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Original Article

Impact of COVID-19 on a brain damage unit

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ABSTRACT

Aim: To report on the impact of COVID-19 on a brain damage unit.
Methods: We reviewed the records of all patients admitted to our brain damage unit. The study included all the significant clinical events from the first positive qualitative real-time reverse-transcriptase −polymerase-chain-reaction assay (April 8th, 2020) for SARS-CoV-2 to the day all patients tested negative (June 8th, 2020).
Results: Of the 20 patients (14 men) (age 57.7 ± 14.9; 2−71 months after brain damage; all with a modified Rankin scale score > 4), 16 tested positive for SARS-CoV-2 and remained positive for a mean of 32.3 days (ranging from 26 to 61). One patient died from COVID-19, while 12 patients were asymptomatic and three suffered mild pneumonia without acute respiratory distress syndrome. All patients received prophylactic subcutaneous heparin. Intravenous methylprednisolone was prescribed for three patients with bilateral pneumonia with excellent results.
Conclusions: Most positive cases (93.7%) were not severe. The good outcome was most likely due to the use of prophylactic anticoagulation therapy, the early use of methylprednisolone for pneumonia and the previously reported immunosuppression amid patients with brain damage. This study hopes to encourage further study into brain damage immunity.

1. Introduction

The havoc caused by the novel severe acute respiratory syndrome coronavirus (SARS-CoV-2) has strained to the limit the ability of scientists worldwide to find effective treatments, elucidate pathophysiological mechanisms and identify severity markers [1−3].

The mortality from SARS-CoV-2 is largely due to bilateral pneumonia, associated with an exaggerated immune response leading to acute respiratory distress syndrome.

This is occasionally combined with hypercoagulability state and multisystemic failure (elevated levels of IL6, C reactive protein, ferritin and D-dimer) [4,5]. Many old time-tested drugs for the disease have empirically "re-purposed" for treatment [6−8]. One of the most used, in the initial phase, was hydroxychloroquine [6,7], although it has subsequently proved to be ineffective and have severe and life-threatening adverse effects [9]. Currently, the only treatment that seems to reduce mortality among those who receive either invasive mechanical ventilation or oxygen alone is dexamethasone [10].

Several comorbidities have been identified as potential susceptibility factors for severe infection and fatal outcomes, such as the preexistence of diabetes mellitus, arterial hypertension, obesity, malnutrition, restrictive and obstructive airway diseases, and low vitamin D levels among others [5,11−13]. Some of these factors are commonly seen in patients admitted to brain damage units.

Patients with long-term hospital stay following stroke or traumatic brain injury patients are at increased risk of more severe infection due to the preexistence of malnutrition, low vitamin D

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levels and reduced respiratory capacity [14–16]. However, there is no reliable information on the impact of COVID-19 on patients with brain damage [3]. We hereby report the impact of COVID-19 impact on a brain damage unit with 20 hospitalized patients, of whom 16 were affected.

2. Methods

In this retrospective observational study, we reviewed the records of all patients admitted to our brain damage unit. The study included all significant clinical events from the first positive qualitative real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay (April 8th, 2020) for SARS-CoV-2 to the day all patients were tested negative (June 8th, 2020). Daily chest auscultation, monitoring of temperature, respiration rate, oxygen saturation, and heart rate were recorded for all patients. Laboratory values of blood cell count, renal, and liver functions were only registered for positive patients. Ferritin, D-dimer, and C reactive protein levels were determined in 15 out of the 16 positive patients. Chest X-rays were only performed on patients with dyspnea or oxygen saturation below 94%. Blood tests or chest X-rays were not given to negative patients.

Basal laboratory data from the last six months (vitamin D, total protein, albumin, vitamin B12, folic acid, thyroid stimulating hormone, ferritin, liver enzymes, creatinine, triglycerides and total cholesterol) and any invasive procedures, diagnosed infections, and bacterial cultures in the last year were obtained from the clinical history of every patient.

This study was performed retrospectively with anonymized clinical data. The legal guardians of all participants provided their informed consent to participate in this study.

3. Statistical analysis

The clinical and laboratory data of the participants was compared using Student's t-tests and Mann-Whitney U tests or Fisher's exact test, when appropriate, for quantitative and nominal variables, respectively. A Kolmogorov-Smirnov test was used to verify normality while the correlations between clinical and laboratory data in positive patients were identified using Spearman's correlation coefficients.

All analyses were performed using SPSS v 19.0 (IBM Corp. Armonk, NY, USA). with a significance level of $p < 0.05$.

4. Results

On April 8th, 2020 (date of the diagnosis of the first case), the mean age of the 20 patients [14, (70%) men] in the brain damage unit was 57.7 years (range: 22–84 years). The mean time (months) since the brain injury was 10.4 (range: 2 to 70) and all had a modified Rankin scale score > 4. Additional demographic data is provided in Table 1.

The first patient to be diagnosed was case number 15. SARS-CoV-2 infection was suspected because of fever (38 °C) and malaise for 48 h. The patient's nasopharyngeal swab test for SARS-CoV-2 by RT-PCR assay was positive on April 8th; the remaining 19 patients were then tested for COVID-19 using the same method, resulting in 15 positives for SARS-CoV-2. The four negative patients were tested up to three times over the following 10 days, all testing persistently negative. However, these patients were isolated and quarantined in a separate area of the hospital but remained in direct supervision of the same medical team. All patients continued their physiotherapy, logopedic and occupational therapy sessions as originally planned if their clinical state permitted. Likewise, all patients remained isolated in their rooms since the diagnosis of COVID-19.

One patient (case 20) died on April 9th from respiratory insufficiency from bilateral pneumonia that led to a cardiac arrest. He had a previous history of recurrent respiratory tract infections since his arrival two months back and was treated with multiple antibiotics with good response, although the final infection was aggravated by inadequate management of respiratory secretions due to dyskinesias secondary to brain damage. The final respiratory infection of this patient had a two-week course before death. The patient tested positive for SARS-CoV-2 the day before he died.

Of the other 15 positive patients, 12 remained asymptomatic and three had mild pneumonia without acute respiratory distress syndrome. Among the comorbidities for severe SARS-CoV-2 infection in positive patients, eight had arterial hypertension, six had diabetes mellitus, eight had dyslipidemia, four had previous heart disease and four had severe chronic obstructive pulmonary disease. No significant differences were observed in the frequency of these diseases among positive and negative patients (Fisher's exact test, all $p > 0.05$). According to the American Thoracic Society guidelines [17], none of our patients had severe respiratory distress criteria.

Five patients with COVID-19 had fever during the first week after diagnosis and four had oxygen saturation below 90%, but only three of these also had dyspnea and bilateral pneumonia in chest-X-rays. Malaise was reported or evidenced by a worse general aspect (in patients who could not communicate) of 12 out of 16 positive patients and one negative patient who also had odynophagia. Three positive patients had moderate diarrhea for less than three days while only one positive case reported anosmia. No new SARS-CoV-2 related symptoms or findings were reported after 10 days from the positive diagnosis of the 15 surviving patients.

Blood tests after diagnosis were only performed on positive patients. Leukopenia was detected in two patients, both had slightly elevated levels of ferritin (less than two times the higher limit set by our laboratory) and moderately elevated C reactive protein; D-dimer levels were otherwise normal. Among the three patients who developed pneumonia, only one had slightly elevated D-dimer levels, while all showed elevated C reactive protein levels (lower than 6 mg/dL) (reference value < 0.5). Two out of three patients had low vitamin D levels. All of them received antibiotic treatment, according to the antibiogram, for six days and respiratory symptoms abated before treatment was ended.

Among the positive cases some basal (before the outbreak) analytic alterations were found. Low vitamin D (11 patients), low vitamin B12 levels (two patients), total protein levels (four patients), high thyroid stimulating hormone (three patients), alteration in liver enzymes non-superior to three times the normal values (three patients) and high cholesterol or triglyceride levels (four patients). None of the negative cases had alterations in these values except one patient who had high cholesterol levels and three with low vitamin D levels. However, there were no differences between basal laboratory values (vitamin D, total protein, albumin, vitamin B12, folic acid, thyroid stimulating hormone, ferritin, liver enzymes, creatinine, triglycerides and total cholesterol) among positive and negative patients (Student's t or Mann-Whitney U tests, when appropriate, all $p > 0.05$).

All patients were receiving low weight subcutaneous heparin (0.5 mg/kg/day), while three positive patients were also given acetylsalicylic acid 100 mg/24 h. When the infection was diagnosed, all positive patients were treated with hydroxychloroquine (600 mg/day) and acetylcysteine (600 mg/day). Intravenous methylprednisolone (40 mg/day) was prescribed for the three patients with bilateral pneumonia as well as for three additional patients with a history of pneumonia in the last month with continuous respiratory secretions. These courses of medication were maintained for five days for all subjects, while treatment with heparin and acetylsalicylic acid continued.

Table 1
Demographic and clinical characteristics of brain damage unit patients (N = 20).

Code	Age	Sex	Months since injury	Etiology of brain injury	Comorbidities	Modified Rankin Scale	Barthel scale
1	64	Man	8	Traumatic brain injury	Arterial hypertension, diabetes mellitus, dyslipidemia and chronic pulmonary obstructive disease	5	0
2	33	Woman	9	Traumatic brain injury	–	5	10
3	22	Man	15	Traumatic brain injury and anoxic encephalopathy	–	5	0
4	62	Man	5	Hemorrhagic Stroke	Arterial hypertension and diabetes mellitus	5	10
5	37	Man	70	Traumatic brain injury	–	5	20
6	60	Woman	2	Carbon monoxide encephalopathy	Dyslipidemia	4	50
7	73	Woman	4	Ischemic Stroke	Arterial hypertension, diabetes mellitus, dyslipidemia and heart disease	5	0
8	63	Man	8	Traumatic brain injury	Arterial hypertension and diabetes mellitus	4	40
9	63	Man	6	Brain tumor surgery complications	Diabetes mellitus,	4	80
10	51	Man	11	Anoxic encephalopathy	Arterial hypertension, diabetes mellitus and heart disease	5	0
11	71	Man	11	Traumatic brain injury	–	5	20
12	66	Man	5	Infectious encephalopathy	Diabetes mellitus and dyslipidemia	5	20
13	65	Man	4	Ischemic Stroke	Arterial hypertension and chronic pulmonary obstructive disease	5	10
14	57	Woman	18	Traumatic brain injury	–	5	0
15	57	Man	1	Hemorrhagic Stroke	Arterial hypertension	4	30
16	48	Man	4	Traumatic brain injury	–	5	0
17	47	Woman	3	Subarachnoid hemorrhage	–	5	0
18	76	Woman	6	Ischemic Stroke	Dyslipemia, heart disease and chronic pulmonary obstructive disease	5	35
19	55	Man	4	Hemorrhagic stroke	Arterial hypertension and dyslipidemia	5	0
20	84	Man	15	Anoxic Encephalopathy	Arterial hypertension, dyslipidemia, heart disease and chronic pulmonary obstructive disease	5	0

Invasive procedures performed in the last year were documented in both groups. For the group of positive cases, these included gastrostomy (eight patients), tracheostomy (nine patients), ventricular drainage (four patients), craniotomy (one patient), vesical catheter (12 patients) and nasogastric catheter (seven patients); for the negative group these were gastrostomy (three patients), tracheostomy (three patients), ventricular drainage (two patients), craniotomy (two patients), vesical catheter (two patients) and nasogastric catheter (two patients). No significant differences were observed in the frequency of previous invasive procedures among positive and negative patients (Fisher's exact test, all $p > 0.05$). A number of infections were diagnosed in the year prior to the COVID-19 pandemic; among the group of positive cases these included skin infection (three patients), respiratory (14 patients), urinary (three patients), central nervous system (three patients); in the group of negative cases these were stage 3 pressure ulcers (two patients), respiratory infection (four patients) and urinary (three patients). No significant differences were observed in the frequency of previous infections among positive and negative patients (Fisher's exact test, all $p > 0.05$). All patients in both groups had at least one bacterial infection in the last year. 13 (81.3%) of positive cases and two (50%) of the negative ones were infected by gram-negative bacteria. See Table 2.

Finally, days to negative RT-PCR assay ranged from 26 to 61 with a mean of 32.3 ± 11.6 days. The time to resolve the infection (i.e., negative RT-PCR) was not correlated with any alteration in clinical or laboratory data (Spearman's correlation coefficients, all $p > 0.05$).

5. Discussion

The outcome of the SARS-CoV-2 outbreak in this cohort is unexpected. Despite having premorbid severe disabilities (arterial hypertension, diabetes mellitus, heart disease and chronically disabled patients) which are well-established risk factors for fatal outcome in SARS-CoV-2 infection [18,19], in majority of them, most of the positive cases (93.7%) did not have a severe affection.

Given our prediction of a severe or fatal outcome, all infected patients, regardless of symptoms, were empirically treated with hydroxychloroquine and acetylcysteine, based on the best available evidence and previous experience with such patients [20] The mild respiratory infections and good outcome in the three most severely symptomatic patients were surprising.

There are several hypotheses that we propose for the good outcome of our patients. The first is the possible protective role that prophylactic anticoagulation therapy could play, given that thrombotic or thromboembolic events have been established as part of the core physiopathology of COVID-19 [21,22]. On the other hand, patients with brain damage reportedly have immunosuppression due to as yet unknown processes [23]. Moreover, a specific monocyte deactivation, with decreased capacity for antigen presentation and depressed secretion of proinflammatory cytokines, has been documented [24]. This is in line with the important role that these cells may have in the dysregulated inflammation in SARS-CoV-2 infection [25] and findings of a possible beneficial role of disease-modifying therapies among multiple sclerosis patients [26]. The history of invasive procedures and positive bacterial cultures in our patients is in keeping with the previously reported immune suppression related to brain damage [23]. Thus, we cannot rule out an immune modulator role of the bacteria, mainly gram-negatives [27]. Of further interest is the prolonged virus clearance in RT-PCR assays (32.3 days) in our patients compared to general population (10.5 days) [28]. Further research is required into the role of brain-damage associated immune suppression in cases of SARS-CoV-2. Finally, we should consider the possibility of varying degrees of virulence in active variants of SARS-CoV-2 [29]. A less virulent variant would explain why none of our patients had an adverse outcome from the disease.

Our findings are in line with those of other studies of highly disabled, spinal injury patients whose outcomes were better than expected [30]. Immune suppression was also been reported [31] in these patients.

We recognize that a principal limitation of this study is the absence of chest X-rays for most positive patients. Chest X-rays were only performed on those with symptoms of respiratory impairment. This study also had several strengths. First, this is the first study to our knowledge that has included hospitalized patients in a single brain damage unit, thus avoiding selection bias. Second,

Table 2
Bacterial cultures in the last year before SARS-CoV-2 infection.

Code	Urine	Respiratory	Skin	Rectum	Bood/cerebrospinal fluid
1	–	–	Klebsiella *pneumoniae*	–	–
2	–	Staphilococcus aureus	–	–	–
3	–	Acinetobacter *baumanii*	–	Acinetobacter baumanii	–
4	–	Staphilococcus aureus	–	–	–
5	–	Staphilococcus aureus	–	–	–
6	Escherichia coli	–	–	–	–
7	–	Staphilococcus aureus, Escherichia coli	–	–	–
8	Klebsiella *pneumoniae*	Klebsiella *pneumoniae*	–	–	–
9	Enterococus, Acinetobacter *baumanii*	–	–	–	Escherichia coli
10	Escherichia coli	Acinetobacter *baumanii*	–	–	–
11	Klebsiella *pneumoniae*	–	–	–	–
12	–	–	–	Citrobacter *freundii*	–
13	–	–	–	–	Staphylococcus *haemolyticus*
14	–	Pseudomona *aeruginosa*, Klebsiella *pneumoniae*	–	–	–
15	–	Acinetobacter *baumanii*	–	Klebsiella *pneumoniae*	–
16	Citrobacter *freundii*	–	Staphilococcus aureus	–	–
17	–	Staphilococcus aureus	–	–	–
18	Pseudomonas *aeruginosa*	Pseudomonas *aeruginosa*	–	–	–
19	–	Staphilococcus aureus, Pseudomona *aeruginosa*, Moraxella *catarrhalis*	–	–	–
20	–	Pseudomonas *aeruginosa*, Staphilococcus aureus	–	Escherichia coli	–

all patients completed the follow-up until infection resolution. Finally, the homogeneity of the empirical medical therapy and complementary physical therapies makes our observations worth consideration.

In closing, despite severe disability and risk factors for a fatal outcome, most positive cases (93.75%) were not severely affected. This outcome may be related to prophylactic anticoagulation therapy, early use of methylprednisolone in those with viral pneumonia and the previously reported immunosuppression amid patients with brain damage. In fact, this study may support the currently available evidence for the importance of innate immune response for the COVID-19 outcome. Our findings may encourage further studies on brain damage immunity and may also offer a different view for the timing of treatment for SARS-CoV-2 infections in highly disabled or institutionalized patients.

Authors' contributions

Dr. Romero collaborated in: 1) the conception, organization of the research project; 2) the statistical analyses; and 3) the writing of the manuscript first draft and the review and critique of the manuscript.

Dr. Ana Bravo-Martín collaborated in: 1) the organization of the research project, and; 2) the review and critique of the manuscript.

Dr. Paulina Oliva-Navarrete collaborated in: 1) the organization of the research project, and; 2) the review and critique of the manuscript.

Dr. Francisco Sánchez-Cuesta collaborated in: 1) the organization of the research project, and; 2) the review and critique of the manuscript.

Dr. Marcos Ríos-Lago in: collaborated in: 1) the organization of the research project, and; 2) the review and critique of the manuscript.

Dr. Benito-León collaborated in: 1) the conception, organization and execution of the research project; 2) the writing of the manuscript first draft and the review and critique of the manuscript.

All authors read and approved the final version of the manuscript.

Declaration of competing interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

References

[1] Maveddat A, Mallah H, Rao S, Ali K, Sherali S, Nugent K. Severe acute respiratory distress syndrome secondary to coronavirus 2 (SARS-CoV-2). Int J Occup Environ Med 2020;11:157–78. https://doi.org/10.34172/ijoem.2020.2202.
[2] Benito-León J, Del Castillo MD, Estirado A, Ghosh R, Dubey S, Serrano JI. Unsupervised machine learning to identify age- and sex-independent severity subgroups among patients with COVID-19: observational longitudinal study. J Med Internet Res 2021;23:e25988. https://doi.org/10.2196/25988.
[3] Roy D, Ghosh R, Dubey S, Dubey MJ, Benito-León J, Kanti Ray B. Neurological and neuropsychiatric impacts of COVID-19 pandemic. Can J Neurol Sci 2021;48:9–24. https://doi.org/10.1017/cjn.2020.173.
[4] Gao Y, Li T, Han M, Li X, Wu D, Xu Y, et al. Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. J Med Virol 2020;92:791–6. https://doi.org/10.1002/jmv.25770.
[5] Xu Z, Li S, Tian S, Li H, Kong L-Q. Full spectrum of COVID-19 severity still being depicted. Lancet 2020;395:947–8.
[6] Gbinigie K, Frie K. Should chloroquine and hydroxychloroquine be used to treat COVID-19? A rapid review. BJGP Open 2020;4:bjgpopen20X101069. https://doi.org/10.3399/bjgpopen20X101069.
[7] Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2021;57:106239. https://doi.org/10.1016/j.ijantimicag.2020.106239.
[8] Ghosh R, Chatterjee S, Dubey S, Lavie CJ. Famotidine against SARS-CoV2: a hope or hype? Mayo Clin Proc 2020;95(8):1797–9. https://doi.org/10.1016/j.mayocp.2020.05.027.
[9] Boulware DR, Pullen MF, Bangdiwala AS, Pastick KA, Lofgren SM, Okafor EC, et al. A randomized trial of hydroxychloroquine as postexposure prophylaxis for covid-19. N Engl J Med 2020;383:517–25. https://doi.org/10.1056/NEJMoa2016638.
[10] Horby P, Lim WS, Emberson J, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med 2021;384:693–704. https://doi.org/10.1056/NEJMoa2021436.

[11] Apicella M, Campopiano MC, Mantuano M, Mazoni L, Coppelli A, Prato SD. COVID-19 in people with diabetes: understanding the reasons for worse outcomes. The Lancet Diabetes & Endocrinology 2020;8:782–92. https://doi.org/10.1016/S2213-8587(20)30238-2.
[12] Sattar N, McInnes IB, McMurray JJV. Obesity is a risk factor for severe COVID-19 infection. Circulation 2020;142:4–6. https://doi.org/10.1161/CIRCULATIONAHA.120.047659.
[13] Panagiotou G, Tee SA, Ihsan Y, Athar W, Marchitelli G, Kelly D, et al. Low serum 25-hydroxyvitamin D (25[OH]D) levels in patients hospitalised with COVID-19 are associated with greater disease severity. Clin Endocrinol 2020;93:508–11. https://doi.org/10.1111/cen.14276.
[14] McHenry MA. Vital capacity following traumatic brain injury. Brain Inj 2001;15:741–5. https://doi.org/10.1080/02699050010013932.
[15] Toman E, Bishop JRB, Davies DJ, Su Z, Criseno S, Mason A, et al. Vitamin D deficiency in traumatic brain injury and its relationship with severity of injury and quality of life: a prospective, observational study. J Neurotrauma 2016;34:1448–56. https://doi.org/10.1089/neu.2016.4494.
[16] Dhandapani S, Manju D, Sharma B, Mahapatra A. Clinical malnutrition in severe traumatic brain injury: factors associated and outcome at 6 months. The Indian J Neurotrauma 2007;4:35–9. https://doi.org/10.1016/S0973-0508(07)80009-8.
[17] Carla A, Pereira B, Boukail H, Audard J, Pinol-Domenech N, De Carvalho M, et al. Acute respiratory distress syndrome subphenotypes and therapy responsive traits among preclinical models: protocol for a systematic review and meta-analysis. Respir Res 2020;21:81. https://doi.org/10.1186/s12931-020-01337-9.
[18] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054–62. https://doi.org/10.1016/S0140-6736(20)30566-3.
[19] Shakespeare T, Ndagire F, Seketi QE. Triple jeopardy: disabled people and the COVID-19 pandemic. Lancet 2021;10;397(10282):1331–3. https://doi.org/10.1016/S0140-6736(21)00625-5.
[20] Jean S-S, Lee P-I, Hsueh P-R. Treatment options for COVID-19: the reality and challenges. J Microbiol Immunol Infect 2020;53:436–43. https://doi.org/10.1016/j.jmii.2020.03.034.
[21] Spiezia L, Boscolo A, Poletto F, Cerruti L, Tiberio I, Campello E, et al. COVID-19-Related severe hypercoagulability in patients admitted to intensive care unit for acute respiratory failure. Thromb Haemostasis 2020;120:998–1000. https://doi.org/10.1055/s-0040-1710018.
[22] Ghosh R, Roy D, Mandal A, Pal SK, Chandra Swaika B, Naga D, et al. Cerebral venous thrombosis in COVID-19. Diabetes & metabolic syndrome. Diabetes Metab Syndr 2021;15:1039–45. https://doi.org/10.1016/j.dsx.2021.04.026.
[23] Dziedzic T, Slowik A, Szczudlik A. Nosocomial infections and immunity: lesson from brain-injured patients. Crit Care 2004;8:266–70. https://doi.org/10.1186/cc2828.
[24] Shimonkevitz R, Bar-Or D, Harris L, Dole K, McLaughlin L, Yukl R. Transient monocyte release of interleukin-10 in response to traumatic brain injury. Shock 1999;12:10–6. https://doi.org/10.1097/00024382-199907000-00002.
[25] Gómez-Rial J, Currás-Tuala MJ, Rivero-Calle I, Gómez-Carballa A, Cebey-López M, Rodríguez-Tenreiro C, et al. Increased Serum Levels of sCD14 and sCD163 indicate a preponderant role for monocytes in COVID-19 immunopathology. Front Immunol 2020:560381. https://doi.org/10.3389/fimmu.2020.560381.
[26] Berger JR, Brandstadter R, Bar-Or A. COVID-19 and MS disease-modifying therapies. Neurol - Neuroimmunol Neuroinflammation 2020;7:e761. https://doi.org/10.1212/NXI.0000000000000761.
[27] Evrard B, Balestrino D, Dosgilbert A, Bouya-Gachancard J-LJ, Charbonnel N, Forestier C, et al. Roles of capsule and lipopolysaccharide O antigen in interactions of human monocyte-derived dendritic cells and Klebsiella pneumoniae. Infect Immun 2010;78:210–9. https://doi.org/10.1128/IAI.00864-09.
[28] Chang D, Mo G, Yuan X, Tao Y, Peng X, Wang F-S, et al. Time kinetics of viral clearance and resolution of symptoms in novel coronavirus infection. Am J Respir Crit Care Med 2020;201:1150–2. https://doi.org/10.1164/rccm.202003-0524LE.
[29] Boehm E, Kronig I, Neher RA, Eckerle I, Vetter P, Kaiser L. Geneva center for emerging viral diseases. Novel SARS-CoV-2 variants: the pandemics within the pandemic. Clin Microbiol Infect 2021;S1198:743–7. https://doi.org/10.1016/j.cmi.2021.05.022.
[30] Rodríguez-Cola M, Jiménez-Velasco I, Gutiérrez-Henares F, López-Dolado E, Gambarrutta-Malfatti C, Vargas-Baquero E, et al. Clinical features of coronavirus disease 2019 (COVID-19) in a cohort of patients with disability due to spinal cord injury. Spinal Cord Series and Cases 2020;6:39. https://doi.org/10.1038/s41394-020-0288-3.
[31] Prüss H, Tedeschi A, Thiriot A, Lynch L, Loughhead SM, Stutte S, et al. Spinal cord injury-induced immunodeficiency is mediated by a sympathetic-neuroendocrine adrenal reflex. Nat Neurosci 2017;20:1549–59. https://doi.org/10.1038/nn.4643.