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Profile Of Strokes In First And Second Waves Of COVID-19: A Study From Tertiary Care Centre

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Abstract

Background: COVID-19 (Novel corona virus) continues to wreck havoc across China, European countries, USA, India and now seems to be heading towards the fourth wave. The aim of this study was to explore the association between neuroimaging findings of brain, COVID-19 infection and non COVID-19 patients who presented with neurological manifestations during the first and second waves.

Methods: The present study is a retrospective, hospital-based, descriptive study of neuroimaging findings (NCCT head, HRCT thorax) in COVID-19 and non COVID-19 patients admitted with neurological manifestations in the Department of Neurology at a tertiary care centre in Rajasthan (India) between July 2020 till June 2021.

Results: The average age during the second wave was less as compared to the first wave (53.87 vs 63.26 years) along with male preponderance during both the waves of COVID-19. Prevalence of strokes including encephalopathy was 0.57% in the first wave and 1.56% in the second wave for the COVID-19 positive patients. Olfactory dysfunction (26.0% vs 35.9%), headache (47.8% vs 12.8%), altered sensorium (78.3% vs 17.9%), paresis (87.0% vs 51.3%), seizures (17.4% vs 2.6%), dysarthria/aphasia (87.0% vs 56.4%) were found to be the major symptoms during both the waves at presentation. Overall, ischemic infarcts were the most common finding in 50% patients. Patients who presented with encephalopathy had a poor prognosis.

Middle cerebral artery was the most common territory involved in both first and second waves among both positive (69.6% vs 35.9%) and negative (34.8% vs 42.9%) patients with ischemic strokes.

Conclusion: The most common neurological manifestations in COVID-19 patients were headache, olfactory dysfunction, strokes, altered mental status and seizures in both the waves. Among ischemic stroke, large vessel occlusion was more common during both the waves of COVID-19 infection. Deaths were more common in COVID-19 positive patients with stroke than in non-COVID-19 patients.

Keywords: NCCT head, COVID-19, HRCT chest, ischemic stroke, stroke, RT-PCR

Introduction:

On 30thJanuary, 2020, WHO declared the SARS-CoV-2 outbreak as a Public Health Emergency of International Concern (PHEIC) and a pandemic on 11th March, 2020.(1)(2) Since then, COVID-19 infection has been creating havoc in the society over the years. Till now, we have seen three waves of the infection and awaiting the fourth wave which has already shown signs of its presence in the world.

The second wave of COVID-19 infection simply took the wind out of sails of healthcare in India with the governments (both centre and states) struggling hard to bring some amount of respite to the citizens and seemingly failing in the process with huge losses in terms of human life and the economic and social impact.

The daily test positivity rate revealed that the spread of infection had been explosive with steep rise in absolute number of cases.(3)(4) It, therefore, becomes imperative to not only look for preventive solutions on a war footing but also to understand what makes this wave of infection so dangerous and fatal in all its manifestations.

A similar phenomenon was seen during the 1918 influenza pandemic.(5)As in all pandemics, COVID-19 second wave turned out to be much more widespread, speedier and lethal across the globe with varying severities hitting India and the US the most. India recorded twice as many cases in this wave and the first one too. Coronavirus disease 2019 (COVID-19) may increase the risk of acute ischemic stroke similar to the increased risk seen within the first 3 days after other respiratory tract infections.(6) In a review of literature in April 2020,(7) the proportion of patients with COVID-19 who had acute ischemic stroke was estimated to be 4.9% during initial hospitalization. Similarly, a lot of other neurological manifestations were also seen during these waves.

We performed this study to identify association between patients presenting with neurological manifestations with radio-imaging findings in COVID-19 positive and negative patients during the two waves.

Materials And Methods:

Design and setting:

The present study is a retrospective, hospital-based, descriptive study conducted in the Department of Neurology of a tertiary care centre in Rajasthan (India).

In the present study, 272 patients who presented with neurological manifestations and had undergone HRCT thorax and NCCT head were included in the study during the period of July 2020 to June 2021. Ethical clearance was taken from the Institutional Ethics Committee.

Study duration- July 2020 to June 2021.

Sample size- All patients who presented in Neurosciences department and in the COVID-19 area during July 2020 to June 2021 and who fulfilled the inclusion criteria.

Inclusion criteria:

All the patients who were admitted with neurological manifestations and who underwent NCCT head and HRCT thorax in the Neurosciences Department and COVID-19 area of a tertiary care centre during the study duration were included in the study.

Exclusion criteria:

Patients without neurological manifestations and those patients in whom HRCT thorax and NCCT head were not performed were excluded from the study.

Methods:

It is a retrospective study where data was collected of all the patients admitted to a tertiary care hospital from **July 2020 to June 2021** with neurological manifestations and patients who underwent HRCT chest and NCCT head. As a protocol, all the patients who were admitted during the COVID-19 pandemic had to undergo HRCT chest and RT-PCR of throat and nasal swab for better isolation of the infected patients. Real-time reverse transcription–polymerase chain reaction (RT-PCR) of throat and nasal swab samples were done and were divided into RTPCR positive or negative patients. The patients with RT-PCR/ HRCT chest positive results (CORADS ≥5) were referred to as COVID-19 positive group. Electronic medical records, laboratory parameters, radiologic examinations (HRCT thorax, NCCT head), and other tests if done were reviewed retrospectively.

Demographic data such as age, sex, previous co-morbidities (hypertension, diabetes, dyslipidaemia, smoking habit, obesity, heart disease, chronic kidney disease [CKD], immunosuppression, cancer, neurologic diseases), and relevant previous treatments were recorded.

Statistical analysis:

Data was recorded as per Performa. The data analysis was computer based; SPSS-22 was used for analysis. For categorical variables chi-square test was used. For continuous variables independent sample's *t*-test was used. *P-value*<0.05 was considered as significant.

Results:

Table 1 show that average age was 63 years and 52 years in the first wave whereas 53 years and 56 years in the second wave among COVID-19 positive and negative cases respectively. Ratio of males to females was 2.28:1 and 1.73:1 in first wave whereas 1.78:1 and 1.39:1 in the second wave of COVID-19 positive and negative patients respectively. Hypertension was the most common co-morbidity among all cases in both waves (87.0% & 25.6%) whereas smoking was the least common (30.4% vs 12.8%). Prevalence of

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neurological manifestations was 0.57% in the first wave and 1.56% in the second wave for the COVID-19 positive patients. The percentage of total deaths in both waves due to neurological manifestations with COVID-19 patients was 40.3% (39.1% vs 41%).

Table 2 shows olfactory dysfunction (26.0% vs 35.9%), headache (47.8% vs 12.8%), altered sensorium (78.3% vs 17.9%), paresis (87.0% vs 51.3%), seizures (17.4% vs 2.6%), dizziness/giddiness (8.7% vs 41.0%) and dysarthria/aphasia (87.0% vs 56.4%) to be the major symptoms during both the waves.

Table 3 shows diffuse cerebral oedema/encephalopathy (17.4% vs 5.1%), intracranial haemorrhage (13.0% vs 35.9%) and ischemic infarct (69.6% vs 59.0%) in the first and second wave for the COVID-19 positive patients. Overall in both the waves, ischemic infarct was the most common finding occupying 50% patients.

Table 4 shows COVID-19 patients with ischemic infarcts as one of the important cause of death in both waves individually and combined (21.7% in first wave & 23.1% in second wave; total of 22.6%) while intracranial haemorrhage was more common cause in COVID-19 negative patients in the first wave (3.6%).

Table 5 shows MCA was the most common territory involved in both first and second wave among both positive (69.6% vs 35.9%; 13.0% vs 25.6%) and negative (34.8% vs 42.9%; 39.3% vs 15.3%) patients with stroke (ischemic and haemorrhagic respectively).

Table 6 shows comparison of parameters of the patients with COVID-19 during both the waves to summarise our findings.

Discussion:

The disease has been evolving with time with newer variants infecting the populations with variable presentations including the cerebrovascular co-morbidities. In this study, the first thing we noticed was the mean age of the patients being affected by stroke which turned out to be younger in second wave (53.87 years) than the first wave (63.26 years). However, in the COVID-19 negative group, the mean age was lesser in the first wave (52.78 years) as compared to the second wave (56.83 years). In a study by Kumar et al, it was concluded that the second wave of COVID-19 in India was slightly different in presentation than the first wave, with a younger demography and lesser co-morbidities.(8) This could also be attributed to the vaccination drive focussed towards the older population along with irresponsible behaviour by the general population towards the preventive rules.

Our study had higher number of males as compared to females in both the waves having neurological condition as well as COVID-19 infection. The ratio of male: female being 2.28:1 in the first wave and 1.78:1 in the second wave. As already known, females are more resistant to infections than men, and this is possibly mediated by several factors including sex hormones and high expression of corona virus receptors (ACE 2) in men and also in life style, such as higher levels of smoking and drinking amongst Indian men as compared to women was seen. Additionally, women tend to have more responsible attitude towards the COVID-19 pandemic than men.(9)

The prevalence of hypertension, diabetes in the patients with COVID-19 negative group during the first wave was found to be much lower as compared to the prevalence in the COVID-19 positive patients (66.1% vs 87.0% and 39.3% vs 82.6% respectively). Furthermore, the second wave seemed to cause stroke even in patients who had fewer co-morbidities as opposed to the first wave. The patients with hypertension constituted 85.95% of the total affected patients in the first wave while in the second wave; the number went down to 25.6%. Similarly, the patients with diabetes constituted 82.6% of the cases in the first wave with the number going down to 7.69% in the second wave. These observations were in correlation to the study by Kumar et al which showed that second wave of COVID-19 affected the patient with lesser co-morbidities. Also, this could be attributed to the vaccination drive towards older population with co-morbidities as described earlier.

The deaths of the patients with COVID-19 positive during the second wave was almost similar to the percentage of deaths during the first wave but it was still higher as compared to the percentage of deaths in the COVID-19 negative group which highlights the associated mortality related to the disease. Newer variants like B.1.351 and B.1.617 were found to be

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highly transmissible with reduced antibody neutralization during the second wave of COVID-19 contributing to the high pathogenicity of the disease. (10)

During the COVID-19 waves, olfactory dysfunction, headache, altered sensorium, paresis, seizures, dizziness/giddiness and dysarthria/aphasia were the major clinical features at presentation in both COVID-19 positive and negative patients. The major clinical features seen in the COVID-19 positive patients were headache, altered sensorium, paresis, dysarthria/aphasia and seizures during the first wave as contrast to olfactory dysfunction and dizziness/giddiness during the second wave. These observations could help us in predicting the severity of the disease and would help in better management of the patients.

The prevalence of neurological complications in the COVID-19 positive patients was higher during the second wave (1.56%) as compared to the first wave (0.57%). This may be attributed to the higher pathogenicity of the more transmissible variants which was more prevalent during the second wave of COVID-19.(10)

In our study, we found that there was an increase in cases of hemorrhagic stroke in the second wave. The number went up from 13.04% to 35.89%. The cases of ischemic infarct were 69.56% and 60% in the first and second wave respectively. While that of encephalopathy were 13.04% and 5.12% respectively. The association of ischemic and hemorrhagic strokes in COVID-19 patients could be attributed to three main mechanisms which appear to be responsible for the occurrence of ischemic strokes in COVID-19. These include a hypercoagulable state, vasculitis, and cardiomyopathy. While the pathogenesis of hemorrhagic strokes in the setting of COVID-19 has not been fully elucidated, it is possible that the affinity of the SARS-CoV-2 for ACE2 receptors, which are expressed in endothelial and arterial smooth muscle cells in the brain, allows the virus to damage intracranial arteries, causing vessel wall rupture.(11)

It is also possible that the cytokine storm that accompanies this disorder could be the cause of hemorrhagic strokes. This massive release of cytokines may also damage and result in breakdown of the blood-brain barrier and cause hemorrhagic posterior reversible encephalopathy syndrome (PRES). Secondary hemorrhagic transformation of ischemic strokes has also been reported in COVID-19 patients. Such transformation may occur in the setting of endothelial damage or a consumption coagulopathy accompanying COVID-19.In SARS-CoV-2 infection, the presence of S-protein could further reduce the expression and function of ACE2 proteins. (11)

In this study, most number of deaths was caused by encephalopathy in both the waves. A similar study reviewed 274 cases of COVID-19, of which 24 (8.8%) developed hypoxic encephalopathy which progressed to death in 23 (95.8%) and recovery in 1 (4.2%).(12) In the present study, the percentage of death in COVID-19 positive patients attributed to ischemic infarct in first wave was 26.31% and that to haemorrhagic stroke was 33.3 %. In the second wave we saw an increase in percentage of deaths in patients with both haemorrhagic (42.8%) and ischemic stroke (39.1%). This may be attributed to the older patients with co-morbidities in the first wave and higher pathogenic variants in the second wave along with health system being exhausted due to increased number of COVID-19 patients.

In our study, the major artery affected in the COVID-19 positive patients during the pandemic during the first wave was middle cerebral artery in both haemorrhagic and ischemic stroke group. But during the second wave, the majority of patients had MCA territory affection along with other territories being involved too. As a whole, the major artery involved in all the groups was middle cerebral artery. In a similar retrospective case-control study it has been shown that COVID-19 is mainly associated with large vessel occlusion strokes rather than the small vessel occlusion strokes.(13) It has also been reported that detection of acute stroke can be a strong prognostic marker of the poor patient outcome as it is the most common neuroimaging finding among the COVID-19 patients. Our results are in agreement with the results of the current analysis which have also found significant cerebrovascular diseases in COVID-19 patients of 28 studies with a pooled proportion of 9.9% (6.8−13.4).(14)

Our findings have also been summarized in Table 6 for better comparison of the data between the two waves of COVID-19. There were a few limitations in

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our study. Firstly, as it was a retrospective study, data collection could not be done completely involving the blood investigations. Secondly, patients with peripheral nervous system involvement could not be proven during the study analysis.

Conclusion:

Our study demonstrates that neurological manifestations are mostly reported in both COVID-19 and non-COVID-19 patients. The most common neurological manifestations in COVID-19 patients were headache, olfactory dysfunction, strokes, altered mental status and seizures in both the waves. Altered sensorium at present was found to be the associated with maximum cases of death in our study. Among ischemic stroke, large vessel occlusion was more common during both the waves of COVID-19 infection.

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Tables:

Table 1: Demographic Profile

Demographic Variables		COVID-19 +ve W1 (%)	COVID-19 -ve W1 (%)	Total W1 (%)	COVID-19 +ve W2 (%)	COVID-19 -ve W2 (%)	Total W2 (%)	Pooled			*p*-value
								+ve (%)	-ve (%)	Total (%)	
Sample Size		23	112	135	39	98	137	62	210	272	---
Age		63.26 ± 13.27	52.78 ± 16.04	54.56 ± 16.05	53.87 ± 14.16	56.83 ± 14.95	55.99 ± 14.74	57.35 ± 14.47	54.67 ± 15.64	55.28 ± 15.39	.000 (S)
Gender (Male:Female)		2.28:1	1.73:1	1.8:1	1.78:1	1.39:1	1.49:1	1.95:1	1.56:1	1.64:1	.643
Co-morbidity	Hypertension	20 (87.0)	74 (66.1)	94 (69.6)	10 (25.6)	45 (45.9)	55 (40.1)	30 (48.4)	119 (56.7)	149 (54.8)	.272
	Diabetes	19 (82.6)	44 (39.3)	63 (46.7)	3 (8.3)	25 (25.5)	28 (20.4)	22 (35.5)	69 (32.9)	91 (33.5)	.197
	Smoker	7 (30.4)	29 (25.9)	36 (26.7)	5 (12.8)	32 (32.7)	37 (27.0)	12 (19.4)	61 (29.0)	73 (26.8)	.216
Neurological Manifestations	IPD patients with neurological manifestations	23	112	135	39	98	137	62	210	272	---
	Total IPD patients during study	4064	16131	20195	2498	25678	28176	6562	41809	48371	---
	Prevalence	0.57%	0.69%	0.67%	1.56%	0.38%	0.49%	0.94%	0.50%	0.56%	---
Death		9 (39.1)	8 (7.1)	17 (12.6)	16 (41.0)	8 (8.2)	24 (17.5)	25 (40.3)	16 (7.6)	41 (15.1)	.000 (S)

Table 2: Clinical Profile of COVID-19 and Non-COVID-19 patients

Clinical Profile	COVID-19 +ve W1 (n=23)	COVID-19 -ve W1 (n=112)	Total W1 (n=135)	COVID-19 +ve W2 (n=39)	COVID-19 -ve W2 (n=98)	Total W2 (n=137)	Pooled			*p*-value
							+ve (n=62)	-ve (n=210)	Total (n=272)	
Olfactory dysfunction (Anosmia/Parosmia)	6 (26.0)	0 (0)	6 (4.4)	14 (35.9)	4 (4.1)	18 (13.1)	20 (32.2)	4 (1.9)	24 (8.8)	---
Headache	11 (47.8)	79 (70.5)	90 (66.7)	5 (12.8)	31 (31.6)	36 (26.3)	16 (25.8)	110 (52.4)	126 (46.3)	.035*
Altered sensorium	18 (78.3)	32 (28.6)	50 (37.0)	7 (17.9)	38 (38.8)	45 (32.8)	25 (40.3)	70 (33.3)	95 (36.0)	.028*
Paresis (mono/hemi/quadriparesis)	20 (87.0)	84 (75.0)	104 (77.0)	20 (51.3)	72 (73.5)	92 (67.2)	40 (64.5)	156 (74.3)	196 (72.1)	.025*
Seizures	4 (17.4)	13 (11.6)	17 (12.6)	1 (2.6)	10 (10.2)	11 (8.0)	5 (8.1)	23 (11.0)	28 (10.3)	.037*

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Dizziness/Giddiness	2 (8.7)	20 (17.9)	22 (16.3)	16 (41.0)	17 (17.3)	33 (24.1)	18 (29.0)	37 (17.6)	55 (20.2)	.014*
Dysarthria or Aphasia	20 (87.0)	106 (94.6)	126 (93.3)	22 (56.4)	35 (35.7)	57 (41.6)	42 (67.7)	141 (67.1)	183(67.3)	.038*

*Significant at .05 level

Table 3: Association between Covid-19 positive/negative and Neuroimaging of Brain

Neuroimaging Findings	COVID-19 +ve W1 (n=23)	COVID-19 -ve W1 (n=112)	Total W1 (n=135)	COVID-19 +ve W2 (n=39)	COVID-19 -ve W2 (n=98)	Total W2 (n=137)	Pooled			*p*-value
							+ve (n=62)	-ve (n=210)	Total (n=272)	
Diffuse Cerebral Edema/ Encephalopathy	4 (17.4)	1 (0.9)	4 (3.0)	2 (5.1)	22 (22.4)	24 (17.5)	6 (9.6)	23 (11.0)	28 (10.3)	.000 (S)
Haemorrhage	3 (13.0)	64 (57.1)	67 (49.6)	14 (35.9)	24 (24.5)	38 (27.7)	17 (27.4)	88 (41.9)	105 (38.6)	
Ischemia	16 (69.6)	45 (40.2)	61 (45.2)	23 (59.0)	52 (53.1)	75 (54.7)	39 (62.9)	97 (46.2)	136 (50.0)	

Table 4: Outcome of Covid-19 positive and Covid-19 negative patients

Neuro-imaging findings of Brain	COVID-19 +ve W1 (n=23)		COVID-19 -ve W1 (n=112)		Total W1 (n=135)		COVID-19 +ve W2 (n=39)		COVID-19 -ve W2 (n=98)		Total W2 (n=137)		Pooled +ve (n=62)		Pooled -ve (n=210)		Pooled Total (n=272)		*p*-value
Outcome	Death	Survived	Death	Survived	Death	Survived	Death	Survived	Death	Survived	Death	Survived	Death	Survived	Death	Survived	Death	Survived	
Diffuse Cerebral Edema/ Encephalopathy	4 (17.4)	0 (0.0)	1 (0.9)	0 (0.0)	4 (3.0)	0 (0.0)	1 (2.6)	1 (2.6)	2 (2.0)	20 (20.4)	3 (2.2)	21 (15.3)	4 (6.5)	1 (1.6)	3 (1.4)	20 (9.5)	7 (2.6)	21 (7.7)	.000 (S)
Haemorrhage	1 (4.3)	2 (8.7%)	4 (3.6)	60 (53.6)	5 (3.7)	62 (45.9)	6 (15.4)	8 (20.5)	2 (2.0)	22 (22.4)	8 (5.8)	30 (21.9)	7 (11.3)	10 (16.1)	6 (2.9)	82 (39.0)	13 (4.8)	92 (33.8)	
Ischemia	5 (21.7)	11 (47.8)	2 (1.8)	43 (38.4)	7 (5.2)	54 (40.0)	9 (23.1)	14 (35.9)	2 (2.0)	50 (51.0)	11 (8.0)	64 (46.7)	14 (22.6)	25 (40.3)	4 (1.9)	93 (44.3)	18 (6.6)	118 (43.4)	

Table 5: Association between Covid-19 positive/negative and territory involved in haemorrhage or ischemia

Territory involved	COVID-19 +ve W1 (n=23)	COVID-19 -ve W1 (n=112)	Total W1 (n=135)	COVID-19 +ve W2 (n=39)	COVID-19 -ve W2 (n=98)	Total W2 (n=137)	Pooled +ve (n=62)	Pooled -ve (n=210)	Pooled Total (n=272)	*p*-value
Haemorrhage										
MCA	3 (13.0)	44 (39.3)	47 (34.8)	10 (25.6)	15 (15.3)	25 (18.2)	13 (21.0)	59 (28.1)	72 (26.5)	.983
ACA	0 (0.0)	4 (3.6)	4 (3.0)	2 (5.1)	1 (1.0)	3 (2.2)	2 (3.2)	5 (2.4)	7 (2.6)	
PCA	0 (0.0)	8 (7.1)	8 (5.9)	1 (2.6)	4 (4.1)	5 (3.6)	1 (1.6)	12 (5.7)	13 (4.8)	
Basilar	0 (0.0)	1 (0.9)	1 (0.7)	0 (0.0)	1 (1.0)	1 (0.7)	0 (0.0)	2 (1.0)	2 (0.7)	
SAH	0 (0.0)	7 (6.3)	7 (5.2)	1 (2.6)	3 (3.1)	4 (2.9)	1 (1.6)	10 (4.8)	11 (4.0)	
Ischemia										
MCA	16(69.6)	39 (34.8)	55 (40.7)	14 (35.9)	42 (42.9)	56 (40.9)	30 (48.4)	81 (38.6)	111(40.8)	.169

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ACA	0 (0.0)	2 (1.8)	2 (1.5)	1 (2.6)	2 (2.0)	3 (2.2)	1 (1.6)	4 (1.9)	5 (1.8)
PCA	0 (0.0)	3 (2.7)	3 (2.2)	4 (10.3)	6 (6.1)	10 (7.3)	4 (6.5)	9 (4.3)	13 (4.8)
Basilar	0 (0.0)	1 (0.9)	1 (0.7)	4 (10.3)	2 (2.0)	6 (4.4)	4 (6.5)	3 (1.4)	7 (2.6)

Table 6: Comparison of parameters in patients with stroke between first and second waves of COVID-19

S. No.	Parameter(s)	First wave	Second wave
1.	Age (in years)	63.26 ± 13.27 (↑)	53.87 ± 14.16
2.	Gender (Male: Female)	2.28:1 (↑)	1.78:1
3.	Co-morbidities (HTN; DM) (%)	87.0; 82.6 (↑)	25.6; 8.3
4.	Death rate (%)	39.1	41.0 (↑)
5.	Seizures (%)	17.4 (↑)	2.6
6.	Paresis (%)	87.0 (↑)	51.3
7.	Dysarthria/aphasia (%)	87.0 (↑)	56.4
8.	Headache (%)	47.8 (↑)	12.8
9.	Altered sensorium (%)	78.3 (↑)	17.9
10.	Dizziness/ giddiness (%)	8.7	41.0 (↑)
11.	Ischemic stroke (%)	69.6 (↑)	59.0
12.	Hemorrhagic stroke (%)	13.0	35.9 (↑)
13.	Cranial vessel(s) involved	Large vessel(s) (mostly)	Large + small vessel(s)
14.	Encephalopathy was associated with poor outcome during both the COVID-19 waves		

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