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ROLE OF COMPUTED TOMOGRAPHY SCAN IN EVALUATION OF NEUROLOGICAL MANIFESTATIONS IN COVID 19 POSITIVE PATIENTS AND ITS CORRELATION WITH D-DIMER VALUE AND GCS: A RETROSPECTIVE COHORT STUDY IN A TERTIARY CARE HOSPITAL IN CENTRAL INDIA

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ABSTRACT

Objective: To investigate the incidence and spectrum of neuroimaging findings and their prognostic role in hospitalized COVID-19 patients in Government Medical College Nagpur along with their correlation with D-Dimer Values and GCS .

Methods: This is a retrospective cohort study of 774 COVID-19 confirmed patients admitted to Government Medical College Nagpur between 1st April 2020 and 31st October 2020. Clinical data were extracted from electronic medical records, and particularly data of all neurological symptoms were extracted from the imaging reports. Four neuro-radiologists evaluated all neuroimaging studies for acute neuroimaging findings related to COVID-19. Plasma D-dimer levels were measured using a particle-enhanced, immunoturbidimetric assay on admission in the 116 patients who came for evaluation of neurological symptoms.

Moreover ,the patients were classified into different groups as mild, moderate and severe based on their GCS scores and was assessed with respect to their neuro-imaging findings.

Results: 15 % of the admitted patients suffered from neurological symptoms. Acute stroke was the most common finding in the patients with positive neuroimaging findings resulting in 34.4% of the patients with positive neuroimaging findings. Other findings were subacute infarcts (13.8%), Chronic lacunar infarcts (20.6%) , Intraparenchymal hemorrhage in 10.4 %, hypertensive encephalopathy in 7 % and subarachanoid hemorrhage in 3.4 %.

Plasma median D-dimer levels were significantly (P = 0.000) higher in Acute stroke patients as compared to COVID 19 positive patients who had negative CT scan imaging features(0.88; interquartile range [IQR], 0.28–2.11 mg/L and 0.31; IQR, 0.17–0.74 mg/L).

Patients who have positive neuroimaging findings presented with a lower GCS whereas patients who had negative neuroimaging findings presented with a higher GCS.

Conclusions: Our study demonstrates acute stroke is the most common neuroloimaging finding in hospitalized COVID 19 Patients. Moreover D-Dimer values are highly predictive of acute ischemic stroke. Patients with positive neuro-imaging findings have poor GCS scores.

KEYWORDS : COVID-19, Computed Tomography scan, D-Dimer

1. INTRODUCTION:

An outbreak of coronavirus disease 2019 (COVID-19) began in Wuhan, China, in December 2019 and has rapidly spread around the world to become a pandemic (1). As of 09th December, India has the second highest number of cases only second to USA with a total of 9,735,975 cases and 141,398 deaths. Several studies have described the spectrum of chest imaging features of COVID-19 (2). However, to date, only a few case reports have described COVID-19–associated neurologic imaging findings (3).

Acute ischemic stroke (AIS) is one of the major causes of death worldwide [4]. D-dimer, the final product of plasma in-mediated degradation of fibrin-rich thrombi, has emerged as a simple blood test that can be used in diagnostic algorithms for the exclusion of venous thromboembolism. D-dimer levels have certain advantages over other measures of thrombin generation, because it is resistant to ex vivo activation, relatively stable, and has a long half-life [5]. The concentration of D-dimer reflects the extent of fibrin turnover in the circulation, because this antigen is present in several degradation products from the cleavage of cross linked fibrin by plasmin[6]. It has been suggested that modestly elevated circulating D-dimer values reflect minor increases in blood coagulation, thrombin formation, and turnover of cross linked intravascular fibrin (which is partly intra-arterial in origin) and that these increases may be associated with coronary heart disease [7]. D-dimer is known to be positively associated with coronary heart disease incidence and its recurrence, which is largely in dependent of conventional risk factors [7]–[8]. In addition, elevated D dimer concentrations have been reported to be associated with cerebral venous sinus thrombosis [9], acute pulmonary embolism [10], spontaneous intracerebral hemorrhage [11], long-term neurologic outcomes in Childhood-Onset Arterial Ischemic Stroke [12]. Previous studies also have suggested that D-dimer levels may be associated specifically with subtypes [13], assessing prognosis [14]–[15] and unfavorable outcome in ischemic stroke patients. Some studies have suggested that D-dimer can be seen as an outcome predictor in ischemic stroke and an indicator of severity of traumatic brain injury [16]–[17]. Unfortunately, there has been little research on the associations between plasma D-dimer level and acute ischemic stroke in COVID-19 Positive patients(COVID-19 being a pro-thrombotic state).

The purpose of our study was to systematically characterize neurologic symptoms and neuroimaging features in hospitalized patients with COVID-19 in Government Medical College Nagpur along with their correlation with D-Dimer Values.

2. MATERIALS AND METHODS:

2.1 Study Design and Patient Population

We used a retrospective cohort study from Government Medical College Nagpur. Institutional review board approval and waivers for informed consent were obtained at all institutions.

Our inclusion criteria included
(a) hospitalized patients who were positive for COVID-19 by means of real-time reverse-transcriptase polymerase chain reaction testing (ICMR approved laboratory in GMC Nagpur) of respiratory secretions obtained by means of nasopharyngeal swab, or oropharyngeal swab from April 01 2020 to October 31 2020;
(b) presence of acute neurologic symptoms (altered sensorium, loss of consciousness and neuro-deficit)during hospital stay; and
(c) Under gone Computed Tomography scans .
We reviewed the electronic medical records to extract clinical, laboratory, and demographic data.

2.2 Image Acquisition

All images were obtained as per standard of care protocols. Computed Tomography scans were done by Siemens 128 slice CT machine in Covid Care Centre in GMC Nagpur.

2.3. Image Interpretation

The neurologic imaging characteristics that were evaluated are listed in Table 1. All scans were initially analyzed by the institution's four radiologists. (Two junior residents and two radiologists of 25 years experience).

Table 1: Neuroimaging Characteristics of Hospitalized Patients with New Onset of Neurologic Symptoms after COVID-19

Neuroimaging characterestics	CT finding
Acute infarct	20/116(17.2%)
Chronic Lacunar infarcts	12/116(10.3%)
Subacute infarct	8/116(6.9%)
Intraparenchymal hemorrhage	6/116(5.2%)
Hypertensive encephalopathy	4/116(3.5%)
Subarachanoid hemorrhage	2/116(1.7%)
Mixed Findings	6/116(5.2%)
Normal	58/116(50%)

2.4 D-Dimer Values:

Plasma D-dimer levels were measured using a particle-enhanced, immunoturbidimetric assay on admission in 116 patients who underwent CT scan.

2.5: GCS values:

Glascow coma scale scoring was done for all the 116 patients. The patients were divided into three groups: GCS 13-15 (mild head insult); GCS 9-12(moderate head insult); and GCS less than 9 (severe head insult).

2.6 Ethics:

The study plan was discussed with the ethical committee of our institution and as it is retrospective observational study, the ethical approval was waived off.

2.7 STATISTICAL ANALYSIS:

Statistical Analysis Continuous variables are presented as mean +/- standard deviations and were compared between patients with altered mental status by using the Student t test; categoric variables are presented as frequencies with percentages. P <.05 was indicative of a statistically significant difference.

3.RESULTS

3.1: Spectrum of neuroimaging findings:

- A total of 774 consecutive hospitalized patients with COVID-19 were reviewed. Of these 774 patients, 116 (15%) met the eligibility criteria (Fig 1). All the 116 patients underwent non-contrast Computed Tomography scans.

Table 2 summarizes the demographic characteristics, medical history, and neurologic characteristics. The most common neurologic symptoms were altered mental status in 68 of the 116 patients (59%).

774 consecutive hospitalized patient with RT-PCR confirmed diagnosis of COVID-19 from April 01 to October 31,2020.

↓

116 patients (15%) developed acute neurological symptoms and referred for neuroimaging and had undergone Non-Contrast Computed Tomographic scans.

↓

1. 58 out of 116 (50%) patients had negative neuroimaging findings.
2. 20 out of 116 (17.2%) patients had acute infarct.
3. 12 out of 116 (10.3%) patients had chronic lacunar infarcts.
4. 8 out of 116 (6.9%) patients had subacute infarcts.
5. 6 out of 116 (5.2%) patients had intraparenchymal hemorrhage.
6. 4 out of 116 patients(3.5 %) had hypertensive encephalopathies.
7. 2 out of 116 patients (1.7%) had subarachanoid hemorrhage.
8. 6 out of 116 patients (5.2%) had mixed findings.

Fig.1 : Study flowchart. COVID-19 = coronavirus disease 2019 RT-PCR = real-time reverse-transcriptase polymerase chain reaction.

Table 2: Characteristics of Hospitalized Patients with COVID-19

Characterestics	Value
Sex	
Male	70(60.3%)
Female	46(39.6%)
Age	
Age <50 years	20(17.2%)
Age >50 years	96(82.7%)
Past Medical History	
Hypertension	56(48.3%)
Diabetes Mellitus	34(29.3%)
Coronary Artery Disease	30(25.9%)
Malignancy	15(12.9%)
HIV	2(1.7%)
Hemoglobinopathy	2(1.7%)
Clinical Features	
Altered Mental Status	68(58.6%)
Neurodeficit	36(31.0%)
Loss of consciousness	30(25.86%)
Seizure	14(12.06%)
Ataxia	3(2.6%)
Hyposmia	3(2.6%)

- Of the 116 patients; 56 patients(48.3%) suffered from hypertension whereas 34 patients (29.3%) suffered from diabetes. There is a considerable overlap in past medical history as there are patients with co-morbid conditions.
- 58 out of 116 patients had normal neuroimaging features.
- 20 out of 116 patients (17.2%) patients showed acute infarct on Non-contrast CT scans. 12 out of the 20 patients show MCA(Middle Cerebral Artery) territory infarcts. 4 out of the 20 patients show infarcts of ICA (Internal carotid artery) territory. 2 out of the 20 patients show combined ICA and MCA territory stroke. 2 out of the 20 patients show acute infarcts involving midbrain and pons. [Fig 2 and 3]

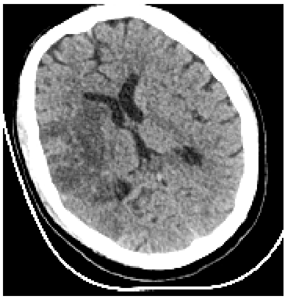

Fig 2 reveals ill defined hypodensity of average attenuation 22HU noted involving right fronto-parieto-temporal region and right gangliocapsular region s/o acute non-hemorrhagic right MCA territory infarct

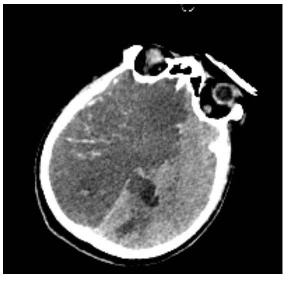

Fig 3 reveals Diffuse ill defined hypo density of average attenuation 22HU noted involving whole of the right cerebral hemisphere with sparing of medial temporal lobe with mass effect , subfalcine and uncal herniation towards left.

- 12 out of the 116 patients (10.3%) showed chronic lacunar infarcts mainly in ganglio-capsular regions.[Fig 4]

Fig 4 reveals chronic lacunar infarct in right thalamus.

- 8 out of 116 patients (6.9%) showed sub acute infarcts. Anterior cerebral territory was involved in 2 cases where Middle cerebral artery was involved in 2 cases . Posterior circulation was involved in remaining 4 cases which involved cerebellum.[Fig 5]

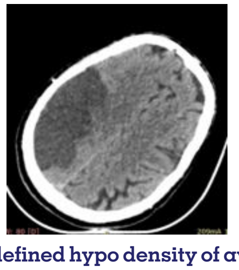

Fig 5 reveals ill defined hypo density of average attenuation 19 HU in right parietal lobe with loss of grey white matter differentiation s/o sub acute infarct in right middle cerebral artery territory.

- 6 out of 116 patients (5.2%) showed intraparenchymal haemorrhage. Two of them involved the midbrain and Pons; two of them involved thalamocapsular region and the rest two involved left gangliocapsular regions.[Fig 6 and 7]

Fig.6 reveals an intraparenchymal hemorrhagic focus of size 0.9x0.7x1.7cm(0.5cc) of average attenuation 58HU noted involving dorsal midbrain and pons.

Fig 7 reveals mixed density intraparenchymal hemorrhage of size 1.9x1.9x1.4cm (vol-2-3cc) noted involving left thalamocapsular region with mild surrounding edema.

- 4 out of 116 patients(3.5%) showed hypertensive encephalopathy predominantly in the occipital lobes. [fig 8]

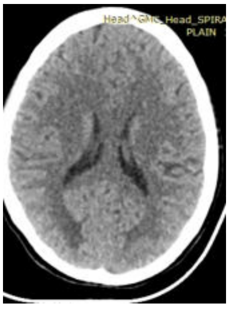

Fig 8 reveals ill defined hypodensities of average attenuation 21HU noted involving subcortical and deep white matter in bilateral fronto-parieto-temporo-occipital lobes, more marked in the occipital lobes.

- 2 out of 116 patients (1.7%) revealed subarachanoid hemorrhage with intraventricular extensions [Fig 9]
- Rest 6 out of 116 patients (5.2%) revealed mixed findings like a combination of acute,subacute and chronic infarct in two cases(1.7%); intraparenchymal hemorrhage and hypertensive encephalopathy in another two cases(1.7%) ; subdural hemorrhage with infarcts in another two cases(1.7%).

Fig 9 reveals Diffuse thick subarachnoid hemorrhage noted involving bilateral fronto-parieto-temporo-occipital regions with intraventricular extension into occipital horns of bilateral lateral ventricles.

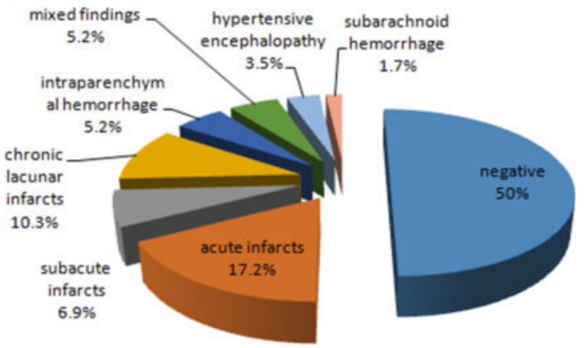

Fig 10 reveals the distribution of neuroimaging finding of the 116 patients who had undergone Non-enhanced computed tomography scan in our study.

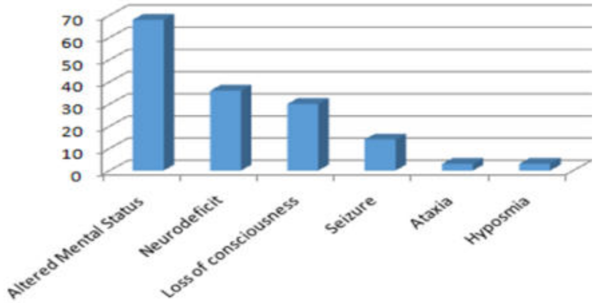

Fig 11 reveals the spectrum of clinical findings with which the 116 patients presented while doing the Computed Tomography scan. Altered mental status is the most common clinical feature.

3.2 GCS values:

Glascow coma scale scoring was done for all the 116 patients. The patients were divided into three groups: GCS 13-15 (mild head insult); GCS 9-12(moderate head insult); and GCS less than 9 (severe head insult).

Table3: Shows the distribution of the patients with respect to neuroimaging findings and Glascow Coma Scale.

GCS	Normal	Acute Stroke	Subacute Infarct	Chronic Lacunar infarct	IPH	Mixed	PRESS	SAH	Total
13 to15	46	5	1	7	1	0	1	0	61
9 to 12	8	2	2	4	2	3	0	1	22
Less than 9	4	13	5	1	3	3	3	1	33

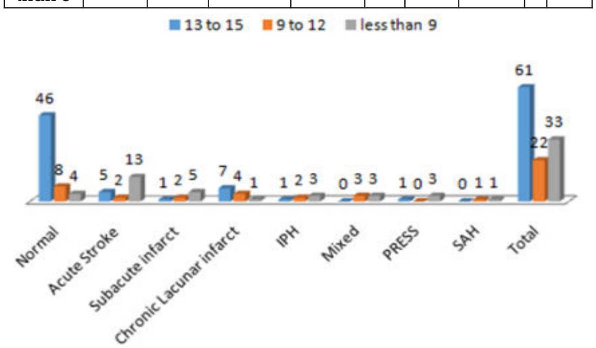

Fig 12 Shows the distribution of the patients with respect to neuroimaging findings and GCS score.

3.3 D-Dimer Correlation:

The results indicated that the Plasma D-dimer levels were significantly (P=0.000) higher in AIS as compared to patients with negative neuroimaging findings. (0.86; IQR, 0.26–2.14 mg/L and 0.33; IQR, 0.15–0.76 mg/L, respectively).

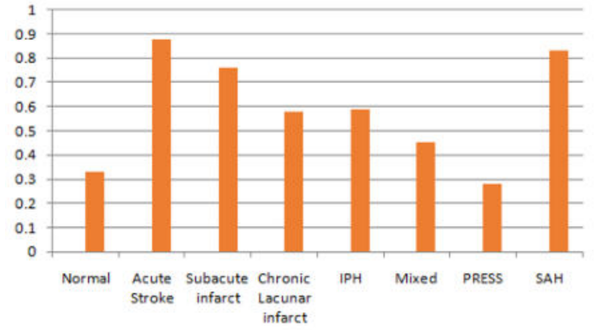

Fig 13: Shows the distribution of neuroimaging findings with Plasma D-Dimer values (Median Values in mg/L).

Table 4: Shows the distribution of neuroimaging findings with Plasma D-Dimer values (Median values in mg/l)

Normal	Acute Stroke	Subacute Infarct	Chronic Infarct	IPH	Mixed	PRESS	SAH
0.33	0.88	0.76	0.58	0.59	0.45	0.28	0.83

4.DISCUSSION:

4.1 Our study demonstrated that the neurologic imaging features of hospitalized patients with COVID-19 were variable, without a specific pattern but dominated by acute ischemic infarcts and intracranial hemorrhages.

Currently, we have a poor mechanistic understanding of the neurologic symptoms in patients with COVID-19, whether these are arising from critical illness or from direct central nervous system invasion of severe acute respiratory syndrome coronavirus 2 (18). Accumulating evidence suggests that a subgroup of patients with severe COVID-19 might have a cytokine storm syndrome that could be a trigger for ischemic strokes, probably related to the prothrombotic effect of the inflammatory response (19). Our results showed a lower prevalence of central nervous system symptoms than the Wuhan experience (20) (15% vs 25%, respectively); however, the prevalence of acute ischemic strokes was higher in our study (17.2% vs 11%).

In conclusion, neurologists and neuroradiologists should be familiar with the broad spectrum of neurologic imaging patterns associated with COVID-19.

4.2:

Glascow coma scale is a good predictor of neurological outcome of the patient. In our study we came into conclusion that patients with lower GCS values presented with positive neuroimaging findings in most of the cases.

4.3

There are several plausible mechanisms through which D-dimer levels could be closely related to stroke. Firstly, increased D-dimer levels may reflect ongoing thrombus formation within cerebral vessels or may be a marker of systemic hypercoagulability. Furthermore, thrombi formed in hypercoagulable states such as high D-dimer levels may be resistant to the endogenous fibrinolytic system . Secondly, some markers of hemostatic function are acute-phase reactants; D-dimer is one of these markers. There is, in fact, some evidence that fibrin degradation products, including D-dimer, may act to stimulate the inflammatory process , and this might provide a further pathological mechanism through which D-dimer is linked to progressing stroke . There is some evidence that Ddimer itself stimulates monocyte synthesis and release of proinflammatory cytokines such as interleukin- 6. Elevated systemic inflammation reflected by high D-dimer levels could also contribute to the stroke severity . Activated inflammation and activated coagulation, in concert with each other, may contribute to the development of stroke. Thirdly, because D-dimer is one of the acute phase reactants, it is possible that elevated D-dimer levels in patients with stroke may be the result rather than the cause of stroke. Although D-dimer was significantly correlated with baseline infarct volume, D-dimer was associated with severity independently of infarct volume. Thus, we consider that it is less likely that elevated D-dimer is merely an epiphenomenon of development of stroke.

In our study we saw that D-Dimer values are raised in patients with positive neuroimaging findings like acute ischemic stroke and subarachanoid hemorrhage with respect to patients with negative neuroimaging findings.

5.Acknowledgement:

We want to acknowledge all the patients along with their families who participated in the study.

6. Conflict of interest:

None

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