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*Coronavirus Pandemic*

# Coexistence of SARS-CoV-2 and cerebrovascular diseases: does COVID-19 positivity trigger cerebrovascular pathologies?

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## Abstract

The objectives of this study were to determine the prevalence of cerebrovascular diseases caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection, and to assess the pharmacological agents used in such cases as reported in the literature. Patient files were retrospectively scanned to determine the prevalence of neurological symptoms of the central nervous system (headache, dizziness, lack of smell and taste, numbness in arms and legs, change in consciousness, muscle weakness, loss of urine and stool control) and cerebrovascular diseases (ischemic cerebrovascular diseases, cerebral venous sinus thrombosis, intracerebral hemorrhage, subarachnoid/subdural hemorrhage) in 2019 novel coronavirus (2019-nCoV) disease (COVID-19) cases (n = 20,099). The diagnostic laboratory, radiology examinations and treatments applied to these cases were recorded. The data from studies presenting cerebrovascular diseases associated with SARS-Cov-2, which constituted 0.035% of all cases, were systematically evaluated from electronic databases. During the treatment of cerebrovascular diseases, it was discovered that high doses of enoxaparin sodium anti-Xa are combined with apixaban or acetylsalicylic acid or clopidogrel or piracetam, and mannitol, in addition to SARS-CoV-2 treatment modalities. While neurological symptoms of the central nervous system are uncommon in cases of SARS-CoV-2 infection, cerebrovascular diseases are far less common, according to the findings of this study. Acute cerebral ischemia was discovered to be the most common cerebrovascular disease associated with SARS-CoV-2. The mortality rate increases with the association between SARS-CoV-2 and cerebrovascular disease.

**Key words:** 2019-nCov; ischemic cerebrovascular diseases; intracerebral hemorrhage; pharmacological treatment protocols; SARS-CoV-2.

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## Introduction

The 2019 novel corona virus (2019-nCoV) disease (COVID-19), resulting from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, is known to cause serious morbidity and high mortality rate in humans [1].

Studies on 2019-nCov [2-4] have reported typical clinical symptoms such as fever, cough, diarrhea, and fatigue. Furthermore, some anomalies have been reported in the characteristic laboratory and radiological examinations [5]. In some studies, it has been discovered that SARS-CoV-2 infection may cause damage to the central nervous system, especially the olfactory bulb, even when the infection is still in its early stages [6,7]. Headache, anosmia, and dysgeusia are defined as common symptoms in the literature, and it has also been reported that disturbance of consciousness and seizures may occur as complications in cases with severe 2019-nCov [7,8]. Furthermore, it has been reported that neurological dysfunction and demyelinating reaction may arise as complications in cases diagnosed with SARS-Cov-2 after inflammation

of the pathogen's immune response and the resulting neural tissue [9-12].

Studies reviewing the neurotropic properties of COVID-19 and what kind of damage the virus causes to the central nervous system, suggest that angiotensin-converting enzyme-2 (ACE2) is the functional receptor of SARS-Cov-2, including glial cells in skeletal muscle and cerebral and spinal neurons [13,14]. Zhou *et al*. [13] explained that COVID-19 targets neurons and glial cells by binding to the ACE2 receptor to enter human cells with the virus, making these structures vulnerable to infection. Some cases of COVID-19 are associated with acute ischemic stroke, cerebral venous sinus thrombosis, cerebral hemorrhage, and acute cerebrovascular disorders such as subarachnoid hemorrhage, meningitis/encephalitis, acute necrotizing hemorrhagic encephalopathy [13], and acute Guillain-Barré syndrome [15].

In addition, when SARS-CoV-2 RNA is detected in the cerebrospinal fluid sample of a case diagnosed with 2019-nCov, it is presumed to be direct evidence to support the theory of neurotrophic involvement of SARS-CoV-2 [13]. However, it has been stated that the mechanisms underlying SARS-CoV-2's neurotrophic properties have yet to be clarified, and that it may reach the central nervous system through a hematogenous or neuronal retrograde pathway, affecting it directly or indirectly [16]. Potentially emerging drug-drug interactions between pharmaceuticals used to treat COVID-19 infection and medications prescribed to treat underlying comorbidities may induce adverse drug reactions in patients, worsening their clinical outcome [17]. There are very few evidence-rich clinical studies in the literature that evaluate the association of SARS-CoV-2 with cerebrovascular diseases and pharmacological treatment modalities.

The aim of this study was to examine patients with central nervous system neurological symptoms and cerebrovascular disease in 20,099 cases with a verified diagnosis of 2019-nCov based on laboratory and radiological examinations, as well as the pharmaceutical agents used in these cases, using the data available in literature.

## Methodology

*Ethical permission*

The data from both patients and healthy volunteers were obtained from hospital information management system databases. Approval to use the relevant data was obtained from the hospital administration (Date: 19/01/2021, Number: 13441514) and the Republic of Turkey Ministry of Health (2021-01-11T23_05_09).

The study involved patients who were admitted to hospital with fever, cough, muscle pain, loss of smell and taste, and malaise, and whose real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test and thorax computed tomography (CT) test confirmed the diagnosis of SARS-CoV-2. Cases with central nervous system neurological symptoms were discovered after SARS-CoV-2 was diagnosed. The data of cases diagnosed with cerebrovascular disorders after radiological examinations CT, magnetic resonance imaging (MRI), and MR-angiography were then included in the study of these cases.

*Materials*

RT-PCR tests were carried out with a commercial kit (Diagnovital HS SARS-Cov-2 Multiplex Real-Time PCR Kit, with BIO-RAD (Model number CFX96 Optics Module, serial number: 785BR25673, Hercules, USA) Touch Real-Time PCR Detection System). The specimens were collected using flocked swab (Cat. 2801110FR, Istanbul Technical University, Istanbul, Turkey) and then transferred to Bio-Speedy® Direct RT-qPCR SARS-Cov-2 (Bioeksen Ar Ge Tek, Istanbul, Turkey).

During biochemical analysis, the fasting blood glucose (FBG) [Cat. 141519008], C-Reactive protein (CRP) [Cat. 1429007], alanine aminotransferase (ALT) [Cat. 140120001], aspartate aminotransferase (AST) [Cat. 140220001] and the MB isoenzyme (CK-MB) [Cat. 142620001], which is found more commonly in the heart muscle than the enzyme creatine kinase (CK) [Cat. 142519013], urea [Cat. 141320002], LDH [Cat. 142719005], and sodium (Na) [Cat. 15720006], were all measured by the Mindray BS2000M (Bio Medical Electronics co. ltd, Shenzen, Chine), a device developed in the People's Republic of China. While Ferritin [Cat. 971200] was tested with the Beckmann Uniceldxi 800, (Brea, California, USA), and Troponin-I [Cat. 18260] was analyzed with the Radiometer-AQT90Flex (Cophenagen, Denmark). D-Dimer [Cat. 200007700] was measured using the Instrumentation Laboratory-ACL TOP 100 (Bedford USA, manufactured in Italy).

Among the commercial kits used in biochemical analysis, FBG (range of variation: 0.3-28 mmol/L), CK-MB (range of variation: 5-6000U/L), AST (range of variation: 4-800 U/L), ALT (range of variation: 4-1000 U/L), and CRP (range of variation: 2-150mg/L) were studied with 99.7% sensitivity. D-Dimer (range of variation: 150-3680 ng/mL) was studied with 94% sensitivity and the ferritin (2-1500ng/mL) kit had 95% sensitivity.

*Search strategy*

The electronic databases PubMed, Medline, Scopus, and Google Scholar were used to retrieve articles published until April 7, 2021, in English-language, and reporting on COVID-19. These databases were searched with the AND/OR option using the keywords "COVID-19", "coronavirus", "2019nCov", "nCOV", "SARS-CoV-2", "ischemic cerebrovascular diseases", "acute ischemic stroke", "cerebral venous sinus thrombosis", "cerebral hemorrhage", "subarachnoid bleeding", "meningitis/encephalitis", "acute necrotizing hemorrhagic encephalopathy", "pharmacological treatment protocols", "apixaban", "acetylsalicylic acid", "clopidogrel", "piracetam", "mannitol", "enoxaparin sodium anti-Xa", and "cortisone/dexamethasone".

The selection criteria for the data to be used in the study were designed to include only studies with a high level of evidence characterizing the clinical or epidemiological characteristics of COVID-19 patients and cases with acute cerebrovascular events treated in neurology/neurosurgery clinics.

The percentage distribution of articles by year was recorded, and a study by Lijmer *et al.* was used to determine the level of evidence of the studies [18-20]. Subsequently, the data were checked considering the Transparent Reporting of the Systematic Review (PRISMA) [19-21]. All bibliographies that may have been missed during the database search were reviewed again [19,20]. Scientific publications such as pre-clinical modeling, case reports, letters, editorial commentaries, reviews, systematic reviews, and meta-analyses were excluded from the study, as were subjects under the age of 18 [19,20].

*The exclusion and inclusion criteria of the cases in the study*

Data from students of dentistry, pharmacy, nursing, or medical faculties, personnel from hospitals or laboratories including volunteers, the cases, employees in the pharmaceutical sector, and people in certain hierarchical structures such as members of the armed forces were excluded from the research.

Aside from the clinical signs of infection such as fever, cough, myalgia, malaise, rhinorrhea, arthralgia, chest pain and shortness of breath, as well as nasopharyngeal swabs, bronchoalveolar lavage fluid, sputum or bronchial aspiration, subjects with confirmed SARS-CoV-2-RNA detection in a respiratory sample with plasma were included in the study.

The study was predicated upon the life, health, dignity, and integrity of the cases/volunteers involved in the study, the right to make decisions about themselves, their privacy, and the confidentiality of their personal information, in compliance with the Declaration of Helsinki. This study was carried out in accordance with the Declaration of Helsinki and ethical frameworks.

During our data collection, diagnoses of a total of 20,090 COVID-19 cases were assessed. Among these cases, those diagnosed with COVID-19 and with acute cerebrovascular symptoms (n = 82) were included in the study. The study included seven cases with diffusion

**Table 1.** Reports of neurological complications associated with COVID-19.

| Case | CVD Type | Location of the lesion | Age (years) | Gender | State of consciousness | Motor deficit | Sense deficit | Cranial nerve involvement | Concomitant diseases | Conclusion |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Thrombo Embolic | Right frontoparietal region | 62 | F | Unconscious | Left upper and lower extremity 1/5 | non-cooperative | Left central facial paralysis | T2DM | Exitus |
| 2 | Thrombo Embolic | Left caudate nucleus head adjacency | 65 | F | Conscious | - | - | - | T2DM | Discharged |
| 3 | Thrombo Embolic | Right temporo-occipital region | 67 | F | Somnolence | - | non-cooperative | - | HT | Discharged |
| 4 | Subdural hematoma | Right temporo-occipital and supratentorial region | 76 | F | Conscious | - | - | - | HT | Discharged |
| 5 | Thrombo Embolic | Left cingulate gyrus and left parietal postcentral gyrus | 54 | M | Conscious | Right upper extremity 2/5, Lower extremity 4/5 | Right hemihypoesthesia | Right central facial paralysis | - | Discharged |
| 6 | Thromboembolic | Right corona radiata posterior | 67 | M | Conscious | 4/5 proximally in all extremities | Glove-sock style hypoesthesia | - | T2DM, HT | Discharged |
| 7 | Thrombo Embolic | Right parietal and parieto-occipital | 89 | M | Somnolence | 3/5 in upper and lower extremities on the left | non-cooperative | - | HT, T2DM | Exitus |

restriction and/or bleeding consistent with acute infusion in diffusion MRI and CT examinations.

*Statistical analysis*

Minitab (version 22) software was used for data evaluation. Descriptive statistics were calculated as percentage (%), minimum (min), maximum (max), or mean ± standard deviation (Mean ± St Dev).

*Ethics approval*

Approval to use the relevant data was obtained from the hospital administration (Date: 19/01/2021, Number: 13441514) and the Republic of Turkey Ministry of Health (2021-01-11T23_05_09).

## Results

A total of 20,099 cases with SARS-Cov-2 infection, who tested positive with both CT thorax and RT-PCR tests for 2019-nCov diagnosis, were treated in hospital. The study focused on cases diagnosed with COVID-19 that had neurological symptoms in the central nervous system (n = 82).

The data of seven of these patients who were found to have diffusion restriction and/or intracerebral hemorrhage, consistent with acute infarction in diffusion MRI and CT examinations, were included in the study. In cases of SARS-Cov-2, the prevalence of cerebrovascular diseases was estimated to be 0.035%.

The mean age of the cases with these symptoms was 68.57 ± 11.15 years (min: 54, max: 89). Diagnoses of type-2 diabetes mellitus (T2DM) and arterial hypertension (HT) were included in the histories of the cases (Table 1).

Four of the patients had motor deficits and two had cranial nerve involvement. Sensory deficits were not present in two cases and could not be evaluated in three non-cooperative patients, while they were present in two others. When the state of consciousness of the participants was assessed, it was discovered that four were conscious, two were somnolent, and one was unconscious.

The biochemical parameters of the cases analyzed at the time of admission to the hospital indicated presence of COVID-19 infection (Table 2). The thoracic CT (Supplementary File), brain CT, and MRI images of the cases were evaluated at the same time. Diffusion MRI sections of these cases were examined in two groups as DWI and ADC mapping. Brain CT and MRI images from radiological examinations of cases with positive 2019-nCov-PCR test outcomes and cases with acute cerebrovascular pathologies were presented demonstratively (Figure 1-4).

In Figure 1A, an axial plane image of a non-contrast brain CT section of an 89-year-old male patient is shown. In the right parietal and parietooccipital regions, diffuse density reduction was observed in a wide area extending from cortical gray matter and subcortical white matter areas to periventricular white matter areas, the gray-white matter distinction has disappeared, and there is erasure in the adjacent hemispheric cortical sulci. Although in the diffusion MRI of the same case the diffuse signal increase is observed in a wide area extending from cortical gray matter and subcortical white matter areas to periventricular white matter areas, in the DWI (Figure 1B) and ADC mapping (Figure 1C) it is observed in a wide area in the right parietal and parietooccipital regions. In addition, diffuse loss of signal at the same localization is observed in ADC mapping. However, these findings indicate a limitation in diffusion.

**Table 2.** Descriptive statistics of biochemical parameters.

| Parameters | Mean ± StDev | Min - Max |
|---|---|---|
| FBG (mg/dL) | 192.57 ± 134.03 | 109 - 488 |
| WBC | 9.59 ± 3.67 | 4.70 - 14.70 |
| CRP | 43.60 ± 43.935 | 1.00 - 121.30 |
| Neutrophil | 7.26 ± 3.71 | 2.76 - 14.10 |
| Lymphocytes | 1.39 ± 0.94 | 0.26 - 3.21 |
| Platelet | 218.43 ± 109 | 81 - 350 |
| The international normalized ratio (INR) | 1.17 ± 0.09 | 1.03 - 1.31 |
| LDH | 370 ± 155 | 190 - 603 |
| D-Dimer | 1566.29 ± 2146.47 | 23 - 6064 |
| AST | 65.38 ± 34.81 | 4.3 - 105.51 |
| ALT | 36.29 ± 19.97 | 15 - 74.44 |
| Urea | 110.29 ± 167 | 27 - 488 |
| Creatine | 1.58 ± 1.64 | 0.73 - 5.27 |
| CK | 106.43 ± 107.89 | 29 - 337.15 |
| CK-MB | 36.71 ± 29.85 | 29 - 337.15 |
| Na | 130.66 ± 25.3 | 78.6 - 162 |
| Troponin-I | 0.02 ± 0.02 | 0.01 - 0.05 |
| Ferritin | 488.51 ± 648.09 | 90.5 - 1500 |

**Figure 1.** Brain CT and diffusion MRI sections of an 89-year-old male and a 67-year-old female patient.

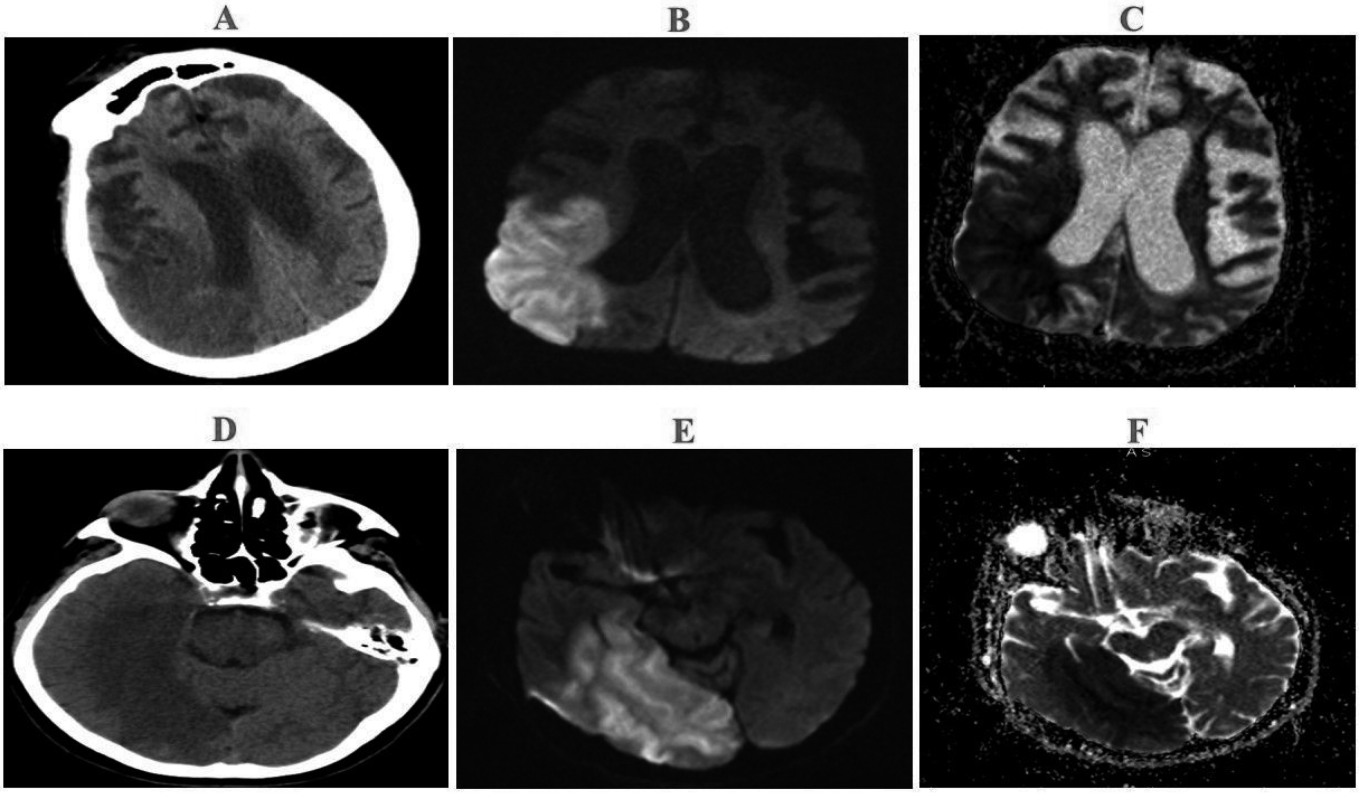
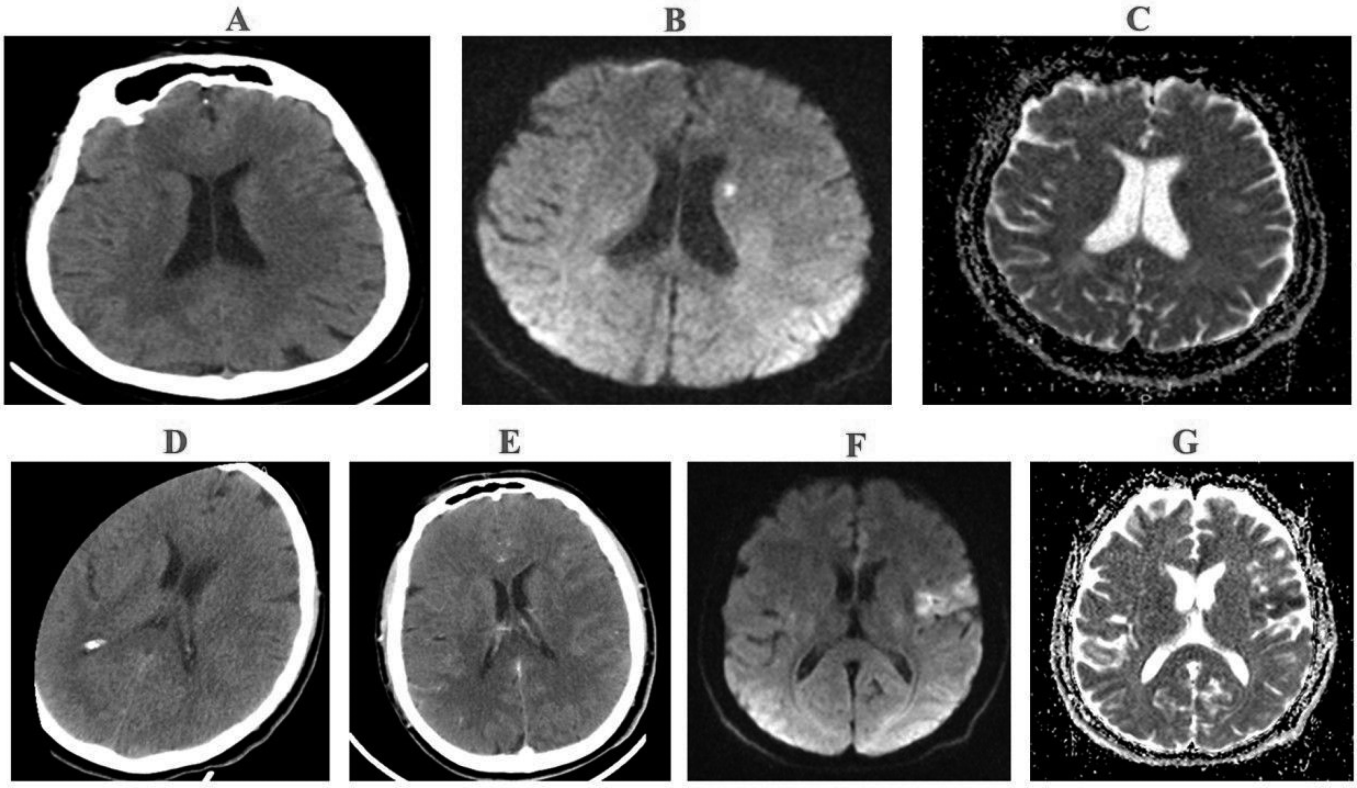



**Figure 2.** Brain CT and diffusion MRI sections of a 65-year-old female patient and a 54-year-old male patient.



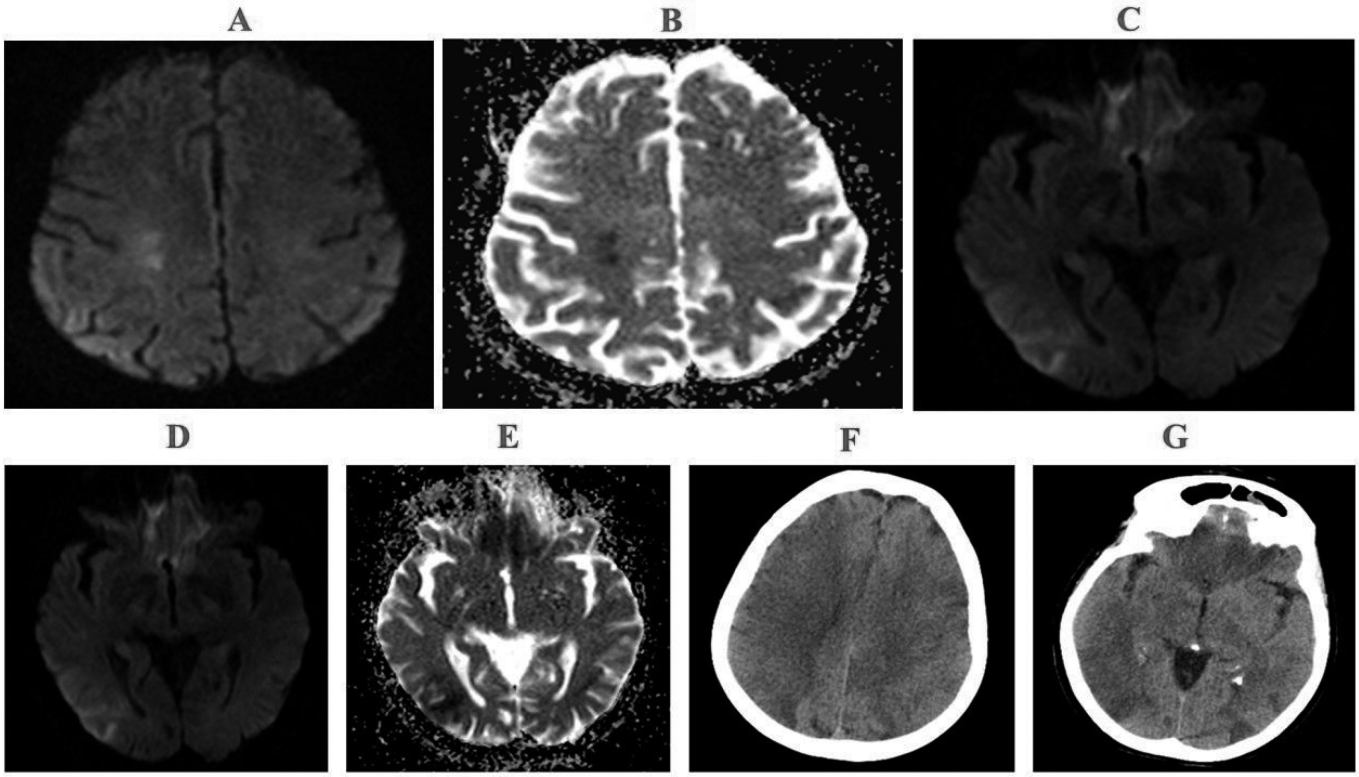
Due to edema, hemispheric cortical sulci around the lesion were removed. All of these findings were indicating an acute infarction.

Hypodense areas in the medial of the right temporooccipital zone, which diffuse the cortical gray and subcortical white matter areas, where the gray-white matter separation disappears and is accompanied by signs of erosion in the adjacent hemispheric cortical sulci due to edema, are striking in the axial non-contrast brain CT section of a 67-year-old female patient (Figure 1D). In the axial plane diffusion MRI images of the case, hyperintense signal recordings in the cortical gray matter and subcortical white matter areas, and DWI sequence (Figure 1E) in the medial of the right temporooccipital region and hypointense signal recordings in ADC mapping (Figure 1F) were observed. These findings were accompanied by narrowing or even deletion in adjacent hemispheric cortical sulci. These findings were considered to be an indication of acute infarction.

No significant finding was found except for a hypodense nodular area with a diameter of 5 mm in the lateral adjacency of the caudate nucleus on the right in the section passing through the ventricular level in the axial non-contrast brain CT sections of a 65-year-old female case (Figure 2A). In Figure 2B and Figure 2C, ADC mapping in the axial plane of the same patient in diffusion MRI sections is not caused by an acute event, is seen as isointense in MRI, and does not produce a selectable signal difference. On the left, the DWI sequence revealed hyperintense nodular areas, and ADC mapping revealed hypointense nodular areas, all consistent with an acute infarction measuring approximately 8 mm in diameter adjacent to the caudate nucleus head. In brain CT sections, this specified area is isodense and not visible. Figure 2D and 2E show the axial contrast-enhanced brain CT sections of the same patient. In diffusion MR images obtained in the axial plane of the same patient, in DWI sequence (Figure 2F) and ADC mapping (Figure 2G) hyperintense signal changes are observed in DWI images consistent with acute infarction in the left cingulate gyrus and left parietal postcentral gyrus, and hypointense signal changes are observed in ADC mapping.

In the diffusion MRI of a 62-year-old female case obtained in the axial plane (Figure 3), a hyperintense nodular area with lobulated contoured DWI sequence (Figure 3A) with a diameter of about 15 mm in the deep white matter area in the right frontoparietal in the sections passing through the supraventricular level, and a hypointense nodular area in ADC mapping (Figure 3B) were observed, and they were interpreted as a sign of diffusion restriction, which was evaluated in favor of acute infarction. In the inferior sections of the same

**Figure 3.** Brain CT and diffusion MRI sections of a 62-year-old female patient.



patient, in the cingulate gyrus in both frontal regions and the cortical gray matter and subcortical white matter areas in the right temporal region, hyperintense areas in DWI sequence (Figure 3C) and hypointense irregularly shaped areas in ADC mapping (Figure 3D) were observed, and they were interpreted as indications of acute infarction. Findings are now settled in the unenhanced brain CT sections in the axial plane obtained two days later in the same patient, and at the supraventricular level (Figure 3E) a large hypodense infarct area in the frontoparietal region that fits the right MCA irrigation area, similarly in the sections passing through lower levels (Figure 3F), and a wide hypodense infarct area in the bifrontal of both ACA irrigation and large hypodense infarct areas in the right temporal are seen.

Images of a 76-year-old female case (Figure 4) show acute subdural hemorrhage areas up to 6 mm in the right temporooccipital region and supratentorial region in the thickest part of non-contrast parenchyma

**Figure 4.** Brain CT image of a 76-year-old female patient, and brain CT and diffusion MRI sections of a 67-year-old male patient.

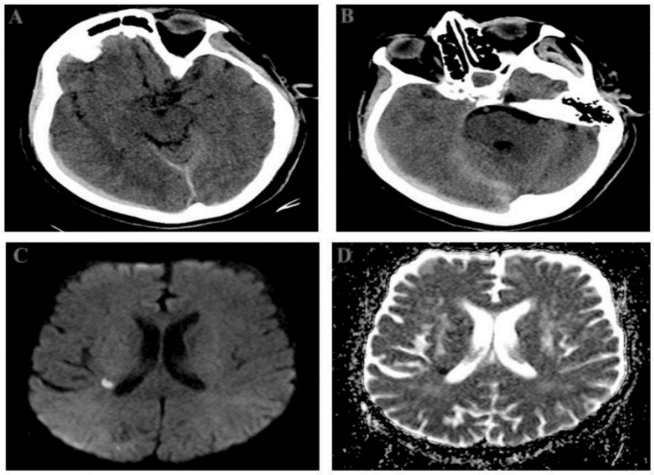



**Table 3.** Findings of research based on keywords related to acute brain, gleaned from electronic databases. The studies are indicated as follows: *Mowla *et al*. [22]; **Moriguchi *et al*. [23]; and ***Poyiadji *et al*. [24].

| Keywords | Case reports | Review | Systematic Review | Meta-analysis | Randomized Controlled Trial | Total (count) |
|---|---|---|---|---|---|---|
| SARS-Cov-2 + acute cerebrovascular diseases | 69 | 89 | 19 | 8 | 0 | 320 |
| Covid-19 + acute cerebrovascular diseases | 77 | 97 | 23 | 11 | 0 | 401 |
| 2019-nCov+ acute cerebrovascular diseases | 69 | 90 | 19 | 8 | 0 | 321 |
| SARS-Cov-2 + ischemic stroke | 54 | 40 | 18 | 3 | 0 | 238 |
| Covid-19+ ischemic stroke | 65 | 49 | 21 | 3 | 0 | 374 |
| 2019-nCov + ischemic stroke | 54 | 40 | 18 | 3 | 0 | 239 |
| SARS-Cov-2 + cerebral venous sinüs thrombosis | 10 | 9 | 2 | 2 | 1(22)* | 25 |
| Covid-19 + cerebral venous sinüs thrombosis | 15 | 9 | 3 | 2 | 0 | 35 |
| 2019-nCov + cerebral venous sinüs thrombosis | 10 | 9 | 2 | 2 | 0 | 25 |
| SARS-Cov-2 + cerebral hemorrhage | 26 | 12 | 4 | 1 | 0 | 73 |
| Covid-19 + cerebral hemorrhage | 28 | 13 | 5 | 2 | 0 | 89 |
| 2019-nCov + cerebral hemorrhage | 26 | 12 | 4 | 1 | 0 | 73 |
| SARS-Cov-2 + intracerebal hemorrhage | 30 | 13 | 5 | 1 | 0 | 96 |
| Covid-19 + intracerebal hemorrhage | 37 | 14 | 6 | 2 | 0 | 130 |
| 2019-nCov + intracerebal hemorrhage | 30 | 13 | 5 | 1 | 0 | 96 |
| SARS-Cov-2 + subarachnoid hemorrhage | 14 | 5 | 1 | 1 | 0 | 48 |
| Covid-19 + subarachnoid hemorrhage | 15 | 5 | 1 | 1 | 0 | 66 |
| 2019-nCov + subarachnoid hemorrhage | 14 | 5 | 1 | 1 | 0 | 48 |
| SARS-Cov-2 + meningitis/encephalitis | 5 | 5 | 2 | 1 | 1(23)** | 13 |
| Covid-19 + meningitis/encephalitis | 5 | 5 | 3 | 1 | 0 | 14 |
| 2019-nCov + meningitis/encephalitis | 5 | 5 | 2 | 0 | 0 | 13 |
| SARS-Cov-2 + acute necrotizing hemorrhagic encephalopathy | 14 | 17 | 3 | 0 | 0 | 44 |
| Covid-19 + acute necrotizing hemorrhagic encephalopathy | 17 | 18 | 3 | 1 | 1(24)*** | 51 |
| 2019-nCov + acute necrotizing hemorrhagic encephalopathy | 14 | 17 | 3 | 0 | 0 | 44 |
| SARS-Cov-2 + acute Guillain-Barre syndrome | 35 | 42 | 15 | 4 | 0 | 113 |
| Covid-19 + acute Guillain-Barre syndrome | 36 | 48 | 15 | 4 | 0 | 124 |
| 2019-nCov + acute Guillain-Barre syndrome | 35 | 42 | 15 | 4 | 0 | 113 |

sections obtained from different levels, (A) and (B), when evaluating non-contrast parenchyma sections in brain CT. In diffusion MRI images obtained 40 days after the first admission to the hospital of a 67-year-old male patient, a hyperintense nodular area of 8 mm diameter in the DWI sequence posterior to the right corona radiata (C), and a hypointense nodular area in ADC mapping (D) were observed, and they were interpreted as compatible with acute infarction.

A total of 90,831 studies were retrieved when 'COVID-19' was used as a keyword. These studies were published between April 7, 2019, and January 10, 2021. 55,114 studies were retrieved when the we searched with '2019-nCov'as the keyword, and 54,786 when we searched with 'Sars-Cov-2' as the keyword [22-24] (Table 3).

Different clinics administered Favipiravir and paracetamol, intravenous moxifloxacin and dexamethasone, or subcutaneous enoxaparin. Favipiravir (Favira 200 mg tablet®, Abdi Ibrahim, Istanbul, Turkey) was administered at 3200 mg/day on the first day, and 600 mg/day for the remaining four days for a total of five days. Moxifloxacin (Moxacin®, Vem Pharmaceutical Industry, Tekirdag, Turkey) was administered at a dose of 400 mg/250 mL/day, Enoxaparin (Clexane®, Sanofi, Istanbul, Turkey) 4000 anti-Xa/0.4 mL/day, dexamethasone (Dexoject®, Tum-Ekip-Pharmaceuticals, Istanbul, Turkey) 8mg/2mL/day, and paracetamol (Parol®, Atabay Pharmaceuticals, Istanbul, Turkey) at a total dose of 1500 mg/day for five days.

In addition to the aforementioned routine COVID-19 therapy, these patients were given apixaban, acetylsalicylic acid, clopidogrel, piracetam, and mannitol. The dose of Enoxaparin sodium anti-Xa was also increased to 0.6 mL/day. Table 4 summarizes the results of a systematic review of these drugs in the literature [25].

## Discussion

It is well known that SARS-Cov-2 can cause acute cerebrovascular disease. Acute ischemic stroke [26], cerebral venous sinus thrombosis [22, 27], cerebral hemorrhage [28], subarachnoid hemorrhage [29], meningitis/encephalitis, and acute necrotizing hemorrhagic encephalopathy have been recorded among the patients [30,31].

The overall number of neurological patients, as well as the associated health burden and social and economic costs, can be large when so many people are infected. Even if the rate of infections that trigger neurological disease will likely remain small, but that serious neurological sequela can remain in these patients [32].

Pharmaceutical preparations such as chloroquine, hydroxychloroquine, favipiravir, lopinavir/ritonavir, azithromycin, clarithromycin, moxifloxacin, acetylsalicylic acid, enoxaparin, dexamethasone, and paracetamol were used as mono or combined in the routine treatment of 2019-nCov cases examined in this review. Besides the aforementioned drugs, the use of atazanavir [17] or tocilizumab [5] have been reported in the literature.

According to the literature, steroids are preferred primarily in acute demyelinating reactions, and alpha and beta interferon therapies approved for the treatment of chronic demyelinating diseases are also used in the treatment of COVID-19, depending on the subsequent treatment response [33]. While interferons are used alone or in combination with ribavirin [34], it is understood that the main agent used to relieve the neurological symptoms that occur with the attacks is steroid (cortisone)-containing pharmaceuticals [30,31]. There are also reports on the use of plasmapheresis, which is an alternative treatment method for removing antibodies from the body if the attack symptoms do not improve adequately despite steroid therapy [35]. In addition, it has been stated that treatment is continued

**Table 4.** Findings from studies based on keywords specific to drugs for acute brain treatment obtained from electronic databases. The * indicates data from Wallentin *et al.* [25].

| Drugs | Case reports | Review | Systematic Review | Meta-analysis | Randomized Controlled Trial | Total (Count) |
|---|---|---|---|---|---|---|
| Apixaban + SARS-Cov-2/Covid-19/2019-nCov | 12 | 1 | 0 | 0 | 1[25]* | 21 |
| Acetyl salicylic acid+ SARS-Cov-2/Covid-19/2019-nCov | 1 | 0 | 0 | 0 | 0 | 1 |
| Enoxaparin sodium+ SARS-Cov-2/Covid-19/2019-nCov | 3 | 1 | 0 | 0 | 0 | 4 |
| Clopidogrel+ SARS-Cov-2/Covid-19/2019-nCov | 5 | 1 | 1 | 0 | 0 | 23 |
| Piracetam + SARS-Cov-2/Covid-19/2019-nCov | 0 | 0 | 0 | 0 | 0 | 0 |
| Mannitol+ SARS-Cov-2/Covid-19/2019-nCov | 0 | 0 | 0 | 0 | 0 | 1 |

with agents such as natalizumab [36] and fingolimod [37], particularly in cases where current demyelinating disease treatments are insufficient.

It has also been reported in the literature that SARS-CoV requires two $Ca^{2+}$ ions to interact with the host cell during its entry phase, and some calcium channel blockers including nimodipine and memantine that can be effective in the treatment of dementia in Alzheimer's disease, have an inhibitory effect in various viral infections [38].

It is still unclear if COVID-19 infections cause aneurysmal dilatations in intracerebral vascular structures or play a role in the rupture of an established intracranial aneurysm [29]. However, it has been suggested that cytokines such as IL-6, IL-β, and TNF-α, which are seen at high levels in systemic circulation during hypercytokinemia caused by the SARS-Cov-2 virus, cause damage to the cerebral blood-brain barrier. Moreover, these causal mechanisms that may contribute to subarachnoid hemorrhage by increasing the risk of rupture of existing intracranial aneurysms due to systemic inflammation, especially collagen destruction in the basal membrane of the cerebral vascular tissue [39].

Samples taken after coronal autopsy of two patients who were deceased after SARS-CoV-2 infection were evaluated histopathologically [40]. In the first case, in the literature severe multifocal cortical infarction with extensive perivascular calcification and numerous megakaryocytes, consistent with a severe multi-territorial cerebral vascular injury, and associated cerebral thrombotic microangiopathy were reported as detected [40]. The autopsy of the second case reported the discovery of brainstem encephalitis centered on the dorsal medulla and subacute regional infarction in the cerebellar cortical area. However, it was reported that in situ hybridization and RT-PCR results for SARS-CoV 2 RNA in samples were negative in both cases [40]. Despite the fact that the cases had calcifying cerebral cortical infarction with associated megakaryocytes and brainstem encephalitis, it was assumed that the absence of viral RNA in post-mortem cerebral tissues might not be a direct result of the viral neuroinvasive effect of such pathologies [40]. They came to the conclusion that these incidents were most likely caused by para-infectious phenomena such as systemic hyperinflammatory and hypercoagulable syndromes [40].

In a study of a 2019-nCov case admitted to the clinic due to interstitial pneumonia and seizures, it was stated that newly diagnosed demyelinating lesions were observed in the cerebral MRI examination [7]. Neurological and respiratory problems decreased, and the patient improved in a case where high-dose steroid therapy was applied; however, in this study the importance of 2019-nCov is emphasized, in that it may cause an immune disorder similar to SARS or play a triggering role in infective processes. It was stressed that rapid invasive therapies should be used in such cases to avoid hypoxic neurotoxicity and damage to the central nervous system [7].

In a study documenting the neuropathological findings of a 73-year-old male patient who was deceased after acute cerebellar hematoma associated with SARS-Cov-2 infection [41], cranial CT images showed a large right cerebellar hematoma and intraventricular hemorrhage with tonsillar herniation, and the patient died after a short time.

Another report described a ruptured intracranial aneurysm that was observed in a patient diagnosed with SARS-Cov-2 infection, whose neurovascular disease may be causally related [29]. Nimodipine, hydration, and low molecular weight heparin prophylaxis were administered as a standard treatment for aneurysmal subarachnoid hemorrhage. Steroids were also applied in addition to this standard treatment [29]. They also underlined that they added steroids to the treatment for the management of the acute phase in order to prevent the high inflammatory state due to cytokine storm, which can be seen in 2019-nCov [29].

A 44-year-old female case who was previously healthy and intact was evaluated in a study that revealed acute hemorrhagic necrotizing encephalitis caused by SARS-CoV-2 infection [30]. The patient had progressive cognitive impairment due to SARS-CoV-2 infection, and signs of acute hemorrhagic necrotizing encephalitis were found in cranial MRI examination. After admission with generalized tonic-clonic seizures and frontal dysexecutive syndrome, a steroid was administered upon detection of cognitive impairment. However, it has been reported that the treatment was ineffective, and the patient died [30].

A 59-year-old female patient with SARS-Cov-2 infection and a history of transfusion-related aplastic anemia was evaluated in a similar study [31]. During the radiological imaging examinations of the patient, who presented to the clinic with seizures and decreased level of consciousness ten days after the onset of subjective clinical findings of fever, cough, and headache, widespread edema was observed in the brainstem. Owing to the patient's loss of consciousness, a cranial MRI was performed, and she was intubated and given mechanical ventilation to protect his airway [31]. In this case, symptoms of progressive brainstem

edema were found alongside symmetrical hemorrhagic lesions in the brainstem, amygdala, putamen, and thalamic nuclei, leading to a diagnosis of hemorrhagic acute necrotizing encephalitis with early brainstem involvement. Following that, the patient was given steroid therapy, and the patient died on the eighth day due to a lack of response [31].

Four additional studies [22-25] were discovered through systematic analysis of the literature; however, when the full texts of these studies were examined, it was noticed that none of them were randomized controlled studies with clinical design.

SARS-CoV-2 can cause thrombotic complications such as coagulopathy and stroke [22]. A series of intracranial sinus vein thrombosis (CVST) cases with SARS-CoV-2 infection are presented in some retrospective and multinational design studies in which CVST is reported to be a rare finding that can be triggered by COVID-19 [22]. Six of the thirteen cases that met the study requirements were discharged, and three of thirteen were deceased [22]. It was emphasized that, CVST is a potential cause of comorbidity in SARS-Cov-2 infected cases [22].

Hyperintensity along the right lateral ventricle wall and hyperintense signal changes in the right mesial temporal lobe and hippocampus on brain MRI could indicate the possibility of meningitis associated with SARS-Cov-2 [23] in another study where the first case of meningitis/encephalitis associated with SARS-Coronavirus-2 was presented [23].

Adverse drug reactions (ADRs) may occur as a result of drug-drug interactions (DDIs) that arise during anti-COVID-19 treatment and comorbidities, raising the risk of hospitalization, delaying recovery, or even causing death. If required, dose adjustments should be made in the care of COVID-19 patients with a comorbid disease. Clinics should also be closely monitored for the incidence of DDI-related adverse events.

Ellul *et al.* state in their study that there are a growing number of case reports that describe a wide range of neurological symptoms, but in most cases, they lack adequate details, indicating the complexity of examining such patients [32].

In studies in which it is reported that 16 (7%) of 214 hospitalized COVID-19 patients in Wuhan, China, and 40 (69%) of 214 COVID-19 patients in French series of 58 intensive care patients with COVID-19, 49 (84%) had neurological complications, including 40 (69%) with encephalopathy due to SARS-CoV-2, it is stated that encephalitis was identified in only eight patients and Guillain Barré syndrome in 19 patients [32]. It was also highlighted that the SARS-CoV-2 pathogen was found in CSF samples from some of the patients [32]. Katsanos *et al*, reported that 1.3% of 67,845 SARS-CoV-2 patients were hospitalized for cerebrovascular events, with an increased risk of ischemic stroke (OR=3.5) [42].

In this study, we found that 0.41% (n = 82) of the cases studied had neurological symptoms related to the central nervous system. Cerebrovascular incidents were seen in 7 (8.5%) of the 82 cases with thromboembolic cerebrovascular disease in six cases and a subdural hematoma in six cases. 2.44% (n = 2) of these cases deceased. The studies accessed through electronic database searches and whose full texts were analyzed did not completely meet the study's selection criteria, and there was no Level I clinical research or study. A heterogeneity test could not be conducted because there was no common literature data, so the statistical findings were presented descriptively. Of the 20,099 cases of SARS-Cov-2 infection whose diagnosis of 2019-nCov was confirmed and both CT thorax and RT-PCR tests were positive, 82 cases with neurological symptoms were examined. Among these cases, it was understood that there were seven cases with diffusion restriction and/or intracerebral hemorrhage consistent with acute infarction in diffusion MRI and CT examinations, and therefore, the probability of cerebrovascular symptoms was found to be 0.035%. While the mean age of cases with these symptoms is noted to be 68.57 ± 11.15 years, it is recognized that T2DM and HT diagnoses are also present in the cases with cerebrovascular symptoms. In addition to the pharmacological agents routinely used in SARS-CoV-2 treatment modalities, it is noted that mannitol infusion and high-dose enoxaparin sodium anti-Xa are administered in conjunction with one of the apixaban/acetylsalicylic acid/clopidogrel/piracetam drugs in the treatment of cerebrovascular diseases.

## Limitations

The study is based on a retrospective design. In addition, the data it used was compiled from cases from the same race.

## Conclusions

Neurological symptoms of the central nervous system were not common in the cases of SARS-CoV-2 that were examined. In addition, cerebrovascular diseases were seen much less frequently, according to the findings of this study. Acute cerebral ischemia was observed to be the most common cerebrovascular pathology associated with SARS-CoV-2. The fact that the mortality rate can increase significantly when

SARS-CoV-2 and cerebrovascular disease coexist, as well as the very low coexistence of SARS-CoV-2 and cerebrovascular pathologies, leads us to believe that COVID-19 does not trigger cerebrovascular pathologies. However, there is still a need for careful clinical, diagnostic and epidemiological studies to help identify the symptoms and burden of neurological disease caused by SARS-CoV-2.

## Authors' contributions

Prof. Dr. Ates and Dr. Yilmaz conceptualized and designed the study, analyzed and interpreted data, supervised data collection, and critically reviewed and revised the manuscript for important intellectual content. Assoc. Prof. M.D. Karaarslan drafted the initial manuscript, acquired data, analyzed the data, interpreted the data, and critically revised the manuscript for important intellectual content. Dr. Ersoz acquired data, analyzed the data, interpreted the data, and revised the manuscript for important intellectual content. Dr. Kasim and Assoc. Prof. M.D. Dogan conceptualized and designed the study, analyzed and interpreted data, and critically reviewed and revised the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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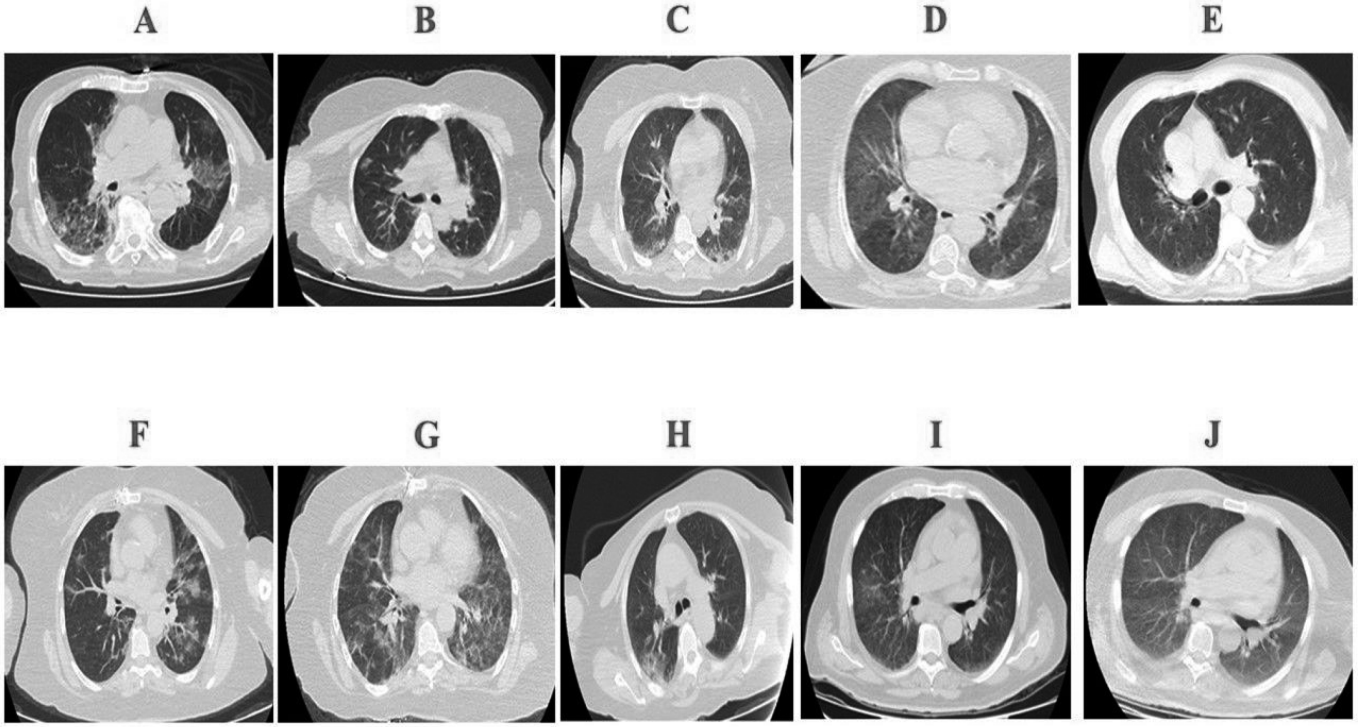
## Annex – Supplementary Items

**Supplementary Figure 1.** Thorax CT images of the cases.




**A:** Image of non-contrast CT sections in the parenchymal window in the axial plane of an 89-year-old male patient. Areas of ground-glass density in the form of large areas of subpleural and central areas of attenuation were found in the right lung's middle lobe medial section, the paramediastinal areas, the lower lobe basal and superior parts, and the left lung's upper lobe lingular segment, which are typical findings of COVID-19 pneumonia. **B and C:** Image of non-contrast chest CT sections in the parenchymal window in the axial plane of a 67-year-old female patient. In sections taken from different levels, ground-glass density attenuation areas, which are a typical finding for COVID-19 pneumonia, were observed in both lungs, in different localizations, particularly in the lower lobes and subpleural areas as patchy and irregularly shaped sporadically, and they appear to coalesce sporadically. **D:** Unenhanced thoracic CT scan in the parenchymal window of a 65-year-old female patient reveals heterogeneous density attenuation areas consistent with mosaic perfusion in the lower lobes of both lungs, the middle lobe of the right lung, and the lingular portion of the left lung in the axial plane. No other findings were detected in the lungs that were compatible with COVID-19 pneumonia. **E:** Image of non-contrast thorax CT sections in the parenchymal window in the axial plane of a 54-year-old male patient. In the parts passing through both lungs, no signs of COVID-19 pneumonia were identified, and no mass or additional infiltration was observed in the parenchyma. Parenchymal vascular structures and aeration seem normal. However, there is minimal ground-glass density in the lower lobe of the right lung, which may be consistent with dependent area stasis. **F:** Patchy and irregularly shaped ground-glass density areas of attenuation with widespread junction tendency were observed in thorax CT sections in the parenchymal window in the axial plane obtained when a 62-year-old female patient was first admitted to the hospital, with involvement seen in the middle lobe and medial of the lower lobe in the right lung, and especially in the lingular segment and lower lobe in the left lung, which were interpreted as typical COVID-19 pneumonia findings. **G:** The infiltration areas were observed to spread further with the decrease in ground-glass density in the parts passing almost the same localization in the control thoracic CT obtained after 14 days of the same patient. **H:** Images of a 76-year-old female case. In non-contrast thorax CT sections obtained in the parenchymal window in the axial plane, an area of attenuation with ground-glass density was observed as a single focus that spreads over a large area of irregular shape in the upper lobe posterior segment adjacent to the major fissure in the right lung, and in the lower lobe superior segment, and was evaluated as consistent with COVID-19. **I:** In the non-contrast thorax CT sections in the parenchymal window in the axial plane of a 67-year-old male patient, areas of attenuation with minimal ground-glass density suspicious for COVID-19 pneumonia without sharp boundaries were observed in the right lung middle lobe lateral segment and subpleural areas in the lower lobes. **J:** The control CT test of the same patient performed after 25 days revealed that the parenchymal aeration, where the areas defined in the previous examination disappeared, had returned to normal.