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Neuroimaging findings of brain MRI and CT in patients with COVID-19: A systematic review and meta-analysis

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ABSTRACT

Purpose: To comprehensively evaluate the incidences of abnormal neuroimaging findings in patients with COVID-19 via a systematic review and meta-analysis.

Method: PubMed-MEDLINE and EMBASE were searched for original articles reporting imaging findings of the brain in adult patients with COVID-19 between January 1, 2020 and October 9, 2020. Abnormal neuroimaging findings were categorized as (1) cerebral microhemorrhages, (2) acute spontaneous intracranial hemorrhage (ICH), (3) acute to subacute infarcts, and (4) encephalitis or encephalopathy. Pooled incidences of neuroimaging findings were assessed using random-effects modeling. Between-study heterogeneity was explored by using the χ² statistic for pooled incidences and the inconsistency index I². The quality of the studies was evaluated using the Risk of Bias Assessment Tool for Nonrandomized Studies. Subgroup meta-regression analysis was performed to identify potential sources of heterogeneity.

Results: Twenty-one eligible papers, including 2125 patients, were identified. The pooled incidences of cerebral microhemorrhages, acute spontaneous ICH, acute/subacute infarcts, and encephalitis/encephalopathy were 6.9 % (95 % confidence interval [CI], 4.9 %–8.9 %), 5.4 % (95 % CI, 3.1 %–7.6 %), 24.0 % (95 % CI, 16.1 %–31.8 %), and 3.3 % (95 % CI, 1.9 %–4.7 %), respectively. Substantial heterogeneities were noted for all neuroimaging findings (I² = 87 %–97 %). Significant publication biases were present in the pooled incidences. In the subgroup meta-regression analysis, patients with mean or median ages over 65 years showed a significantly lower incidence of encephalitis/encephalopathy (P < 0.001). Furthermore, studies reported that patients in ICU had significantly higher incidences of cerebral microhemorrhages (P < 0.001) and encephalitis/encephalopathy (P < 0.001).

Conclusions: Considerable incidences of abnormal neuroimaging findings have been reported in patients with COVID-19. Acute to subacute cerebral infarction was the most prevalent neuroimaging finding.

1. Introduction

In December 2019, the epidemic of coronavirus disease 2019 (COVID-19)—caused by the severe acute respiratory syndrome virus (SARS-CoV-2)—was first reported in Wuhan, China. The rapid spread of COVID-19 has made it a public health emergency of international concern [1]. As of October 21, over 40 million people were confirmed to be infected with SARS-CoV-2 globally, with over 700,000 confirmed deaths worldwide [2]. While SARS-CoV-2 is mostly known for causing severe respiratory distress, a growing number of neurologic manifestations have been reported [3,4]. In one study from Wuhan, China, 28.2 % of the patients with COVID-19 showed an altered mental status or acute cerebrovascular disease [3]. Also, in patients who recovered from COVID-19, neurologic symptoms were reported to be present in 55 % of the patients [5].

Since the initial case reports describing COVID-19-associated acute hemorrhagic necrotizing encephalopathy [6], other neuroimaging findings in patients with COVID-19 have been reported, including

Abbreviations: ADEM, acute disseminated encephalomyelitis; CI, confidence interval; COVID-19, coronavirus disease 2019; ICH, intracranial hemorrhage; PRES, posterior reversible encephalopathy syndrome; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; I², Higgin’s inconsistency index.

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encephalitis/meningitis [7–9], hemorrhagic posterior reversible encephalopathy syndrome (PRES) [10,11], acute disseminated encephalomyelitis (ADEM) [12,13], cerebral venous thrombosis [14–16], and acute ischemic stroke [8,16,17]. Over the past several months, the number of publications reporting COVID-19-related neuroimaging findings since the outbreak of SARS-CoV-2 has been unprecedented and evolving. However, most publications are case reports/series, which have low evidence levels to establish the prevalence of specific neuroimaging findings in COVID-19.

Considering the dire nature of the pandemic, the current meta-analysis aims to collate currently available literature reporting various neuroimaging findings of COVID-19 to provide more research evidence, thereby improving radiologists’ diagnostic confidence upon encountering COVID-19-related neuroimaging findings.

2. Materials and methods

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18]. The institutional review board of our institution approved this study.

2.1. Literature search

PubMed-MEDLINE and EMBASE databases were searched for studies published between January 1, 2020 and July 30, 2020. The search terms were as follows: (Coronavirus disease OR Novel coronavirus OR 2019-nCoV OR SARS-CoV-2 OR Covid-19 OR Severe Acute Respiratory Syndrome Coronavirus 2) AND (Brain) AND (CT OR computed tomography OR MRI OR magnetic resonance imaging). The search was updated on October 9, 2020. The references of the selected articles were further...
| First author | Study period, all in 2020 | Affiliation | modality (n) | image analysis (experience) | Number of patients with neuroimaging | sex, male (%) | Age, mean ± SD/median (range) | study design | Multicenter study | microbleed | Acute/subacute infarct | non-traumatic ICH | Encephalitis/encephalopathy |
|--------------|--------------------------|-------------|--------------|-----------------------------|--------------------------------------|--------------|-------------------------------|--------------|----------------|-------------|-----------------|----------------|-----------------------------|
| Fitsiori     | NR                       | University Hospitals of Geneva and Faculty of Medicine of Geneva, Geneva | MRI 2 | neuroradiologists (NR) | 9 | 7 (77.8) | 67.7 ± 9 | retrospective no | 9 | 2 | 0 | 0 |
| Chougar      | March 23 - May 7         | Pitie-Salpetrier Hospital, Paris | MRI 2 | neuroradiologists (NR) | 73 | 48 (65.8) | 58.5 ± 15.6 | retrospective no | 8 | 17 | 0 | 12 |
| Xiong        | January 18 - March 20    | 56 hospitals in Hubei and Sichuan | CT NR | NR | 28 | NR | NR | retrospective yes | NR | 10 | 0 | 0 |
| Helms        | March 3 - April 3        | Strasbourg, France | MRI NR | median, 63 | 13 | NR | median, 63 | retrospective yes | 0 | 3 | 0 | 8 |
| Paterson     | April 9 - May 15         | University College London, Queen Square Institute of Neurology, London | MRI (13); CT (3) | NR | 16 | 9 (56.3) | 58.8 ± 12.5 | retrospective yes | 4 | 8 | 0 | 11 |
| Coolen       | 3/31 - 4/24              | CUB Hospital Erasme, Brussels | MRI 3 | neuroradiologists (NR) | 19 | 14 (73.7) | mean, 77 (49–94) | prospective no | 0 | 2 | 0 | 2 |
| Jain         | March 1 - April 14       | New York University Langone Health | MRI (48); CT (323 one examination; 131 > 1 examinations) 4 | neuroradiologists (fellowship-trained) | 454 | 275 (60.7) | median, 64 | retrospective yes | 0 | 26 | 0 | 1 |
| Radmanesh    | April 5 - April 25       | NYU Langone Medical Centers | MRI 2 | neuroradiologist2 (6 and 9 years of experience) | 27 | 9 of 11 reported (81.8) | 53 (38–64) (11 patients in ICU) | retrospective no | 7 | 11 | 4 | 5 |
| Hernández-Fernández | March 1 - April 19 | Hospital Universitario de Albacete, Castilla-La Mancha, Spain | CT (23) / both CT and MRI (6) 1 | neuroradiologist (NR) | 23 | 18 (78.3) | 66.8 | retrospective no | 4 | 17 | 5 | 1 |
| Kremer       | March 23 - April 27      | 16 Hospitals in France | MRI 3 | neuroradiologists (9, 20, 25 years of experience) | 37 | 30 (81.1) | 61 ± 12 | retrospective yes | 9 | NR | 20 | 27 |
| Kandemirli   | March 1 - April 18       | 8 Hospitals in Istanbul, Turkey | MRI 2 | neuroradiologists (both, 29 years of experience) | 27 | 21 (77.8) | 63 (34–87) | retrospective yes | 0 | 1 | 1 | 12 |
| Radmanesh    | March 1 - March 31       | NYU Langone Medical Centers | CT (207) / MRI (11) / both CT and MRI (24) 1 | neuroradiologist (6 years of experience) | 242 | 150 (62) | 68.7 ± 16.5 | retrospective no | 134 | 13 | 11 | 26 |
| D’Amore      | February 21 - May 21     | Hospital of Circolo and Macchi | CT (27) / both CT and MRI (4) 3 | neuroradiologists | 27 | 7 (46.7) | mean 68 (21–88) | retrospective no | 0 | 6 | 4 | 2 |

(continued on next page)
| First author | Study period, all in 2020 | Affiliation | modality (n) | image analysis (experience) | Number of patients with neuroimaging | sex, male (%) | Age, mean ± SD/median (range) | study design | Multicenter study | microbleed | Acute/subacute infarct | non-traumatic ICH | Encephalitis/encephalopathy |
|--------------|--------------------------|-------------|--------------|----------------------------|-------------------------------------|---------------|--------------------------|-------------|-----------------|-----------|---------------------|-----------------|-------------------------|
| Klironomos   | March 2 - May 24         | Department of Neuroradiology, Karolinska University Hospital | CT (174) / MRI (43) (both CT and MRI, 32) | (6, 7, 10 years of experience) | 11 neuroradiologists, 1 radiology resident (mean ± SD, 11.5 ± 5.7 years of experience) | 185 | 138 (74.6) | 62 ± 14 | retrospective | no | 29 | 25 | 27 | 31 |
| Yoon         | March 3 - May 6          | Department of Radiology, Massachusetts General Hospital | CT (141) / MRI (21) / both CT and MRI (31) | 2 neuroradiologists (NR) | | 150 | 98 (65.3) | 63.6 ± 16 | retrospective | no | 7 | 13 | 2 | 7 |
| Sheth        | October 30, 2019 – May 20, 2020 | Department of Neurology, Yale University School of Medicine | Portable MRI (20) | 1 neuroradiologist (NR) | | 20 | 17 (85) | 60 ± 8 | Prospective | No | 0 | 3 | 1 | 3 |
| Shahjouei    | March 27 – May 1         | 99 tertiary centers in 11 countries | CT or MRI | Local radiologists (NR) | | 156 | 109 (70) | 66 ± 15 | Retrospective | Yes | 0 | 123 | 27 | 0 |
| Sawlani      | March 1 – May 31         | Queen Elizabeth Hospital Birmingham academic quaternary-care center and affiliated community hospital | CT (172) / MRI (36) | 2 neuroradiologists (NR) | | 167 | NR | NR | Retrospective | No | 12 | 21 | 3 | 0 |
| Lin          | March 4 – May 9          | Perelman School of Medicine at the University of Pennsylvania | CT (269) / MRI (51) (both, 42) | 2 neuroradiologists (10 years) | | 278 | 165 (59) | 64 (50–75) | Retrospective | No | 3 | 31 | 10 | 0 |
| Freeman      | March 1 – June 18        | Perelman School of Medicine at the University of Pennsylvania | MRI | 3 neuroradiologists (NR) | | 59 | NR | Nr | Retrospective | No | 2 | 10 | 0 | 0 |
| Agarwal      | March 1 – May 10         | 3 tertiary care hospitals of an academic medical center | MRI | 2 neuroradiologist (fellow) | | 1115 | 82 (71.3) | NR | Retrospective | Yes | 25 | 47 | 0 | 0 |

NR = not reported; NA = not applicable; SD = standard deviation; DWI = diffusion-weighted imaging; T1WI = T1-weighted imaging; T2WI = T2-weighted imaging; CE-T1WI = contrast-enhanced T1-weighted imaging; FLAIR = fluid attenuated inversion recovery; SWI = susceptibility-weighted imaging.
screened to search for potentially relevant articles. Two reviewers (Y.C. and M.K.L.) independently performed the literature search, and any disagreement regarding study inclusion was resolved by consensus. The authors were not blinded to the authors, institutions, or journals while selecting studies or extracting data. EndNote version X9 (Thomas Reuters, New York City, NY, USA) was used for literature management.

2.2. Eligibility criteria

Studies investigating imaging findings (CT or MRI) of the brain in patients with COVID-19 were eligible for inclusion. The included studies met the following criteria: (1) Population: Patients diagnosed with COVID-19 with a sample size greater than five patients. (2) Study design: Both retrospective and prospective observational studies were included. (3) Outcomes: Studies reporting sufficient details on imaging findings of the brain from either CT or MRI (i.e., cerebral microhemorrhages, acute/subacute infarction, acute spontaneous intracranial hemorrhage (ICH), encephalitis/encephalopathy).

The exclusion criteria were as follows: (1) reviews, editorials, and letters; (2) case reports or case series with < 5 patients; (3) partially overlapping patient cohorts; (4) articles not written in English, and (5) non-human studies. Two reviewers independently reviewed the literature in consensus.

2.3. Data extraction

From the selected articles, the following data were extracted into standardized formats: (a) study characteristics: authors, affiliations, country of origin, study duration, study design, and sample size; (b) patients’ demographic and clinical characteristics: age, sex, imaging modality and its specifications, number of neuroradiologist reviewers, indication for imaging (neurologic symptoms or others), and patients in ICU (reported or not reported). Likelihood ratio tests were used to compare the random-effects models in subgroup analysis.

Between-study heterogeneity was calculated by using the I² statistics for pooled estimates (P < 0.05, indicating significant heterogeneity) and the Higgin’s inconsistency index (I²), where I² values of 0%–40%, 40%–60%, 60%–90%, and 90%–100% indicated insignificant, moderate, substantial, and considerable heterogeneity, respectively [8]. Publication bias was evaluated using funnel plots and Egger’s test, with a P-value < 0.1 indicating significant bias [20].

Publication bias-adjusted pooled incidences were also calculated via the trim-and-fill method [21], where agreement between the unadjusted and adjusted pooled incidences and estimates may indicate little publication bias. All statistical meta-analyses were performed using R (v.3.6.1, R Foundation for Statistical Computing, Vienna, Austria). A P-value of <0.05 was considered statistically significant.

3. Results

3.1. Literature search

An overview of the selection process for studies from the literature search is depicted in Fig. 1. The initial literature search identified 231 articles. After the removal of duplicates, 183 articles were screened for eligibility. Among these, 164 were excluded after reviewing their titles and abstracts (84 case reports/series, 50 review/letters/editorials, 28 articles with irrelevant content, 1 non-English article, and 1 non-human study). The full texts of the remaining 19 articles were thoroughly reviewed; five articles were further excluded due to lack of neuroimaging findings [22,23], partially overlapping patient cohorts [24],

| Table 2 |
| --- |
| Summary of the meta-analytically pooled incidences for abnormal neuroimaging findings in patients with COVID-19. |
| **Summary estimate** | **Trim-and-fill estimate** |
| Cerebral microhemorrhages | Pooled incidences (%) [95 % CI] | P-value for heterogeneity | I² (%) | P-value for publication bias | No. of missing studies | Adjusted pooled proportions (%) [95 % CI] |
| 6.9 [4.9–8.9] | <0.001 | 94 | <0.001 | 10 | 1.6 [0–3.7] |
| Spontaneous acute ICH | 5.4 [3.1–7.6] | <0.001 | 87 | <0.001 | 4 | 4.0 [1.7–6.4] |
| Acute/subacute infarct | 24.0 [16.1–31.8] | <0.001 | 97 | 0.014 | 0 | 24.1 [16.3–31.9] |
| Encephalitis/encephalopathy | 3.3 [1.9–4.7] | <0.001 | 92 | <0.001 | 10 | 0.8 [0–2.5] |

ICH = intracranial hemorrhage; CI = confidence interval; I² = Higgins’ inconsistency index.

* P-value by the Cochran’s Q method to test the heterogeneity of the pooled data (P < 0.05 indicates significant heterogeneity).

* Higgins’ inconsistency index (0–40% may indicate insignificant heterogeneity; 30–60%, 50–90%, and 75–100% may indicate moderate, substantial, and considerable heterogeneity, respectively).

* Egger’s test (P < 0.10 indicates significant publication bias).

2.4. Quality assessment

Quality assessments of the included studies were independently performed by two reviewers using the structured criteria of the Risk of Bias Assessment Tool for Non-randomized Studies (RoBANS) [7].

2.5. Statistical analyses

The primary outcomes of this meta-analysis were the pooled incidences of abnormal neuroimaging findings, including cerebral microhemorrhages, acute/subacute infarcts, acute spontaneous ICH, and encephalitis/encephalopathy. Meta-analytic pooling was performed using the inverse variance method to calculate weights. Pooled incidences with 95% confidence intervals (CIs) were obtained using Der Simonian-Laird random-effects modeling [19]. Subgroup meta-regression analysis was performed based on patients’ median age (>65 or ≤65 years), imaging modality (MRI or CT/MRI), origin of publication (Europe, USA, or Asia), single/multi-center design, indication for imaging (neurologic symptoms or others), and patients in ICU (reported or not reported). Likelihood ratio tests were used to compare the random-effects models in subgroup analysis.

Between-study heterogeneity was calculated by using the I² statistics for pooled estimates (P < 0.05, indicating significant heterogeneity) and the Higgin’s inconsistency index (I²), where I² values of 0%–40%, 40%–60%, 60%–90%, and 90%–100% indicated insignificant, moderate, substantial, and considerable heterogeneity, respectively [8]. Publication bias was evaluated using funnel plots and Egger’s test, with a P-value < 0.1 indicating significant bias [20].

Publication bias-adjusted pooled incidences were also calculated via the trim-and-fill method [21], where agreement between the unadjusted and adjusted pooled incidences and estimates may indicate little publication bias. All statistical meta-analyses were performed using R (v.3.6.1, R Foundation for Statistical Computing, Vienna, Austria). A P-value of <0.05 was considered statistically significant.

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high risks of bias based on the quality assessment [25], and not in the field of interest [26]. Between the two studies with overlapping cohorts, the study with a more recent study period was chosen. An updated literature search for studies published between July 30, 2020 and October 9, 2020 resulted in 346 studies, of which seven studies met the same eligibility criteria [27–33]. Overall, 21 articles with a total of 2125
patients were included [4, 27–46]. No additional eligible study was found after a search of references within the included studies.

3.2. Characteristics of the included studies

The characteristics of the 21 included studies are summarized in Table 1. Of the 21 studies, all study designs were retrospective, except for two prospective studies [28, 39]. Nine studies were multi-center studies [4, 29, 31, 33, 36, 38, 40, 42, 43] whereas the other 12 were performed at single centers [27, 28, 30, 32, 34, 35, 37, 39, 41, 44–46]. The cohort sizes ranged from 9 to 454 patients. The countries of origin of the selected studies were heterogeneous, including China [40], Turkey [42], Europe [4, 30, 35–37, 39, 41, 43, 45, 46], and the USA [27, 28, 31–34, 38, 44]. One study was a multinational study involving all three continents [29]. Brain MRI was the only neuroimaging modality used in ten of the studies [4, 28, 32, 33, 37, 39, 41–44] whereas ten studies used brain CT and/or MRI [27, 28, 31–34, 36, 38, 45, 46]; one study used only brain CT [40].

3.3. Pooled incidences of COVID-19-associated abnormal neuroimaging findings

In the included studies, 42.6 % (906/2125) of the patients showed abnormal neuroimaging findings on brain CT or MRI. The pooled incidence of cerebral microhemorrhages in 20 studies (excluding one study that used brain CT alone [40]) was 6.9 % (95 % CI: 4.9 %–13.8 %; $I^2 = 94 \%$) [Table 2 and Fig. 2(a)]. The pooled incidence of acute spontaneous ICH in the included studies (n = 21) was 5.4 % (95 % CI: 3.1 %–7.6 %; $I^2 = 87 \%$) [Table 2 and Fig. 3(b)]. In 20 studies (excluding one study that excluded patients with infarction) [47], the pooled incidence of acute to subacute infarct was 24.0 % (95 % CI: 16.1 %–31.8 %; $I^2 = 97 \%$) [Table 2 and Fig. 3(c)]. The pooled incidence of encephalitis or encephalopathy was 3.3 % (95 % CI: 1.9 %–4.7 %; $I^2 = 92 \%$) [Table 2 and Fig. 3(d)].

All four types of abnormal neuroimaging findings demonstrated significant publication bias on funnel plots (i.e., asymmetric distribution of studies) (Fig. 4) and in Egger’s tests ($P < 0.05$). Moreover, except for the acute/subacute infarct category, the trim-and-fill estimates were inconsistent with the pooled incidences, indicating publication bias (Table 2). All included studies had significant between-study heterogeneities ($P < 0.001$).

3.4. Subgroup meta-regression analysis

The results of the subgroup meta-regression analysis are summarized in Table 3. In the subgroup analysis of cerebral microhemorrhages, studies using only MRI demonstrated significantly higher incidences (13.8 %) than those using either CT or MRI (3.1 %) ($P < 0.001$). Regionally, studies published in Europe showed higher pooled incidences of cerebral microhemorrhages (14.0 %) than those in the USA (4.1 %) or Asia (3.0 %) ($P < 0.001$). Moreover, studies that reported patients in ICU showed higher pooled incidences (11.8 %) than those not reporting patients in ICU (3.2 %) ($P < 0.001$).

For the incidence of encephalitis/encephalopathy, imaging modality (MRI, 6.9 % vs. CT/MRI, 2.1 %; $P < 0.001$), region (Europe, 12.9 % vs. USA, 1.8 % and Asia, 2.6 %; $P < 0.001$), median/mean age ($>65$ years, 1.7 % vs. $\leq 65$ years, 10.5 %; $P < 0.001$), and patients in ICU (11.1 % vs. not reported, 0.7 %; $P < 0.001$) demonstrated significant differences.

While considerable heterogeneities remained in most subgroup analyses, little heterogeneity was observed in encephalitis/encephalopathy for older patients ($I^2 = 8\%$).

Fig. 4. Funnel plots of pooled incidences of (a) cerebral microhemorrhage, (b) acute spontaneous ICH, (c) acute/subacute infarct, and (d) encephalitis/encephalopathy in patients with COVID-19. COVID-19 = coronavirus disease 2019; ICH = intracranial hemorrhage.
were smell and taste disorders and headaches, indicating the involvement of the various COVID-19-related neurologic manifestations, emphasizing CI

4. Discussion

In the present meta-analysis evaluating the pooled incidences of abnormal neuroimaging findings in patients with COVID-19, acute to subacute infarcts were the most common [24.0 %, 95 % CI = 16.1 %–31.8 %], followed by cerebral microhemorrhages [6.9 %, 95 % CI = 4.9 %–8.9 %], acute spontaneous intracerebral hemorrhages [5.4 %, 95 % CI = 3.1 %–7.6 %], and encephalitis/encephalopathy [3.3 %, 95 % CI = 1.9 %–4.7 %]. Substantial heterogeneities were observed across types of imaging findings. These results add evidence for the consideration of abnormal neuroimaging findings in patients with COVID-19. Therefore, our results may increase the awareness of COVID-19-related neuroimaging findings among radiologists.

A recent systematic review by Nepal et al. comprehensively reviewed the various COVID-19-related neurologic manifestations, emphasizing clinical symptoms [48]. They found that the most common symptoms were smell and taste disorders and headaches, indicating the involvement of the central nervous system. The difference between their study and the present study was that their study consisted of many case reports/series without neuroimaging findings, and meta-analytic assessment was not available. The current study attempted to focus on specific COVID-19-related neuroimaging findings with meta-analytic outcomes.

As for the possible pathogeneses underlying various neuroimaging findings, the severe coagulopathy often present in COVID-19 patients might be responsible for the relatively common incidence of disseminated cerebral microhemorrhages [49]—as a milder form of acute spontaneous ICH. However, a study by Rudmanesh et al. showed that among seven critically ill COVID-19 patients with cerebral microhemorrhages, none showed overt disseminated intravascular coagulation [44]. They postulated that cerebral microhemorrhages could be a late complication of critical-stage COVID-19 related to hypoxemia or a form of small vessel vasculitis. Therefore, the underlying mechanism of the development of cerebral microhemorrhages remains to be elucidated.

Patients with encephalitis and encephalopathy were grouped since their imaging patterns were often non-specific, including leptomeningeal enhancement [43], acute hemorrhagic necrotizing encephalopathy [44], diffuse leukoencephalopathy [44], and increased white matter signal intensities after accounting for age [34], ADEM, and PRES [39,41,45]. These manifestations suggest that SARS-CoV-2 causes acute brain injury via unexplained mechanisms. Although these aspects are not fully elucidated, a recent review by Li et al. suggested various potential routes of invasion of SARS-CoV-2 into the central nervous system [50]. According to Li et al., the potential entry routes include the vascular, peripheral nerve, lymphatic, and cerebrospinal fluid pathways. Thus, the various abnormal neuroimaging findings might have different underlying routes of invasion, as suggested by Li et al.
However, concrete associations between routes of invasion and neuroimaging findings cannot be established without sufficient evidence.

Notably, the included studies demonstrated substantial heterogeneity and publication bias, indicating that interpretations of pooled incidences should be performed with caution. Even in subgroup analysis, the potential sources of heterogeneities were only found for encephalitis/encephalopathy in older patients—demonstrating minor heterogeneities. Interestingly, plausible sources of heterogeneity, such as study regions and multi-center settings, did not cause heterogeneities. Thus, the various COVID-19-related neuroimaging findings might involve a broad spectrum of underlying interrelated mechanisms, making it difficult to identify sources of heterogeneities.

Importantly, the pooled incidences of abnormal neuroimaging findings in the current study should not be interpolated to the overall population of patients with COVID-19; the included studies consisted mostly of patients who had severe neurologic manifestations, were admitted to the ICU, or were under mechanical ventilation. Furthermore, the mean and median patients ages in all included studies were over 58 years, indicating that the patients belonged to older age groups that are more vulnerable to severe disease [47]. Therefore, such predispositions would make the patients included in this study more susceptible to developing abnormal neuroimaging findings.

Several limitations need to be addressed. First, the literature search period was limited to several months; however, due to the ever-increasing concerns on the spread of COVID-19 globally, rapid collation of available evidence is needed to understand the various COVID-19-associated neuroimaging findings. Additionally, in most selected studies, confounding variables such as underlying comorbidities were not statistically adjusted for the neuroimaging findings, nor were there control groups. Again, considering the urgency of the COVID-19 pandemic, a careful review of patients’ medical records must have been difficult. Moreover, the causal relationship between COVID-19 infection and abnormalities in imaging findings is not fully established; abnormal neuroimaging findings might be due to systematic confounding factors such as DM, mechanical ventilation, and the multi-drug regimen for respiratory distress with hypoxia. Finally, nearly all the diagnoses of encephalitis and encephalopathy were not definite without serologic confirmation. These limitations necessitate a future prospective study with adjustment for comorbidities and a more detailed analysis to confirm the association between COVID-19 and neuroimaging findings.

In conclusion, the current systematic review and meta-analysis demonstrated a considerable incidence of abnormal neuroimaging findings related to COVID-19. The findings of this study may help increase awareness of the wide range of COVID-19-related neuroimaging findings among radiologists worldwide.

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CRediT authorship contribution statement

Yangsean Choi: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. Min Kyoung Lee: Data curation, Investigation, Resources, Supervision, Validation.

Declaration of Competing Interest

The authors report no declarations of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejrad.2020.109393.

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