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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  $\chi^2$  statistic for pooled incidences and the inconsistency index  $I^2$ . 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 ( $I^2 = 87\%–97\%$ ). 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;  $I^2$ , Higgin's inconsistency index.

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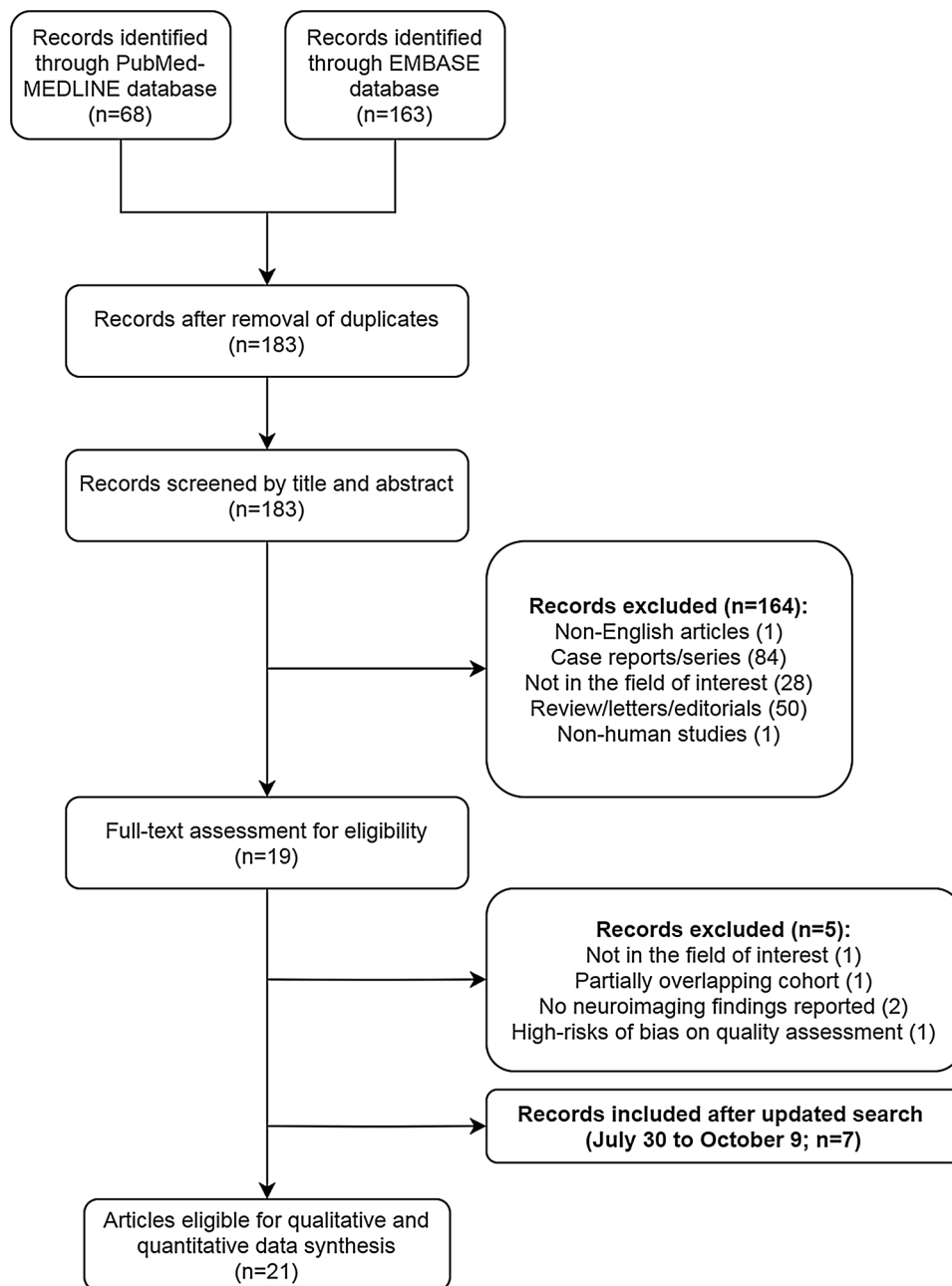


Fig. 1. Flow diagram depicting the study eligibility criteria.

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

**Table 1**  
The clinical characteristics of the included studies.

First author	Study period, all in 2020	Affiliation	modality (n)	image analysis (experience)	Number of patients with neuroimaging	sex, male (%)	Age, mean $\pm$ 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 $\pm$ 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 $\pm$ 15.6	retrospective	no	8	17	0	12
Xiong	January 18 - March 20	56 hospitals in Hubei and Sichuan	CT	NR	28	NR	NR	retrospective	yes	NR	10	0	0
Helms	March 3 - April 3	Strasbourg, France	MRI	NR	13	NR	median, 63	retrospective	yes	0	3	0	8
Paterson	April 9 - May 15	University College London, Queen Square	MRI (13); CT (3)	NR	16	9 (56.3)	58.8 $\pm$ 12.5	retrospective	yes	4	8	0	11
		Institute of Neurology, London											
Coolen	3/31–4/24	CUB Hôpital Erasme, Brussels	MRI	3 neuroradiologists (NR)	19	14 (73.7)	mean, 77 (49–94)	prospective	no	2	0	1	2
Jain	March 1 - April 13	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 $\pm$ 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 $\pm$ 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)

Table 1 (continued)

First author	Study period, all in 2020	Affiliation	modality (n)	image analysis (experience)	Number of patients with neuroimaging	sex, male (%)	Age, mean $\pm$ SD/median (range)	study design	Multicenter study	microbleed	Acute/subacute infarct	non-traumatic ICH	Encephalitis/encephalopathy
Klironomos	March 2 - May 24	Foundation, Varese, Lombardia, Italy 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 $\pm$ SD, 11.5 $\pm$ 5.7 years of experience)	185	138 (74.6)	62 $\pm$ 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 $\pm$ 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 $\pm$ 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 $\pm$ 15	Retrospective	Yes	0	123	27	0
Sawhani	March 1 - May 31	Queen Elizabeth Hospital Birmingham	CT (172) / MRI (36)	2 neuroradiologists (NR)	167	NR	NR	Retrospective	No	12	21	3	0
Lin	March 4 - May 9	academic quaternary-care center and affiliated community hospital	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 tertial care hospitals of an academic medical center	MRI	2 neuroradiologist (fellow)	1115	82 (71.3)	NR	Retrospective	Yes	25	47		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 < 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 and experience, proportion of patients in ICU, reported neurologic symptoms, and indications for imaging; (c) outcomes: incidences of four types of neuroimaging findings (acute spontaneous ICH, acute/subacute infarct, cerebral microhemorrhages, and encephalitis/encephalopathy). One reviewer (blinded) extracted the data, and the second reviewer (blinded) confirmed the data's validity. The acute spontaneous ICH was defined as acute brain hemorrhage identified on brain CT without a history of trauma; acute/subacute infarct, cerebral microhemorrhages, and encephalitis/encephalopathy were diagnosed based on diffusion-weighted, susceptibility-weighted, and T2-weighted/fluid-attenuated inversion recovery imaging with or without contrast-enhanced T1-weighted imaging, respectively. For encephalitis/encephalopathy, variable neuroimaging findings were included, such as abnormal signal intensities or enhancement in white matter, basal ganglia or cortex, PRES or diffuse leukoencephalopathy.

**Table 2**

Summary of the meta-analytically pooled incidences for abnormal neuroimaging findings in patients with COVID-19.

	Summary estimate			Trim-and-fill estimate		
	Pooled incidences (%) [95 % CI]	P-value for heterogeneity <sup>a</sup>	I <sup>2b</sup> (%)	P-value for publication bias <sup>c</sup>	No. of missing studies	Adjusted pooled proportions (%) [95 % CI]
Cerebral microhemorrhages	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; I<sup>2</sup>=Higgins' inconsistency index.

<sup>a</sup> P-value by the Cochran's Q method to test the heterogeneity of the pooled data (P < 0.05 indicates significant heterogeneity).

<sup>b</sup> Higgins' inconsistency index (0–40 % may indicate insignificant heterogeneity; 30–60 %, 50–90 %, and 75–100 % may indicate moderate, substantial, and considerable heterogeneity, respectively).

<sup>c</sup> Egger's test (P < 0.10 indicates significant publication bias).

### 2.4. Quality assessment

Quality assessments of the included studies were independently performed in consensus 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' mean/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  $\chi^2$  statistics for pooled estimates (P < 0.05, indicating significant heterogeneity) and the Higgin's inconsistency index (I<sup>2</sup>), where I<sup>2</sup> values of 0%–40 %, 30 %–60 %, 50 %–90 %, and 75 %–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],

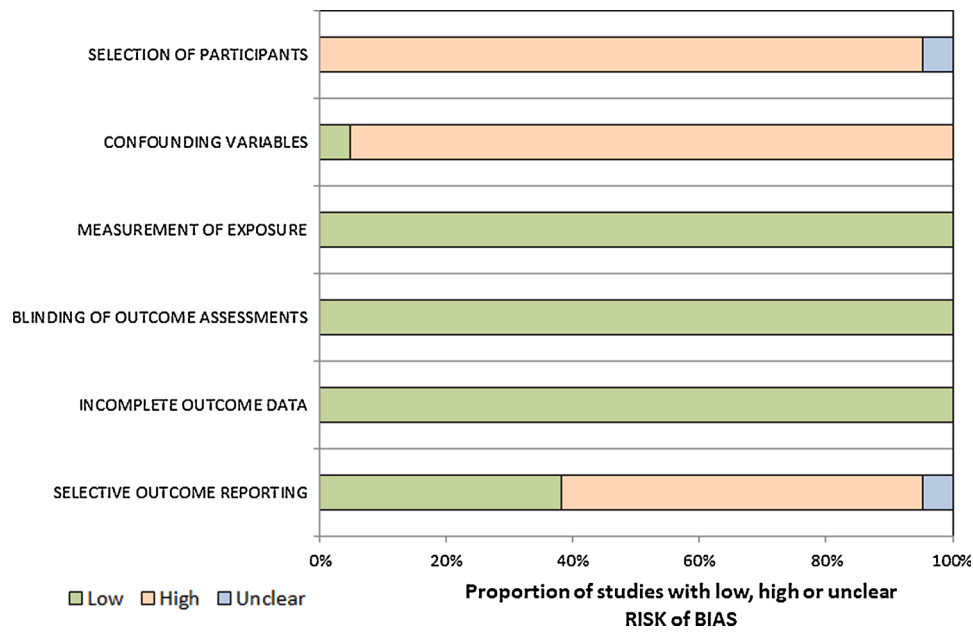


Fig. 2. The RoBANS criteria of the included studies. RoBANS = Risk of Bias Assessment Tool for Nonrandomized Studies.

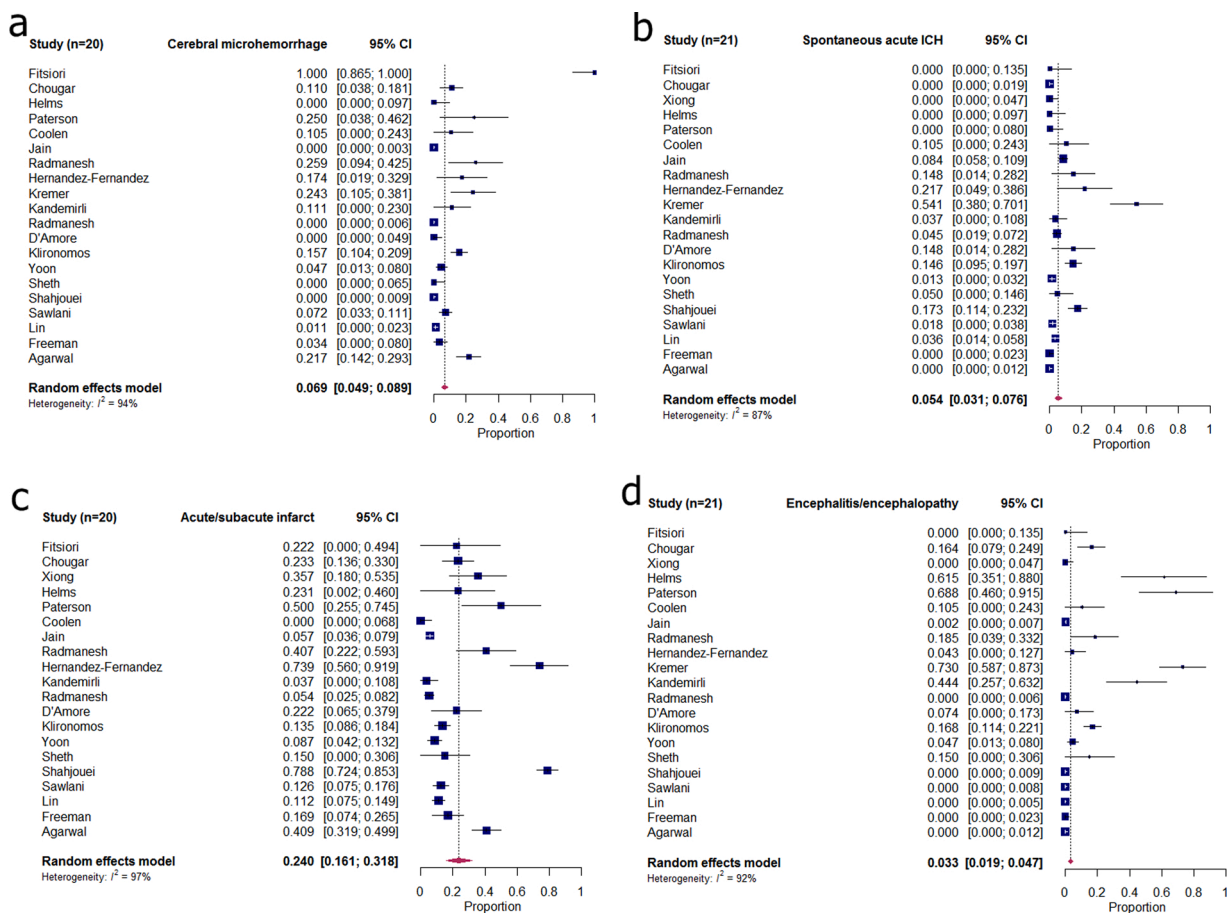
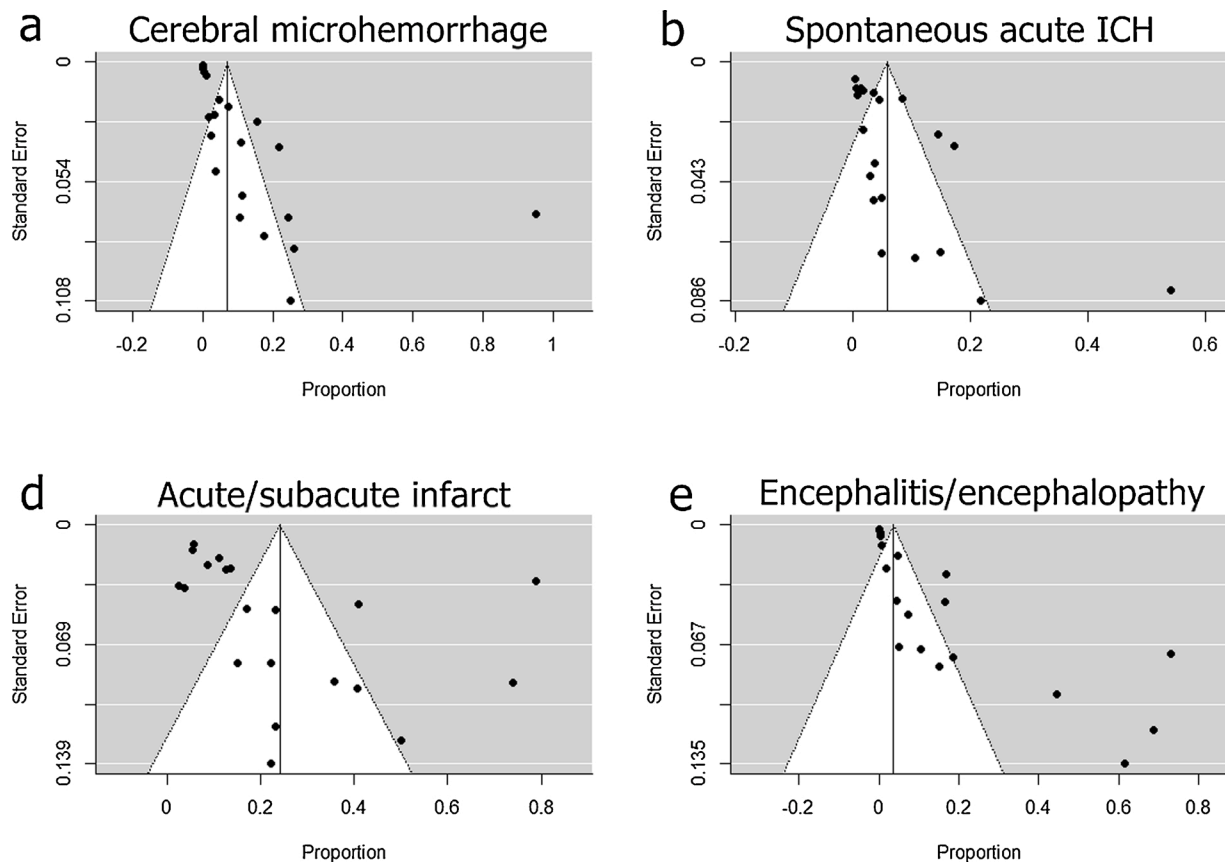


Fig. 3. Forest plots of pooled incidences of (a) cerebral microhemorrhage, (a) acute spontaneous ICH, (c) acute/subacute infarct, and (d) encephalitis/encephalopathy in patients with COVID-19. COVID-19=coronavirus disease 2019; ICH = intracranial hemorrhage.

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



**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.

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 [27,29–31,34–36,38,45,46]; 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 Figs. 2,3(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 ( $I^2 = 8$  %).



**Table 3**  
Subgroup meta-regression analysis of COVID-19 related neuroimaging findings.

Covariate	Cerebral microhemorrhages			Acute/subacute infarct			Spontaneous acute ICH			Encephalitis/encephalopathy		
	Pooled incidences (%) [95 % CI]	I <sup>2</sup> (%)	P	Pooled incidences (%) [95 % CI]	I <sup>2</sup> (%)	P	Pooled incidences (%) [95 % CI]	I <sup>2</sup> (%)	P	Pooled incidences (%) [95 % CI]	I <sup>2</sup> (%)	P
Imaging modality												
MRI	13.8 [10.5–17.2]	96	<0.001	20.0 [7.9–32.2]	89	0.413	3.9 [0.6–7.3]	83	0.458	6.9 [4.2–9.7]	95	<0.001
CT or MRI	3.1 [1.0–5.2]	86		27.1 [16.4–37.7]	98		6.1 [3.3–8.9]	86		2.1 [0.4–3.7]	88	
Region <sup>a</sup>												
Europe	14.0 [10.6–17.4]	96	<0.001	22.5 [14.7–30.3]	89	0.389	7.1 [3.4–10.8]	89	0.149	12.9 [9.3–16.4]	96	<0.001
USA	4.1 [1.1–7.1]	88		17.0 [9.1–24.8]	92		3.5 [0.1–7.0]	87		1.8 [0–4.7]	64	
Asia	3.0 [0–8.8]	63		13.9 [1.7–26.0]	82		2.4 [0–7.8]	0		2.6 [0–7.4]	91	
Mean/median age <sup>b</sup>												
>65 years	10.1 [5.6–14.7]	98	0.326	33.4 [17.2–49.6]	99	0.27	10.6 [4.8–16.4]	76	0.25	1.7 [0–5.2]	8	<0.001
≤65 years	6.9 [3.4–10.3]	88		18.0 [5.6–30.4]	81		6.6 [2.9–10.2]	89		10.5 [7.6–13.4]	96	
Multicenter												
Yes	5.7 [1.8–9.6]	87	0.119	30.4 [16.8–44.0]	99	0.257	6.1 [2.6–9.5]	92	0.525	3.3 [1.1–5.5]	95	0.545
No	9.9 [6.7–13.1]	96		20.0 [9.0–31.1]	88		5.0 [1.8–8.1]	78		4.3 [2.1–6.4]	85	
Indication for imaging <sup>c</sup>												
Neurologic symptoms	6.1 [3.8–8.3]	95	0.053	23.2 [12.4–33.9]	98	0.624	7.8 [4.4–11.1]	88	0.574	5.0 [2.9–7.1]	93	0.054
Not reported or other clinical indication	11.8 [5.6–17.9]	78		29.2 [8.6–49.7]	78		4.3 [0–10.2]	85		9.7 [4.7–14.7]	95	
Patients in ICU												
Reported	11.8 [8.8–14.8]	96	<0.001	17.2 [5.3–29.1]	79	0.118	6.2 [2.8–9.5]	87	0.544	11.1 [8.2–14.0]	96	<0.001
Not reported	3.2 [0.6–5.7]	84		30.9 [19.1–42.7]	98		4.8 [1.6–7.9]	88		0.7 [0–2.7]	63	

CI = confidence interval; ICH = intracranial hemorrhage; I<sup>2</sup> = Higgin’s inconsistency index.

<sup>a</sup> A multinational study by Shahjouei et al involving all three continents was not included.

<sup>b</sup> Three studies (Sawhani et al, Freeman et al, and Agarwal et al) not reporting mean/median ages were excluded for cerebral microhemorrhages; four studies (Xiong et al, Sawhani et al, Freeman et al, and Agarwal et al) were excluded in other three categories for the same reason.

<sup>c</sup> Three studies (Lin et al, Freeman et al, and Agarwal et al) not reporting indication for neuroimaging were excluded.

### 3.5. Quality assessment

The quality assessment, according to RoBANS, indicated moderate overall quality, with all studies satisfying at least three of the six criteria (Fig. 2). Notably, for the “selection of participants” domain, none of the studies confirmed neuroimaging findings among the study participants at study initiation.

## 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 studies, and subgroup analysis did not reveal specific sources of potential heterogeneity. Substantial publication biases were present among all types of imaging findings. These results add evidence for the considerable incidence 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 pathogenesis 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 Radmanesh 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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