GAS Journal of Clinical Medicine and Medical Research (GASJCMMR)

OPEN ACCESS

Volume 2, Issue 1, 2025 Journal Homepage: https://gaspublishers.com/gasjcmmr/ ISSN: 3049-1568
Email: gaspublishers@gmail.com

Observation on Efficacy and Safety of Intraveinous Bolus Artesunate Therapy among Clinically Proven Acute Covid-19 Induced Encepthalopathy

Pradhan B[1], Barik H.[2]

[1,2,] GAS Journal of Clinical Medicine & Medical Research

Received: 01.01.2025 | **Accepted:** 05.01.2025 | **Published:** 06.01.2025

***Corresponding Author:** Pradhan B[1], Barik H.[2]

DOI: 10.5281/zenodo.14910317

Abstract **Original Research Article**

The spike glycoprotein of SARS-CoV-2 (COVID-19) helps the virus to bind the ACE2 receptor to enter the host cells. ACE2 receptors are present in lung, heart, kidney, liver and brain. COVID-19 is now recognized as a multi-organ disease with a broad spectrum of manifestations. COVID-19-induced encephalopathy was defined as a rapidly developing (less than 4 weeks) pathophysiological process in the brain leading to decreased level of consciousness ranging from altered consciousness, mild confusion, delirium to deep coma are hallmark clinical features. Clinical diagnosis of covid-19 induced encephalopathy was made among hospitalized patients with negative oropharyngeal swab RT-PCR tests presented with clinical features of encephalitis by adopting a diagnostic criteria, if they met ≥ one of the following diagnostic criteria, such as elevated inflammatory markers i.e. serum LDH, CRP, Ferritin, D-dimer level and decreased lymphocyte, eosinophils and platelet counts, with associated X-ray chest, HRCT and MRI of brain findings suggestive of encephalitis, after exclusion of classical medical etiologies such as electrolyte disturbances, other infections, drug or alcohol toxicity or withdrawal, metabolic disorders, low perfusion state or acute central nervous system conditions, such as stroke or meningitis. Furthermore, confirmation of recent exposure to COVID-19 was made by testing of COVID-19 specific antibodies in selected cases. They were empirically treated with off label high dose Artesunate IV bolus Artesunate and it was observed that, Artesunate therapy appears to be very effective and safe decreases the morbidity and mortality among the clinically diagnosed COVID-19- induced encephalopathy.

Keywords: Central nervous system, SARS-CoV-2, COVID-19-induced Encephalopathy, Bolus Intravenous Artesunate

INTRODUCTION:

COVID-19 can present with central nervous system manifestations, such as headache, encephalitis and encephalopathy. COVID-19 encephalopathy has been defined as a rapidly developing (less than 4 weeks) pathophysiological process in the brain leading to delirium, decreased level of consciousness or coma after exclusion of classical medical etiologies, such as electrolyte disturbances, infection, drug or alcohol toxicity and/or withdrawal, metabolic disorders, low perfusion state or acute central nervous system conditions, such as stroke or meningitis.[1] The spike glycoprotein of SARS-CoV-2(COVID-19) helps the viruses to bind the ACE2 receptor to enter the host cells.ACE2 receptors are present in lung, heart, kidney and brain. COVID-19 is now recognized as a multi-organ disease with a broad spectrum of manifestations. ACE2 receptor presence has been demonstrated on neurons and endothelial cells that facilitate SARS-CoV-2 virus entry to the brain. Another speculated route of entry to the brain is via the olfactory system as olfactory mucosa has a relatively high expression of the ACE2 receptor and SARS-CoV-2 may spread to the brain across the

cribriform plate. In the brain, the virus can affect the brainstem and lead to dysregulation of vital respiratory and cardiac functions. The virus can travel retrogradely via axonal transport to the brain from the gut or lungs. Virus can circumvent the blood-brain barrier and enter the brain through vascular endothelium via transcytosis or the infection of endothelial cells. Alternatively, the virus can reach the brain by Trojan horse mechanism via infected leukocytes migration across the blood- brain barrier or paracellularly via disrupted tight junctions in the endothelial cells due to inflammation caused by the viremia. Encephalitis is an acute, diffuse, inflammatory condition of the brain, clinically characterized by fever, headache, seizure, focal neurological deficits, extrapyramidal signs and altered consciousness. Delirium is usually a common manifestation of mild to moderate encephalopathy in patients with COVID-19. The etiology of encephalopathy can be multiple: toxic, metabolic, anoxic-ischemic, sepsis, and inflammatory. Cortical and subcortical T2/FLAIR signal changes are common MRI neuroimaging abnormalities. The patients having encephalopathy/encephalitis are either severely or critically ill in published COVID-19 associated encephalopathy, mainly in older (>50 years) patients.[2] The predominant pathophysiological mechanisms of acute COVID- 19 include the following : direct viral toxicity, endothelial damage and microvascular injury; immune system dysregulation and stimulation of a hyperinflammatory state; hypercoagulability with resultant in situ thrombosis and microthrombosis and maladaptation of the ACE2 pathways. The mechanisms contributing to neuropathology in COVID-19 can be grouped into overlapping categories of direct viral infection, severe systemic inflammation and neuron inflammation, microvascular thrombosis.[3]

Another route not dependent on viremia includes the coordination of dynein and kinesins proteins in the transport of the virus into the CNS using infected motor or sensory nerves. Primarily SARS-CoV-2 infection of host target cells occurs to unciliated bronchial epithelial cells and type II pneumocytes in the lung through the ACE2, Basigin (BSG; CD147), and Neuropilin-1 (NRP-1). Higher expression of BSG and NRP-1 was reported in many brain cell types, where as ACE2 are highly expressed in the brain microvasculature and it is more likely that SARS-CoV-2 would utilize these receptors to enter the CNS. COVID-19 patients could present with confusion and delirium as early signs of COVID-19 without any of the respiratory symptoms. It has been estimated that 9% of COVID-19 patients have altered mental status could be the result of direct invasion of the brain or damage resulting from high levels of inflammatory mediators due to immune response to SARS-CoV-2 infection. Several studies reported increase in neutrophil-lymphocyte ratio (NLR), C-reactive protein (CRP) and serum ferritin in COVID-19 patients with ischemic stroke. Following the occurrence of ischemic stroke, the production of proinflammatory mediators from activated immune cells and ischemic brain tissue could further promote brain injury. Lung infection by SARS-CoV-2 results in severe inflammation, acute respiratory distress syndrome (ARDS). ARDS leads to hypoxia and inflammation-induced encephalopathy and seizures. Some COVID-19 patients develop seizures as a consequence of hypoxia, metabolic derangements, severe inflammation, organ failure, and cerebral affection. Seizures in some COVID-19 patients have been reported due to SARS-CoV-2-induced brain damage, high levels of inflammatory mediators, and viral-induced encephalitis or meningitis. Infection with SARS-CoV-2 reduces the seizures threshold which can worsen the case in epileptic patients or it can lead to seizures in patients without any history of seizures. Seizures could be one of the initial symptoms in COVID-19 patients.[4]

STRATEGIES OF DIAGNOSIS AND TREATMENT OF CLINICAL COVID-19-INDUCED ENCEPHALOPATHY:

During the second wave(β variant) of COVID-19 pandemic , patients with negative oropharyngeal swab RAT and RT-PCR test report at point of care, admitted in the department of general medical wards (in the western part of Odisha state of India,VIMSAR, Burla,Sambalpur, during September-Novembr,2021); clinically presented with altered sensorium with signs and symptoms of central nervous system manifestations were clinically diagnosed/suspected as cases of COVID-19-induced encephalopathy, if they met ≥ one of the following criteria, such as elevated inflammatory markers i.e. serum LDH, CRP, Ferritin and elevated

D-dimer levels and decreased lymphocyte, eosinophils and platelet counts,[5] and/or associated with X-ray chest, HRCT suggestive of COVID-19 infection and MRI of brain findings of encephalopathy. Furthermore, COVID-19 specific serologic antibodies tests for TAb/IgM, and IgG were done at appropriate time to confirm the recent COVID-19 exposure in selected cases. After obtaining inform consent from patient's relatives, empirical Artesunate 4mg/kg/bw IV bolus (in 2-10 minute) twice daily administered at the time of diagnosis for five days. Morbidity, mortality outcome and any adverse reactions to IV Artesunate therapy were noted up to the point of discharge of patients.

SCIENTIFIC RATIONALE OF IV BOLUS ARTESUNATE THERAPY FOR COVID-19 INFECTION:

There was no approved safe and effective therapeutics were available at that time of COVID-19 pandemic. Artesunate exhibit in-vitro antiviral activity against a number of pathogenic human viruses. Artesunate recently been repurposed as a potential COVID-19 drug, attributed to its ability to inhibit spike-protein mediated and TGF-β-dependent early steps in the infection process as well as its ability to disrupt the post-entry intracellular events of the SARS-CoV-2 infection required for replication. Artesunate have anti-inflammatory activity and could reduce the systemic levels of inflammatory cytokines that contribute to cytokine storm and inflammatory organ injury in COVID-19 patients. Artesunate could bind the SARS-CoV-2 spike protein in a way that would interfere with its docking onto the human ACE2 receptor protein, which is the first step in the host infection process of the COVID-19 virus. Artesunate may prevent the worsening of the health condition of patients with mild-moderate COVID-19 when administered early in the course of their disease.[6] Ruiyuan Cao, et al in their study found that EC_{50} (50% effective concentration) of Artesunate was 12.8±5.30μM and Dihydroartemisinin (DHA) had 13.31±1.24μM against SARS-CoV-2 in-vitro could inhibit SARS-CoV-2 replication in a dose-dependent manner, might function at the post-entry stage of SARS-CoV-2, indicating Artesunate could be a potential antiviral agent against COVID-19 infection.[7] Bae JY et al, in their study in Vero cells Artesunate inhibited SARS-CoV-2 replication with IC_{50} of 53.06 μM and CC_{50} of > 100 μM. Interestingly, Artesunate in Calu-3 cells**,** (which are derived from human airway epithelial cells was more representative of susceptible cells in actual human airway infection) inhibitory effect had IC_{50} of 1.76 μM and CC_{50} > 100 μM, which was better than in Vero cells and reduced viral replication in a dose-dependent manner.[8] Zhou Y et al proved that Artesunate was most potent among artemisinin derivatives in different cells line i.e. Vero E6 cells, human hepatoma Huh7.5 and human lung carcinoma A549-hACE2 cells line with EC_{50} of 7-12 μg/ml and Artemether EC_{50} of 53-98μg/ml.[9] Gilmore K et al in their Vero E6 cells study found that , Artesunate EC_{50} had 7-12 μg/ml or (0.7-1.2 μM) was more potent than other Artemisinin derivatives and Cmax of Artesunate exceeding EC_{50} can be achievable clinically in plasma and tissue concentrations of 15μg/ml. The typical doses of 2 - 2.4 mg/kg IV bolus Artesunate produce Cmax of between 19.4 and 29.7μg/ml. In studies of animal tissue Artesunate concentration were several fold higher than plasma concentrations in lung, kidney, intestine, and spleen.[10]

Artesunate 120mg IV bolus administration produced a Cmax of 11,343ng/ml (42μM) with t½ of 0.05 hrs and Cmax of DHA was 2646ng/ml with t½ of 0.67 hrs (total 13,987ng/ml), which were greater than EC_{50} of Artesunate and DHA against SARS-CoV-2.[11] In another study 120mg IV bolus Artesunate produced a Cmax of 29.5 μM with elimination $t^1/_2$ of 2.7 min and Cmax for DHA was 9.3 μM with $t\ ^1/_2$ of 40 min versus 100mg oral AS produce Cmax of DHA of 2.6 μM, $t\ ^1/_2$ of 39 min.[12] Artemisinins administration leads to autoinduction of hepatic drug metabolism and reduces its own bioavailability. The plasma concentrations of same daily dose of AS were ⅓rd less on day 3 onwards than of day 1.[13] The PK variability following 120mg IV bolus AS with high Cmax occurs with first exposure time and the Cmax variability ranges from 735-1890ng/ml(AS+DHA) and this variability was 25 fold among different clinical trials. There is large inter-individual PK/PD variability and such low drug concentrations in some patients may explain treatment failure in malaria treatment. Thus, low dose regimen of AS to be avoided.[14] High dose IV bolus Artesunate preferred to achieve higher free

peak plasma levels (Cmax) of DHA and have higher bioavailability to enter the human cells in comparison to Artemether and Arteether which are mostly bound to plasma proteins.[15] Patients with severe COVID-19 may have many critical and variable conditions and with different co-morbidities with variable severity scores that may determine the drug's PK/PD characteristics and prognosis. Thus, current dose of 120mg IV AS produce variable Cmax ranging from 735-1890ng/ml with greater inter individual variability have lower Cmax. The 4-8mg/kg loading dose is safe and in phase I-II study of IV AS 4-8mg/kg loading doses were extremely well tolerated in humane volunteers and malaria patients.[16] Artesunate Cmax is more important than AUC in producing improved efficacy and IV bolus Artesunate provide sufficient high Cmax in patients and avoid inter-individual variability in PK/PD. Artesunate IV bolus injection following 4mg/kg produce Cmax of 36,100ng/ml and following 8mg/kg Cmax of 89,340ng/ml.[17] The optimal doses and dose intervals for Artesunate and DHA have not been determined. Therefore, in the absence of well controlled dose-ranging studies and valid pharmacodynamic relationships widely used empirical regimens remain unchallenged.[18] Coronavirus replication cycle is around 8-10 hrs.[19, 20] Artesunate has Cmax dependent effects and IV bolus infusion (in 2-10 minutes) initiated with 4-8mg/kg at interval of 8-10 hr or 12hly can achieve higher plasma Cmax for the first exposure given for a short course of ≥ 3 to 5 days to cover 9 to 15 replication cycles in early stage (<7 days) of robust viral replication can prevent disease progression as well as avoided auto-induction of its own metabolism leading to low Cmax. Artemisinin and its derivatives i.e. Artesunate have anti-inflammatory and immunomodulatory functions through inhibiting pathogenic T cell activation and suppressing B cell activation and expanding regulatory T cells.[21] Artemisinin possess anti-inflammatory and anti-oxidant properties against lipopolysaccharide (LPS)-induced acute lung injury in mice.[22] Artesunate have in-vitro antiviral properties against wide varieties of viruses including SARS-CoV-2 and also have anti-inflammatory, immunomodulatory, antioxidant, anticytokine, multiorgan protective effects may be useful even in the later stages of hyperinflammation to reduce morbidity and mortality in COVID-19 induced cytokine storm/ARDS.[23]

Artesunate effectiveness in clinical trial of COVID-19 patients: In a prospective study of 43 cases of COVID-19 patients divided into routine treatment group (n=25) and Artesunate group (n=18) 60 mg IV twice daily along with routine treatment for 10 days. Among Artesunate group, time for significant improvement of symptoms was (days: 3.33±1.91 vs. 4.84±2.19), RT-PCR negative conversion time was (days: 4.72±2.16 vs. 6.68±3.76), lung lesion absorption starting time (days: 5.39±2.36 vs. 7.48±3.78), lung lesion absorption >70% time (days:14.11±4.16 vs. 17.04±4.42) and length of hospital stay (days: 16.56±3.71 vs. 18.04±3.97) were significantly shorter, than those in routine treatment group with fewer adverse reactions.[24] Pradhan B et al reported IV bolus Artesunate(4mg/kg/bw) twice daily for 5 days appears to be very effective with excellent safety profile with faster resolution of symptoms, improves oxygen saturation rapidly in hypoxic patients and decreased morbidity and mortality among clinically diagnosed moderate to severe clinically diagnosed COVID-19 infected patients.[25]

Cases presentations:

Case. 1. A 48 years old female presented to ED with history of fever for 8 days, GTCS 3-4 episodes with altered sensorium for 1 day. On examination (O/E) her BP was 90/60mmHg, PR 90/min, SpO2 -96 %(RA). She was stupor with neck stiffness and plantar response was extensor. Screening of RT-PCR oropharyngeal swab test for COVID-19 was negative. On investigation serum ferritin was 544ng/ml,CRP-36mg/L,LDH-349IU/L,D-dimer-0.1mg/L,ESR-107mm1sthr,TLC-0.4X10^3/µL,L-1.7X10^3/µL,N-4.35X10^3/µL,TPC 0.42X10^3/µL and Neutrophil-67.7%, Lymphocyte-27.1%, Monocyte-4.4%, Eosinophil-0.3%, Basophils-0.3%. Chest x-ray showed bilateral(B/L) basal GGO opacities. For GTCS she was treated initially with IV Lorazepam followed by IV phosphenytoin, but as convulsion was continuing and IV Valproic acid was added and convulsion was controlled. She was empirically treated with Artesunate IV bolus 240mg twice daily and broad spectrum IV antibiotics. On 4th day of treatment she regained her consciousness and able to

take orally. On 8th day her serum ferritin was 38ng/ml, CRP-5mg/L and MRI of brain showed features of meningoencephalitis. Serologic test for COVID-19 specific antibody on 20th days from symptom onset was positive for Total Antibody (TAb) 5.6 (CLIA) suggesting recent COVID-19 exposure.

Case. 2. A 20 years old female presented to ED with history of fever since 10 days, headache and vomiting since 6 days and altered sensorium for 2 days. O/E she was stupor with BP 100/70mmHg, PR -108/min, Spo2-97% (RA), with neck stiffness and bilateral lateral rectus palsy and plantar extension. Screening of oropharyngeal swab RT-PCR test for COVID-19 was negative. On investigations of routine blood tests,TLC-12.43x10^3/µL,and Neutrophil- 51.1%,Lymphocyte-47.4%,Monocyte-1.35%,Eosinophils-0.1%,Basophils-0.01%,Hb-9.9gm%, TPC-203X10^3/µL, CRP was 31.5mg/L, serum Ferritin was 721ng/ml. Chest x-ray showed bilateral ground glass opacities (GGO) in peripheral lung fields characteristic of COVID-19. She was empirically treated with IV bolus Artesunate 240mg twice daily and IV antibiotics. She regained her consciousness on 3rd day. On 5th day serum CRP was 5mg/l, Ferritin was 493ng/ml and on 7th day CRP was 0.5mg/L, serum Ferritin was 399ng/ml and D-dimer 0.7mg/L. CT scan of brain was normal. Serologic test for COVID-19 specific antibodies on 14th day from onset of symptoms was negative (IgG of 0.09, IgM was 0.14), probably due to shorter duration of illness not yet developed antibodies.

Case. 3. A 23 years old female presented with fever since 4 days and altered sensorium with delirium and irritability since 1 day. O/E her BP was 90/50mmHg, PR-92/min, RR-30/min, SpO2-97 %(RA), with features of encephalopathy. On investigations Hb-8gm%,TLC-9.3x10^3/µL,PLT-98X10^3/µL,Urea-22mg%,Creatinine-0.9mg%,Na^+-140mEq/L,K^+-3.3mEq/L.Total bilirubin-0.2mg%, direct-0.1mg%,AST-32U/L,ALT-39U/L,HIV, HCV, HbsAg, QBC & ICT for malaria , Dengue and Scrub typhus tests were negative. Serum CRP level was 20mg/L, serum Ferritin - 529ng/ml. She was treated with IV Artesunate 240mg IV bolus twice daily for 5 days and broad spectrum IV antibiotics. She markedly improved on 3rd day of treatment and fully consciousness. On investigations her Hemoglobin level was 8.1gm%,WBC-6.89X10^3/µL, PLT-197X10^3/µL, Na^+ -14mEq/L, K^+ -3.0mEq/L, CRP-0.5mg/L, serum Ferritin was 116ng/ml. CECT of brain showed features of encephalitis. Blood sample for serologic test for COVID-19 specific TAb antibody positive- 1.7 and IgG 3.49 OD ratio positive (>1) on 20th day from symptom onset suggestive of recent COVID-19 exposure.

Case. 4. A 45 years old female presented to ED with chief complains of dry cough since 10 days, Headache for 2 days and abnormal body movement for 1 day and 3 episodes of GTCS, followed by altered sensorium. O/E, her BP was 100/80mmHg, PR-80/min, PaO2-98 %(RA), and plantar response were extensor. On investigation TLC-11.4 X10^3/µL, Neutrophils- 95%,Lymphocytes- 2.6%,Monocyte-1.8%,Eosinophils -0%,Basophils -9% and TPC-94X10^3/µL. Serum Na^+-105mEq/L, K^+-2.6mEq/L, HIV, HCV, HbsAg, QBC and ICT for malaria, Dengue , Scrub typhus were negative. On biochemical test serum ferritin was 906ng/ml, LDH-719IU/L,CRP-16.3mg/L,Urea-35mg/dl,Creatinine-1.6mg/dl. Chest x-ray showed bilateral patchy GGO right side more than left side. She was treated with IV anticonvulsant and potassium for correction of hypokalemia. She was treated with IV bolus Artesunate 240mg twice daily for 5 days, IV Ceftriaxone and Vancomycine. On 5th day her serum K^+ was 3.7mEq/L, Serum Na^+-132mEq/L. CSF analysis on 3rd day showed leukocyte 3 cells/mm^3, glucose 77mg%, total protein 10mg%,chloride 118mmol/L,ADA 2IU/L. On 15th day from symptoms onset COVID-19 specific antibody, IgG was positive (>1) with index value of 1.7 and 21.75 BAU/ml (ELFA Method) against S1 spike protein. MRI of brain showed features of encephalitis. She was improved and became conscious and left against medical advice on 7th day of treatment.

Case 5. A 44 years old female referred from a secondary care hospital with history of fever since 5 days, vomiting 3 days and 4 episodes of GTCS with alerted sensorium and bleeding from mouth due to tongue bite admitted to ICU, her BP was 90/60mmHg, PR-88/min, SpO2-98%(RA), she was treated with IV bolus Artesunate 240mg BD, IV antibiotics and anticonvulsants to control convulsions, and prophylaxis Enoxaparine 40 IU SC OD . Her chest x-ray showed patchy opacities in

bilateral lung fields. Routine blood investigations:-TLC-11820/µL, N-7570/µL, L-4030/µL, M-220/µL, E-0.5/µL, TPC-1.48lahk/µL, Hb-4.5gm/dl. QBC, ICT for malaria, HIV, HbsAg, HVC, Dengue, Scrub typhus tests were negative. Serum Ca^{++}-1.0mg/dl,Na^{+}-141mEq/L,K^{+}-3.9mEq/L,Urea-23mg/dl,Creatinine-1.0mg/dl,serum total protein-6.9mg/dl, Albumin-4.2mg/dl,RBS-179mg/dl, Serum total Cholesterol was 165mg/dl,HDL-25mg/dl,LDL-39mg/dl,TG-161mg/dl. Total bilirubin-0.8,direct-0.5,AST-444U/L, ALP-272U/L, ESR-20mm, CRP-25.7mg/L, Ferritin-615ng/ml, D-dimer-4.4mg/L. CT scan of brain was normal. On 3rd day she was still stupor with PR-108/min, RR-38/min, SpO2-96% (RA), BP-80/60mmHg with vasopressor isoprenaline IV infusion. Serum Na^{+} was 139mmol/L, K^{+} 3.0mmol/L, Ca^{++}0.8mg/dl, Urine microscopy showed pus cells-10/hpf and blood and urine culture had no growth. On 5th day she had again bout of convulsions with bradycardia (PR-50/min), with her serum calcium was 0.8mg/dl and serum k^{+} was 6.3mmol/L, treated with IV calcium gluconate (10%, 50ml) infusion and k-binding through nasogastric tube. Free radical scavenger Edaravone 60mg in 100 ml NS IV infusion in 30 minute twice daily added. On 7th day her serum K^{+} was 6.6mEq/L, serum Ca^{++} was 0.9mg/dl,LDH-746IU/L, Ferritin-348ng/ml, D-dimer-2.2. On 8th day Na^{+}-133mEq/L,K^{+}-4.54mEq/L, and on 9th day serum K^{+}-3.9mEq/L,Ca^{++}0.8mg/dl. On 10th day her serum Na^{+} was 130mEq/L, K^{+}3.7mEq/L, Ca^{++}-0.9mg/dl,D-dimer-2.3mg/L. Her conditions improved and regained her consciousness and pulse rate was 80/min and she was extubated with O_2 4L/min and SpO2 was 100%. On 11th day she was on NIV with CPAP mode and on 12th day her serum Na^{+} was 133mEq/L,K^{+}-3.3mEq/L, Ca^{++}1.1mg/dl and was on T-Pipe with NIV pressure support. Injection vitamin D_3 60K IM given for low serum D_3 level. On 13th day patient's blood sample sent for COVID-19 specific antibody against RBD S1 spike protein was come to positive (>1) for IgG 3.4 index value and 69.73 BAU/ml indicating recent exposure to COVID-19. On 14th day patient was again stupor with decreased oxygen saturation for which again intubated for mechanical ventilation and at that day her serum K^{+} was 5.7mEq/L,CRP-200mg/L,D-dimer-8.8mg/L, Na^{+}-136mEq/L,K^{+} 5.7mEq/L, Ca^{++} -0.9mg/dl and on 15th day, serum Na^{+} was 136mEq/L,K^{+}-4.4mEq/L, Ca^{++}-0.9mg/dl. IV Methylprednisolone 40mg IV tid started for 7 days. On 16th day serum Na^{+} was 134mEq/L,K^{+}-3.1mEq/L and Ca^{++}-0.8mg/dl. On 17th day her serum K^{+} was 2.9mmol/L and again treated with IV infusion of KCL and magnesium sulfate twice and on 18th day her serum K^{+} was 5.7mEq/L,Na^{+}-135mEq/L,Ca^{++}-1.0mg/dl,D-dimer-4.1mg/L,Ferritin-667ng/ml and her Hb was 7.7gm/dl and received one blood transfusion .On 19th day serum Na^{+} was 136mEq/L,K^{+}-3.9mEq/L, Ca^{++}-0.8mg/dl, Mg^{++}-1.3mg/dl,Hb-8.1gm/dl and patient regained her consciousness and self extubated with nasal O2 therapy. On 21th day her serum Na^{+} was 138mEq/L, K^{+}-3.7mEq/L, Ca^{++}-0.9mg/dl,Hb-7.1gm/dl and patient able to take orally and all anticonvulsants and antibiotics were given orally and discharged on 22th day. This was a case of clinical COVID-19-induced encephalopathy presented with GTCS and recurrent dys-electrolytemia.

Case 6. A 16 years old female presented with history of intermittent fever since 15 days and loose motion for 4 days with altered sensorium for one day. O/E she was stupor, BP-94/48 mmHg, PR-84/min, PaO2-89 %(RA), RR-30/min.On routine blood tests TLC 9650/µL, N-46%, L-53.4%, M-0.4%, E-0.1%, B-0%. Hb-7.2gm%,TPC-75000/µL.RBS-143mg%,Urea-41mg/dl,Creatinine-0.7mg/dl,Na^{+}-137meq/L,K^{+}-4.4meq/L, serum calcium 0.8mg/dl. Serum total bilirubin-1.2mg/dl, Direct-0.8mg/dl, AST-236IU/L, ALT- 122IU/L,ALP-171IU/L. Serum Ferritin was 1000ng/ml,CRP-21.8mg/L,ESR-20mm 1st hr. QBC, ICT for malaria , Dengue, Scrub typhus, Leptospira , HIV, HVB, HVC tests were negative. Chest X-ray showed bilateral GGO typical of COVID-19 and treated with IV bolus Artesunate 240mg twice daily along with IV antibiotic. On 4th days her chest x-ray showed some resolution of opacities. She regained her consciousness on 3rd day and fully conscious on 5th day. Her serum sample was positive for COVID-19 spike S1 domain specific antibody with 5.77 Index value (>1 index value positive) and 117.30 BAU/ml (>1 BAU/ml) suggestive of recent exposure.

Case 7. A 17 years old male presented with history of fever since 8 days and altered sensorium since 4 days. His BP was 100/60mmHg, PR-84/min, Spo2-94 % (RA). Chest X-ray showed bilateral patchy opacities in both lower zones, right side > left side.

On investigations TLC- 10,810/mm^3, Hb- 12.8gm%, TPC -1.7 lakh/µL,CRP-70mg/L, Ferritin-800ng/ml,LDH-750U/L,RBS-153mg/dl, serum urea 71mg/dl, Creatinine- 1.2mg/dl, Na^+ -138mEq/L,K^{+-} 4.7mEq/L, Serum bilirubin total-1.8mg%,direct-0.9mg%,AST -386U/L,ALP-130U/L,ALP-218U/L, Serum amylase-120. MP-QBC and ICT for malaria negative, Dengue, Scrub typhus negative, Leptospira negative. He was treated with IV bolus Artesunate 240mg twice daily. On second day he regained his consciousness and discharged on 3rd day.

Case 8. A 25 years old female presented with history of high grade fever and general weakness for seven days and dry cough, one episode of hemoptysis and bleeding gum while brushing her teeth for 2 days. Her TPC count was 20 $x10^9$ /L, admitted to a secondary care hospital and received 4 units of platelet transfusion at secondary care hospital before admitted to our tertiary care hospital. On investigations on 12th day of symptoms, TLC count was 7.06$X10^3$/L,N-74%,L-19.8%,E-0.9%,M-5.0%,TPC-95$X10^9$/L.Hb-11.2gm%, Dengue, Scrub typhus, QBC, ICT for malaria was negative. ESR-48mm ,CRP-100mg/L, serum ferritin-400ng/ml,D-dimer-0.3mg/ml, blood Urea-13mg%, Creatinine-0.8mg%, Na^+-138mEq/L, K^+-3.6mEq/L, Ca^{++}-0.mg/dl, total bilirubin-04.mg/dl and direct-02.mg/dl, AST-14U/L,ALT-15,ASP-7U/L. Chest x-ray showed bilateral lower lobe GGO. She received 4 units of platelet transfusion. She was afebrile on 8th day of admission, but developed altered sensorium with irritability and then become stupor, with plantar extensor response. Her BP was 70/50mmHg. MRI of brain report was unremarkable. She was treated with IV bolus Artesunate 240mg twice daily. On 10th day of hospitalization she regained her consciousness. COVID-19 spike specific antibody was positive for IgG 42.04 index value and 854.6 BAU/ml on 15th day.

Case 9. A 25 years old female presented with history of high grade fever for 15 days with intermittent dry cough and breathlessness for 10 days and altered sensorium for 5 days. On examination she was stupor and her BP-80/60mmHg, SpO2-85 % (RA). On routine blood investigations TLC-3020/µL, L-34%, E-0.2%, N-63%, TPC-2.09lakh/µL, Hb-9.4gm%, CRP-63.3mg/L, LDH-929U/L, Serum ferritin-480ng/ml, D-dimer-1.2mg/L,Urea-92mg%,Creatinine-2.4mg%,Na^+-146mEq/L,K^+-4.4mEq/L,RBS-70mg%,HIV,HCV,HBV, Dengue, Scrub typhus, MP-QBC,ICT Malaria were negative. Total Cholesterol-163mg%,HDL-26mg%,LDL-48mg%,VLDL-82mg%,TG-409mg%. She was treated with IV bolus Artesunate 240mg BD, IV antibiotic and vasopressor with nasal O_2 support. On 3rd day she became afebrile and fully conscious on 4th day with SpO2-97 % Room Air. On fifth day of admission her chest x-ray showed Right lower lobe GGO.TLC-4160/µL, N-68% L-32%,E-0.3%, Hb-8.7gm%, TPC-3.8Lakh/µL, CRP-32mg/L, serum Ferritin-655ng/ml, D-dimer-1.2mg/L,Urea-64mg%,Creatinine-1.2mg%, Na^+-143mEq/L, K^+-4.4mEq/L, RBS-110mg/dl. On 6th day SpO2-98 %(RA) and her BP was 120/80mmHg without use of vasopressor.

Case 10. A 61 years old male presented with history of headache, blurring of vision 20 days and altered sensorium 1 day. On examination his BP was 70/40mmHg, PR-110/min, Spo2 98% (RA), stupor and plantar responses were extensor. On investigations, TLC-13000/µL,N-93%,L-3.3%,M-3.1%,E-0.1%,TPC-2.1Lakh/µl,Hb-12gm%,CRP-54.6mg/L,ferritin-595ng/ml,D-dimer-0.1mg/L, RBS-148MG%, Urea-38mg%, Creatinine-1/3mg%,Na^+-127mEq/L,K^+-3.3mEq/L, serum total protein-8gm%, albumin-5.1mg%, total bilirubin-1mg%,direct-0.4mg%,AST-48U/L,ALT-53U/L,ALP-108U/L. HIV, HCV, HBV, MP-QBC, ICT Malaria, Dengue, Scrub typhus negative. MRI of brain showed acute infraction of left medial temporal lobe and posterior thalamus and left lateral midbrain. Chest x-ray showed bilateral upper lobe opacities with peripheral GGO in right upper zone. He was treated with IV bolus Artesunate 240mg BD. On 3rd day patient conscious, afebrile, oriented with stable vital status and BP was 110/70mmHg without vasopressor , PR-92/min,Spo2-96%(RA) and able to take orally.

Case 11. A 42 years old male known type 2 DM on OADs presented with history of fever since 8 days, decreased urination, dry cough and altered sensorium for 2 days. On examination he was on shock with

systolic BP-60mmHg, PR-56/min, and Spo2-98 %(RA). On investigations TLC-14200/µL,N-88%,L-7.2%,M-4%,E-0.3%,TPC-21000/µL,Hb-15.4gm%,Urea-222mg%,Creatinine-5.2mg%, Na^+-131mEq/L, K^+- 3.6mEq/L, C^{++}-0.8mg/dl, serum Uric acid- 13.2mg%, HbA1c 7.2%, CRP- 89mg/L, Ferritin 761ng/ml, D-dimer 4.6mg/L. Serum total bilirubin 4.2mg%, direct-3.4mg%, AST-191 U/L,ALT-92U/L,ALP-181U/L and Trop-I negative. QBC, ICT for Malaria, Dengue, and Scrub typhus were negative, urine microscopy showed 18-20 pus cells/hpf. X-ray chest showed bilateral opacities, right side lung > left. Bolus IV Artesunate started from 2nd day of admission. On 3nd day,TLC-1498/µL, N-88%,L-7%,M-4.5%,E-0.1%,TPC was 64000/µL after 3 units of RDP infusion. Urea-233mg%, Creatinine- 3.5mg%,Na^+-136mEq/L, K^+-3.2mEq/L, Ca^{++}-0.9mg/dl. MRI of brain on 4th day showed small acute infarction in left frontal white matter in DW1. Patient fully conscious on 5th day and urine output was 1.5 liter/day.

Case 12. A 28 years old female presented with history of child birth by LSCS one month back and developed fever for 2 days and loss of consciousness for 1 day. On examination her BP was 150/90mmHg, PR-84/min, she was stupor. On 2nd day investigations showed TLC-35000/µL, N-69%,L-21%, E-0.6%,M-8.4%,TPC-45000/µL,Hb-6.1gm%,CRP-38mg/L,LDH-750U/L,Ferritin-390ng/ml, ESR-52mm,Urea-32mg%, Creatinine-0.7mg%, Na^+-145mEq/L,K^+3.4mEq/L, Ca^{++} 1.0mg/dl. Total bilirubin-0.3mg%, direct- 0.08mg%, total protein 7.5gm%, Albumin-4gm%,Uric acid -6.1mg%. Chest x-ray showed bilateral patchy opacities right side > left side. She was treated with IV bolus Artesunate 240mg twice daily. On 3rd day MRI study of brain showed left ganglio-capsular hemorrhage with midline shift. On 4th day blood investigations showed TLC-8000/µL,N-74%,L-16%,M-6%,E-2.3%,Hb-11.7gm%,TPC-1.3 Lakh/µl, Scrub typhus, Dengue and MP-QBC, ICT malaria was negative. On 5th day patient regained her consciousness, oriented and able to take orally. On 9th day repeat MRI of brain showed large sub-acute intracerebral hemorrhage in the left ganglio-capsular area and left coronaradiata with mass effect and midline shift. She was discharged with residual Rt. side Hemiparesis.

Case 13. A 60 years old male presented with high grade continuous fever for 2 days with vomiting and altered sensorium. O/E he was in delirious and disoriented. His BP was 110/70mmHg, PR-90/min, RR-22/min, Spo2-89% (RA), febrile with neck rigidity. On investigations TLC-13270/µL, N-76.8%,L-18.0%, M-5.0%,TPC-1,14000/µL,TRBC-4.3million/µL,Hb-13.2gm%,ESR-53mm, serum ferritin-1000ng/ml, CRP-200mg/L, D-dimer-1.9mg/L. MP-QBC and ICT , Scrub typhus, Dengue tests were negative. HIV, HBV, HBC were non-reactive. Serum urea was 53mg/dl, Creatinine-1.2mg/dl, Na^+-140mEq/L, K^+-0.9mEq/L, Ca^{++}-3.4mg/dl, Serum total bilirubin 0.6mg/dl, direct-0.4mg/dl, AST-37IU/L, ALT-94IU/L, ALP-492IU/L, total serum protein-6.0gm/dl, Albumin-1.7gm/dl, total cholesterol-118mg/dl, HDL-20mg/dl, TG-190mg/dl, VLDL-38mg/dl, HDL-32mg/dl. CT scan of brain showed age related cortical atrophy. CSF study showed TLC-05/m^3, Polymorph-03, mononuclear cells-02, AFB not found, gram's stain negative, ADA test negative. X-ray chest showed bilateral lower lobe opacities with GGO pattern right side > left side. He was treated with IV bolus Artesunate 240mg BD and IV antibiotic. He recovered his consciousness after 42 hours of Artesunate therapy and became afebrile and able to take orally.

Case 14. A 15 years old male presented with high grade intermittent fever for 7 days three days back and had multiple episodes of seizure for 1 day. O/E he was drowsy and disoriented, PR-110/min, BP was 90/60mmHg, and plantar responses extensor, Spo2 was 65 %(RA) and 98% with O_2 therapy. On investigations on the 2nd day,TLC-11280/ µL,N-43.0%,L-53.3%,M-2.6%,E-0.2%,TPC-1.72000/µL,Hb-10.7gm/dl, Urea-19mg/dl,Creatinine-0.7mg/dl, Na^+-137mEq/L,K^+-4.4mEq/L, Ca^{++}-1.1mg/L, total bilirubin- 0.2mg/dl ,direct-0.1mg/dl,AST-123IU/L,ALT-158IU/L,ALP-138IU/L, serum ferritin was 776ng/ml,LDH-860U/L, D-dimer was 4.0mg/L,MP-QBC,ICT , Scrubtyphus , HBV,HBC HIV tests were negative , Dengue IgM was falsely positive (as on 4th day repeat tests for Dengue IgM and IgG were negative). He was treated with IV bolus Artesunate 240mg twice daily, IV anticonvulsants and antibiotic

and became conscious on 3rd day and Spo2 was 100% (RA). His chest x-ray showed bilateral peripheral inhomogeneous opacities and band of consolidation around the left heart border suggesting COVID-19 infection.

Case 15. A 17 years old female presented with chief complains of fever since 3 days and multiple episodes of convulsion followed by loss of consciousness for one day. O/E her BP was 110/60mmHg, PR-162/min, RR-24/min, Spo2-94 %(RA), comatose with extensor plantar responses. She was treated with IV bolus Artesunate (240mg) twice daily, IV antibiotics and anticonvulsants. There was no further convulsion. On 2nd day investigations showed TLC-5820/µL,N-51.3%,L-40.24%,M-8.0%,E-0.2%B-0.3%.TPC-1.21 lakh/µL,Hb-9.7gm/dl, CRP-100mg/L, serum Ferritin-214ng/ml, LDH-1200U/L, D-dimer-1.6mg/L. Serum total bilirubin-0.2mg/dl, direct-0.1mg/dl,AST-44U/L,ALT-32U/L,ALP-64U/L.Chest x-ray showed band of consolidation (GGO) over the left border of heart and patchy opacities in the right lower zone. She improved her consciousness and able to take orally on 3rd day. Repeat chest x-ray on 3rd day showed resolution of the consolidations. On 6th day blood investigations, CRP was 1.6mg/L, Ferritin-87ng/ml, D-dimer-0.5mg/L, serum Urea-12mg/dl, Creatinine-0.8mg/dl, serum Na^+-144mEq/L,K^+-4.1mEq/L, Ca^{++}-1.1mg/L. MRI of brain and contrast MRI study showed no obvious abnormality.

Case 16. A 45 years old female presented with chief complains of fever since 7 days, headache followed by altered sensorium for 3 days. On examination her BP was 90/60mmHg, PR-82/min, Spo2-95 %(RA). She was treated with IV bolus Artesunate, IV antibiotic. On 2nd day she had one episode of GTCS treated with IV anticonvulsants and there was no further convulsion. Routine blood test showed FBS-145mg/dl, serum Urea-43mg/dl,Creatinine-0.8mg/dl, serum Na^+-149mEq/L,K^+-3.8mEq/L, serum Ca^{++}-1.0mg/dl, serum total protein-6.2gm/dl,Albumin-2.4gm/dl, total serum cholesterol-106mg/dl,HDL-18mg/dl,LDL-48mg/dl,VLDL-32mg/dl,TG-160mg/dl. Serum bilirubin total 0.8mg/dl, direct-0.4mg/dl, AST-168U/L, ALP-150U/L, ALP-130U/L. ESR was 65mm , LDH-976U/L,CRP-93.03mg/L, Serum Ferritin->1000ng/ml. Dengue, Scrub typhus , HIV,HVB,HCV and MP-QBC,ICT tests were negative. Chest x-ray showed band of GGO around the left border of heart and right side of hilum suggesting COVID-19 infection and CT scan of brain had no abnormalities. On 3rd day her serum Na^+-151mEq/L,K^+-3.6mEq/L,Urea-55mg/dl, Creatinine-0.8mg/dl and ECG within normal limit. On 4th day she recovered her consciousness. On 8th day CRP level decreased to 32.1mg/L, Ferritin-292ng/ml and D-dimer was 5.1mg/L.

Case 17. A 33 years old male presented with fever since 8 days, altered sensorium 4 days. O/E BP-130/80mmHg,PR-89/min,Spo2-96%(RA),neck rigidity present, plantar extensor response. He was treated with bolus IV Artesunate 240mg twice daily and IV Antibiotic. On investigations TLC-4490/µL,N-91.1%,L-8.0%,E-0.1%,M-0.8%,B-0%.MP-QBC, ICT , HIV, HBV, HBC, Dengue, Scrub typhus tests were negative. Serum CRP-24.2mg/L, Ferritin-498ng/ml, LDH-317IU/L,D-dimer-0.5mg/L. Serum total bilrubin-0.73mg/dl, direct-0.13mg/dl, ALP-12,AST-30,ALP-109,serum total protein-7.5gm/dl, Albumin-4.2gm/dl, Chest x-ray showed right lower lobe GGO > than left side suggestive of COVID-19. On 2nd day he was conscious but irritable with normal vital status. On 4th day fully regain his consciousness and FBS-141mg/dl, RBS-234mg/dl, HbA1c-6.5%, blood Urea-26mg/dl, Creatinine-1.0mg/dl, serum Na^+-143mEq/L,K^+-3.7mEq/L, Ca^{++}-1.0mg/dl. On 5th day MRI study of brain showed multiple discreet FLAIR /T_2 hyerintense lesions with ill defined margin in bilateral supratentorial brain representing infective/ inflammatory white matter disease. On 6th day contrast MRI study of brain showed tiny enhancing lesion in bilateral Centrum semiovale, high frontopareital lobes and left insular cortex suggestive of infective etiology. On 9th day CSF study showed 57 cells/cmm, mostly lymphocytes, total protein-34.7mg/dl, glucose-62mg/dl, ADA-14IU/L (>40 positive) and discharged on 13th day.

Table 1. Clinical profiles of Rapid Antigen and RT-PCR negative hospitalized Clinically Proven Acute COVID-19 induced encephalopathy patients and their outcome with IV Bolus Artesunate Therapy:

Case No	Age & Sex-M/F	Symptoms	Co - morbidities	CRP mg/L (N-0 - 6)	Ferritin ng/ml (N-30-220- M,) (20-110 F)	LDH IU/L (N-240-480)	D-dimer mg/L (N-0.5-1)	X-ray chest, HRCT, MRI brain	COVID-19 Specific Antibodies	Outcome& duration of hospital stay.
1	48 F	Fever- 8 days, GTCS-4 –with altered sensorium-1 day	Nil	36	544	349	0.1	B/L basal patchy pneumonia	TAb-5.6+ve(>1) (CILIA)	Survived, 7 days
2	20 F	Fever-10 days, headache, vomiting, altered sensorium 2 days	Nil	31.5	721	Not done	Not done	Chest x-ray-B/L peripheral lung field GGO		Survived, 10 days
3	23 F	Fever-4 days, altered sensorium, delirium1 day.	Nil	20	529	Not done	Not done	CECT brain– Encephalitis.	TAb-1.7 & IgG-3.49 +VE	Survived,12 days
4	45 F	Cough-10 days, headache 2 days, abnormal body movements 1 day, GTCS 3 episodes, altered sensorium 1 day.	Nil	16.3	906	719	Not done	X-ray chest B/L patchy GGO rt.>left side.MRI brain Encephalitis.	IgG index value1.7 & BAU/ml 21.75 (ELFA)+ VE	Survived, 7 days
5	44 F	Fever with UTI -5 days, vomiting, GTCS with SE 1 day.	Nil	25.7 & 200	615		4.4 & 8.8	B/LL Opacities >in right side	IgG 3.7 index value & 69.73 BAU/ml +ve	Survived, 22 days
6	16 F	Fever 15 days, loose motion 4 days, altered sensorium 1 day	Nil	21.8	1000	Not done	Not done	Chest x-ray B/L infiltrate with GGO	IgG 5.77 index value & 117.3 BAU/ml +ve (>1).	Survived, 6 days

7	17 M	Fever 8 days, altered sensorium 4 days, confused disoriented.	Nil	70	800	750	Not done	Chest x-ray B/L patchy opacities right side >left side.		Survived, 3 days
8	25 F	Fever & weakness 7 day. Gum Bleeding 2 day	Nil	100	400	Not done	Not done	B/LL opacities right side > left side.	IgG 42.02 index value & 854.6 BAU/ml +ve.	Survived, 12 days
9	25 M	Fever 15 days, dry cough & SOB 10 days, and altered sensorium 5 days.	Nil	63.3	480 & 655	929	1.2	Chest x-ray right LL opacities		Survived, 7 days
10	61 M	Headache, blur vision 20 days, altered sensorium 1 day.	Nil	54.6	595	Not done	Not done	B/L upper & mid zone GGO Rt > Left. MRI brain left medial temporal & posterior thalamus & left lateral midbrain infarction		Survived, 7 days
11	42 M	Fever 8 days, dry cough, decreased urination & altered sensorium 2 days.	T2D M	89	761	Not done	4.6	MRI brain – small acute infarction left frontal lobe, x-ray chest B/L opacities RT >Left side		Survived, 7 days

12	28 F	LSCS 1 month back, fever 2 days, loss of consciousness 1 day	NIL	38	390	750	Not done	X-ray chest B/L peripheral GGO, Rt > Left.MRI brain – large left ICH gaglio-capsular area & left coronarad iata.		Survived, 9 days
13	60 M	Fever 29 days, vomiting & altered sensorium 2 days	Nil	200	>1000	Not done	1.9	CSF study -5 mononuclear cells, x-ray chest B/L lower lobe opacities Rt > Left		Survived, 7 days
14	15 F	Fever 15 days, GTCS 1 day, altered sensorium 1 day	NIL	Not done	776	860	4.0	Chest x-ray B/L peripheral GGO and bands of consolidation of lung over left border of heart.		Survived, 7 days
15	17 F	Fever-3 days, multiple episodes of convulsions & loss of conciousness-1 day	Nil	100	214	1200	1.6	GGO over right atrial border & left ventricle. MRI of brain-normal		Survived, 7 days.

16	45 F	Fever -7 days, headache , altered sensorium 3 days	Nil	65	>1000	976	5.1	Band of GGO surrounding left border of heart,CT-brain normal		Survived, 8 days
17	33 M	Fever 8 days, Altered sensorium 4 days	Nil	24.2	498	317	0.5	1st MRI-Inflammatory white matter disease. Contrast MRI-infective etiology.	CSF-57cell /ccm, mostly lymphocyt, protein-34.7mg/dl,ADA -14IU/L	Survived, 11 days

DISCUSSION:

Sherry HY. et al studied a total of 3083 patients (82%) across cohorts had any neurological manifestation and described concomitant COVID-19 neurological manifestations, including symptoms such as headache, myalgia, anosmia, and ageusia as well as neurological syndromes such as encephalopathy, stroke, and coma among others. Acute encephalopathy was the most common clinically captured neurological sign and/or syndrome in all cohorts of 49% patients. The next most common neurological signs and/or syndromes were coma (17%) and stroke (3%). The most common self-reported symptoms included headache 37% and anosmia or ageusia in 26%. Furthermore, the presence of neurological signs or syndromes with COVID-19 significantly increased (5-fold higher) risk of dying during acute hospitalization. Presence of preexisting neurological disorders was associated with increased risk of developing neurological signs and/or syndromes and independently associated with exacerbation of existing neurological pathology, development of de novo neurological syndromes, or neurological complications.[26] Virginie Lambrecq et al, to better define the features of COVID-19-related encephalopathy(CORE), enrolled 78 RT-PCR positive hospitalized COVID-19 adults or COVID-19 associated pneumonia on a CT scan of the chest were underwent EEG to identify a subgroup of patients with CORE and they combined EEG with clinical, biological, and MRI findings. Before the patients underwent EEG the most frequent neurologic manifestations were delirium , movement disorders , including tremor , dyskinesia , akathisia , myorrhythmia , and myoclonus , anosmia , seizures including status epilepticus , focal seizures , and generalized seizures , and oculomotor disorders. There were 57 patients underwent MRI and 41 had abnormalities i.e. acute ischemic lesions , multiple micro-hemorrhages, white matter-enhancing lesions , basal ganglia abnormalities, and metabolic lesions (i.e. central pontine myelinolysis).Twenty patients had perfusion abnormalities, almost entirely hypoperfusion.The results of MRI scans were more frequently unremarkable than EEG findings 28% vs 12%. Sixty-nine patients showed pathologic EEG findings, including metabolic-toxic encephalopathy features, frontal abnormalities, periodic discharges, and epileptic activities. Fifty-five patients showed biological abnormalities, including dysnatremia, kidney failure, and liver dysfunction the same day as the EEG. The results of cerebrospinal fluid analysis were negative for SARS-Cov-2 for all tested patients. Nine patients who had no identifiable cause of brain injury outside COVID-19 were defined as COVID-19-related encephalopathy. The results from this cohort of hospitalized patients with COVID-19 suggest there are clinical, EEG, and MRI patterns that could delineate specific COVID-19-related

encephalopathy.[27] C.Delorme et al reported four cases of COVID-19-related encephalopathy and described the clinical features of COVID-19-related encephalopathy and their metabolic correlates using brain 2-desoxy-2-fluoro-D-glucose (FDG)-positron emission tomography (PET)/computed tomography (CT) imaging (FDG-PET/CT). The diagnosis was made in patients with confirmed COVID-19 who presented with new-onset cognitive disturbances, central focal neurological signs, or seizures. All patients underwent cognitive screening, brain MRI, lumbar puncture and brain (FDG-PET/CT). The delay between first COVID-19 symptoms and onset of neurological symptoms were between 0 and 12 days. None of these patients had MRI features of encephalitis or significant cerebrospinal fluid (CSF) abnormalities. SARS-CoV-2 RT-PCR in the CSF was negative for all patients. All patients presented with a consistent brain FDG-PET/CT pattern of abnormalities, namely frontal hypometabolism and cerebellar hypermetabolism. All patients improved after immunotherapy.[28]

COVID-19 can present with central nervous system manifestations, such as headache, encephalitis and encephalopathy, peripheral nervous system manifestations, such as anosmia, ageusia and Guillian- Barre syndrome, and skeletal muscle manifestations, such as myalgia and myasthenia gravis reported either in the early stage or within the course of the disease. Systematic review showed that COVID-19 can be manifested by a wide spectrum of neurological symptoms.[29] A previous study has shown that serological assays exhibit diagnostic accuracy for COVID-19 only after 14 days of symptom onset, allowing appropriate antibody seroconversion in the host. The accuracy and limitations of existing serological methods for SARS-CoV-2 antibody detection have been openly debated and are an ongoing area of research and refinement.[30]

Our case series highlight that COVID-19 infection can present with clinical manifestations of encephalopathy. In this case series, patients presented with encephalopathy as the initial main clinical manifestation and diagnosis was confirmed by follow up positive SARS-CoV-2 serological test. COVID-19 infection can present with asymptomatic or pauci-symptomatic, diagnosed by early detection of elevated inflammatory biomarkers and imaging studies i.e. chest x-ray, HRCT of chest, among clinically suspected COVID-19-induced encephalopathy. These finding underscores the value of measuring the inflammatory and coagulation markers and imaging study during the etiological workup of patients who experienced atypical manifestations of COVID-19, given that a negative result from an RT-PCR test is expected..

Conclusions:

RT-PCR nasopharyngeal swab test frequently gives false negative results and under diagnose COVID-19 infection. COVID-19 infections are associated with early elevated inflammatory blood biomarkers and associated coagulation dysfunction. This case series highlights that, COVID-19 infected patients can presented with features of encephalopathy in the second wave of COVID-19 pandemic. As COVID-19 is a highly inflammatory disease, diagnosed early by measurement of elevated inflammatory biomarkers and imaging studies.COVID-19 specific serological tests in the appropriate time further confirm the evidence of COVID-19 infection. An early identification of COVID-19 infection has public health implications, which can presents with variable clinical manifestations. Artesunate has pleotropic effects i.e. antiviral, anti-inflammatory, anti-cytokine, anti-oxidant, immunomodulatory, organ protective effects etc. The main stay of treatment in this case series was with use of high dose IV bolus Artesunate and all responded very well without any adverse effects. This novel innovative observation and treatment warrants confirmation in other locations with high volumes of unexplained encephalopathy during this COVID-19 pandemic with high index of suspicion of COVID-19 infection. Furthermore, future randomized, double blind placebo controlled trials are needed to examine the association of COVID-19-induced encephalopathy among RT-PCR positive cases and their response to IV bolus Artesunate.

Limitation of study: - Case control observational study was not done due to clinically marked decrease in mortality and morbidity associate with IV bolus Artesunate therapy which was safe and very effective.

Acknowledgement: We were grateful to all the patients and their relatives, who given their consent for our innovative investigations and treatment approaches.

Conflict of interest: Nil.

REFERENCES

1. Uginet Marjolaine, Gautier Breville, Frédéric Assal,Karl Olof Lövblad, Maria Isabel Vargas, Jérôme Pugin et al. COVID-19 encephalopathy: Clinical and neurobiological features. J Med Virol. 2021; 93:4374–4381.DOI: 10.1002/jmv.26973.
2. Garg RK, Palatals VK, Gupta A. Encephalopathy in patients with COVID-19: A review.J Med Virol. 2021; 93:206–222. DOI: 10.1002/jmv.26207.
3. Ani Nalbandian, Kartik Sehgal, Aakriti Gupta, Mahesh V. Madhavan, Claire McGroder et al. Post-acute COVID-19 syndrome. Nature Medicine. April 2021; Vol. 27: 601–615.
4. Shehata GA, Lord KC, Grudzinski MC , Elsayed, M Abdelnaby, R. Elshabrawy H.A. Neurological Complications of COVID-19: Underlying Mechanisms and Management. Int. J. Mol. Sci. 2021, 22, 4081. https://doi.org/ 10.3390/ijms22084081.
5. JD Santotoribo, DN-Jurado, EL-Balsalobre. Evaluation of Routine blood Tests for Diagnosis of Suspected Coronavirus Disease 2019.Clinical Lab.9/2020 June 8; 66:xxxx. Doi.10.7754/Clin.Lab.2020.200522.
6. Fatih M Uckun, Saran Saund, Hitesh Windlass, Vuong Trieu. Repurposing Anti-Malaria Phytomedicine Artemisinin as a COVID-19 Drug. Frontiers in Pharmacology. 19 March 2021. doi: 10.3389/ fphar. 2021. 649532.
7. Ruiyuan Cao, Hengrui Hu, Yufeng Li, Xi Wang, Mingyue Xu, Jia Liu. et al. Anti-SARS-CoV-2 Potential of Artemisinins In-Vitro. ACS Infect Dis. July 31, 2020. https://dx.doi.org/10.1021/acsinfecdis.0c0 05 22.
8. Bae Joon Yong, Gee Eun Lee, Heedo Park, Juyoung Cho, Yung-Eui Kim, Joo-Yeon Lee, Chung Ju, Won-Ki Kim, Jin Il Kim, Man-Seong Park. Pyronaridine and artesunate are potential antiviral drugs against COVID-19 and influenza. bioRxiv preprint doi: https://doi.org/10.1101/2020.07.28.22510 2.
9. Zhou Yuyong, Kerry Gilmore, Santsecharay Ramirez,Eva Settels,Kerla A,Gammeltofe,Long V,Ulrik Fahnee,Shan Feng,Anna Offersgaard,Jakob Trimpert,Jens Bukh,Klaus Osterricder,Judith M Gottwein,Pater H Seeberder.In vitro efficacy of artemisinin-based treatment against SARS-CoV-2.Science Reports/(2021)11:14571/https://doi.org/10 .1038/s41598-021-93361-y. www.nature.com/sciencetific reports /
10. Gilmore K, Y Zhou Y, Ramirez S, Long V. Pham, Fahnøe U, et al, In vitro efficacy of Artemisinin-based treatments against SARS-CoV-2, bioRxiv preprint doi: https:// doi.org./ 10.1101/ 2020.10.05.326637. October 5 2020.
11. Ilett KF, Batty KT. Powell S. M Binh, T Q, Thu l., Phuong HL, Hung NC, Davis TM. The pharmacokinetic properties of intramuscular Artesunate and rectal Dihydroartemisinin in uncomplicated falciparum malaria. Br. J. Clin. Pharmacol.2002; 53, 23−30.
12. Kevin T. Batty, Le Thi Anh Thu,Timothy M. E. Davis, Kenneth F. Ilett,Truong Xuan Mai,Nguyen Canh Hung,Nguyen Phuc Tien,Shane M. Powell, Huynh Van

Thien,Tran Quang Binh & Nguyen Van Kim. A pharmacokinetic and pharmacodynamic study of intravenous vs oral artesunate in uncomplicated falciparum malaria. Br J Clin Pharmacol 1998; 45: 123–129.
13. Gordi T, Xie R, Huong NV, Huong DX, Karlsson MO, Ashton M. A semi physiological pharmacokinetic model for artemisinin in healthy subjects incorporating autoinduction of metabolism and saturable first pass hepatic extraction.Br J Clin Pharmacol.2005; 59:189–98.
14. Karbwang J , Na-Bangchang K, Thanavibut A, Molunto P. Plasma concentrations of artemether and its major plasma metabolite Dihydroartemisinin following a 5 day regimen of oral artemether in patients with uncomplicated falciparum malaria. Ann Trop Med Parsit.1998; 92:31-36.
15. Li Q, Xie LH, Haeberle A, Zhang J, Weina P.The evaluation of radiolabel Artesunate in tissue distribution in rats and protein binding in human. Am J Trop Med Hyg.1006; 75:817-826.
16. Li Q, Milhous WK, Weina PJ. Artemisinin in malaria therapy. Overseas press (India) Pvt. Ltd. First Edn.2003.p-10, 82, 84, 98.
17. Qisui Li,Lowis R Catilena ,Kevin J Leary,George A,Saviolakis R,Scott Miller ,Victor Melendez,,Peter J Weina. Pharmacokinetic profiles of Artesunate after single intraveinous dose at 0.5.,1,2,4 and 8mg/kg in healthy volunteers; A phase I study. Am J Trop Med Hyg.81(4);2009;pp-615-621.doi.10.4269/ajtmh.2009.09.0150.
18. Kevin T. Batty, Le Thi Anh Thu,Timothy M. E. Davis, Kenneth F. Ilett,Truong Xuan Mai,Nguyen Canh Hung,Nguyen Phuc Tien,Shane M. Powell, Huynh Van Thien,Tran Quang Binh & Nguyen Van Kim. A pharmacokinetic and pharmacodynamic study of intravenous vs oral artesunate in uncomplicated falciparum malaria. Br J Clin Pharmacol 1998; 45: 123–129.
19. YM Bar-On, A Flamholz, R Phillips, R Milo. Science Forum .SARS-CoV-2 (COVID-19) by the numbers. eLife.2020; 9:e57309. DOI https://doi.org/10.7554/eLife.57309.p- 1-15.
20. Fehr AR, Periman S, (2015), Coronavirus: an overview of their replication and pathogenesis. Method Mol Biol.1282; 1-23.
21. Chenchen Shi, Haipeng Li,Yifu Yang, Lifei Hou. Anti-Inflammatory and Immunoregulatory Functions of Artemisinin and its Derivatives. Mediators of Inflammation. Volume 2015, Article ID 435713. http://dx.doi.org/ 10. 1155/ 2015/ 435713. Hindawi Publishing Corporation.
22. Zhao D, Zhang J, Xu G, and Wang Q. (2017). Artesunate protects LPS-induced acute lung injury by inhibiting TLR4 expression and inducing Nrf2 activation. Inflammation 40, 798–805. doi: 10.1007/ s 10753-017-0524-6.
23. Dr (Prof.) Butungeshwar Pradhan et al. Artesunate: an Artemisinin Derivative having Antiviral Properties with Multiple Pleotropic Effects is a Perfect Potential Agent for the Treatment of Symptomatic COVID-19 Infection and Related Hyper inflammation States. JMSCR .Volume 08 Issue 10 October, 2020.p-215-225.
24. Lin Y,Wu F,Xie Z,Song X,Zhu X,Zhu Q, Wei J,Tan S,Liang L.Ging B L. Clinical study of Artesunate in the treatment of coronavirus disease 2019.Europe PMC. 01 Apr 2020, 32(4):417-420. DOI: 10.3760/ cma.j.cn121430-2020031200412. PMID: 3252734.
25. Pradhan Bet al. Efficacy Outcomes on morbidity and mortality of Intravenous Bolus Artesunate Therapy among Rapid Antigen Test and RT-PCR Negative Hospitalized Moderate to Severe Clinically Proven COVID-19 Patients: A Breakthrough large case series. Journal of Medical Science and Clinical Research. Volume 09 Issue 08 August 2021.p-121-137.
26. Sherry H.Y. Chou, Ettore Beghi, Raimund Helbok, E.M Joshua Sampson, Valeria Altamirano, Shraddha Mainali, Claudio Bassetti, Jose I. Suarez, Molly McNett . Global Incidence of Neurological Manifestations Among Patients Hospitalized With COVID-19- A Report for the GCS-Neuro COVID Consortium and the ENERGY Consortium. JAMA Network . 2021; 4(5):e2112131.

doi:10.1001/ jamanetwork open. 2021.12131.
27. Virginie Lambrecq, Aurélie Hanin,Esteban Munoz-Musat, Lydia Chougar,Salimata Gassama, Cécile Delorme,Louis Cousyn et al. Association of Clinical, Biological, and Brain Magnetic Resonance Imaging Findings With Electroencephalographic Findings for Patients With COVID-19. JAMA. March 152021; 4(3):e211489. doi:10.1001/jama network open.2021.1489.
28. C Delorme,O Paccoud, A Kas, A Hesters,S Bombois,P Shambrook ,A Boullet, D Doukhi. et al. COVID-19-related encephalopathy: a case series with brain FDG-positron-emission tomography/computed tomography findings. European Journal of Neurology 2020, 27: 2651–2657.doi:10.1111/ene.14478.
29. Z.H Ousseiran,et al.Neurological manifestations of COVID-19: a systematic review and detailed comprehension. International Journal of Neuroscience.27 Sep 2021. https://doi.org/10.1080/ 00207454.2021.1973000.
30. Tian Ming Tu, Christopher Ying Hao Seet, Jasmine Shimin Koh,Carol Huilian Tham, Hui Jin Chiew, Jasmyn Angon De Leon, et al. Acute Ischemic Stroke During the Convalescent Phase of Asymptomatic COVID-2019 Infection in Men. JAMA Network Open. 2021;4(4):e217498. doi: 10.1001/ jamanetwork open. 2021.7498.