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Research article

Research on clinical-paraclinical and evolutive aspects in patients with post spinal cord injury (SCI) statuses and Covid-19 – a systematic literature review

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Abstract: The COVID-19 pandemic has generated a lot of interest among doctors as well as scientists around the world. Studies on the impact of the Covid-19 pandemic, including in people with post SCI sufferance, are ongoing, aiming to understand the pathophysiological mechanisms of SARS-CoV2 in target tissues, to optimize related methods of diagnosis and treatment in both, initial and later phases of the disease – e.g.: "long Covid" status – and thus, to make a substantial contribution to the quality of life improvement of the affected patients.
After using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (acronym PRISMA) method to quest for afferent knowledge, it resulted a quite small number (12) of articles, most of them indirectly approaching this topic. Therefore, is important to deepen this niche – which is scarcely approached – in order to find new therapeutic approaches able to combat COVID-19-associated to SCI manifestations – like, for instance, to check whether the principle of intermittent hypoxia treatment is effective and worth to be included in the rehabilitation treatment protocols – as neither an indubitable effective drug or vaccine, or respectively, cure for SCI, has been provided so far.

Keywords: Spinal cord injury, Paraplegia, Tetraplegia, COVID-19, intermittent hypoxia treatment

1. Introduction

The 2019 coronavirus pandemic (COVID-19) led to drastic measures to limit the spread of severe acute respiratory syndrome (SARS-CoV-2). Stay-at-home policies and express instructions to defer non-urgent medical cases have limited clinical visits. In this context, telemedicine had a pragmatic role to provide follow-up care to patients[i].Many European states introduced various countermeasures against the spread of SARS-CoV-2, which varied from country to country, with some banning and mixing between households and outdoor activities, allowing certain types of activities (e.g. Poland, Germany and the UK) and others recommending only social distancing precautions (e.g. Sweden)[ii].
The COVID-19 pandemic has led to the closure of outpatient clinics in public hospitals to limit its spread, especially among the most vulnerable patients. It had a negative effect on the care of chronic patients, as it is well known that all of them – including and especially with neurological conditions – require regular and accurate monitoring[iii].
Phylogenetic studies described various types of coronaviruses (CoVs), including middle east respiratory syndrome (MERS) and severe acute respiratory syndrome coronavirus (SARS), which are divided into four groups of alpha (229E and NL63), beta (OC43 and

HKU1), gamma and delta coronaviruses[iv]. Recently, a new strain of coronavirus was discovered, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The manifesting disease caused by this new virus was called Covid-19[iv]. Studies had shown that when SARS-CoV-2 enter lung tissue cells and proliferate, it causes alveolar and interstitial inflammatory oedema and secretion, leading to damaged alveolar gas exchange and central nervous system (CNS) hypoxia. In addition, SARS-CoV2 enters the nasal passage and provokes neuronal inflammatory responses through immune system dysregulation. SARS-CoV-2 also invades the spinal cord and causes acute inflammation of grey and white matter (e.g. myelitis), including with urinary and bowel incontinence[iv].

Medical imagery, including chest radiography and computed tomography (CT), are widely utilized in COVID-19 patients, both at the time of baseline diagnosis and throughout the disease course[v].

Initially, SARS-CoV-2 was considered a respiratory pathogen. However, it practically behaved as a virus that causes a multisystem involvement. In addition to pulmonary, renal, gastrointestinal, hematological and neurological manifestations, there have also been reported. It is now known that several central and peripheral nervous system disorders can occur following SARS-CoV-2 infection[vi]. Among severe central nervous system (CNS) manifestations, stroke, demyelinating disorders and seizures were commonly reported, as well as spinal cord complications associated with COVID-19 . On the other side, patients with known primary demyelinating disorders may experience an exacerbation of pre-existing neurological features[vi].

So, COVID-19 can evoke a range of neurosensory conditions belonging to infectious, inflammatory, demyelinating and degenerative classes.

Various studies suggested that patients with physical disabilities may be considered susceptible to mental health disorders like depression, worry, fear and anxiety. Therefore, it is extremely important to evaluate the psychological state of people with physical disabilities during the onset of COVID-19, too[vii].

Many (mainly) non-specific options, including antiviral agents and antiinflammatory protocols, are available with varying therapeutic effect. However, some changes to these general protocols, are necessary including to ensure the delivery of therapeutic(s) to the specific components of the CNS[viii].

SCI is often an irreversible condition that leads to weakening of muscle activity in the limbs and the trunk, sensory and respectively, bladder and bowel, functioning impairments, below the lesion level. Treatment modalities for SCI are limited to maximizing residual function [e.g. physiatric interventions such as: paired associative stimulation (PAS) that is a combination of transcranial magnetic stimulation (TMS) with peripheral nerve stimulation (PNS) – capable to induce a long-term potentiation (LTP)-like effect in the central nervous system] and minimizing the range of complications (mainly – but not exclusively – through rehabilitative nursing[ix]). The effects of various protocols have been studied in a lot of neurologic conditions both for diagnostic and therapeutic purposes. However, as there is no cure for SCI, there is a need for more experimental treatments to help patients with SCI improve muscle activity and increase independence[x].

The COVID-19 vaccines have brought a ray of hope to effectively fight this pandemic and save human lives. Four main types of vaccines are currently in use, including viral vector vaccines, COVID-19 mRNA vaccines, inactivated or attenuated virus vaccines and protein vaccines. Yet, post-authorization, a spectrum of serious neurological (and at other somatic and/or psychological levels) other complications was reported as cerebral venous sinus thrombosis, Bell's palsy, transverse myelitis, acute disseminated encephalomyelitis and Guillain-Barré syndrome. However, a causal association of these adverse events is controversial and large prospective studies are needed to prove causality[xi].

Little is known about the influence of the COVID-19 vaccines in specific conditions such as patients with neuromotor disorders. One operational review of United States Veterans

Health Administration (VHA) medical records related to COVID-19 infections and vaccinations presents preliminary data on vaccine breakthrough in Veterans with spinal cord injuries[xii].

COVID-19 pandemic has affected the population worldwide, evidencing new challenges and opportunities for several kinds of emergent and existing technologies. There are studies which presented the Social Assistive Robotics (SAR) as a potential tool to support clinical care areas. Robot-assisted therapies as Lokomat were successful for neurorehabilitation during and also after the COVID-19 pandemic[xiii].

At least a part of the SCIs are incomplete, presenting some degree of spontaneous functional recovery in weeks or months following the injury. This is assigned to plasticity in uninjured spinal pathways or other areas of the central nervous system. Unfortunately, the spontaneous recovery of motor and/or sensory function can be modest and rarely allows complete recovery. Thus, a major focus of contemporary clinical researches in the field of SCI tends to enhance CNS plasticity and functional recovery[xiv]. In this context, acute intermittent hypoxia (AIH) claim to be one of the therapeutic modality that enhances neuroplasticity.

The essential feature of intermittent hypoxia (IH) is repeated or recurrent episodes of low oxygen (hypoxia), interspersed with periods of normoxia. Recent studies reveal that IH has varied effects on multiple systems which depend of: a) the duration of hypoxia, b) the severity of hypoxemia, c) the number of cycles/day, d) the pattern of IH presentation (consecutive days vs. alternating days) and e) the protocol duration. Among these, the severity of hypoxia and the number of cycles per day are the most correlated with its effects. It was demonstrated that with low cycle numbers per day and mild to moderate hypoxic episodes, beneficial effects are more predominant[xv].

Material and methods

It is very important to study the bibliographic resources, in order to understand the actual stage of knowledge about our field of interest: SCI – particularly paraplegia – in the Covid-19 era. For this purpose, we collected data from: Elsevier[xvi], NCBI PubMed[xvii] and NCBI PMCentral[xviii] library data bases, also from the Physiotherapy Evidence Database (PEDro)[xix] using, contextually, four combinations of keywords/ syntaxes (Table1).

We also used the ISI Web of Knowledge/Science database in order to check whether the articles selected by the PRISMA method from the above mentioned databases are published in journals indexed in the Institute for Scientific Information (ISI – ex-Thomson Reuters – Clarivate Analytics) database[xx]. We conducted a systematic review of the related literature, using the widely and internationally accepted PRISMA method [xxi] (Fig.1). The medical databases were searched for the articles published between 01.01.-03.12.2021, which were open access, written in English. As a result, articles which did not meet the above mentioned criteria – including not published in journals indexed in ISI Thompson Reuters data base – were not considered eligible. The remaining articles were further filtered using the PEDro scoring algorithm[xxii], to evidence their quality – eligible only those ranked with a minimum (PEDro inspired) score[xxii] of 4 ("fair quality") – according to the number of citations, after applying an adapted calculation formula[xxiii] (Table 2).

Several works which are not ISI Thompson Reuters indexed, including the Romanian related literature, were consulted as they are suggestive, in order to understand the pathogenic and clinical aspects of Covid-19 disease, especially in patients with SCI (see References).

Table1 Keywords combinations using for search of medical databases

Keyword combinations	Elsevier	PubMed	PMC	PEDro	Total
"Spinal cord injury" + "Tetraplegia" + "COVID-19"	0	0	37	0	37
"Spinal cord injury" + "Paraplegia" + "COVID-19"	0	0	51	0	51
"SCI" + "Tetraplegia" + "COVID-19"	0	0	29	0	29
"SCI" + "Paraplegia" + "COVID-19"	0	0	47	0	47
Total	0	0	164	0	164

Fig.1 The specific diagram of our PRISMA type of search and selection

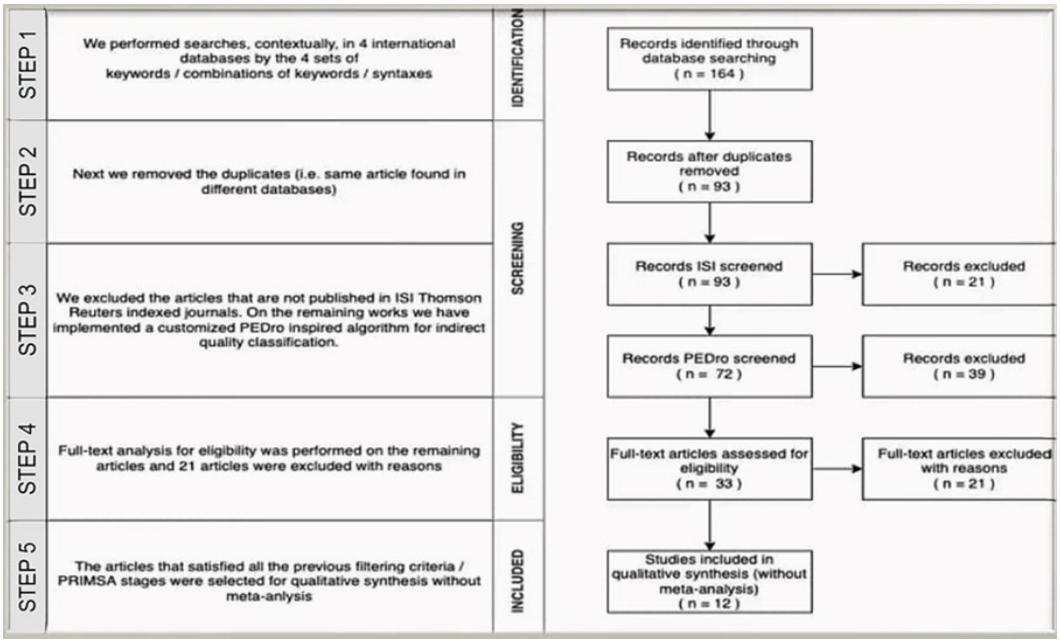

Table 2 The list of the selected articles, following to the PRISMA method

No.	Article	Citation count	Reference count	PEDro score
1	Fakhri et al, Targeting Neurological Manifestations of Coronaviruses by Candidate Phytochemicals: A Mechsanistic Approach - Front Pharmacol. 2020; 11: 621099. Published online 2021 Jan 20. doi: 10.3389/fphar.2020.621099	9	265	10
2	Amene Saghazadeh, Nima Rezaei, Biosensing surfaces and therapeutic biomaterials for the central nervous system in COVID-19 - Emergent Mater. 2021 Mar 10 : 1–20. doi: 10.1007/s42247-021-00192-8 [Epub ahead of print]	3	182	10

3	Mondal et al, COVID-19 and emerging spinal cord complications: A systematic review - Mult Scler Relat Disord. 2021 Jun; 51: 102917. Published online 2021 Mar 21. doi: 10.1016/j.msard.2021.102917	9	45	10
4	Céspedes et al, Long-Term Social Human-Robot Interaction for Neurorehabilitation: Robots as a Tool to Support Gait Therapy in the Pandemic - Front Neurorobot. 2021; 15: 612034. Published online 2021 Feb 23. doi: 10.3389/fnbot.2021.612034	10	43	10
5	Ravindra Kumar Garg, Vimal Kumar Paliwal, Spectrum of neurological complications following COVID-19 vaccination - Neurol Sci. 2021 Oct 31 : 1–38. doi: 10.1007/s10072-021-05662-9 [Epub ahead of print]	6	147	10
6	Piotr Urbański, Łukasz Szeliga, Tomasz Tasiemski, Impact of COVID-19 pandemic on athletes with disabilities preparing for the Paralympic Games in Tokyo - BMC Res Notes. 2021; 14: 233. Published online 2021 Jun 14. doi: 10.1186/s13104-021-05646-0	6	21	8
7	Patel et al, Diaphragm and Phrenic Nerve Ultrasound in COVID-19 Patients and Beyond: Imaging Technique, Findings, and Clinical Applications - J Ultrasound Med. 2021 Mar 27 : 10.1002/jum.15706. doi: 10.1002/jum.15706 [Epub ahead of print]	4	45	7
8	Summaka et al, Assessing the psychological impact of COVID-19 outbreak and its related factors on Lebanese individuals with physical disabilities - Disabil Health J. 2021 Jul; 14(3): 101073. Published online 2021 Feb 18. doi: 10.1016/j.dhjo.2021.101073	4	41	6
9	Chesnel et al, Efficiency and satisfaction with telephone consultation of follow-up patients in neuro-urology: Experience of the COVID-19 pandemic - Neurourol Urodyn. 2021 Mar; 40(3): 929–937. Published online 2021 Mar 6. doi: 10.1002/nau.24651	4	29	6
10	Pohjonen et al, Omitting TMS component from paired associative stimulation with high-frequency PNS: A case series of tetraplegic patients - Clin Neurophysiol Pract. 2021; 6: 81–87. Published online 2021 Feb 20. doi: 10.1016/j.cnp.2021.01.004	3	28	5
11	Tarantino et al, The effects of COVID-19 pandemic counter measures on patients receiving botulinum toxin therapy and on their caregivers: a study from an Italian cohort - Neurol Sci. 2021; 42(8): 3071–3077. Published online 2021 May 6. doi: 10.1007/s10072-021-05282-3	3	18	4
12	Sankary et al, Breakthrough cases of COVID-19 in vaccinated United States Veterans with spinal cord injuries and disorders - Spinal Cord. 2021 Aug 17 : 1–2. doi: 10.1038/s41393-021-00690-w [Epub ahead of print]	3	5	4

Results

After getting through the steps of the PRISMA method (Fig1), a total of 12 articles were selected (Table2). Although none are directly related to our subject of study, the articles

reflected the impact of COVID-19 pandemic on healthcare system, in particular on people with spinal cord injury. Most of these articles are case-report studies. One article was a systematic literature review regarding Covid-19 emerging spinal cord complications. Therefore, we extended the panel of relevant related bibliographic resources.
As a result, several works which are not ISI Thompson Reuters indexed, including the Romanian related literature, were consulted as they are suggestive, in order to better understand pathogenic and clinical aspects of Covid-19 disease, especially considering the particularities of patients with SCI, as well as to study the principle of intermittent hypoxia treatment.

Discussion

Regarding the COVID-19 pandemic, people with SCI represent a unique diagnostic challenge. Being very fragile due to their physical condition, they are quite vulnerable group at risk for severe evolutions[xxiv].
The prognosis of spinal cord injuries depends on a number of factors as level and severity of the lesion, etiology, the type of interventions administered, complications of the disease, patient-specific genetic factors. Also, age and type of lesion are factors that influence the neurological and functional recovery[xxiv].
In the last two decades, a number of studies have demonstrated that acute AIH can induce neuroplasticity in the injured spinal cord, thereby influencing functional recovery of limbs and respiratory capacity. AIH is a very attractive approach as it can non-invasively induce spinal plasticity proved by a remarkable functional impact in animal models and in a limited number of human studies. Initial observations suggest that AIH can be effectively coupled with traditional rehabilitation methods (e.g., locomotor training) and more experimental approaches, such as stem-cell transplantation[xiv].
Due to potentially adverse effects of AIH (e.g. autonomic dysreflexia, neuroinflammation, reactive gliosis or hypertension), it is very important to find optimal protocols including the number, frequency, and severity of hypoxic episodes, that can be safely applied.
Recent researches demonstrated that low-moderate doses of repeated acute hypoxia (rAIH) do not induce pathology[xiv].

Conclusions

There are a few therapeutic options available after the acute, post-injury period, when spontaneous recovery mechanisms are exhausted and further functional improvement is less probable. The applications of IH are numerous, both in health and pathological states, but require future research to develop protocols that optimize the balance between efficacy and safety. The benefits of this research may be considerable since low-dose of IH appears to represent an appropriate method to enhance lost functions in patients with SCI.
Combined with exercise or other physical and pharmacological methods, rAIH may offer a new direction to improve functional movements in people with SCI, especially – from safety reasons – to be possibly applied in such paraplegic patients**.**
We conclude that protocols including rAIH + walking execises may be potentially effective to ameliorate overground walking in persons with chronic incomplete post SCI patients, especially paraplegics.

Conflict of interests: The authors declare no conflict of interest.

References:

1. i Chesnel et al, Efficiency and satisfaction with telephone consultation of follow-up patients in neuro-urology: Experience of the COVID-19 pandemic - Neurourol Urodyn. 2021 Mar; 40(3): 929–937. Published online 2021 Mar 6. doi: 10.1002/nau.24651

2. ii Piotr Urbański, Łukasz Szeliga, Tomasz Tasiemski, Impact of COVID-19 pandemic on athletes with disabilities preparing for the Paralympic Games in Tokyo - BMC Res Notes. 2021; 14: 233. Published online 2021 Jun 14. doi: 10.1186/s13104-021-05646-0
3. iii Tarantino et al, The effects of COVID-19 pandemic countermeasures on patients receiving botulinum toxin therapy and on their caregivers: a study from an Italian cohort - Neurol Sci. 2021; 42(8): 3071–3077. Published online 2021 May 6. doi: 10.1007/s10072-021-05282-3
4. iv Fakhri et al, Targeting Neurological Manifestations of Coronaviruses by Candidate Phytochemicals: A Mechsanistic Approach - Front Pharmacol. 2020; 11: 621099. Published online 2021 Jan 20. doi: 10.3389/fphar.2020.621099
5. v Patel et al, Diaphragm and Phrenic Nerve Ultrasound in COVID-19 Patients and Beyond: Imaging Technique, Findings, and Clinical Applications - J Ultrasound Med. 2021 Mar 27 : 10.1002/jum.15706. doi: 10.1002/jum.15706 [Epub ahead of print]
6. vi Mondal et al, COVID-19 and emerging spinal cord complications: A systematic review - Mult Scler Relat Disord. 2021 Jun; 51: 102917. Published online 2021 Mar 21. doi: 10.1016/j.msard.2021.102917
7. vii Summaka et al, Assessing the psychological impact of COVID-19 outbreak and its related factors on Lebanese individuals with physical disabilities - Disabil Health J. 2021 Jul; 14(3): 101073. Published online 2021 Feb 18. doi: 10.1016/j.dhjo.2021.101073
8. viii Amene Saghazadeh, Nima Rezaei, Biosensing surfaces and therapeutic biomaterials for the central nervous system in COVID-19 - Emergent Mater. 2021 Mar 10 : 1–20. doi: 10.1007/s42247-021-00192-8 [Epub ahead of print]
9. ix Hoeman SP - Rehabilitiation Nursing. Prevention, Intervention and Outcomes - Mosby Inc., an affiliate of Elsevier Inc., St. Louis, 2008
10. x Pohjonen et al, Omitting TMS component from paired associative stimulation with high-frequency PNS: A case series of tetraplegic patients - Clin Neurophysiol Pract. 2021; 6: 81–87. Published online 2021 Feb 20. doi: 10.1016/j.cnp.2021.01.004
11. xi Ravindra Kumar Garg, Vimal Kumar Paliwal, Spectrum of neurological complications following COVID-19 vaccination - Neurol Sci. 2021 Oct 31 : 1–38. doi: 10.1007/s10072-021-05662-9 [Epub ahead of print]
12. xiiSankary et al, Breakthrough cases of COVID-19 in vaccinated United States Veterans with spinal cord injuries and disorders - Spinal Cord. 2021 Aug 17 : 1–2. doi: 10.1038/s41393-021-00690-w [Epub ahead of print]
13. xiii Céspedes et al, Long-Term Social Human-Robot Interaction for Neurorehabilitation: Robots as a Tool to Support Gait Therapy in the Pandemic - Front Neurorobot. 2021; 15: 612034. Published online 2021 Feb 23. doi: 10.3389/fnbot.2021.612034
14. xiv Elisa J. Gonzalez-Rothi, Kun-Ze Lee, Erica A. Dale, Paul J. Reier, Gordon S. Mitchell, and David D. Fuller, Intermittent hypoxia and neurorehabilitation 15 DEC 2015https://doi.org/10.1152/japplphysiol.00235.2015
15. xv Angela Navarrete-Opazo, and Gordon S. Mitchell, Therapeutic potential of intermittent hypoxia: a matter of dose 15 NOV 2014https://doi.org/10.1152/ajpregu.00208.2014
16. xvi https://www.elsevier.com/
17. xvii https://www.ncbi.nlm.nih.gov
18. xviii https://www.ncbi.nlm.nih.gov
19. xix http://search.pedro.org.au/search
20. xx *https://apps.webofknowledge.com; **Acquisition of the Thomson Reuters Intellectual Property and Science Business by Onex and Baring Asia Completed – https://web.archive.org/web/20161205133655/http://ipscience.thomsonreuters.com/news/ip-and-science-launched-as-independent-company/
21. xxi *http://prismastatement.org/documents/PRISMA%202009%20flow%20diagram.pdf; **Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & PRISMA Group (2009), Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS medicine, 6(7), e1000097
22. xxii https://www.strokengine.ca/glossary/pedro--score/
23. xxiii Onose, G., Popescu, N., Munteanu, C., Ciobanu, V., Sporea, C., Mirea, M. D., ... & Mirea, A., Mobile Mechatronic/Robotic Orthotic Devices to Assist–Rehabilitate Neuromotor Impairments in the Upper Limb: A Systematic and Synthetic Review, Frontiers in neuroscience, 2018, 12 (https://www.frontiersin.org/articles/10.3389/fnins.2018.00577/full
24. xxiv Prof. Univ. Dr. Gelu Onose – Universitatea de Medicină şi Farmacie ”Carol Davila”, Spitalul Clinic de Urgenţă ”Bagdasar-Arseni”, Bucureşti,Editura Universitară „Carol Davila” Bucureşti, 2011 Platforma de ghiduri de practică profesională pentru specialitatea Recuperare, Medicină Fizică şi Balneologie