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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Is a high chest CT severity score a risk factor for an increased incidence of long-term neuroimaging findings after COVID-19?

Ahmet Turan Kaya, Asst. Prof, and Burcu Akman, Asst. Prof

Objectives: We aimed to determine the incidences of neuroimaging findings (NIF) and investigate the relationship between the course of pneumonia severity and neuroimaging findings. Materials and methods: Our study was a retrospective analysis of 272 (>18 years) COVID-19 patients who were admitted between “March 11, 2021, and September 26, 2022”. All patients underwent both chest CT and neuroimaging. The patient’s chest CTs were evaluated for pneumonia severity using a severity score system (CT-SS). The incidence of NIF was calculated. NIF were categorized into two groups; neuroimaging positive (NIP) and neuroimaging negative (NIN). Consecutive CT-SS changes in positive and negative NIF patients were analyzed. Results: The median age of total patients was 71; IQR, 57-80. Of all patients, 56/272 (20.6%) were NIP. There was no significant relationship between NIP and mortality (p = 0.815) and ICU admission (p = 0.187). The incidences of NIF in our patients were as follows: Acute-subacute ischemic stroke: 47/272 (17.3%); Acute spontaneous intracranial hemorrhage: 13/272 (4.8%); Cerebral microhemorrhages: 10/272 (3.7%) and Cerebral venous sinus thrombosis: 3/272 (10.7%). Temporal change of CT-SSs, there was a statistically significant increase in the second and third CT-SSs compared to the first CT-SS in both patients with NIP and NIN. Conclusion: Our results showed that neurological damage can be seen in the late period and neurological damage may develop regardless of pneumonia severity. Keywords: COVID-19—CT severity score—Brain CT—Brain MRI—Stroke—Neuroimaging © 2022 Elsevier Inc. All rights reserved.
stroke may occur due to coagulopathy secondary to vascular endothelial damage.15–17

Studies investigating neurological damage post-
COVID-19 usually included the first year of the pandemic and patients were not followed for more than 2 years.18–23 While these studies investigated neurological complications in inpatients, post-discharge patients were not investigated. The relationship between the course of pneumonia severity and neurological damage has not been investigated.

Therefore, we aimed to determine the incidences of neuroimaging findings (NIF) in the post-COVID-19 period and investigate the relationship between the temporal changes in pneumonia severity in consecutive chest CTs and NIF.

Methods

Study population

This is a single-center, retrospective analysis of patients admitted to our hospital between “March 11, 2021, and September 26, 2022”. This study was approved by the Ethical Committee of Amasya University Faculty of Medicine and was conducted according to the Declaration of Helsinki and Good Clinical Practice (02 December 2021, number: 12/155). Patient information was obtained from electronic records and censored. Since the study was retrospective, the ethics committee did not find it necessary to obtain written informed consent from the patients.

Data collection

In our study, we obtained electronic medical records of individuals who applied to other associated clinics in addition to the “COVID-19 clinic and/or post-COVID-19 follow-up clinic”. The first electronic data search resulted in a list of a total of 21,878 case records. Patients with positive RT-PCR were evaluated if they had chest CT scans in addition to neuroimaging (with or without contrast) scans. In patients with more than one COVID-19 positive, the date of the first RT-PCR positive was accepted. Patients with a time interval of more than 10 days between RT-PCR and first chest CT were excluded from the study. The first positive neuroimaging was enrolled in the study in patients with more than one neuroimaging. If sequential neuroimaging is negative, the last neuroimaging was enrolled in the study. As a result, 272 patients were included in the study (Fig. 1).

Inclusion criteria

Patients over 18 years of age, with positive RT-PCR test, and with neuroimaging (brain CT and/or MRI) and chest CT were included in the study.

Exclusion criteria

Patients with chronic-stage infarcts and hemorrhages confirmed by neuroimaging before the study time interval were excluded.

Fig. 1. Workflow diagram of the study.
Clinical and laboratory data

Demographic information of the patients, comorbidities, history of hospitalization or intensive care unit (ICU) admission, and survival were recorded from electronic medical records.

Imaging protocols

Chest and brain imaging were performed in the routine protocols of our hospital. The chest and brain CT scans were performed using the multidetector CT (MDCT) scanner 128-slice GE Healthcare Revolution EVO CT (GE Medical Systems; Milwaukee, WI). All brain MRI examinations were performed on a 1.5 Tesla scanner (Avanto, Siemens Healthcare).

Image analysis

Two radiologists (ATK, BA) with 9 and 15 years of experience in general radiology evaluated chest and neuroimaging together. Firstly, neuroimaging findings were categorized into two groups; neuroimaging positive (NIP) and neuroimaging negative (NIN). After, NIP was categorized into four subgroups; 1) Acute-subacute ischemic stroke (ASIS) (Fig. 2); 2) Acute spontaneous intracranial hemorrhage (ICH); 3) Cerebral microhemorrhages (CMH); 4) Cerebral venous sinus thrombosis (CVST) (Fig. 3).

In addition, the NIP group was divided into two groups “white matter changes” (WMC) and “grey matter changes (GMC)” according to the localization of the changes. Radiologists evaluated the patients’ first and, if available, second and/or third chest CTs for pneumonia severity. They used the extent of parenchymal involvement per lobe using a computed tomography severity score (CT-SS) on a total 25-point scale (0 = 0.1% - 1% - 5.2% - 6% - 25%, 3 = 26% - 50%, 4 = 51% - 75% and 5 = >= 75%).

Statistical analysis

Statistical analyzes were performed by using IBM SPSS Statistics for Windows, Version 25.0 (IBM, Armonk, New York, USA). The normal distribution of the variables was examined using Kolmogorov-Smirnov. In the descriptive analysis, continuous and categorical variables were compared according to neuroimaging groups and subgroups. Pearson Chi-square or Fisher tests were used to comparing categorical variables. The Mann-Whitney U test was used to compare the neuroimaging groups. Median and interquartile ranges (IQR) were used for the results. p < 0.05 was considered statistically significant. The statistical significance of the temporal changes of CT-SSs according to neuroimaging groups was examined with the Friedman test. Pairwise comparisons were made using the Wilcoxon test. After Bonferroni’s correction, p < 0.017 was considered statistically significant.

Fig. 2. (A) 53-year-old male patient has a positive RT-PCR test for COVID-19. He was discharged after being treated in Non-ICU in our hospital. 464 days after the RT-PCR positive date, brain CT and DWI were performed in our hospital due to neurological complaints. Focal ground glass opacities were present in both lung peripheries. Chest CT-SS:6. (B) Axial DWI image showed hyperintense cerebellum in the right paramedian area, (C) ADC images had hypointense acute ischemic infarct with diffusion restriction (Open arrow).
Fig. 3. A 48-year-old female patient had a positive RT-PCR test for COVID-19 (First CT-SS= 14; Second CT-SS= 15; Third CT-SS= 10). She was discharged after her treatment in the Non-ICU in our hospital. Brain CEMRI and MRV were performed in our hospital due to neurological complaints 24 days after the RT-PCR positive date. In the axial FLAIR (a) and coronal T2W (b) images, there were hyperintense edematous gray matter changes (GMCs) in both parietal lobe gyri (white arrows), and there was an increase in signal due to a filling defect in the superior sagittal sinus (SSS) in the T2W coronal image (magnified area).
**Results**

**Demographic results and frequencies of neuroimaging findings**

272 patients (median age = 71; IQR, 57-80) were included in our study. Of these patients, 56/272 (20.6%) were neuroimaging positive (NIP). 144/272 (52.9%) of our patients were male and there was no significant relationship between patients with NIP and gender ($p = 0.621$). 60/272 (22.1%) of our patients died, and there was no significant relationship between patients with NIP and mortality ($p = 0.815$). 60/272 (22.1%) of our patients were admitted to the ICU. There was no significant relationship between patients with NIP and ICU admission ($p = 0.187$). The incidences of NIP in our patients were as follows: ASIS, 47/272 (17.3%); ICH, 13/272 (4.8%); CMH, 10/272 (3.7%) and CVST, 3/272 (1.1%). CVST was present in all 3/272 (1.1%) patients who underwent MRV. There was no significant relationship between patients with NIP and inpatient or ICU admission ($p = 0.535$; $p = 0.187$). In the patients with NIP, chronic cardiovascular diseases 48/56 (85.7%) and chronic neurological diseases 47/56 (83.9%) were significantly more common ($p = 0.017$; $p < 0.001$) (Tables 1 and 2). Of the 272 patients included in our study, 138 had second a chest CT and 45 had a third chest CT.

**The relationship between ICU admission and NIF**

The most common NIF was ASIS 13/47 (21.7%) in the ICU admission group, which was not statistically significant ($p = 0.887$). The rate of WMC in the ICU group compared to the non-ICU group was [25% (15/60) versus 12.7% (27/212)], which was statistically significantly higher ($p = 0.02$). There was a statistically insignificant increase in NIF (excluding CMH) rates in the ICU group compared to the non-ICU group ($p > 0.05$) (Table 3).

**Relationship between mortality and NIF**

There was no significant relationship between NIF and mortality ($p > 0.05$). In the ex-patients, the highest incidence of NIF was ASIS [10/50 (16.0%)]. But it was not statistically significant ($p = 0.887$). There was a statistically insignificant decrease in NIF rates in the ex-patients compared to the alive patients ($p > 0.05$) (Table 3).

**Relationship between NIF and CT-SS**

The median age of patients with NIP was 71.5 (IQR; 63.25 – 82.75), which was not statistically significant compared to the negative group ($p = 0.098$). There was no significant relationship between patients with NIP, and CT-SS values of the first, second, and third chest CT scans ($p = 0.247$; $p = 0.832$; $p = 0.978$). The time interval between RT-PCR and the first chest CT was 1.24±2.33 (0-9) days. The time interval between RT-PCR and neuroimaging was 94.62±172.37 (0-692) days. The time interval between the first chest CT and neuroimaging was 93.38±172.55 (0-692) days. There was no significant relationship between the patients with NIP and the time interval between RT-PCR and the first CT ($p = 0.257$). In the patients with NIP, the median time interval (days) between RT-PCR and neuroimaging was 22.24 (IQR, 4.44-141.23); the median time interval (days) between chest CT and neuroimaging was 20.81 (IQR, 2.37-141.23). These time intervals were statistically higher than in patients without NIP ($p = 0.023$; $p = 0.01$) (Table 4).

**Relationship between follow-up chest CT-SS and NIF**

We compared the course of consecutive CT-SS values according to neuroimaging groups. There was a statistically significant increase between the first CT-SS and second CT-SS ($p < 0.001$; $p < 0.001$) and first CT-SS and third CT-SS ($p = 0.001$; $p = 0.014$) values in both patients with NIP and patients with NIN, respectively (Fig. 4) (Table 5).

**Discussion**

In our study, we investigated the incidences of post-COVID-19 neuroimaging findings (NIF) and the relationship between the temporal changes in pneumonia severity in consecutive chest CTs and acute-subacute neurological pathologies. The incidence of patients with neuroimaging positive (NIP) was 20.6% (56/272). In the patients with NIP, the highest incidence was acute-subacute ischemic stroke (ASIS) [47/272 (17.3%)], while the lowest incidence was cerebral microhemorrhages (CMH) [10/272 (3.7%)] in the subgroup analysis. ASIS had the highest incidence of NIF in patients who were admitted to ICU [13/60 (21.7%)] and in the ex-patients group [10/60 (16.7%)]. There was no significant relationship between patients with NIP and CT-SS values. When we analyzed the temporal change, there was a statistically significant increase in the second and third CT-SSs compared to the first chest CT in both patients with NIP and NIN.

SARS-CoV-2 can cause brain damage through both direct and indirect pathways. Four different pathways are thought to be effective in direct damage. First, SARS-CoV-2, which reaches the brain tissue by a hematogenous route, may attach to the ACE-2 receptor, causing endothelial damage, slowing blood flow, and disrupting the
blood-brain barrier.\textsuperscript{25,26} Secondly, it may be due to inflammatory damage of the virus that reaches the brain retrogradely from peripheral nerves.\textsuperscript{26} Third, the virus can enter via the neuronal pathway between the respiratory tract and the brain stem.\textsuperscript{27} Fourth, some authors claim that the virus enters the intestinal epithelial cells via ACE-2 receptors, which are abundant there, and reaches the brain by the neuronal spread.\textsuperscript{28} The indirect pathway can be divided into brain damage secondary to hypoxia, especially in critical COVID-19 patients, and severe inflammatory response syndrome (SIRS) due to an excessive immune response to the viruses. Increased IL-6 in the CSF samples is important evidence for cytokine storms.\textsuperscript{26} In addition, thromboembolism may be seen due to familial hypercoagulation disorder, multi-organ dysfunction secondary to SIRS, antiphospholipid antibody syndrome, viral myocarditis, and triggered atrial fibrillation.\textsuperscript{29–32} Some studies hold hypertension and empirical anticoagulation therapy responsible for the development of ICH and CMH.\textsuperscript{33–35} They also reported that severe coagulopathy is effective in the pathogenesis of CMH.\textsuperscript{36} Neurological complications were reported by approximately 37% in studies and reviews conducted in the early period of the pandemic, and this rate has been reduced in

| Table 1. Frequencies of demographic data and neuroimaging findings. |
|---------------------------------------------------------------|
| **Frequency** | **Percent** |
| **Gender** | | |
| Female | 128 | 47.1 |
| Male | 144 | 52.9 |
| **Inpatients?** | | |
| Outpatients | 72 | 26.5 |
| Inpatients | 200 | 73.5 |
| **ICU?** | | |
| Non-ICU | 212 | 77.9 |
| ICU | 60 | 22.1 |
| **Survival** | | |
| Alive | 212 | 77.9 |
| Death | 60 | 22.1 |
| **Neuroimaging** | | |
| Negative | 216 | 79.4 |
| Positive | 56 | 20.6 |
| **Neuroimaging localizations** | | |
| WMC | | |
| Negative | 230 | 84.6 |
| Positive | 42 | 15.4 |
| GMC | | |
| Negative | 234 | 86.0 |
| Positive | 38 | 14.0 |
| **Neuroimaging findings** | | |
| ASIS | | |
| Negative | 225 | 82.7 |
| Positive | 47 | 17.3 |
| ICH | | |
| Negative | 259 | 95.2 |
| Positive | 13 | 4.8 |
| CMH | | |
| Negative | 262 | 96.3 |
| Positive | 10 | 3.7 |
| CVST | | |
| Negative | 25 | 9.2 | 89.3* |
| Positive | 3 | 1.1 | 10.7* |
| Not performed** | 244 | 89.7 |
| **Neuroimaging methods** | | |
| Brain CT | | |
| Not performed | 4 | 1.5 |
| Performed | 268 | 98.5 |
| CECT | | |
| Not performed | 255 | 93.8 |
| Performed | 17 | 6.3 |
| Brain MRI | | |
| Not performed | 214 | 78.7 |
| Performed | 58 | 21.3 |
| CEMRI | | |
| Not performed | 257 | 94.5 |
| Performed | 15 | 5.5 |
| Brain DWI | | |
| Not performed | 87 | 32 |
| Performed | 185 | 68 |
| MRV | | |
| Not performed | 269 | 98.9 |
| Performed | 3 | 1.1 |

*Valid Percent
**MRV or Contrast-enhanced neuroimaging wasn’t performed ICU: Intensive care unit; WMC: White matter changes; GMC: Grey matter changes; Acute-subacute ischemic stroke (ASIS); ICH: Acute – subacute spontaneous intracranial hemorrhage; CMH: Cerebral microhemorrhages; CVST: Cerebral venous sinus thrombosis; CECT: Contrast enhanced CT; CEMRI: Contrast enhanced MRI; DWI: Diffusion-weighted imaging; MRV: Magnetic Resonance Venography
the late period of the pandemic with the development of vaccination and appropriate treatments. For example, Ladopoulos et al. reported that the main factor in the etiology of ASIS is large vessel occlusion. This may be due to the lack of experience with the infection in the early period of the pandemic and inadequate anticoagulant therapy. In the studies that included in the early period of the pandemic, the incidence ranges were reported as ASIS: 1.76%-59.9%; ICH: 5.4%-69.2%; CMH: 0.8%-58.7% and CVST: 0.08%-5.5%, respectively. In our study, NIF incidences were ASIS: 17.3%; ICH: 4.8%; CMH: 3.7% and CVST: 10.7%, respectively. In a study of hospitalized patients in New York, the incidence of ASIS was reported as 0.9%. Yaghi et al. and Tan et al. reported that the reasons for the different results in neuroimaging incidence studies were severe patients who were intubated and sedated, incomplete imaging due to difficulty in mobilization due to isolation, and long MRI scan time. As a result of delays due to these reasons, ASIS may have a falsely low incidence because hemorrhagic transformation developing after ASIS is interpreted as ICH. Due to the small number of participants in reviews of CVST-positive COVID-19 patients, case reports are generally included rather than clinical trials. This reduces the reliability of the reported incidence of CVST. In our study, only 3 patients underwent MRV and all had CVST. In addition, since sinuses and veins can be evaluated in brain CECT and CEMRI, a total of 28 patients were analyzed in terms of CVST. MRV or any contrast-enhanced neuroimaging modality was not performed on 244 patients. Therefore, we calculated the valid percent as 2/28 (10.7%) while CVST was positive in 3/272 (1.1%). This was the reason for our higher prevalence compared to other studies. In another review, Choi et al. reported that the prevalence may vary depending on the difference in imaging modalities used in the studies. Chi-square or (*) Fisher tests were used to compare categorical variables according to neuroimaging groups.

### Table 2. Comparison of positive neuroimaging with demographic data and comorbidities.

| Neuroimaging | Negative | Positive | p value |
|--------------|----------|----------|---------|
| Gender       |          |          |         |
| Female       | 100      | 28       | 0.621   |
| Male         | 116      | 28       |         |
| Total        | 216      | 56       |         |
| Inpatients or outpatients | | | |
| Outpatients  | 59       | 13       | 0.535   |
| Inpatients   | 157      | 43       |         |
| Total        | 216      | 56       |         |
| ICU          |          |          |         |
| Non-ICU      | 172      | 40       |         |
| ICU          | 44       | 16       | 0.518   |
| Total        | 216      | 56       |         |
| Survival     |          |          |         |
| Alive        | 169      | 43       |         |
| Death        | 47       | 13       | 0.815   |
| Total        | 216      | 56       |         |
| Pulmonary diseases | | | |
| Absent       | 177      | 43       |         |
| Present      | 39       | 13       |         |
| Total        | 216      | 56       |         |
| Cardiovascular disease | | | |
| Absent       | 65       | 8        | 0.017   |
| Present      | 151      | 48       |         |
| Total        | 216      | 56       |         |
| Neurological diseases | | | |
| Absent       | 151      | 9        | 0.001   |
| Present      | 65       | 47       |         |
| Total        | 216      | 56       |         |
| Diabetes mellitus | | | |
| Absent       | 170      | 46       |         |
| Present      | 46       | 10       | 0.571   |
| Total        | 216      | 56       |         |
| Kidney diseases | | | |
| Absent       | 204      | 49       | 0.069   |
| Present      | 12       | 7        |         |
| Total        | 216      | 56       |         |
| Liver diseases* | | | |
| Absent       | 215      | 56       | 0.999   |
| Present      | 1        | 0        |         |
| Total        | 216      | 56       |         |

Chi-square or (*) Fisher tests were used to compare categorical variables according to neuroimaging groups.
Table 3. Comparison of neuroimaging findings with ICU admission and survival.

| Neuroimaging | Non-ICU | ICU | p value | Non-ICU | ICU | p value |
|--------------|---------|-----|---------|---------|-----|---------|
| WMC          |         |     |         |         |     |         |
| Negative     | 185     | 87.3 | 45      | 75      | 0.02|         |
| Positive     | 27      | 12.7 | 15      | 25      |     |         |
| Total        | 212     | 60   | 60      |         |     |         |
| GMC          |         |     |         |         |     |         |
| Negative     | 185     | 87.3 | 49      | 81.7    | 0.27|         |
| Positive     | 27      | 12.7 | 11      | 18.3    |     |         |
| Total        | 212     | 60   | 60      |         |     |         |
| ASIS         |         |     |         |         |     |         |
| Negative     | 178     | 84   | 47      | 78.3    | 0.309|         |
| Positive     | 34      | 16   | 13      | 21.7    |     |         |
| Total        | 212     | 60   | 60      |         |     |         |
| ICH*         |         |     |         |         |     |         |
| Negative     | 203     | 95.8 | 56      | 93.3    | 0.492|         |
| Positive     | 9       | 4.2  | 4       | 6.7     |     |         |
| Total        | 212     | 60   | 60      |         |     |         |
| CMH*         |         |     |         |         |     |         |
| Negative     | 204     | 96.2 | 58      | 96.7    | 0.999|         |
| Positive     | 8       | 3.8  | 2       | 3.3     |     |         |
| Total        | 212     | 60   | 60      |         |     |         |
| CVST*        |         |     |         |         |     |         |
| Negative     | 21      | 91.3 | 4       | 80      | 0.459|         |
| Positive     | 2       | 8.7  | 1       | 20      |     |         |
| Total        | 23      | 5    | 2       |         |     |         |

WMC: White matter changes; GMC: Grey matter changes; ASIS: Acute-subacute ischemic stroke; ICH: Acute — subacute spontaneous intracranial hemorrhage; CMH: Cerebral microhemorrhages; CVST: Cerebral venous sinus thrombosis.
Chi-square or (*) Fisher tests were used to compare categorical variables according to ICU admission and survival.

Table 4. Comparison of positive neuroimaging with CT-SS’s and time intervals.

| Neuroimaging | Age | First CT-SS | Second CT-SS | Third CT-SS | Time from RT-PCR test to First Chest CT (days) | Time from RT-PCR test to Neuroimaging (days) | Time from First Chest CT to Neuroimaging (days) |
|--------------|-----|-------------|--------------|-------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| N            | Mean | SD          | Min. | Max. | Median | 25th | 75th | p value* | N       | Mean | SD          | Min. | Max. | Median | 25th | 75th | p value* | N       | Mean | SD          | Min. | Max. | Median | 25th | 75th | p value* |
| Age          |      |             |      |      |        |      |      |         |         |      |             |      |      |        |      |      |         |      |      |         |      |      |        |      |      |         |      |      |         |      |      |        |      |      |         |      |      |         |
| Negative     | 216  | 66.68       | 16.20| 22   | 94     | 71.00| 56.00| 79.00   | 0.098   | 216  | 67.61       | 15.80| 22   | 94     | 71.00| 57.00| 80.00   | 0.009  | 35   | 12.17       | 7.38 | 0    | 25     | 13.00| 8.00 | 16.00   | 0.978  | 216  | 87.39       | 164.79| 0    | 9     | 8.00 | 1.80 | 73.00   | 0.023  | 216  | 86.07       | 164.98| 0    | 675    | 5.00 | 0.06 | 73.00   | 0.01   |
| Positive     | 56   | 71.00       | 13.72| 32   | 94     | 71.50| 63.25| 82.75   |         | 56   | 7.95        | 7.14 | 0    | 25     | 6.00 | 2.00 | 12.75   |         | 56   | 12.22       | 198.07| 0    | 692    | 22.24| 4.44 | 141.23  |         | 56   | 121.63       | 198.32| 0    | 692    | 198.32| 4.44 | 141.23  |         | 56   | 93.36        | 172.55| 0    | 692    | 7.95 | 0.41 | 79.00   |         |
| Total        | 272  | 67.61       | 15.80| 22   | 94     | 71.00| 57.00| 80.00   |         | 272  | 7.14        | 7.00 | 0    | 25     | 5.00 | 0.00 | 11.00   |         | 138  | 11.54       | 7.38 | 0    | 25     | 12.00| 6.00 | 16.25   |         | 272  | 121.11       | 6.63 | 0    | 25     | 13.00| 8.00 | 15.50   |         | 272  | 121.22       | 172.37| 0    | 692    | 9.39 | 2.00 | 79.00   |         | 272  | 93.38        | 172.55| 0    | 692    | 7.95 | 0.41 | 79.00   |         |

* Mann-Whitney U test was usedCT-SS: CT Severity Score SD: Standart Deviation; Min: Minimum; Max: Maximum.
7.9–32.2] and 27.1% [16.4–37.7]; ICH: 3.9% [0.6–7.3] and 6.1% [3.3–8.9]; CMH: 13.8% [10.5–17.2] and 3.1% [1.0–5.2], respectively. 20 As seen in this study, a higher prevalence was reported when CT and/or MRI was performed in ASIS and ICH compared to patients who only underwent MRI, while it was reported to be lower in CMH. 20 Kim et al. reported that, unlike this study, there was no statistically significant difference in the rates of COVID-19 patients with NIP between the studies that used and did not use MRI. 21

The long time interval in our study also included the vaccination program that started in the first half of 2021 in our country. Although complications especially ASIS and CVST have been reported post-COVID-19 vaccination, Rahming et al. reported in their review that there was no significant increase in the overall incidence of stroke in the population of individuals administered COVID-19 vaccines. 39 According to our results, we thought that the main cause of positive neuroimaging in our patients who were COVID-19 positive before vaccination and who were vaccinated afterward was the infection itself.

In our study, the incidence of NIP in patients admitted to the ICU [26.7% (16/60) vs 18.9% (40/212)] showed a statistically insignificant increase compared to the non-ICU group (p = 0.187). Like our study, Choi et al. also reported that the incidence of NIP in patients admitted to ICU (11.8 % vs. 3.2%) was higher compared to the non-ICU group. 20 Kim et al. compared the incidence of NIP in studies that included critically ill patients with other studies. The incidence of NIP was 9.1% in studies that included critically ill patients, which was higher than in other studies (1.6%). 21 In three different reviews including critically or ICU admitted patients, the incidence ranges of NIP were reported as ASIS: 3.37%–17.2%; ICH: 6.2%–11.3%; CMH: 8.8%–14.8% and CVST: 1.8%–15.6%, respectively. 20–22 The fact that most of the patients admitted to the ICU were intubated suggests that they may have a history of hypoxia. The increase in the incidence of NIP in this group may be due to this reason in our study and Choi et al.’s study. 20 Since this group of patients has a low level of consciousness or is under sedation, neurological deficits of the patients may be hidden and examination may be difficult. Therefore, the need for neuroimaging should be kept in mind in clinically critical patients and patients admitted to the ICU. In our study, the incidence of NIP in patients admitted to ICU was similar to the literature, and ASIS: 21.7%; ICH 6.7%; CMH: 3.3%, and CVST: 20%. There was no statistically significant difference in NIP between the ICU and non-ICU groups. Kim et al. compared NIP with other studies in critically ill patients and reported that there was no significant difference between the two groups, similar to our study. 21 In particular, they argued that the development of ASIS was due to an increased risk of thrombosis due to hypercoagulability, not due to the systemic inflammatory response secondary to acute respiratory distress syndrome (ARDS). 21 This may explain the non-significant ASIS increase in the ICU admission group in our study.

Mogensen et al. reported the highest rate of neuroimaging findings in patients who died, as ICH (49.7%). The incidence of ASIS was 30% in their study. 18 In our study, the most common incidence of NIF in patients who died was ASIS: 16.7%; CMH: 3.3% and ICH: 1.7% respectively. The low incidence in our study may be due to the increase
in knowledge in diagnosis and treatment because the first case was seen late compared to other countries. Lang et al. reported a statistically insignificant increase in the mortality rate in the patients with NIP (21%) compared to patients with NIN (17%) in their study (p = 0.945).40 Similarly, in our study, there was a statistically insignificant increase in the mortality rate in the patients with NIP (23.2%) compared to patients with NIN (21.8%) (p = 0.815).

In our study, we investigated the effect of increased pneumonia severity on the incidence of NIP. We analyzed the temporal change of CT-SSs in three consecutive chest CTs. There was no significant increase in CT-SS in the patients with NIP compared to the patients with NIN. In addition, there was a statistically significant increase in the second and third CT-SS compared to the first CT-SS in both patients with NIP and NIN. This showed us that the increase in CT-SS was not only associated with NIP. Mahammedi et al. also investigated the effect of CT-SS on patients with NIP.41 While our study included inpatients, outpatients, and discharged patients, other studies included only inpatients. They analyzed the highest CT-SS value in patients with more than one chest CT and reported significantly higher CT-SS in the group with NIP, unlike our study.41 They reported a higher incidence of neurological symptoms in patients with severe respiratory disease.41 Lang et al. also reported that the CT-SS value was high in the patients with NIP, but there was no significant predictor of acute NIP in multivariate analysis.40 The difference in results in our study is consistent with the literature. It has been reported that not only high CT-SS but also silent hypoxia, metabolic disorder, intubation history, advanced age, history of ICU admission, cardiovascular diseases, autoimmune diseases, angiopathies, and proinflammatory cytokines are effective in brain damage.42–44

| Neuroimaging Negative | N | Mean Rank | Sum of Ranks | p value** |
|------------------------|---|-----------|--------------|-----------|
| Second CT-SS- First CT-SS | Negative Ranks | 20<sup>a</sup> | 25.78 | 515.50 | <0.001 |
| Positive Ranks | 75<sup>b</sup> | 53.93 | 4044.50 |
| Ties | 14<sup>c</sup> | 12.28 | 110.50 |
| Total | 109 | 19.38 | 484.50 |
| Third CT-SS- First CT-SS | Negative Ranks | 9<sup>d</sup> | 13.33 | 266.50 | 0.001 |
| Positive Ranks | 25<sup>e</sup> | 19.38 | 261.50 |
| Ties | 1<sup>f</sup> | 21.79 | 10 |
| Total | 35 | 31 |
| Third CT-SS- Second CT-SS | Negative Ranks | 20<sup>g</sup> | 5.25 | 3.50 | <0.001 |
| Positive Ranks | 12<sup>h</sup> | 14.70 | 367.50 |
| Ties | 3<sup>i</sup> | 3.50 | 51.50 |
| Total | 35 | 21.79 | 51.50 |

**Wilcoxon Signed Ranks Test was used. p < 0.017 was considered statistically significant.

<sup>a</sup>Second CT-SS < First CT-SS
<sup>b</sup>Second CT-SS > First CT-SS
<sup>c</sup>Second CT-SS = First CT-SS
<sup>d</sup>Third CT-SS < First CT-SS
<sup>e</sup>Third CT-SS > First CT-SS
<sup>f</sup>Third CT-SS = First CT-SS
<sup>g</sup>Third CT-SS < Second CT-SS
<sup>h</sup>Third CT-SS > Second CT-SS
<sup>i</sup>Third CT-SS = Second CT-SS
SARS-CoV-2 virus, which reaches the brain in a retrograde way from peripheral nerves.\textsuperscript{45}

Although the interval between positive neuroimaging after SARS-CoV-2 infection is not clear in the literature, Li et al. reported it as about 12 days.\textsuperscript{46} In our study, the median time between the first positive RT-PCR and the first positive neuroimaging was 22.24 days (IQR: 4.44-141.23, p=0.023). As seen in Table 4, the time interval are obtained over a much longer period.

To our knowledge, our study was the first to investigate the incidence of ischemic and hemorrhagic strokes post-COVID-19 with the longest time interval of more than two years. It was also the first study to evaluate the effect of temporal variation of CT severity of pneumonia on neuroimaging findings.

Our study had some limitations. First, it was a retrospective single-center study. Secondly, no analysis was performed to show the virus in the cerebrospinal fluid during the NIP period of the patients. Third, a histopathological examination of the brain tissue after mortality was not performed. Finally, it is difficult to definitively associate new neurological findings post-COVID-19 with this disease.

In conclusion, our results showed that since neurological damage can be seen in the late period, careful follow-up should be done in risky groups and neurological damage may develop regardless of the severity of the disease.

Ethics Committee Approval

This retrospective and the single-center study was approved by the Ethical Committee of Amasya University Sabuncuo�lu Serefeddin Education and Research Hospital (02 December 2021, number: 12/155). The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Informed Consent

The study is retrospective, patient information was obtained from electronic records and censored. Since the study was retrospective, the ethics committee did not find it necessary to obtain written informed consent from the patients.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author, [ATK].

Authors’ contribution statements

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version of the paper.

Declaration of Competing Interest

The authors declare they have no conflicts of interest.

CRediT authorship contribution statement

Ahmet Turan Kaya: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Supervision. Burcu Akman: Methodology, Writing – original draft, Writing – review & editing, Supervision.

Funding

No funding was received to assist with the preparation of this manuscript. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Johns Hopkins Coronavirus Resource Center. COVID-19 Map - Johns Hopkins Coronavirus Resource Center. Johns Hopkins Coronavirus Resource Center; 2020. p. 1.
2. Lu Y, Li X, Geng D, et al. Cerebral Micro-Structural Changes in COVID-19 patients – an MRI-based 3-month follow-up study. EClinicalMedicine 2020:25
3. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 2020;77:1.
4. Gulko E, Oleksk ML, Gomes W, et al. MRI brain findings in 126 patients with COVID-19: initial observations from a descriptive literature review. AJNR Am J Neuroradiol 2020;41:2199.
5. Mahajan A, Of JH-AJ, 2020 undefined, Novel coronavirus: what neuroradiologists as citizens of the world need to know. Am Soc Neuroradiol.
6. Zhou P, Yang X, Wang X, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. nature.com.
7. Moonis G, Filippi CG, Kirsch CFE, et al. The Spectrum of neuroimaging findings on CT and MRI in adults with COVID-19. 102214/AJR2024839 2020;217:959–74.
8. Zubair A, McAlpine L, Gardin T, SF J, 2020 Undefined, Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: a review. jamanetwork.com.
9. Moriguchi T, Harri N, Goto J. A First Case of Meningitis/Encephalitis Associated with SARS-Coronavirus-2 undefined. Elsevier; 2020.
10. Paniz-Mondolfi A, Bryce C, Grimes Z, et al. Central nervous system involvement by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). J Med Virol 2020;92:699-702.
11. Zhou L, Zhang M, Wang J, Dis JG-TMI, 2020 undefined. Sars-Cov-2: underestimated damage to nervous system. text2fa.ir 2020.
12. Huang Y, Jiang D, Brain JH, Behavior undefined, immunity and, 2020 undefined. SARS-CoV-2 detected in cerebrospinal fluid by PCR in a case of COVID-19 encephalitis. ncbi.nlm.nih.gov.
13. Xu J, Zhong S, Liu J, et al. Detection of severe acute respiratory syndrome coronavirus in the brain: potential role of the chemokine MIG in pathogenesis. Clin Infect Dis 2005;41:1089-1096.
14. Zhang Q, Ding Y, Hou J, LH-D 1 jun yi da xue xue, 2003 undefined. Detection of severe acute respiratory syndrome (SARS)-associated coronavirus RNA in autopsy tissues with in situ hybridization. europepmc.org.

15. Libby P. COVID-19 is, in the end, an endothelial disease. Eur Heart J 2020: academic.oup.com.

16. Oxley T, Mocco J, Majidi S. Large-vessel stroke as a presenting feature of Covid-19 in the young. Mass Med Soc 2020;382:e60.

17. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med 2020;46:1089-1098.

18. Mogensen MA, Wangaryattawanich P, Hartman J, et al. Special report of the RSNA COVID-19 task force: systematic review of outcomes associated with COVID-19 neuroimaging findings in hospitalized patients. Br J Radiol 2021;94:20210149.

19. Ladopoulos T, Zand R, Shahjouei S, et al. COVID-19: neuroimaging features of a pandemic. J Neuroimaging 2021;31:228.

20. Choi Y, Lee MK. Neuroimaging findings of brain MRI and CT in patients with COVID-19: a systematic review and meta-analysis. Eur J Radiol 2020;133:109393.

21. Kim PH, Kim M, Suh CH, et al. Neuroimaging findings in patients with COVID-19: a systematic review and meta-analysis. Korean J Radiol 2021;22:1875.

22. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endothelitis in COVID-19. Lancet (London, England) 2020;395:1417.

23. Zhang Y, Xiao M, Zhang S, et al. Coagulopathy and anti-phospholipid antibodies in patients with Covid-19. N Engl J Med 2020;382:e38.

24. Libby P. COVID-19 is, in the end, an endothelial disease. Eur Heart J 2020: academic.oup.com.

25. Chang YC, Yu CJ, Chang SC, et al. Pulmonary sequelae of acute respiratory syndrome coronavirus-2 infection: a systematic review and meta-analysis. Eur J Neurol 2021;28:3478.

26. Chang YC, Yu CJ, Chang SC, et al. Pulmonary sequelae in convalescent patients after severe acute respiratory syndrome: evaluation with thin-section CT. Radiology 2005;236:1067-1075.

27. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host–virus interaction, and proposed neurotropic mechanisms. ACS Chem Neurosci 2020;11:965.

28. Esposito G, Pesce M, Seguella L, Sanseverino W, Lu J, Sarnelli G. Can the enteric nervous system be an alternative entrance door in SARS-CoV2 neuroinvasion? Brain Behav Immun 2020;87:93.

29. Zhang L, Yan X, Fan Q, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J Thromb Haemost 2020;18:1324.

30. Zhang Q, Ding Y, Hou J, LH-D 1 jun yi da xue xue, 2003 undefined. Detection of severe acute respiratory syndrome (SARS)-associated coronavirus RNA in autopsy tissues with in situ hybridization. europepmc.org.

31. Libby P. COVID-19 is, in the end, an endothelial disease. Eur Heart J 2020: academic.oup.com.