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Systematic Review

Neuroimaging Findings of Brain Computed Tomography and Magnetic Resonance Imaging of COVID-19 Patients: Systematic Review and Meta-Analysis

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ABSTRACT

Novel Corona virus-2019 (SARS-CoV-2) has been spreading in continents around the globe and effective treatment has yet not been developed against this novel infection. The victims of COVID-19 tend to develop abnormal neuroimaging features on brain-CT and MRI Imaging. **Objective: T**o assess the incidences of abnormal neuroimaging features in the sufferers of SARS-CoV-2 infection. **Methods:** PubMed, Science Direct. Research Gate, Medline and Google Scholar were searched till 28th March 2021 to highlight the incidences of abnormal neuroimaging features in the sufferers of SARS-CoV-2 infection. After screening of literature, only twenty-one (21) articles were included. All data extracted from them was further analysed through meta-analysis. **Results:** Twenty-one (21) eligible articles with one thousand six hundred and forty-four (1644) verified COVID-19 patients were included. The average age of SARS-CoV-2 patients is 65.20 years with 67.1% males and 32.9% females. Brain CT scan (46.2%), brain MRI (41.3%) and both brain CT and brain MRI (12.5%) were used to detect neuroimaging features. The pooled incidences of acute or sub-acute infarctions were most common (25.88%), followed by cerebral micro-bleed (20.05%), encephalitis/encephalopathy (14.53%), and acute spontaneous non-traumatic intracranial haemorrhages (7.55%). **Conclusions:** The current systematic review concluded that during the spread of the current COVID-19 pandemic, many SARS-CoV-2 patients manifested neurologic symptoms. Out of these neurological manifestations, acute or sub-acute infarction and cerebral micro-bleed are most common.

INTRODUCTION

SARS-CoV-2 manifested its first infection case in December 2019 in Wuhan and then spread to the entire world rapidly [1]. Due to its rapid spread to countries around the globe, the World Health Organization announced on 11thMarch, 2020 this infection as a global pandemic [2]. Until 20-10-2020 millions of people had been infected by this novel virus around the globe and has caused eleven hundred thousand deaths [3]. The cause of COVID-19 infection is novel corona virus. SARS-CoV-2 has single-stranded RNA virus with small diameter of about 65-125 nm in size [4]. At the level of nucleotides, it is 80% similar to other viruses of the Coronaviridae family. It is 90% identical to the RaTG13-2013 virus that has its natural flora in bats. The spike protein (S), an envelope protein (E), membrane protein (M), and nucleocapsid protein (N) are four basic genes which encode structural proteins in the coronaviruses [5]. The enveloped RNA virus bears spikes on its surface, which is made-up of glycoprotein. This virus

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is known as coronavirus due to these spikes, which give crown like appearance to it [6]. The transmission of COVID-19 infection is through direct and indirect contact [7]. The respiratory droplets spread through coughs, sneezes and talks by infected person and have the potential to infect other healthy individuals [8]. So, isolation of infected patients, room ventilation and as well as utilization of disinfectants can stop the spread of infection [9]. SARS-CoV-2 can infect individuals of all age groups. Although, the old age adults and patients of associated diseases i.e. hypertension, diabetes mellitus, heart disorders, respiratory disorders, hepatic disorders and kidney failure are more vulnerable to develop SARS-CoV-2 infection. The clinical manifestations of SARS-CoV-2 infection can be the appearance of any symptom to as severe as acute respiratory distress syndrome, which requires emergency treatment of the infected person [10]. The associated neurological complications of COVID-19 are diverse in their type. The number of patients who manifest neurological manifestations is low in number. However, it is very important to conduct neuroimaging examination of severely ill SARS-CoV-2 patients to differentiate neurological manifestations of COVID-19 [11]. In this regard, cerebral CT scan and n-MRI are the important imaging modalities to be considered for the assessment of neurological manifestations. Without the help of these imaging modalities, it is impossible to differentially diagnose the diverse neurological complications [12]. A number of neurological manifestations are also reported in higher numbers in SARS-CoV-2 infected individuals particularly in critically ill patients [13-15]. Recent researches from the United States and China, the following neurological clinical features i.e. haemorrhagic or ischaemic stroke, vertigo, headache, musculoskeletal malfunctioning, disorientation, Guillain-Barré syndrome (GBS), or acute necrotizing encephalopathy, without any evidence of direct viral invasion into the brain, are also found in SARS-CoV-2 infected individuals [16-18]. The infected individuals with severe coronavirus disease may present with encephalitis as well as with intracranial arterial cerebrovascular accident on their CT and MRI examinations [25].

METHODS

SARS-CoV-2 has affected several millions of people around the entire globe. The COVID-19 victims tend to develop abnormal neuroimaging features on brain-CT and MRI. This systematic review could provide an evaluation of incidences of abnormal neuroimaging patterns in sufferers of SARS-CoV-2 infection. Science Direct Google Scholar, Research Gate, Medline and PubMed were used to perform search of literature. The studies were selected according to this inclusion criterion: (a) The minimum required information was verified COVID-19 adult patients with neuroimaging features on brain CT or/and n-MRI with no previous history of any brain disorder (b) all RT-PCR confirmed COVID-19 positive laboratory test patients with brain imaging, (c) brain MRI and CT scan radiological features of COVID-19 (d) Neurological imaging positive features of coronavirus patients, (e) studies containing more than 5 participants (d) all English language published original studies. In this review study, the data analysis was performed with the help of Microsoft excel 2010 and (SPSS 24, IBM, Armonk, NY) version 21.

RESULTS

Early screening of literature identified ninety articles. After removal of 18 duplicate articles, 62 were reviewed for their title and abstract, 41 articles were excluded due to inappropriate information. In this systematic review and Meta-analysis, only 21 articles were included. Twenty-one research articles (total of 1664 patients) met the inclusion criteria and included. The data were characterized based on the manifestation of neuroimaging features i.e. cerebral microbleeds, acute spontaneous ICH, acute/sub-acute infarct and encephalitis (encephalopathy) on brain CT or/and brain MRI of COVID-19 verified adult patients. The whole process of screening of literature is shown by the figure 1. In this systematic review, infected individuals had average age of 65.20 years. Percentage of gender ratio was 67.1% males and 32.9% females respectively. Table 1 contains the information on number of patients with neuroimaging, study design, imaging modality, age, the number of verified COVID-19 patients who presented with microbleeds, acute/sub-acute infarct, non-traumatic ICH, encephalitis/encephalopathy. Out of 21 studies included in our systematic review, 95.2% of studies were retrospective and 4.8% of studies were prospective. The percentage of multi-center studies was 45%. To detect the abnormal neuroimaging features in COVID-19 patients following imaging modalities were used: brain CT scan (46.2%), brain MRI (41.3%), and both brain CT and brain MRI (12.5%). Pooled analysis of this systematic review showed that the abnormal neuroimaging findings in SARS-CoV-2 infected individuals were found with the following percentages: microbleeds 20.05%, acute/sub-acute infarct 25.88%, non-traumatic ICH 7.55%, and encephalitis/encephalopathy 14.53 %. According to figure2, the percentage of individuals who presented with microbleeds was NA, 7.19%, 55.37%, NA, 17.39%, 25%, 0%, 24.32%, NA, 100%, 10.96%, NA, 0%, 10.53%, 0% 15.68%, 0%, 0%, 3.39%, 21.74%, and 20.59%, respectively. According to figure 3, in the studies the percentage of individuals who presented with acute/sub-acute infarct was 25.68%, 12.57%, 5.37%, 31.48%, 73.91%, 50%, 3.70%, NA, 26.56%, 22.22%, 23.29%, 35.71%, 23.08%, 0%, 22.22%

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13.51%, 15%, 78.85%, 16.95%, 40.87%, and 5.88%, respectively According to figure 4, in the studies the percentage of COVID-19 infected individuals who presented with non-traumatic ICH was 2.25%, 1.80%, 4.55%, 5.56%, 21.74%, 0%, 3.70%, 54.05%, NA, 0%, 0%, 0%, 0%, 5.26%, 14.81%, 14.59%, 5%, 17.31%, 0%, 0%, and 26.47%, respectively. According to figure 5, the percentage of individuals who presented with encephalitis/encephalopathy was 39.64%, 0%, 10.74%, 2.78%, 4.35%, 68.75%, 44.44%, 72.97%, 12.50%, 0%, 16.44%, 0%, 61.54%, 10.53%, 7.41% 16.76%, 15%, 0%, 0%, 0%, and NA, respectively.

First Author	Study design	patients	Imaging modality	Age (mean ± SD)	Micro-bleed%	Acute/Sub-acute Infarct %	Non-traumatic ICH %	Encephalitis/ encephalopathy %
Meppiel *et al.* [19]	Retrospective	222	CT(35), MRI(157)	65 (53-72)	NA	25.68%	2.25 %	39.64 %
Sawlani *et al.* [20]	Retrospective	167	CT (172)/ MRI(36)	NR	7.19%	12.57%	1.80 %	0 %
Radmanesh *et al.* [21]	Retrospective	242	CT(207)/MRI(11)/ both CT and MRI(24)	68.7 ± 16.5 years	55.37%	5.37%	4.55 %	10.74 %
Mahammedi et al. [22]	Retrospective	108	Brain CT(107), MRI (20) head CTA (17)	69 ± 15	NA	31.48%	5.56 %	2.78 %
Fernández *et al.*[23]	Retrospective	23	CT(23), both CT and MRI(6)	66.8	17.39%	73.91%	21.74 %	4.35 %
Paterson *et al.* [24]	Retrospective	16	MRI(13), CT(3)	58.8 ± 12.5	25%	50%	0 %	68.75 %
Kandemirli *et al.* [25]	Retrospective	27	MRI	63 (34-87)	0%	3.70%	3.70 %	44.44 %
Kremer *et al.* [26]	Retrospective	37	MRI	61 years±12	24.32%	NA	54.05 %	72.97 %
Kremer *et al.* [27]	Retrospective	64	MRI	66 (range 20-92) years	NA	26.56%	NA	12.50 %
Fitsiori *et al.* [28]	Retrospective	9	MRI	67.7 ± 9	100%	22.22%	0 %	0 %
Chougar *et al.* [29]	Retrospective	73	MRI	58.5 ± 15.6	10.96%	23.29%	0 %	16.44 %
Xiong *et al.* [30]	Retrospective	28	CT	NR	NA	35.71%	0 %	0 %
Helms *et al.* [31]	Retrospective	13	MRI	Median, 63 years	0%	23.08%	0 %	61.54 %
Coolen *et al.* [32]	Prospective	19	MRI	mean, 77 (49-94)	10.53%	0%	5.26 %	10.53 %
D'Amore *et al.* [33]	Retrospective	27	CT(27)/, both CT and MRI(4)	mean 68 (21-88)	0%	22.22%	14.81 %	7.41 %
Klironomos *et al.* [34]	Retrospective	185	CT(174)/ MRI(43) both CT and MRI,(32)	62 ± 14	15.68%	13.51%	14.59 %	16.76 %
Sheth *et al.* [35]	Prospective	20	Portable MRI	60 ± 8	0%	15%	5 %	15 %
Shahjouei *et al.* [36]	Retrospective	156	CT/MRI	66 ± 15	0%	78.85%	17.31 %	0 %
Freeman *et al.* [37]	Retrospective	59	MRI	NR	3.39%	16.95%	0 %	0 %
Agarwal *et al.* [38]	Retrospective	115	MRI	NR	21.74%	40.87%	0 %	0 %
Büttner *et al.* [39]	Retrospective	34	CT/MRI	67.5 years ± 17.6 years	20.59%	5.88%	26.47 %	NA
	NR= Not Reported NA= Not Available CT=Computed Tomography MRI= Magnetic Resonance Imaging							

Table 1: Neuroimaging Radiological Findings of COVID-19 patients

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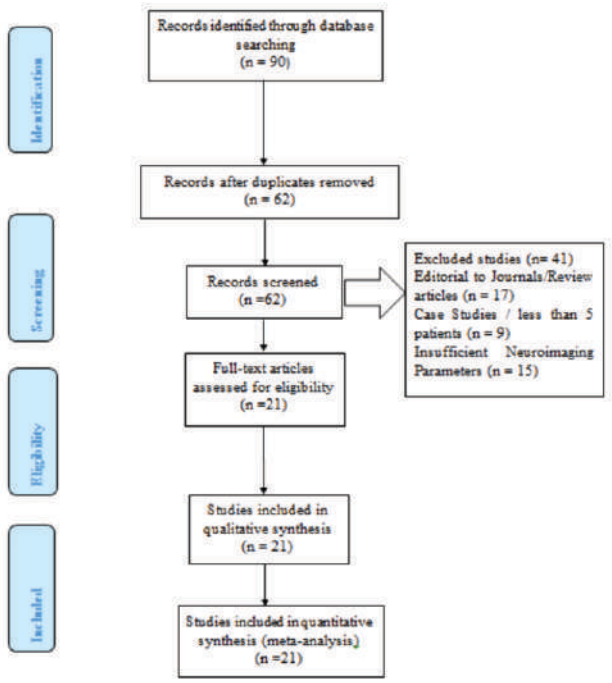

Figure 1: PRISMA-Literature searched flow Diagram

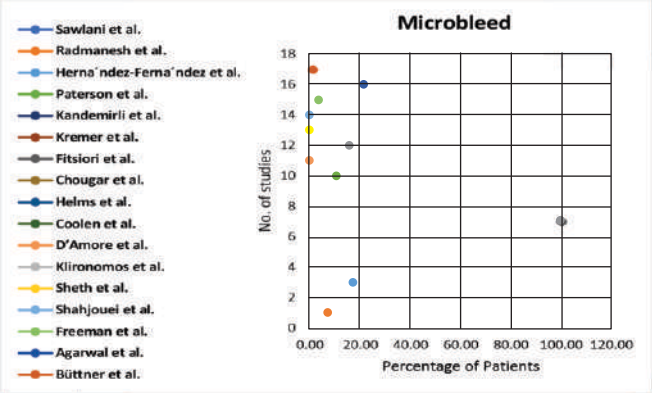

Figure 2: Percentage of patients showing micro-bleed

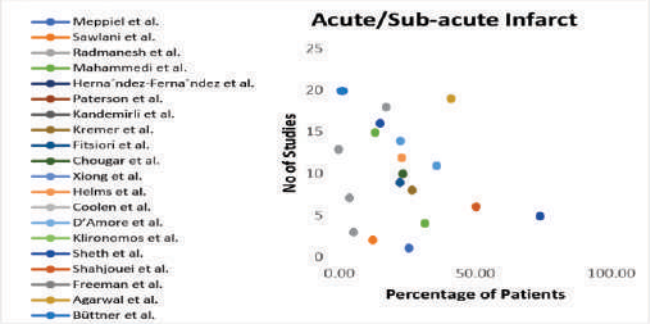

Figure 3: Percentage of patients showing acute/sub-acute infarct

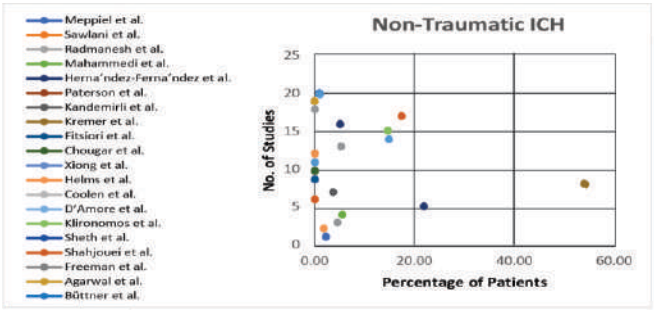

Figure 4: Percentage of non-traumatic ICH on Neuroimaging

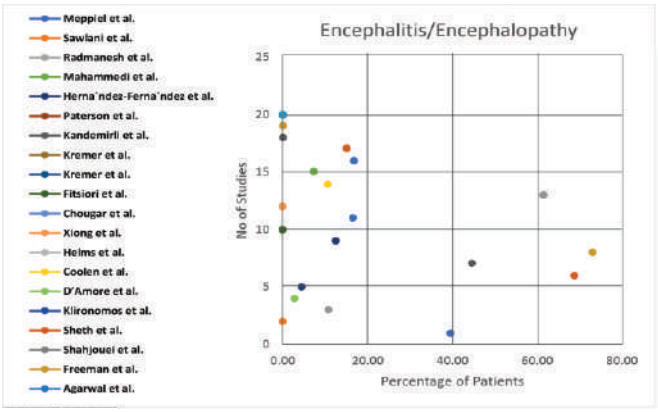

Figure 5: Percentage encephalitis/encephalopathy

DISCUSSION

COVID-19 infection that emerged from the Hubei Province of China has now spread across the world. In response to increasing number of cases of COVID-19 infection around the globe, on 30th January 2020, the World Health Organization (WHO) imposed a global health emergency [40]. The route of spread of this novel infection is person-to-person spread that mainly occurs through direct contact or through droplets spread by sneezing or coughing of the infected individual. Primarily this infection was reported to start in those individuals who visited seafood market in Wuhan province China, where live species of animals were sold out, so it laid the hypothesis that COVID-19 has an animal origin. The classical clinical presentation at onset of COVID-19 infection is pyrexia, non-productive cough and myalgia, while other clinical features include headache, haemoptysis, diarrhoea, difficulty in breathing and lymphopenia [41]. Present evidence suggests that COVID-19 infected individuals commonly had neurological manifestations presented as 6% acute stroke, skeletal muscle injury (19%) and consciousness impairment (15%) [42]. According to a recent study conducted on 214 COVID-19 patients it was found that, along with systemic and respiratory symptoms, 36.4% of total SARS-CoV-2 infected individuals manifested neurological symptoms [16]. According to a review article of characteristics COVID-19, it was found that all age groups

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have a risk to develop corona virus pneumonia and the infected individuals has median age around 50 years [43]. In this review, the infected individuals are presented with mean age of 65.20 years with the prevalence of infection in males 67.10% and females 32.90%. A review was conducted by Katal et al., on 28 eligible articles to assess the imaging findings of COVID-19 infected individuals with neurological manifestations associated with COVID-19. According to the results of this review, 40% of the COVID-19 patients did not manifest any abnormal neuroimaging findings, while others displayed abnormalities on neuroimaging in various parts of the brain including acute cerebrovascular infarction or haemorrhage, transverse myelitis, meningitis, demyelinating disorders (ADEM) and encephalitis/encephalopathy. The most common abnormal neuroimaging characteristic in COVID-19 infected individuals were both ischemic and haemorrhagic cerebrovascular events that were found in 27% of the COVID-19 patients [44]. A meta-analysis conducted by Choi et al., effectively reviewed several COVID-19 associated neurologic characteristics. This review was conducted on twenty-one articles comprising 2125 verified COVID-19 patients. The pooled incidences of abnormal neuroimaging characteristics in SARS-CoV-2 infected individuals, acute or sub-acute infarctions were the most common (24%), followed by cerebral micro-bleed (6.90%), acute spontaneous non-traumatic intracranial haemorrhages (5.40%), and encephalitis/encephalopathy (3.3%). This study reported a lower incidence of encephalitis/encephalopathy in patients with mean/median ages over 65 years ($P < 0.001$). Furthermore, a higher incidence of cerebral micro-haemorrhages was reported in ICU patients ($P<0.001$) [45]. Another review was conducted by Egbert et al., to comprehensively assess the incidence of neurological dysfunctions in COVID-19 patients. Twenty-six articles, including three hundred and sixty-one (361) verified COVID-19 patients, were identified. The 34% cases manifested brain abnormalities on the following modalities: cerebral-CT, MRI, PET and EEG. The most classical brain abnormalities were hyper-intensities of brain white matter (WM) on MRI (53% cases) and hypo-densities on cerebral-CT (23% affected cases), followed by micro-bleed, haemorrhages, and infarction [46]. Another review conducted by Munhoz et al., reported the following features associated with COVID-19 infection: fatigue 10.7-54%, loss of smell sensation 5.1-88%, headache 8-34%, cerebrovascular disease 2.8-5.7%, and encephalopathy 9% [47]. In our review, we found a significant association of neurological complications with 2019-nCoV infection. So for those SARS-CoV-2 infected patients who manifest neurological symptoms, it is vital to consider neuroimaging for diagnostic workup. The clinicians and radiologists should also be aware of neuroimaging characteristics of COVID-19 patients so they can assess the COVID-19 patients in a better way.

CONCLUSIONS

This review concluded that during the spread of current COVID-19 pandemic, many COVID-19 patients manifested neurological finding on imaging examination that suggested a possible association between COVID-19 infection and Central Nervous System. Out of these neurological manifestations, acute or sub-acute infarction and cerebral micro-bleed are most common. The clinicians and radiologists should also be aware of neuroimaging characteristics of COVID-19 patients so they can assess the COVID-19 patients in a better way.

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