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Original Research Article

Assessment of Patients with Intracerebral Hemorrhage during the Pandemic COVID-19 Learning from Experience

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Abstract

Aim: We assessed the patients with intracerebral hemorrhage during the pandemic Covid 19.

Methods: The study protocol was approved by the Hospital COVID- 19 Paras HMRI Hospital, Patna, Bihar, India. All research was performed in accordance with guidelines and regulations, and the respective authors declare a statement confirming that informed consent was obtained from all of the participants' parents and/or their legal guardians. Overall, a total of 50 patients from the PANDEMIC registry fulfilled the inclusion criteria.

Results: The demographic and clinical characteristics of patients from the PANDEMIC registry, as well as the results for all individual-level patient data (total n = 100, with n = 50 from the PANDEMIC registry.

Conclusion: ICH in COVID-19 patients is rare, but it has a very poor prognosis. Different subtypes of ICH seen in COVID-19, support the assumption of heterogeneous and multifaceted pathomechanisms contributing to ICH in COVID-19. Further clinical and pathophysiological investigations are warranted to resolve the conflict between thromboembolic and hemorrhagic complications in the future.

Keywords: COVID-19, Intracerebral Hemorrhage, Pathophysiological Mechanisms, Neurological Consequences, Complications.

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Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), manifests most commonly as a respiratory disease. However, a growing body of clinical data shows that neurological manifestations significantly contribute to the clinical spectrum of the disease and are especially relevant in critically ill patients. [1-3] In addition to other neurological manifestations, cerebrovascular disease has frequently been linked to acute SARS-CoV2 infection. [4-6] To account for the SARS-CoV2- associated hypercoagulable state, several pathophysiological mechanisms have been proposed, including both direct and indirect effects of the viral infection. Apart from hypercoagulable features, SARS-CoV2-associated endothelitis and microangiopathy are also postulated to contribute to hemorrhagic stroke. [7-9] Intracranial hemorrhage (ICH) in COVID-19 patients, therefore, might either be due to hemorrhagic transformation of ischemic stroke, primary hemorrhagic stroke, or

traumatic ICH. Accordingly, the relevance of SARS-CoV2 related effects for the pathogenesis of these ICH subtypes might be heterogeneous.

The clinical course of COVID-19 is most severe in the elderly, and in patients with concomitant diseases such as hypertension and diabetes mellitus (DM), which are known to be the main factors in the development of ICH. [10] Stroke has been reported as a complication of COVID-19. Most strokes among COVID-19 patients are arterial ischemic, though ICH has also been reported. ICH represented an infrequent complication among patients hospitalized with COVID-19 at our center, and patients with COVID-19 and ICH had other risk factors for ICH. However, our patients along with others in the literature suggest that several mechanisms may contribute to ICH in the setting of COVID-19.

Coronavirus infection 2019 (COVID-19) is a dangerous infectious disease that occurs as an acute respiratory viral infection with specific complications, which may include pneumonia, which leads to acute respiratory distress syndrome or respiratory failure with a high risk of death. Among the main complications of COVID-19 on the nervous system are encephalopathy, encephalitis, acute disseminated encephalomyelitis, meningitis, ischemic stroke, and intracerebral hemorrhage (ICH) and other diseases. [11]

We assessed the patients with intracerebral hemorrhage during the pandemic Covid 19.

Materials and Methods

The study protocol was approved by the Hospital COVID- 19 Paras HMRI Hospital, Patna, Bihar, India for 14 months. All research was performed in accordance with guidelines and regulations, and the respective authors declare a statement confirming that informed consent was obtained from all of the participants' parents and/or their legal guardians. Overall, a total of 50 patients from the PANDEMIC registry fulfilled the inclusion criteria.

We performed a retrospective chart review of all hospitalized cases with confirmed COVID-19 infection seen at Hospital COVID-19 Clinics. Diagnosis of ICH was confirmed on neuroimaging with computed tomography (CT) of the brain.

COVID-19 infection nucleic acid tests were performed on nasopharyngeal swabs using quantitative real-time polymerase chain reaction (qRT-PCR). Patients were included in the case series if they had tested positive for COVID-19 prior to their ICH and had continuing clinical features related to COVID- 19. Inclusion criteria were defined as patients with acute ICH on CT neuroimaging and additional radiological assessment of the chest who were positive for COVID-19 and suffered from acute neurological symptoms during a hospital stay. Each of the scans had an electronic clinical and, if applicable, pathology report associated with it. Electronic reports were reviewed to extract clinical, laboratory, pathology, and demographic data. Patients were excluded if they had a secondary ICH from the hemorrhagic transformation of ischemic infarction, brain tumor, cerebral aneurysm, or vascular malformation. Baseline patient characteristics were retrieved from medical records, including symptom onset, Glasgow Coma Scale (GCS), and modified Rankin Scale (mRS) at last medical evaluation or at discharge. Additionally, vascular risk factors (hypertension, dyslipidemia and DM), laboratory parameters (C-reactive protein, D-dimer, etc.), and invasive procedures such as craniotomy from patients' clinical records and follow-up CT were obtained. Any missing or uncertain records were collected and clarified through direct communication with health care clinicians.

Results

Table 1: Baseline characteristics

Baseline Characteristics	PANDEMIC (n = 50)	Individual Patient Data (n = 100)
Age (years), median (IQR)	64.0 (57.0–76.0)	61.0 (53.8–71)
M/F	35/15	35/65
Critical disease (LEOSS), n (%)	32/50 (64)	60/100 (60)
ECMO, n (%)	17/50 (34)	20/100 (20)
Time from COVID-19 diagnosis to ICH diagnosis (days), median (IQR)	21.0 (15.5–31.3)	15 (8.0–22.5)
Non-neurological symptoms		
Fever	4/50 (8)	40/100 (40)
Respiratory symptoms	28/50 (56)	70/100 (70)
Myalgia/arthralgia,	4/50 (8)	8/100 (8)
Malaise	4/50 (8)	10/100 (10)
Neurological symptoms		
Focal neurological deficits, n (%)	8 (16)	20 (20)
Altered level of consciousness, n (%)	30 (60)	50 (50)
Encephalopathy, n (%)	1 (2)	4 (4)
Headache, n (%)	-	15 (15)
Anisocoria, n (%)	16 (32)	24 (24)
Seizure, n (%)	-	6 (6)
ICH		
IPH, n (%)	30 (60)	48 (48)
SAH, n (%)	24 (48)	30 (30)
SDH/EDH, n (%)	20 (10)	5 (5)
Laboratory values		
White blood cells (109/L), median (IQR)	20.3 (15.0–26.8)	15.8 (12.5–22.2)
Platelet count (109/L), median (IQR)	121.5 (70.5–185)	176.0 (97.3–261.5)
C-reactive protein (mg/L), median (IQR)	340.0(231 – 402)	220.0 (54.5–340)
INR, median (IQR)	1.4 (1.2–1.8)	1.3 (1.1–1.6)
aPTT (s), median (IQR)	58.0 (44.0–75.0)	58 (38.8–68)
D-dimer (mg/L), median (IQR)	17.9 (7.8–23.9)	6.8 (2.4–18)

Overall, a total of 50 patients from the PANDEMIC registry fulfilled the inclusion criteria. The demographic and clinical characteristics of patients from the PANDEMIC registry, as well as the results for all individual-level patient data (total n = 100, with n = 50 from the PANDEMIC registry.

Table 2: Outcome

Baseline Characteristics	Favorable Outcome (mRS 0–2)	Non-Favourable Outcome (mRS 3–6)	P Value
Age (years), median (IQR)	60.5 (43.25–67.25)	60.0 (53.0–71.0)	0.329
M/F	25/50	35/100	0.730
Critical disease (LEOSS), n (%)	10 (20)	35 (35)	0.001
ECMO, n (%)	-	20 (20)	0.147
Time from COVID-19 diagnosis to ICH diagnosis (days), median (IQR)	9.5 (1.8–13.5)	16.0 (10.0–24.5)	0.012

Non-neurological symptoms			
Fever	25 (50)	30 (30)	0.567
Respiratory symptoms	34 (68)	70 (70)	0.745
Myalgia/arthralgia,	5 (10)	8 (8)	0.986
Malaise	11 (22)	8 (8)	0.834
Neurological symptoms			
Focal neurological deficits, n(%)	10 (20)	20 (20)	0.576
Altered level of consciousness, n(%)	15 (30)	50 (50)	0.768
Encephalopathy, n (%)	-	4 (4)	0.786
Headache, n (%)	20 (40)	15 (15)	0.456
Anisocoria, n (%)	-	24 (24)	0.476
Seizure, n (%)	-	6 (6)	0.654
ICH			
IPH, n (%)	10 (00)	48 (48)	0.135
SAH, n (%)	20 (40)	30 (30)	0.468
SDH/EDH, n (%)	-	5 (5)	0.983
Laboratory values			
White blood cells (109/L), median (IQR)	20.3 (15.0–26.8)	15.8 (12.5–22.2)	0.769
Platelet count (109/L), median (IQR)	121.5 (70.5–185)	176.0 (97.3–261.5)	0.673
C-reactive protein (mg/L), median (IQR)	340.0 (231.0–402.0)	220.0 (54.5–340.0)	0.670
INR, median (IQR)	1.4 (1.2–1.8)	1.3 (1.1–1.6)	0.850
aPTT (s), median (IQR)	58.0 (44.0–75.0)	58 (38.8–68.0)	0.678
D-dimer (mg/L), median (IQR)	17.9 (7.8–23.9)	6.8 (2.4–18.0)	0.587

Discussion

Corona virus disease (COVID-19) has become the most difficult challenge for modern medicine, as it has manifested into a world- wide pandemic by infecting over61 million people as of November 24, 2020.The etiological factor is coronavirus2(SARS-CoV2), which infects the host cells by binding through the surface spike protein (mediatedbytransmembraneserineprotease 2)to the human angiotensin converting receptor (ACE2). [12-14]

On an individual patient level, the critical disease stage (20.0% vs. 66.7%, p = 0.001), time from COVID-19 diagnosis to ICH diagnosis (9.5 days vs. 16.0 days, p = 0.012), headache (40.0% vs. 11.5%, p = 0.014) and palliative care (0% vs. 38.4%, p = 0.016) correlated with outcomes at discharge (mRS 0–2 vs. mRS 3–6). The critical stage of COVID-19 and headaches in the context of IPH were previously described as predictors for worse outcomes. [15,16] However, in our study, headache predicted a better functional outcome (mRS 0–2). The discrepancy to already published data may be explained by a bias that could have developed because headache had been coded for both, COVID-19 and ICH. Although bleeding diathesis has been a fundamental factor in ICH in both COVID-19 and non-COVID-19 patients [17,18], and a significant proportion of patients had anticoagulation and showed changes in the respective biological biomarkers (aPTT, INR) in this cohort, we did not find anticoagulation to be a significant variable in our study. However, as we were not able to specify whether patients received prophylactic or

therapeutic dose anticoagulation in a large fraction of the overall data, the effect on the outcome might be underestimated.

By pooled analysis of aggregate level data, we provided detailed descriptive statistics but refrained from meta-regression due to incomplete data sets and thus insufficient statistical power. The patients with ICH during active COVID-19 were predominantly male with a median age of 58.8 years (95% CI 54.8; 62.9). Basic epidemiological data are thus comparable to already published cohorts of COVID-19. [16,19] The majority of patients experienced a critical phase of the disease, with respiratory symptoms and an altered level of consciousness being the dominant clinical features. The high proportion of patients with critical stage of COVID-19 is consistent with the studies reporting a relative increase in neurological symptoms with a more severe disease. [20] The median time from COVID-19 diagnosis to the diagnosis of ICH was 21.5 days (95% CI 14.9; 28.0), which might be due to the diagnostic difficulties in critically ill patients, or due to COVID-19-specific vasculopathy in the subacute stage of disease, or both. The high proportion of patients receiving ECMO further illustrates the severity of disease in this cohort. Yet, with a recent analysis reporting similar rates of IPH in COVID-19 and propensity score matched controls without COVID-19 [21], it appears unlikely that the viral infection is an independent risk factor further aggravating the already existing substantial risk of ICH during ECMO therapy. [22]

Conclusion

ICH in COVID-19 patients is rare, but it has a very poor prognosis. Different subtypes of ICH seen in COVID-19, support the assumption of heterogeneous and multifaceted pathomechanisms contributing to ICH in COVID-19. Further clinical and pathophysiological investigations are warranted to resolve the conflict between thromboembolic and hemorrhagic complications in the future.

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