



Neuropathic Pain Associated with COVID-19: a Systematic Review of Case Reports

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Abstract

Purpose of Review Researchers suggests that patients with COVID-19 develop neuropathic pain within weeks or months following infection and that patients with neuropathic pain and COVID-19 sometimes present with deterioration of neurologic complications and pain exacerbation. The objective of this systematic review is to discuss the case-reports having neuropathic pain during and after COVID-19 infection.

Recent Findings Case reports that has described about patients getting neuropathy or neuropathic pain around the disease either immediately or late post COVID were included. The data was extracted and qualitatively synthesised. Literature was searched and 939 articles were found. 12 articles were screened as per the eligibility criteria and finally, 6 case reports on neuropathic pain in Covid-19 were selected from the database and manual search and finalised for analysis. 2 cases of herpes zoster and post herpetic neuralgia, 2 cases of intense burning pain, 1 case of trigeminal neuralgia and 1 of brachial plexopathy included for the review.

Summary Covid 19 viral neurogenic invasion is something very newly discovered topic of discussion in the field of research. With the passage of time, more cases will emerge and more data will be available for research. The review is registered in Prospero with no. CRD42021257060.

Keywords COVID-19 · Coronavirus · Pain · Neuropathic · Neurology

Introduction

Neuropathic pain is the pain that results due to any lesion or disease of the somatosensory nervous system, as per the International Association for the Study of Pain (IASP) [1,

2]. There are different causative neurobiological mechanisms, clinical features, and aetiology of the present lesion for this broad category of pain. Non-nociceptive pain is the most broadly known and accepted term for neuropathic pain because there is no nociceptive stimulus present. Neuropathic pain can be very disturbing for the patient and may have chronic effects if not treated timely and properly. Neuropathic

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pain is described as throbbing, piercing, or burning pain by the patients. Patients also complain of hyperalgesia, which is a feeling of more pain than it should be felt when a normally causing pain stimulus is given. Patients complain of allodynia which is the pain caused by painless stimulus. Neuropathy and neuropathic pain can be triggered by many viral infections. Peripheral neuropathy is caused by immune-mediated mechanisms and not by direct nerve disease. This is supported by viral genome studies on peripheral neuropathy [3, 6]. Inflammation of the peripheral nerves and ganglia as well as tissue damage causes the development of pain. Some viral infections, such as herpes zoster virus, human immunodeficiency virus (HIV), Epstein-Barr virus, cytomegalovirus, enteroviruses, and tropical viruses, have been shown to cause neuropathic pain [4, 5]. Neuropathic pain has also been documented in patients recovering from the SARS virus, a coronavirus that caused a worldwide outbreak in 2003 [5]. Viral infections can injure the peripheral nervous system, by directly effecting the microbe and secondary immune overactivation. Infection through SARS-CoV-2 and any neurogenic symptoms points towards post-infectious response resulting from compromised immunity [1]. SARS-CoV-2 infection-associated Guillain-Barre syndrome (GBS)-related case reports have been documented in China and Europe [7–9].

This review will specifically throw light on the case reports of patients with neuropathic pain, developed around COVID-19 infection.

Methods

Data Source and Searches

Literature for this systematic review (PROSPERO Registration: CRD42021257060) has been searched electronically from January 2020 to July 2021 in Web of Science, Medline (PUBMED), SCOPUS, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL). Search was done using highly sensitive strategies in combination with the following terms: “Covid-19”, “Covid”, “Corona”, “Pain”, “Neuropathy”, “Neurological”, “Neuropathic pain”, “Neuralgia”, “Case study”, and “Case-report”. Publications in English language only will be included. Additional studies were searched by analysing the references from relevant articles.

Study Selection and Data Extraction

Two reviewers (NRD and DJ) independently evaluated and scrutinised the full text articles for eligibility as per criteria for eligibility. Any kind of conflict between reviewers was sorted by involving third reviewer (VG) and mutual consent. Both individually extracted data in accordance with the year of publication, type of study, and each and every information

related to participants like the disease onset, epidemiology, and signs/symptoms, investigations, pain severity, and conclusions. We included case reports with pain related to neurological manifestations and any kind of neuropathic pain associated with SARS-CoV-2 infection. Interventional, comparative, and prospective studies were excluded.

Integration of Results

The data was extracted and qualitatively synthesised. Because the number of reports and patients is restricted, and also the study design, underlying pathology, condition, intervention, investigations procedure, and outcome measures were of heterogeneous nature, quantitative analysis could not be conducted.

Ethical Permit

Published case reports have been included in this systematic review. This work did not include any details about the personal lives of the patients. This study did not include any human participants. We did not seek ethical approval from a committee.

Evaluation of the Risk of Biases

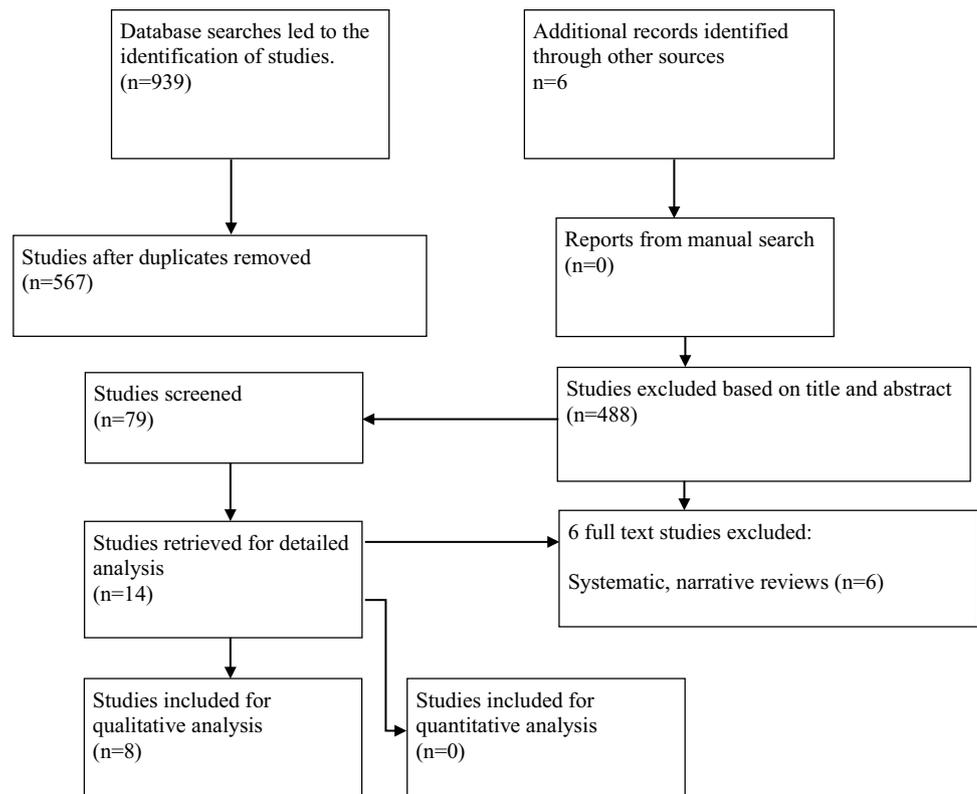
Moola et al. [10] devised the critical evaluation checklist for case reports. We incorporated it for the evaluation of risk of bias in the included studies. If a case report met 5 of the 8 appraisal criteria, it was considered to be of acceptable quality and hence included in the systematic review. Assessment was done by two independent reviewers (NRD and DJ).

Results

Literature was searched and 939 articles were found. Fourteen articles were screened as per the eligibility criteria, and finally, 8 case reports on neuropathic pain in COVID-19 were selected from the database and manual search and finalised for analysis. The process for search criteria, selection, and exclusion of studies is represented in Fig. 1.

Evaluating Bias Risk

Table 1 displays the bias risk that has been evaluated with the help of the Critical Appraisal Checklist for Case Reports [10]. The first assessment criterion was patient demographics; five of six studies included information on gender, age, and, in some cases, employment (Yes: 5). The second factor was patient histories and timelines; just one study out of six did not include these (Yes: 5, No: 1). The third criteria were an accurate description of the patients' present

Fig. 1 Selection process

clinical status; all six studies met this requirement (Yes: 6). The fourth criterion was a detailed explanation of the clinical state, evaluation, and outcomes; all studies, with the exception of one, addressed these in depth (Yes: 6). The fifth assessment criterion is a clear explanation of intervention and therapy processes; in all six investigations, broad remarks were given about them (Yes: 6). The sixth requirement required a detailed account of post-intervention clinical circumstances, which were not provided. Pain and symptom reduction were clearly documented in most of the six investigations, although not in as much detail as pre-intervention settings (Yes: 6). The seventh criteria were information on unforeseen or unfavourable occurrences; just one research did not explain this (Yes: 5). Finally, the eighth criteria were if the case report gave takeaway lessons; four studies were deemed beneficial since they covered numerous testing and thorough explanations for unusual occurrences.

The majority of case reports adequately recorded the patient's demographic features, clinical history according to chronology, the patient's current clinical condition at presentation, diagnostic tests or evaluation procedures, and the outcomes. Following the pre-specified criteria, all 8 case reports were assessed to be of acceptable quality and so included in this systematic review. Four of the eight investigations (Andrew R. Shors [14]; Timo Siepmann [17]; Javier Molina-Gil MD et al. [15]; Mario Cacciavillani et al.

[18]) did not describe the important takeaways. Table 1 summarises the findings.

Evidence Synthesis

Cases were from the USA ($n=3$), the UK ($n=1$), Spain ($n=1$), China ($n=1$), Germany ($n=1$), and Italy ($n=1$). Age of patients ranged from 40 to 70 years overall, and there were 5 men and 3 women (Table 2). In all patients, COVID-19 was diagnosed with RT-PCR.

Neuropathic pain and neuropathic symptoms started between 4 to 45 days after the symptoms onset and diagnosis of COVID-19 in 4 patients, but conversely, in four case reports, onset of neuropathic symptoms developed 3 to 15 days before COVID-19 diagnosed (Table 2).

Two case reports had patients with herpes zoster [13, 14], one with intense burning pain [12], one with trigeminal neuralgia [15], one with brachial plexopathy [11], one with small fibre polyneuropathy [16], and two with neuralgic amyotrophy [17, 18]. Three patients, one with burning pain, and two with herpes zoster infection, did not have any investigations done.

Gabapentin, oxycodone, acetaminophen, amitriptyline, nortriptyline, pregabalin, and diazepam were the choice of drugs to control neuropathic symptoms in patients with brachial plexopathy, intense burning pain, neuropathic pain,

Table 1 Critical appraisal of case reports included in this review

Study ID	1. Were patient's demographic characteristics clearly described?	2. Was the patient's history clearly described and presented as a timeline?	3. Was the current clinical condition of the patient on presentation clearly described?	4. Were diagnostic tests or assessment methods and the results clearly described?	5. Was the intervention(s) or treatment procedure(s) clearly described?	6. Was the post-intervention clinical condition clearly described?	7. Were adverse events (harms) or unanticipated events identified and described?	8. Does the case report provide takeaway lessons?	Overall appraisal: Include <input type="checkbox"/> Exclude <input type="checkbox"/> <input type="checkbox"/> Seek further info <input type="checkbox"/>
Catherine Young Han et al. [11]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Include
Feyzullah Aksan et al. [12]	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Include
Andrew R. Shors [14]	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Include
Xueqin Cao et al. [13]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include
Javier Molina-Gil MD et al. [15]	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Include
Mathew McWilliam et al. [16]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include
Timo Siepmann et al. [17]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Include
Mario Cacciavillani et al. [18]	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Include

Table 2 Description of the characteristics of the patients

Author and year (title) Patient	COVID-19 symptom onset and method of diagnosis	Neuropathic pain/condition (presentation)	Investigations done	Interventions (drugs)	Results	Conclusions
Catherine Young Han et al. [11] Brachial plexopathy as a complication of COVID-19	Age: 52 years Gender: male Past history: hypertension and diabetes mellitus Place: USA	Severe upper extremity weakness and neuropathic pain in the left hand and forearm	MRI, NCV, EMG	Gabapentin, oxycodone, acetaminophen, physical therapy. Wrist sprain	Neuropathic pain resolved and improvement in other symptoms also	Covid-19 induced hypercoagulability can cause microthrombotic complications in multiple organ systems. In this patient, microthrombi occluded vasa nervorum supplying the brachial plexus causing brachial plexopathy. Early investigations and therapy should be considered
Feyzullah Aksan et al. [12] A COVID-19 patient with intense burning pain	Age: 45 years Gender: female Past history: hypertension, obesity, COPD, asthma Place: USA	Neck and back pain ranging from C1 to L5, encompassing the paraspinal and trapezius muscle areas	None	Acetaminophen, NSAID, oxycodone, tramadol, gabapentin	Gabapentin relieved pain and hypersensitivity to touch also improved	Infection caused neuropathic pain in this patient and gabapentin was effective
Andrew R. Shors [14] Herpes zoster and severe acute herpetic neuralgia as a complication of COVID-19 infection	Age: 49 years Gender: female Past history: nothing Place: USA	Itchy rash on trunk, several vesicles and papules on face. Skin burning, allodynia with sinus and tooth pain, severe neuralgia	None	Valacyclovir 1 g 3 times daily, gabapentin, topical lidocaine	Partial control of symptoms	In this patient, viral infection causes inflammation at the dorsal root ganglion and led to strong herpes response
Xueqin Cao et al. [13] Herpes zoster and postherpetic neuralgia in an elderly patient with critical COVID-19: a case report	Age: 70 years Gender: female Past history: diabetes, myasthenia gravis (on medications) Place: China	small red papules on the right side of waist with sharp pain (9 on 11-PNRS)	None	IV acyclovir and prednisolone (20 mg orally), infrared therapy, pregabalin, ibuprofen	Gradual relief in symptoms (took medicines for pain management for one and half month)	COVID-19 infection decreases T lymphocytes and myasthenia gravis also caused dysregulation of regulatory T cells and elevated IL-6. This caused immunosuppressive illness herpes zoster in this patient. Early anti-viral therapy helped the patient

Table 2 (continued)

Author and year (title)	Patient	COVID-19 symptom onset and method of diagnosis	Neuropathic pain/condition (presentation)	Investigations done	Interventions (drugs)	Results	Conclusions
Javier Molina-Gil MD et al. [15] Trigeminal neuralgia as the sole neurological manifestation of COVID-19: a case report	Age: 65 years Gender: male Past history: nothing Place: Spain	Three days after neurological pain started RT-PCR, D-dimer	Sudden excruciating pain in the right V1 region triggered by light touch	Cranial Magnetic Resonance with MR angiography, blood count, infectious serologies, RFT, LFT, thyroid profile	Diazepam 10 mg and pregabalin 300 mg	Relief in pain	COVID-19 virus invades the CNS retrogradely and bind to angiotensin and convert it to enzyme type 2, presenting trigeminal Neuralgia
Mathew McWilliam et al. [16] Neuropathic pain post-COVID-19: a case report	Age: 61 years Gender: male Past history: none Place: UK	One week before the onset of neuropathic pain RT-PCR	A brief sensation of burning throughout the body, followed by paraesthesia and scorching pain in both feet and hands	ESR, IgG, CBC, liver function, renal, folic acid, B ₁₂ , glycated haemoglobin-bin(HbA1C), calcium, cholesterol, vitamin D, thyroid function tests MRI brain, whole spine and brachial plexus, NCVs, CSF analysis	Amitriptyline, 10 mg; nortriptyline, 10 mg; ineffective Pregabalin 25 mg, minimal benefit Pregabalin 75 mg, continued	Pain score reduced to 2/20 from 7/10 score	This patient is suspected to have a post-infectious autoimmune small fibre polyneuropathy which is a sensory neuropathy that predominantly affects small fibres and their functions
Timo Siepmann et al. [17] Neuralgia amyotrophy following infection with SARS-CoV-2	Age: 52 years Gender: male Past history: none Place: Germany	One week before the onset of pain RT-PCR	Severe constant pain in the right shoulder intensified on shoulder extension, shifted distally with paraesthesia in fingers, followed by progressive weakness of the hand	NCV, EMG of the hand muscles and nerves, MRI and nerve ultrasound of the median nerve. CSF analysis	Oral prednisolone (1 mg/kg weight)	Little pain relief with no improvement in muscle power	This patient of mono-neuropathic brachial neuritis on the dominant side after SARS-CoV-2 infection suggests a probable link between neuralgic amyotrophy and COVID-19
Mario Cacciavillani et al. [18] Pure sensory neuralgia amyotrophy in COVID-19 infection	Age: 52 years Gender: male Past history: none Place: Italy	15 days before the onset of pain RT-PCR	Excruciating pain in the left upper limb followed by hypoesthesia and dysesthesia	NCV, EMG of left upper limb muscles and ultrasound of the left upper limb nerves	Acetaminophen	Pain resolved completely, hypoesthesia and dysesthesia was present	Neuralgic amyotrophy might manifest itself as pure sensory involvement. Infections like covid-19 that occur before or after an immune-mediated pathophysiologic process are thought to be probable triggers

RT-PCR Reverse Transcription-Polymerase Chain Reaction, MRI Magnetic resonance imaging, NCV nerve conduction velocity, COPD chronic obstructive pulmonary disease, NSAID non-steroidal anti-inflammatory drug, IJ-PMRS 11 point numeric rating scale, MRI magnetic resonance imaging, CMV cytomegalovirus, EBV Epstein Barr virus, HAV hepatitis A virus, AHBc anti-hepatitis B virus, HIV human immunodeficiency virus, IgM immune globulin M, CSF Cerebrospinal fluid, RFT Renal Function Test, LFT Liver Function Test, ESR Erythrocyte Sedimentation Rate

small fibre polyneuropathy, sensory neuralgic amyotrophy, and trigeminal neuralgia. Tramadol, analgesia, ibuprofen, infrared therapy, and topical lidocaine were given to relieve pain. Acyclovir was given in both patients of herpes zoster and post-herpetic neuralgia.

Patient with brachial plexopathy observes severe weakness in the left upper extremity along with neuropathic pain in the left hand and forearm. One patient had intense burning pain in neck and back along C1 to L5 region, including the paraspinal area and trapezius muscle area. Patients with herpes zoster and post-herpes neuralgia had rash on waist and papules on face with burning sensation and severe pain. Trigeminal neuralgia patient felt sudden severe pain in the right side of face that was triggered by light touch. A severe burning sensation throughout the body followed by tingling, numbness, and burning pain in both feet and hands was observed in patient who had neuropathic pain due to small fibre polyneuropathy. Severe constant pain in the right upper limb followed by paraesthesia and progressive weakness and left upper limb followed by hypoesthesia and dysesthesia along with motor weakness was seen in both cases of neuralgic amyotrophy respectively.

All patients showed gradual improvement in symptoms.

Discussion

Neuropathic pain is the pain observed directly due to peripheral or central nervous system dysfunction without stimulation of nociceptors [19]. The problem in neuropathic pain is due to the abnormal processing of perception and is usually seen in people with neurological diseases. Nociceptive pain is a physiological response as a result of tissue damage that will initiate the pain. Unlike neurogenic pain, neuropathic pain does not involve transient disturbances of the central or peripheral nervous system and therefore produces prolonged pain [20].

Coronaviruses can cause neuropathic pain either directly or indirectly. Recent evidence suggests that angiotensin-converting enzyme 2 (ACE2) serves as a “cytokine storm” doorway for SARS-CoV-2 entrance into cells and the release of tumour necrosis factor alpha (TNF- α) [21]. COVID-19 patients suffer from neurological symptoms, including peripheral neuropathies. Loss of olfactory and gustatory senses, visual damage, and neuropathic pain are the most commonly reported peripheral nerve symptoms. Myalgia or joint pain (arthralgia), sore throat, and headache are all pain-related symptoms. Many individuals with COVID-19 have experienced peripheral nervous system involvement, including painful neuropathies. Mao et al. reported dysgeusia (5.6%), dyssomnia (5.1%), visual disturbances (1.4%), and neuralgia (2.3%) as peripheral nervous system effects. This might be due to invasion of virus in the peripheral

nerves, extended immobilisation during a severe illness, or both [22].

During the COVID-19 outbreak, patients exhibiting neurological signs and experiencing various sorts of discomfort must not be neglected. This is the very first systematic review performed to analyse cases/patients (case reports) of neuropathic pain developed due to underlying neurological disorder during or post-COVID-19 infection. Though many case reports are published on neurological involvement post-COVID-19 viral infection, we took only those patients who had pain as the most dominant symptom. Of the 939 studies searched in the database, only eight studies were selected and reviewed. Eight case reports of patients belonged to different regions of the world are reviewed. They all got neuropathic pain, went through the necessary tests and treatments, and eventually recovered.

Reviews on neurological symptoms, manifestations, complications, and comorbidities post-COVID-19 have been conducted in the last 2 years [22–30]. One literature commentary described the long-term pain syndromes like testicular pain, headache, chronic pain, and chest pain related to COVID-19 infection [31]. The first study to report neurological involvement in SARS-CoV-2 patients indicated that neurological symptoms were substantially more prevalent in individuals with “severe” illness, as characterised by respiratory symptoms [23]. Headache, insomnia, myalgia, ageusia, and dizziness were common neurological manifestations of COVID; less common were cases of seizure, stroke, Miller fisher syndrome, encephalitis, and GBS [25–28]. One systematic review has been published in 2020, reviewing the case reports on post-COVID-19 Guillain–Barre Syndrome [32]. We, that is why, did not consider GBS patient’s case reports for this review. We specifically concentrated on patients with neuropathic pain or neurological conditions causing pain as one of the most prominent symptom. Neuropathic pain is very less reported worldwide.

Mechanism for viral invasion in the nervous system in the brachial plexopathy case would be the formation of microthrombi resulted due to COVID-19-induced hypercoagulable state [33]. These microthrombi caused nerves infarction supplying the brachial plexus, thence resulting in brachial plexopathy. The cell-mediated immune response, particularly T cells, is declined, mostly CD4+ and CD8+, caused by immunosuppressive illnesses like COVID-19 [34–36]. This decline in immunity and dysregulation of T cells causes the reactivation of latent varicella zoster which lies dormant in the body, resulting in herpes zoster infection.

COVID-19 virus infects epithelial, dendritic, and mononuclear cells early in the infection, generating enhanced production of cytokines and chemokines. The virus transmission is facilitated by the late and inadequate production of interferons, which play a role in building innate immunity against viral infections [37]. Nerve injury due to

pro-inflammatory cytokines and other mediators of the systemic immune dysregulation might be the reason for intense burning pain in the patient.

There is a direct mechanism associated with COVID-19 headache and facial pain generation due to the invasion and dissemination of the virus in the CNS which occurs when the virus binds to the superficial receptors of the angiotensin converting enzyme type 2 found in the trigeminal nerve terminals of the nasal cavity [38]. An indirect stimulation of the trigeminal-vascular system in response to a cytokine storm, with a rise in systemic inflammatory indicators such as calcitonin gene-related peptide, is also hypothesised.

Post-infectious small fibre neuropathy due to involvement of small somatic or autonomic fibres and their functions might be the possible mechanism behind neuropathic pain in Small fibre Polyneuropathy patient. Neuralgic amyotrophy in two patients would be caused by a direct viral infection of the brachial plexus or the autoimmune response to preceding SARS-COV infection [39].

Conclusion

Synthesis and analysis case reports on neuropathic pain post-developed post-COVID-19 infection are performed in this review. Although not many cases are reported worldwide, there are many reviews discussing the neurological expression of COVID-19 and other coronavirus infections. Practitioners and investigators should keep neuropathic symptoms in mind as they see COVID-19 patients and conduct the diagnostic as well as treatment procedure accordingly. One limitation of the present review is not recruiting studies having cases of GBS and such neurological disorders that did not have pain as one of the significant symptom.

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Compliance with Ethical Standards

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Informed Consent Not applicable.

Conflict of Interest The authors declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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