------------------------|--------------|--------------|-------|
| Demographics & past medical history |              |              |       |
| Mean age                       | 70±15        | 70±15        | 0.946 |
| Female                         | 17%          | 50%          | <0.001|
| Hypertension                   | 68%          | 71%          | 0.691 |
| Diabetes mellitus              | 43%          | 32%          | 0.149 |
| Dyslipidemia                   | 8%           | 14%          | 0.293 |
| Coronary heart disease         | 30%          | 36%          | 0.464 |
| Congestive heart disease       | 8%           | 14%          | 0.312 |
| Atrial fibrillation (at admission) | 8%      | 16%          | 0.229 |
| Atrial fibrillation (detected during hospital stay) | 19%      | 15%          | 0.489 |
| Smoking (active)               | 6%           | 22%          | 0.017 |
| Alcohol                        | 0%           | 5%           | 0.161 |
| Previous stroke                | 22%          | 24%          | 0.780 |
| Stroke characteristics & treatment |          |              |       |
| NIHSS admission                | 12±7         | 9±8          | 0.034 |
| NIHSS 24th hour                | 11±7         | 8±8          | 0.064 |
| NIHSS at discharge             | 6±7          | 7±7          | 0.737 |
| Symptom onset-to-door time (minute) | 2145±3852  | 1084±2375    | 0.016 |
| IV tPA use                     | 10.8%        | 7.6%         | 0.492 |
| IV tPA (door-to-needle time) (minute) | 127±31     | 121±39       | 0.801 |
| Mechanical thrombectomy use    | 8.1%         | 16.3%        | 0.189 |
| MT (Door-to-groin puncture time) (minute) | 162±34     | 208±57       | 0.189 |
| Hospitalized                   | 92%          | 78%          | 0.084 |
| ICU care                       | 76%          | 50%          | 0.003 |
| Invasive mechanical ventilation | 60%         | 25%          | <0.001|
| Heparin                        |              |              |       |
| Any                            | 73%          | 62%          | 0.150 |
| Intravenous                    | 19%          | 36%          | 0.045 |
| Subcutaneous                   | 16%          | 3%           | 0.003 |
| Low molecular weight           | 38%          | 23%          | 0.042 |
| Aspirin                        | 41%          | 47%          | 0.431 |
| Clopidogrel                    | 16%          | 22%          | 0.417 |
| In-hospital metrics            |              |              |       |
| Brain computed tomography      | 95%          | 98%          | 0.184 |
| Cervicocranial tomographic angiography | 65%    | 88%          | <0.001|
| Brain magnetic resonance imaging | 89%       | 93%          | 0.363 |
| Craniocervical magnetic resonance angiography | 63%   | 67%          | 0.598 |
| Thoracic echocardiography      | 14%          | 60%          | <0.001|
| Stroke etiology (CCS)          |              |              |       |
| Cardioembolism                 | 40%          | 34%          | 0.081 |
| Largery artery disease         | 22%          | 22%          |       |
| Small artery disease           | 16%          | 10%          |       |
| Cryptogenic other              | 16%          | 7%           |       |
| Cryptogenic embolism           | 3%           | 10%          |       |
| Uncommon                       | 0%           | 6%           |       |
| Undetermined                   | 3%           | 11%          |       |
| Outcome                        |              |              |       |
| Median modified Rankin scale   | 6±4          | 3±3          | <0.001|
| Median modified Rankin scale in survived | 2±3       | 3±2          | 0.143 |
| modified Rankin scale ≤2       | 24%          | 45%          | 0.014 |
| Mortality                      | 54%          | 8%           | <0.001|
| Median of length of stay in hospital (days) | 11±14    | 5±13         | 0.002 |
| Median of length of stay in hospital (in survived, days) | 10±45     | 5±12         | 0.223 |

Abbreviations: CCS: Causative Classification of Stroke; ICU: Intensive Care Unit; IV tPA: Intravenous tissue-type plasminogen activator; MT: Mechanical Thrombectomy; NIHSS: The National Institutes of Health Stroke Scale.
No difference was found in the rates of systemic thrombolytic use (10.8% vs 7.6%, \( p = 0.492 \)) for COVID-19 positive and negative, respectively) and thrombectomy (8.1% vs 16.3%, \( p = 0.189 \)). Intensive care admission and mechanical ventilation use were significantly higher in cases with COVID-19, as expected. The overall anticoagulant use rate was not significantly different in COVID-19 cases. Physicians involved in stroke cases with COVID-19 preferred subcutaneous unfractionated or low molecular weight heparin over intravenous heparin. (Table 1).

In all of the patients with COVID-19 infection, at least one cervico-cranial angiography (either CT or MR angiography) was performed, but if one of them was done, the other was usually not obtained. CT angiography appears to be less preferred in this situation. Transthoracic echocardiography was performed significantly less frequently in SARS-CoV-2 positive cases.

Stroke etiological sub-classification did not indicate a difference in patients with COVID-19 (\( p = 0.881 \)). Both groups had cardioembolism (40% in COVID-19 positive and 34% in COVID-19 negative) as the most prevalent etiological category. Other cryptogenic category was numerically higher in the COVID-19 positive group (Table 1).

Acute stroke patients diagnosed as having COVID-19 were hospitalized for about 2 times longer (Table 1). Mortality rate was obviously higher in stroke patients with COVID-19 (54% vs 8%, \( OR = 16.5, 95\% CI \), 7.1–38.3, adjusted for NIHSS and age, \( p < 0.001 \)). The good prognosis rate at discharge was also significantly lower (24% vs 45%, \( OR = 0.39, 95\% CI \), 0.18–0.85, \( p = 0.014 \)). However, when adjusting for NIHSS (\( OR = 0.79, 95\% CI \), 0.75–0.83, \( p < 0.001 \)) and age (\( OR = 0.97, 95\% CI \), 0.95–0.99, \( p = 0.002 \), per 1 year), having COVID-19 did not significantly decrease the good prognosis rate (\( OR = 0.56, 95\% CI \), 0.22–1.44, \( p = 0.228 \)). There was no difference in the minimal / no disability rate in terms of having COVID-19 infection (16% vs 15%, \( p = 0.761 \)). IV tPA was given to 4 SARS-CoV-2 positive cases. One patient died of systemic causes, one was discharged with mRS 1 and two as mRS 3. Three patients who underwent thrombectomy died due to systemic reasons albeit excellent procedure success (Supplementary Table 1).

**Coagulation and inflammation profile**

C-reactive protein, erythrocyte sedimentation rate, fibrinogen and ferritin levels were significantly higher in COVID-19 (+) hospitalized ischemic stroke cases. Lymphocyte count was significantly lower and leukocyte count was significantly higher. Procalcitonin levels showed a numerical elevation (Table 2). No difference was observed between SARS-CoV-2 positive and negative patients in terms of hematological markers such as activated partial thromboplastin time, INR, D-dimer, platelet, hemoglobin and homocysteine levels.

Anti Nuclear Antigen, anti-dsDNA antibody and ENA panel positivity rates were not different in COVID-19 stroke cases. While the ANA titer was 1/100 in 9 COVID-19 positive cases and 1/320 in one, it was 1/100 in 10 cases, 1/160 in one case and 1/320 in two cases in the COVID-19 negative group. Anti-phospholipid antibodies including lupus anticoagulant, anti-cardiolipin antibodies and beta-2 glycoprotein 1 were studied in more than 70% of the acute stroke COVID-19 positive patients and in all of the cryptogenic cases but were never found to be positive (Table 2).

Coagulation factor levels could be studied in a small number of patients, but there was no sign that there might be a significant difference between the two groups. Hereditary thrombophilia was studied in 56% of SARS-CoV-2 (+) cases and in the entire cryptogenic COVID-19 stroke group. Factor V Leiden and prothrombin G20210A mutation homozygous form were not detected in the study group. No difference was found in SARS-CoV-2 positive cases in terms of heterozygosity. The distribution of polymorphism in MTHFR C677T, MTHFR A1298C and PAI-1 gene also did not differ in the COVID-19 positive stroke group (Table 2).

**Transient ischemic attack**

There were a total of 110 cases diagnosed with TIA. Five percent of these were SARS-CoV-2 PCR positive. Only 36 (33%) of the cases could be hospitalized. Others were referred to either the stroke outpatient clinics or other centers (Supplementary figure 1). The basic characteristics of 4 COVID-19 positive (OMS score 4 in one and 5 in three) and 32 SARS-CoV-2 negative hospitalized cases were documented in the supplementary table-2. In the COVID-19 positive group, one case was classified as large artery disease and 3 cases as cryptogenic, and in the COVID-19 negative group, 10 cases were classified as cryptogenic, 8 cases as large artery disease, 4 cases as cardioembolism, 4 cases as other uncommon and 6 cases as undetermined.

**Intracerebral hematoma**

A total of 46 (9%) were diagnosed with acute intracerebral hemorrhage. 2 patients were positive for SARS-CoV-2 PCR. 32 (70%) patients were hospitalized, the remaining 14 patients were referred from the emergency service to other centers (Supplementary figure 1). The clinical and laboratory data of the groups are provided in detail in the supplementary table-3. In SARS-CoV-2 (+) cases, one of the intracerebral hemorrhages was caused by warfarin overdose and the other was of hypertensive type. Two patients were treated in the intensive care unit and one passed away.

**Discussion**

We herein describe the clinical and etiological features of stroke in patients who are positive for COVID-19. This is the first prospective study data presented from Turkey. Our ischemic stroke patients were of similar age to
contemporary controls. The issue of interplay between age, COVID-19 infection and stroke risk has not been clarified yet. While the COVID-19 positive patients are older in some prior series, they were found to be younger in others. The frequency of male was higher in our series. While no gender difference was detected in some studies, male dominance was also found in others. Increase of stroke incidence may be related to the more frequent or severe course of the disease in men. Unlike some of the previous studies, we found that vascular risk and comorbidity profile in COVID-positive stroke cohort was not significantly different from COVID-negative ones. A

### Table 2. Blood markers in hospitalized patients with acute ischemic stroke.

| Blood markers (studied in all) | COVID-19 (+) | COVID-19 (-) | P   |
|--------------------------------|--------------|--------------|-----|
| N 37                          | 355          |              |     |
| Blood markers (studied in all) |              |              |     |
| C-reactive protein            | 9.32±9.96    | 3.93±7.31    | <0.001 |
| Procalcitonin                 | 4.51±16.89   | 1.24±7.78    | 0.054  |
| Erythrocyte sedimentation rate| 40±29        | 25±22        | 0.001  |
| Activated partial thromboplastin time | 25.49±5.23 | 26.29±16.2   | 0.765  |
| Prothrombin time (as INR)     | 1.31±0.41    | 1.17±0.41    | 0.055  |
| D-dimer                       | 5.27±6.58    | 4.33±10.04   | 0.585  |
| Fibrinogen                    | 460±186      | 365±140      | 0.005  |
| Ferritin                      | 456±497      | 158±683      | 0.015  |
| Platelet                      | 229±101      | 229±101      | 0.701  |
| Hemoglobin                    | 12.16±2.84   | 12.93±2.38   | 0.067  |
| Lymphocyte count              | 1.09±0.68    | 1.81±1.15    | <0.001 |
| Leukocytes count              | 10.81±3.7    | 9.36±4.07    | 0.039  |
| Homocysteine                  | 19.4±9.05    | 15.9±10.65   | 0.121  |

### Blood markers (studied in selected cases)

|                | COVID-19 (+) | COVID-19 (-) | P   |
|----------------|--------------|--------------|-----|
| Anti Nuclear Antigen |            | 70%          | 12% |
| Positive        | 42%          | 34%          | 0.721 |
| Anti-dsDNA Antibody |            | 70%          | 11% |
| Positive        | 0%           | 6%           | 0.221 |
| ENA Panel       |              | 70%          | 11% |
| Positive        | 0%           | 0%           | -   |
| Anti-phospholipid antibody | 70%       | 26%          |     |
| Positive        | 0%           | 17%          | 0.023 |
| Factor V Leiden |              | 56%          | 6.5% |
| Positive        | 10%          | 9%           | 0.957 |
| Prothrombin G20210A mutation | 56%     | 7.2%         |     |
| Positive        | 0%           | 12%          | 0.148 |
| MTHFR C677T polymorphism |         | 56%          | 7.2% |
| Positive        | 29%          | 52%          | 0.076 |
| MTHFR A1298C polymorphism |       | 56%          | 7.2% |
| Positive        | 24%          | 39%          | 0.206 |
| PAI-1 gene polymorphism |       | 56%          | 7.2% |
| Positive        | 19%          | 40%          | 0.002 |
| Factor VIII     |              | 56%          | 7.2% |
| Positive        | 19%          | 40%          | 0.002 |
| Factor V        |              | 56%          | 7.2% |
| Positive        | 19%          | 40%          | 0.002 |
| Factor X        |              | 56%          | 7.2% |
| Positive        | 19%          | 40%          | 0.002 |
| Factor XIII     |              | 56%          | 7.2% |
| Positive        | 19%          | 40%          | 0.002 |

Abbreviations: MTHFR: Methylenetetrahydrofolate reductase; PAI: Plasminogen activator inhibitor.
lower prevalence of smoking that we noted was noted in several prior studies without apparent reason.\textsuperscript{11,13}

We have confirmed that the clinical picture of COVID-positive stroke cases is more severe (such as high NIHSS, high rate of ICU admission and mechanical ventilation).\textsuperscript{9,11,13} In COVID-19 positive cases, the interval between symptom-onset and arrival to the hospital was longer. In other words, COVID (+) patients arrived later. Reasons for this delay may involve symptom scanning and notification to central transfer system by the emergency medical service in the pre-hospital setting. Among the causes of high stroke severity observed in COVID-19 cases, neurological examination deterioration due to infection can be encountered. Other causes can include a tendency to large artery occlusion and the clinical progression already due to late arrival.

We found no difference in terms of in-hospital time metrics such as door-to-needle or door-to-groin time in contrast to 15–25 min of prolongation in these metrics has been reported in the literature\textsuperscript{10}. We applied IV tPA in a total of four COVID-19 (+) patients and interventional therapy in three patients. Although the immediate results of the interventional procedure were very good in all three patients, we could not prevent death due to severe systemic diseases. Due to limited number of patients treated we cannot make any further comments on the success of acute stroke treatment in the settings of COVID-19 infection. Possibly, multi-national registries or meta-analysis will be able to produce solutions in this regard. The data collected so far suggests that it is not reasonable to expect a change in the benefit of recanalization therapies.\textsuperscript{10,14}

When compared to SARS-CoV-2-negative stroke patients, SARS-CoV-2-positive stroke patients were found to have higher mortality rates, worse functional outcomes at discharge and longer duration of hospitalization.\textsuperscript{2,9-11,13} Our data supported the finding of increased mortality rate, but we could not document presence of COVID-19 infection as an independent predictor of functional prognosis after adjustment by age and NIHSS.

We found that the rate of cryptogenic stroke did not increase in SARS-CoV-2 positive cases. Our cryptogenic stroke rate was approximately one-fifth, but rates of up to two-thirds were reported in the literature.\textsuperscript{13,15} The reason for this excess may be the possibility of COVID-19-specific stroke, as well as the inability to transfer from the ICU to examination suites due to the severity of the pulmonary disease, or the refusal to perform close contact tests such as transthoracic echocardiography. In our study, the rate of transthoracic echocardiography was also low, but this was compensated by long-term bedside cardiac monitoring and at least one cervicocranial angiography for each patient. Our data suggest that there is no type of ischemic stroke unique to COVID-19, or at least not very common.

Supporting the literature data, we found that acute phase reactants such as CRP, erythrocyte sedimentation rate and fibrinogen and disease severity markers such as ferritin were higher in the COVID-19 group. In addition, as expected lower lymphocytes and higher leukocytes counts was remarkable in COVID-19 patients.

In the hypercoagulable panels we tested on the day of stroke, we did not detect any changes specific to COVID-19 patients. In particular, the antiphospholipid antibodies we measured in more than two-thirds of the patients and in all of the cryptogenic cases did not come out as positive in any of the COVID 19 positive cases. In the literature, SARS-CoV-2 infection and antiphospholipid antibody positivity have been debated since the beginning of the pandemic.\textsuperscript{16,17} In the light of the data added later, we can formulate the connection of antiphospholipid antibodies with COVID-19 infection as follows: The presence of antiphospholipid antibodies in catastrophic COVID-19 infection may contribute to arterial and venous thromboembolic events.\textsuperscript{18} Apart from that, the prevalence of these antibodies is low in COVID-19. If it is found to be positive, it is almost always in low titer and transient. In most cases, this is an epiphenomenon not precipitating vascular thrombotic events.\textsuperscript{19}

Our study is not devoid of limitations: Having a single center and a limited number of patients is a limitation. Especially the number of TIA and intracerebral hemorrhage cases and the number of patients for whom IV tPA and interventional treatment were administered were low. But, we have presented these data so that it can be used in data combination. As a result, we added new findings on etiology, prognosis and thromboinflammation within the scope of COVID-19 infection and ischemic stroke connection. Stroke and COVID-19 infection association will continue to be studied.

Declaration of Competing Interest

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2021.105919.

References

1. Logrosino G, Beghi E. Stroke epidemiology and COVID-19 pandemic. Curr Opin Neurol 2021;34:3-10.
2. Tsivgoulis G, Palaiodimou L, Zand R, Lioutas VA, Krogias C, Katsanos AH, et al. COVID-19 and cerebrovascular diseases: a comprehensive overview. Ther Adv Disord 2020;13:1756286420978004.
3. Topcuoglu MA, Arsava EM, Kursun O, Akpinar E, Erbil B. The utility of middle cerebral artery clot density and burden assessment by noncontrast computed tomography in acute ischemic stroke patients treated with thrombolysis. J Stroke Cerebrovasc Dis 2014;23:e85-e91.
4. WHO-working-group-on-the-clinical-characterisation-management-of-covid-infection. A minimal common
outcome measure set for COVID-19 clinical research. Lancet Infect Dis 2020;20:e192-e1e7.

5. Topcuoglu M, Arsava E, Özdemir A. COVID-19 pandemisinde akut iskemik inme tedavisi: uzman görüşü (in English: Acute ischemic stroke treatment in COVID-19 pandemia: Expert Opinion). Türk Beyin Damar Hastalıkları Dergisi 2020;26:81-84.

6. Brott T, Adams Jr. HP, Olinger CP, Marler JR, Barsan WG, Biller J, et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke 1989;20:864-870.

7. Rankin J. Cerebral vascular accidents in patients over the age of 60. II. Prognosis. Scott Med J 1957;2:200-215.

8. Ay H, Furie KL, Singhal A, Smith WS, Sorensen AG, Koroshetz WJ. An evidence-based causative classification system for acute ischemic stroke. Ann Neurol 2005;58:688-697.

9. Annie F, Bates MC, Nanjundappa A, Bhatt DL, Alkhouli M. Prevalence and outcomes of acute ischemic stroke among patients < /=50 years of age with laboratory confirmed COVID-19 infection. Am J Cardiol 2020;130:169-170.

10. Srivastava PK, Zhang S, Xian Y, Xu H, Rutan C, Alger HM, et al. Acute ischemic stroke in patients with COVID-19: an analysis from get with the guidelines-stroke. Stroke 2021. 10.1161/STROKEAHA.121.034301:STROKEAHA121034301.

11. de Havenon A, Ney JP, Callaghan B, Delic A, Hohmann S, Shippey E, et al. Impact of COVID-19 on outcomes in ischemic stroke patients in the United States. J Stroke Cerebrovasc Dis 2021;30:105535.

12. Lau ES, McNeill JN, Paniagua SM, Liu EE, Wang JK, Bassett IV, et al. Sex differences in inflammatory markers in patients hospitalized with COVID-19 infection: Insights from the MGH COVID-19 patient registry. PLoS One 2021;16:e0250774.

13. Yaghi S, Ishida K, Torres J, Mac Grory B, Raz E, Humbert K, et al. SARS-CoV-2 and stroke in a New York healthcare system. Stroke 2020;51:2002-2011.

14. Pezzini A, Grassi M, Silvestrelli G, Locatelli M, Rifino N, Beretta S, et al. Impact of SARS-CoV-2 on reperfusion therapies for acute ischemic stroke in Lombardy, Italy: the STROKOID network. J Neurol 2021. 10.1007/s00415-021-10497-7.

15. Ramos-Araque ME, Siegler JE, Ribo M, Requena M, Lopez C, de Lera M, et al. Stroke etiologies in patients with COVID-19: the SVIN COVID-19 multinational registry. BMC Neurol 2021;21:43.

16. Castillo-Martinez D, Torres Z, Amezca-Guerra LM, Pineda C. Are antiphospholipid antibodies just a common epiphenomenon or are they causative of immune-mediated coagulopathy in COVID-19? Clin Rheumatol 2021. 10.1007/s10067-021-05724-5.

17. Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, et al. Coagulopathy and antiphospholipid antibodies in patients with COVID-19. N Engl J Med 2020;382:e38.

18. Xiao M, Zhang Y, Zhang S, Qin X, Xia P, Cao W, et al. Antiphospholipid antibodies in critically ill patients with COVID-19. Arthritis Rheumatol 2020;72:1998-2004.

19. Borghi MO, Beltagy A, Garrafa E, Curreli D, Cecchin G, Bodio C, et al. Anti-phospholipid antibodies in COVID-19 are different from those detectable in the anti-phospholipid syndrome. Front Immunol 2020;11:584241.