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COVID-19

The interrelation of COVID-19 and neurological modalities

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Dear Chief Editor,

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the etiological agent of COVID-19, is associated with nervous system complications [1]. Several worldwide investigations reported myriad neurological symptoms ranging from nonspecific and moderate (headache, anosmia, convulsions, myalgia, and confusion) to severe like stroke, encephalitis, and Guillain–Barré syndrome in COVID-19 patients. It is estimated that one-fourth of COVID-19 patients develop neurological manifestations [1]. This indicates the neurotropic ability of SARS-CoV-2. The virus is predicted to enter the brain through hematogenous spread and/or retrograde neuronal transport along the olfactory tract, eventually affecting the brain homeostasis sooner or later in an individual's lifetime [1]. Moreover, it is essential to appraise if a prevailing neurological condition exaggerates COVID-19 or if neurological complications are driven by SARS-CoV-2.

In the current study, we included three COVID-19 patients [patient 1 (patient ID: KIMSIP308271), patient 2 (patient ID: KIMSIP306421) and patient 3 (patient ID: KIMSIP308347)] diagnosed according to the WHO guidelines with neurological alterations (Table S1). Earlier reports suggest that peripheral inflammation is initiated and heightened due to rapid SARS-CoV-2 replication. Also, elevated serum inflammatory markers are significantly related to COVID-19 severity [1]. The recruitment of cells at the infection site enhances the inflammatory responses with an aggravated release of cytokines/chemokines. This peripheral cytokine storm alters the brain permeability, facilitating virus invasion. SARS-CoV-2, on its interaction with angiotensin-converting enzyme -2 (ACE-2) on the brain vascular endothelium, and glial cells may enter the brain [1]. Once in the brain, it can elicit a powerful inflammatory reaction by activating CNS-resident immune cells, causing encephalitis, meningitis, or meningoencephalitis [1]. The use of IVIg therapy in COVID-19 treatment suggests that inhibition of the innate immune cells' and cytokines, neutralization of activated complement, and modulation of B- and Treg-cells help curb the neuroinflammatory reactions [2]. Patient 1 was diagnosed with meningoencephalitis and elevated serum inflammatory molecules (Table 1). Thus, supporting the plausibility of neuroinflammation to SARS-CoV-2 mediated cytokine storm. Patient 2 with Parkinsonism presented comorbidities and succumbed to death before any predominant neuroinflammatory signs could be noticed. Thus, by visualizing the clinical outcomes, viral infections in patients with neurological ailments may be treated accordingly.

Cytokine storm is also marked by an increased interleukin and tumor necrosis factor-α production, which promotes lymphocyte apoptosis [3]. The enhanced inflammatory molecules result in lymphopenia, as observed in the investigated cases. Lymphocytes can undergo lysis upon infection through ACE-2. The deteriorating effect on lymphoid organs may further reduce the lymphocyte turnover. The severe COVID-19 cases, i.e., patients 1 and 2, showed similar pathologies and need for ICU (Fig. 1a). Moreover, patient 1 displayed acute respiratory distress syndrome (ARDS). According to a report, the risk of ARDS escalated significantly with increased neutrophils and

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Table 1 Comparative levels of serum inflammatory markers, LDH, CRP, D-dimer, and procalcitonin (PCT) in patients with neurological manifestations on the day after admission

Patient ID (age/sex)	Serum inflammatory markers (normal range)			
	LDH (135–214 IU/L)	CRP (<5mg/L)	D dimer (<0.50)	PCT (>10ng/mL)
KIMSIP308271 (70yrs/male)	*584.2 (2.72)	30.69 (6.13)	8.1 (16.2)	0.37
KIMSSIP306421 (67yrs/male)	-	39.39 (7.87)	-	1.43
KIMSIP308347 (46yrs/male)	*492.79 (2.30)	37.72 (7.54)	4.37 (8.74)	0.1

The levels and fold change (FC) values of LDH, CRP, and D-dimer compared to the normal range were elevated in all the cases representing peripheral inflammation

*The FC in the case of LDH is compared to the higher limit value of the normal range, i.e., 214 IU/L

decreased lymphocytes [4]. We correlated these observations in patient 1 (Table S2). Besides increased LDH is related to higher myocardial injury, ARDS, and mortality [5]. D-dimer and PCT found to be high in severe COVID-19 patients were markedly upregulated in patient 1 (8.1) and pateint 2 (1.43) respectively (Table 1). Enhanced D-dimers can be related to greater risks of cardiovascular diseaseand ARDS observed in patient 1 (Table S1). Moreover, myocardial injury observed in patient 1 is related to increased mortality. A study reported that 19.7% of the COVID-19 patients had a myocardial injury [6].

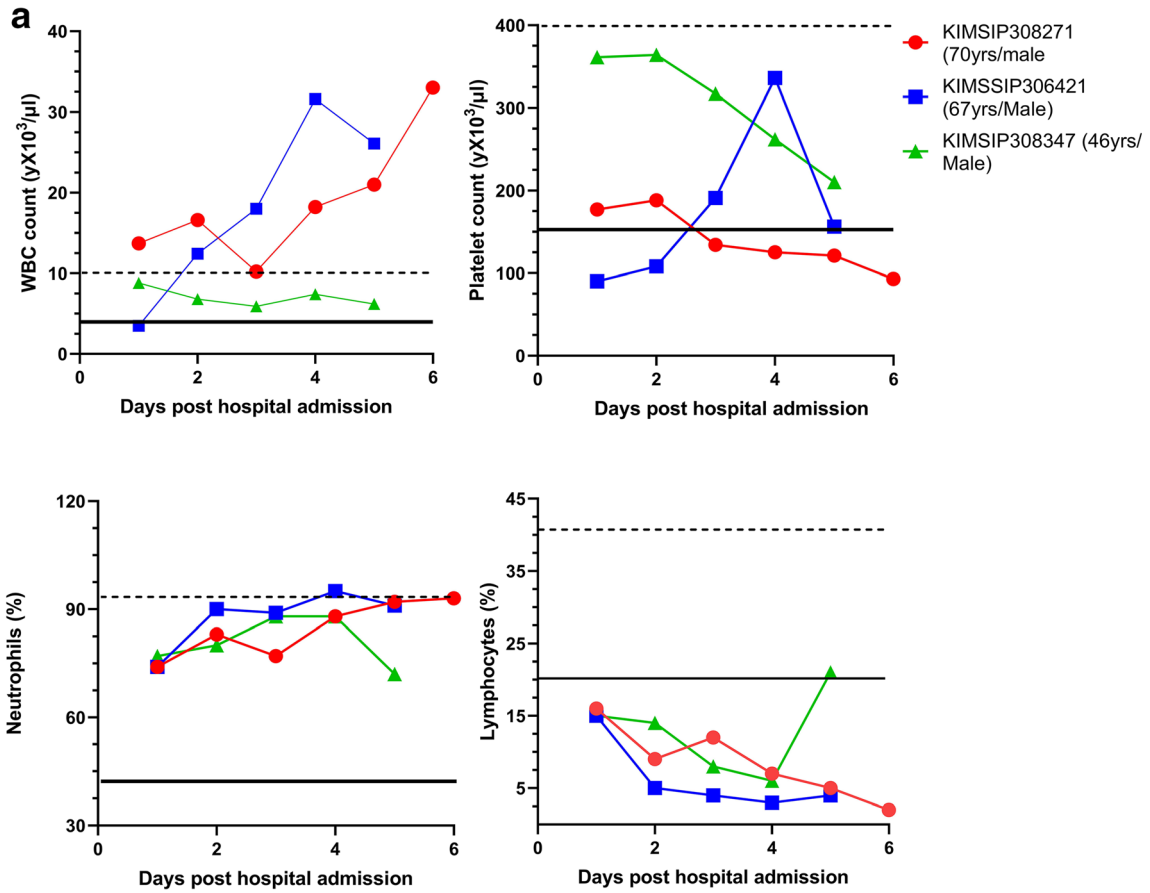

Fig. 1 **a** Graphical representation of WBC count, platelet count, neutrophils %, and lymphocytes % of the patients on subsequent hospitalization days. The dashed line represents the upper limit of the normal range, whereas the solid line represents the lower value of the normal range. Briefly, leukocytosis is observed in patient 1 (patient ID: KIMSIP308271) and 2 (patient ID: KIMSIP306421) unlike patient 3 (patient ID: KIMSIP308347). The platelet counts gradually reduced in the case of patients 1and 3 in contrast to patient 2. Lymphopenia and increased levels of neutrophils are observed in all three cases. **b** Graphical representation of biochemical parameters of the patients on day 1 of admission into the hospital. The dashed line represents the upper limit of the normal range, whereas the solid line represents the lower value of the normal range. Hyponatremia, increased SGOT, and urea level was found in all cases. *The lower range for SGOT is zero

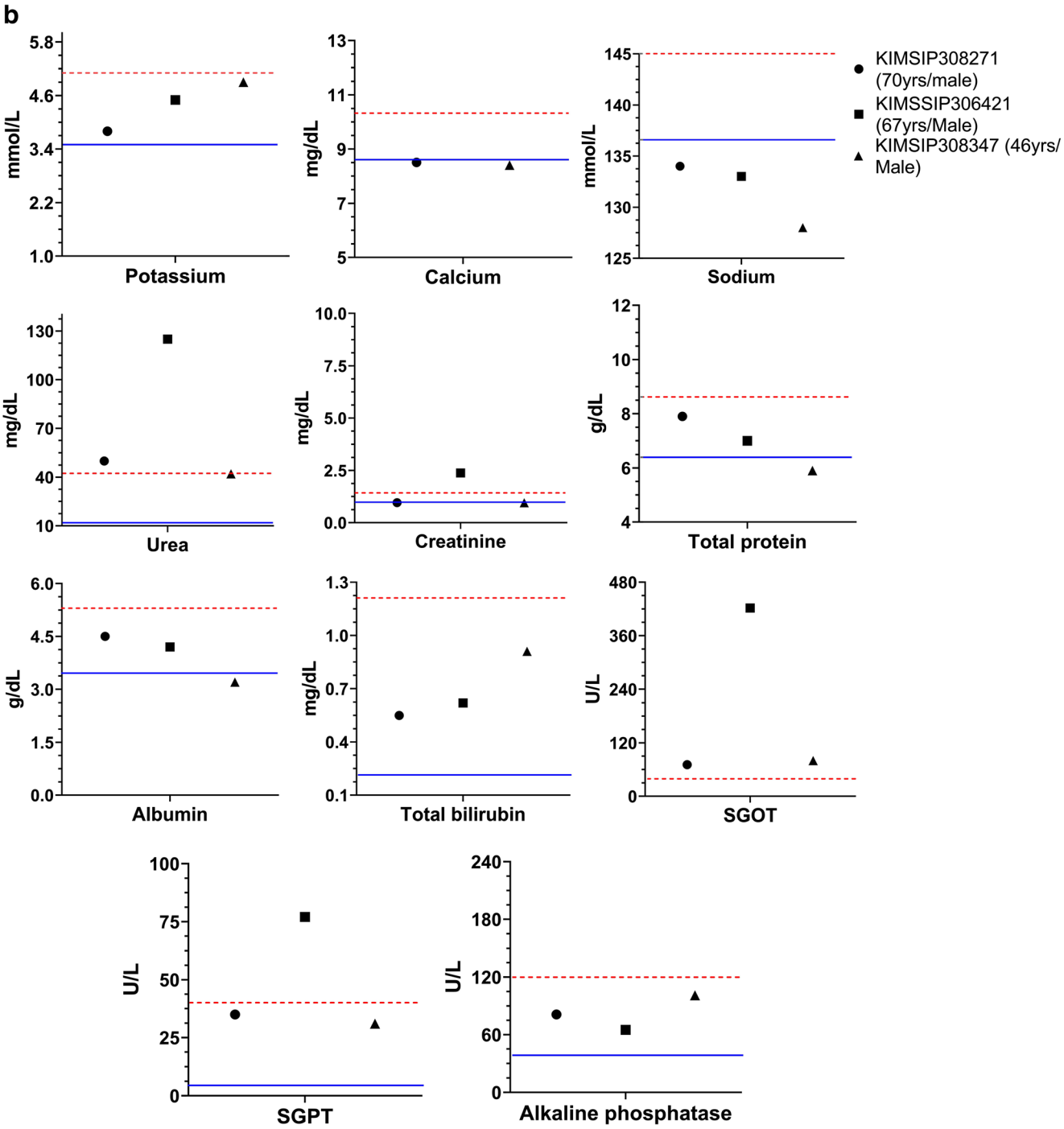

Fig. 1 continued.

Apart from neurological manifestations, patient 2 displayed multiple comorbid conditions like hypertension, acute kidney injury (AKI), liver dysfunction, BPH, and septicemia (Fig. 1b; Table S1). AKI in patient 2 may have appeared due to inflammation (Fig. 1b). SARS-CoV-2 can affect multi-organs, including the kidney, and induce hemodynamic instability resulting in deranged renal parameters [3]. Moreover, virus-driven cytopathic alterations could be responsible for liver function test (LFT) abnormalities in COVID-19 (Fig. 1b) [7]. A detailed study is needed to unravel the influence of SARS-CoV-2 on the liver. Patients with neurological outcomes and less severe COVID-19 or peripheral inflammatory reactions may recover, like patient 3. Conclusively, we noticed that an exaggerated SARS-CoV-2 mediated peripheral immune reaction like

in patient 1 might have affected the patient's brain causing condition like meningitis. Also, severe COVID-19 in patients with prevailing neurological complications and various comorbidities like ARDS, AKI, and hypertension (e.g., patient 2) may result in life-threatening situations. Thus, an elevated peripheral immune cell response and prevailing comorbidities are crucial in determining the severity of COVID-19 and chances of developing neurological symptoms in a patient. Additionally, SARS-CoV-2 can aggravate the existing neurological conditions leading to worsening of brain functionalities later in life. Thus, long-term monitoring of less severe COVID-19 cases with neurological alterations, such as the third patient's case, is crucial. Nonetheless, medication for the treatment of COVID-19 in such cases should include drugs with sufficient blood-brain barrier permeability to regulate the brain homeostasis, simultaneously taking care of the consequences of SARS-CoV-2 infection in the peripheral blood system.

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Author contribution SJ, MS, PD, PKP, NKM, and HCJ analyzed and interpreted the data; BB and KM collected and sorted the clinical data; and SJ, NKM, and HCJ were contributors in writing the manuscript. All authors read and approved the final manuscript.

Declarations

Ethics approval The study was conducted according to the principles of the declaration of Helsinki upon approval by the research ethics committee of KIMS (KIIT/KIMS/IEC/372/2020), School of Biotechnology Kalinga Institute of Industrial Technology, Bhubaneswar (KIIDU/KSBT/2020/345), and Indian Institute of Technology Indore (BSBE/IITI/IHEC-05/2020).

Conflict of interest The authors declare that they have no competing interests.

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