

## SARS-COV-2 INFECTION AND INVOLVEMENT OF PERIPHERAL NERVOUS SYSTEM: A CASE SERIES OF CARPAL TUNNEL SYNDROME AGGRAVATION OR NEW ONSET WITH COVID-19 DISEASE AND A REVIEW OF LITERATURE

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### Abstract.

**Introduction:** COVID-19 may be asymptomatic or have a typical presentation with fever, cough, anosmia, lymphocytopenia. In some cases, it occurs with a “chimeric” presentation, with more subtle and ambiguous symptoms which may be initially misdiagnosed and are referred to in long covid condition. A possible central and peripheral nervous system involvement has been recognized. We present our experience and review the literature about association between carpal tunnel syndrome (CTS) and hand’s arthritis presenting a case series of patients who firmly state that their condition of CTS arised or got worse during a typical presentation of COVID-19. The outbreak of COVID-19 has resulted in significant global healthcare implications. While the respiratory manifestations of COVID-19 have been widely studied, there is emerging evidence suggesting potential associations between COVID-19 and various other health conditions. This review of the literature aims to investigate the potential relationship between COVID-19 and the development or exacerbation of CTS. By synthesizing the available literature on this topic, we aim to provide a comprehensive overview of the current knowledge and enhance our understanding of the potential implications of COVID-19 on CTS.

**Case series:** In this article we report 13 cases of typical presentations of COVID-19 with fever, myalgia, and respiratory system involvement, with a simultaneous aggravation of the median nerve pre-existing neuralgia and some cases that developed a median nerve neuralgia during COVID-19, which came to the attention of the hand surgeon. Some cases had stable symptomatic CTS and were on waiting list for surgical carpal tunnel release, some cases were previously asymptomatic and developed a median nerve neuralgia during COVID-19. All patients referred to a rapid worsening of acral paraesthesia and neuralgic pain of the same quality of CTS and in the median nerve topography. Some patients developed typical COVID-19 symptoms and died; the others were surgically treated.

**Conclusion:** CTS could be an atypical presentations of COVID-19 or a condition of long-covid disease and clinical and epidemiological significance needs to be fully studied. We presented cases of worsening of the median nerve neuralgia which presented among other symptoms of COVID infection. We conclude a causal relation may exist and needs to be further investigated.

**Key words.** Covid, Coronavirus, Carpal Tunnel Syndrome, neuralgia, peripheral nervous system, nerve, arthritis, elderly.

### Introduction.

COVID-19 (SARS-Cov-2 disease) may have an asymptomatic course or a typical presentation with fever, cough, anosmia, lymphocytopenia [1,2].

Unusual findings have also been described [1]. Of these less typical presentations, those affecting the nervous system, either central or peripheral, are not uncommon [3,4].

Carpal tunnel syndrome (CTS) is a common peripheral nerve entrapment disorder characterized by compression of the median nerve at the wrist, leading to hand and wrist pain, numbness, and weakness. While CTS is typically associated with repetitive hand movements and occupational factors, emerging evidence suggests that viral infections may also play a role in its pathogenesis. Given the broad spectrum of systemic manifestations observed in COVID-19, investigating a potential link between COVID-19 and CTS is warranted.

In this article, we report some cases of typical presentations of COVID-19 with fever, myalgia, and respiratory system involvement, with a simultaneous aggravation of the median nerve pre-existing neuralgia, and some cases that developed a median nerve neuralgia during COVID-19, which came to the attention of the hand surgeon. The aim of this article is to describe this unusual symptom we recognized as possibly due to COVID-19, based on clinical observation and known considerations on pathophysiology of the coronavirus infection.

### Materials and Methods.

We analyzed all patients who had come to the attention of our Hand Surgery Unit, from 2020 to the present day, complaining of symptoms referable to CTS and related by them to Covid-19 infection. We included patients who already had a known diagnosis and a reported worsening of symptoms as well as patients with new-onset symptoms. All the patients included underwent Electroneurography and Electromyography to confirm the diagnosis.

### Results.

In the present article we report 13 cases of patients who firmly state that their condition of CTS aroused or got worse during a typical presentation of COVID-19 (Table 1). Some cases, which had stable symptomatic CTS and were on waiting list for surgical carpal tunnel release, referred a typical presentations of COVID-19 with fever, myalgia, and respiratory system involvement, with a simultaneous aggravation of the median nerve pre-existing neuralgia. Some cases were previously

**Table 1.** Case Series. \*clinical improvement was obtained with open carpal tunnel release, after conservative treatment and an observational period of 2-3 months.

Patient	Sex	Age	Side	New onset or disease worsening	Comorbidities	Covid-19 Symptoms					Outcome
						Fever	Myalgia	Respiratory	Gastro-intestinal	Other	
1	M	90	Both	New onset	high blood pressure, diabetes	Yes	Yes	Yes			Death
2	F	82	Left	Worsening	high blood pressure, glaucoma	Yes	Yes	Yes			Death
3	M	66	Both	Worsening		Yes	Yes	Yes			Clinical improvement*
4	F	41	Both	Worsening		Yes	Yes	Yes			Clinical improvement*
5	M	52	Both	Worsening	benign prostatic hypertrophy	Yes	Yes	Yes	Yes		Clinical improvement*
6	M	60	Both	Worsening		Yes	Yes	Yes			Clinical improvement*
7	M	80	Both	New onset	high blood pressure	Yes	Yes	Yes		Skin lesions	Clinical improvement*
8	M	54	Both	New onset	high blood pressure	Yes	Yes	Yes			Clinical improvement*
9	F	84	Both	New onset	high blood pressure	Yes	Yes	Yes			Clinical improvement*
	F	46	Both	Worsening		Yes	Yes	Yes			Clinical improvement*
10	F	58	Left	New onset		Yes	Yes	Yes			Clinical improvement*
11	F	72	Both	New onset	high blood pressure	Yes	Yes	Yes	Yes		Clinical improvement*
12	M	80	Left	Worsening	high blood pressure	Yes	Yes	Yes			Death
13	F	68	Right	New onset		Yes	Yes	Yes			Clinical improvement*

asymptomatic and developed a median nerve neuralgia during COVID-19. All patients referred to a rapid worsening of acral paraesthesia and neuralgic pain of the same quality of CTS and in the median nerve topography during or immediately after COVID-19. Three patients developed typical COVID-19 symptoms and died; the others were surgically treated.

After an observational period of 2-3 months and conservative treatment [5-7], clinical improvement was obtained with open carpal tunnel release in all patients. Surviving patients had a 12-month post-operative follow-up. All 10 patients treated surgically benefited from the surgical treatment.

Two further patients who suffered from a pre-existing median nerve neuralgia (due to a documented CTS) referred to us because of aggravation of the symptoms immediately before CD COVID-19 onset. These two patients were excluded from our case series, because we did not obtain any clinical follow-up, but we think that they may nevertheless be worthy of description and may enhance the very sparse literature on this subject.

#### Case One.

The first case is a 68-year-old male patient with a confirmed diagnosis of bilateral CTS (CTS), mild on the right and moderate

on the left hand, according to Padua classification [8], who had been on waiting list for carpal tunnel release on left hand for two months. He was also hypertensive, treated with a sartan. In March 2020, he reported an abrupt worsening of symptoms and contacted by phone his referring surgeon. He referred to bilateral acral paraesthesia and neuralgic pain of the same quality of CTS and in the median nerve topography, rapidly worsening over the last two days. To confirm median nerve topography and exclude polyneuropathy we asked explicitly for the presence of “pins and needles” on the fifth finger and on the back of the hand, which the patient denied. On the left-hand pain was greater than the contralateral side, with a Numerical Rating Scale (NRS) of 7/10 on the left vs 5.5/10 on the right, and its intensity was more persistent and fixed all day long without circadian oscillations, and sleep was impaired. At the first contact he referred slight evening fever (37.2°) and slight myalgia, without cough and dyspnea. He had not taken any new medication in the past month. We indicated prompt contact with the general practitioner for complete re-evaluation. Moreover, we offered our re-evaluation for the neuropathy.

Six days after, the patient's wife contacted us by phone reporting that later, the day after the first contact, the patient developed typical presentation of COVID-19 with fever (39.0°C) and dyspnea. He immediately accessed the nearest emergency department, where a throat swab was performed for a nucleic acid SARS-Cov-2 identification test (or PCR test), which was positive. He was hospitalized and died two days later of respiratory failure; autopsy was not performed.

### Case Two.

The second patient is a 69 year old male, with obesity, diabetes, hypertension in treatment with metformin, ace-inhibitor and a beta blocker. He was in follow-up for secondary post traumatic right ankle osteoarthritis and confirmed diagnosis of bilateral CTS, minimal on the left and moderate on the right hand, according to Padua classification.[8] He had been on waiting list for carpal tunnel release on right hand for three months. In March 2020 he reported a quick worsening of pain and contacted us by phone. He reported acral paraesthesia and neuralgic pain in the median nerve topography on both hands, with a NRS of 6/10 on the left-hand vs 4.5/10 on the right, worsening over the preceding three days. He denied pain or paresthesia on the fifth finger and on the back of the hand. Pain was present for the whole day. We offered our re-evaluation for the worsening of pain. The day after the first contact, neuralgic pain of the median nerve territory attributable to CTS slightly decreased on both sides (NRS of 5/10 on the left-hand vs 4/10 on the right), while fever until 37,5°C and a worsening diffuse musculoskeletal pain started (visual analogue scale 7/10), with a highest intensity on the right ankle (visual analogue scale 7/10). Over the following three days, body temperature raised until 39.5°C and he presented cough. He accessed the emergency department, where a throat swab was positive for SARS-Cov-2 (PCR test). Furthermore, he presented Leucopenia (3.44, min 4), Lymphocytopenia (19.7%, normal >20%), thrombocytopenia ( $86 \times 109/L$ , normal >120), high transaminase (61 UI/L, normal range 7 - 45), high LDH (254 UI/L, normal <250), high C-reactive protein (13.4 mg/L, normal <5) normal coagulation screening (INR, aPTT, D-Dimer, fibrinogen), blood glucose: 147 mg/dL. Patient died of unspecified causes related to COVID-19 few months later.

### Review of Literature.

The review of the literature reported in the present article was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive search of electronic databases, including PubMed/MEDLINE, Embase, and Scopus, was conducted. Keywords and MeSH terms related to COVID-19, CTS, and neuropathy were used. Studies published between January 2020 and July 2023 were included. Studies reporting on patients diagnosed with COVID-19 and presenting with new-onset CTS or exacerbation of pre-existing CTS were considered for analysis. The review of the literature was performed according to the flow chart in figure 1.

### Review questions

The review questions were formulated following the PICO scheme (population, intervention, comparison, and outcome) as follows:

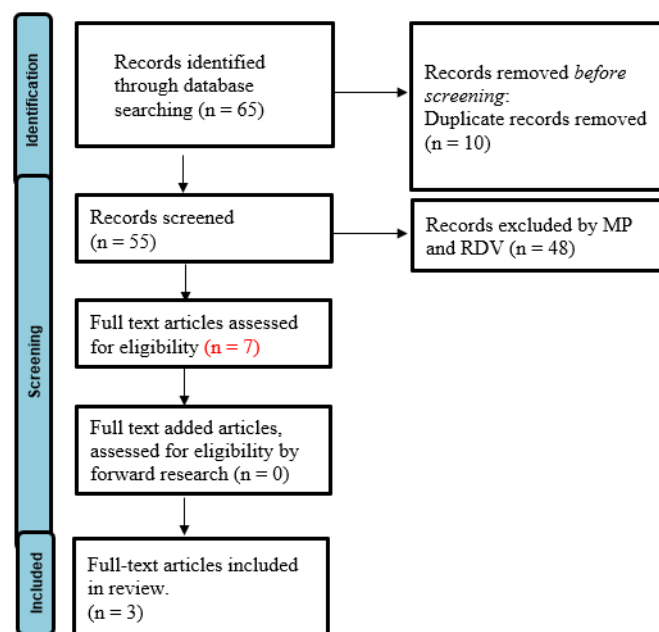


Figure 1. Study flow chart.

Did patients who suffered from COVID-19 contagion (P) have a new onset rather than worsening of already known CTS (C)? Did they need carpal tunnel release surgery (I)? What clinical evolution should we expect (O)? Can be the clinical outcome (O) be influenced by comorbidities (P)?

### Inclusion and exclusion criteria

Full-text articles were analyzed evaluating the correlation between CTS and COVID-19 contagion/disease. Articles written in English were only included. No publication date limits were set. Exclusion criteria were studies on animals, unpublished reports, cadaver or in vitro investigations, review of the literature, abstracts from scientific meetings, and book chapters.

### Search strategy and study selection

MEDLINE via PubMed and Scopus were searched using the keywords: “SARS-CoV-2”, “Covid 19”, “Carpal tunnel”, “Carpal tunnel syndrome”, and heir MeSH terms in any possible combination. Forward research was performed onto the reference list of the selected studies, in order to identify the study of interest. The search was reiterated until July 23, 2023.

### Data extraction and analysis

Two independent reviewers (M.P. and R.D.V.) extracted the data from the studies included. Any discordances were solved by consensus with a third author (V.C.). For each study, the following data were collected: demographic features (sex, age), involved side, new onset CTS or worsening of an already known CTS, diagnostics, associated lesions/symptoms, comorbidities, clinical outcome, and follow-up. Numbers software (Apple Inc., Cupertino, CA, USA) was used to tabulate the collected data. Categorical variables are presented as frequency and percentages. Continuous variables are presented as means and standard deviation. Only one decimal digit was reported and was rounded up.

## Results from review of the literature

After the screening of 65 articles by title and abstract, 9 studies were considered eligible for the full-text analysis [9-17]. After reading the full text, only 3 studies that met inclusion criteria were included in the present review. Among the included studies, one had a level of evidence I [11], while two had a level of evidence IV [14,15].

Fleischer et al. concludes that objectifiable affection of the nervous system is rare in post-COVID-19 syndrome, thus psychosomatic factors can explain peripheral nervous system symptoms [11].

Tullie et al. described a case of CTS post their second dose of AZD1222 (ChAdOx1 nCoV-19) vaccination [15]. In our opinion, the clinical history of this specific case is heterogeneous with respect to the objective of our research.

Only Roncati et al. have currently described cases similar to the cases we report in this article [14].

1. A 51-year-old man (with low level of vitamin D in anamnesis) who developed a left side (monolateral) carpal and cubital nerve syndrome. He underwent decompressive surgery.

2. A 47-year-old man who developed a right side (monolateral) carpal and cubital nerve syndrome. He underwent decompressive surgery. He developed a LADA (latent autoimmune diabetes in adults) in the post Covid-19 disease.

As a conclusion, literature is currently extremely scarce in relation to the association between CTS and COVID-19 disease; the data we have obtained from our search do not allow us to answer our questions.

## Discussion.

Our clinical practice has highlighted the possible relationship between COVID-19 and CTS, however the literature that analyzes the relationship between CTS and COVID-19 is sparse. However, a correlation between the two diseases has already been reported [14].

The literature produced on this subject is scarce, and there is no evidence to confirm the pathophysiological mechanism that determines peripheral neuropathy of the median nerve. Based on the present literature we cannot come to any evidence-based conclusions on this issue.

However, the involvement of the peripheral nervous system has been described in COVID-19, both in motor and in sensory form and has been attributed to various possible causes: the "cytokinetic storm", hypoxic state, acute and chronic inflammatory state, immune mechanisms [18].

CTS is a high prevalence disease [19]. The clinical picture is linked to a chronic compression of the nerve at the wrist that firstly results in endoneurial connective tissue thickening and goes on with the demyelination of the fibers and an axonal degeneration [6,7,19,20].

Good clinical compensation can occur in some cases, thus patients only refer to the physician when CTS is severe, when the nerve injury is permanent, the sensory impairment is persistent and muscular denervation is clinically relevant. On the other hand, there are some patients with slightly positive electromyography/electroneurography and with mainly very intense sensory impairment [20].

In cases where COVID-19 also presents with symptoms similar to the CTS, COVID-19 represents a "storm" that hangs over the median nerve that is probably already at the limit of its functioning due to a more or less compensated chronic inflammation.

This would also explain why surgical decompression is effective to relieve symptoms, according to the literature and as observed in our clinical practice [14]. What the chances of post-surgery recovery are in these patients are still to be assessed, as the long-term evolution of this disorder remains unknown.

Typical presentations of COVID-19 include cough or more serious respiratory impairment, or a completely asymptomatic course, but more subtle presentations, such as isolated anosmia, have been recently described [1,2].

COVID-19 should be recognized in the very first onset, to avoid, with adequate isolation, exposure of household contacts and clinical personnel [21]. We suggest that in some cases COVID-19 occurs with a "chimeric" clinical presentation, with more subtle and ambiguous symptoms which may be easily misdiagnosed at first evaluation [1,3,22-25].

We suggest that, in the cases described, a correlation between the Sars-Cov-2 and sudden neuralgic pain worsening in patients affected by CTS exists and recognizing it can lead to quicker recognition of the patient's illness and a better management. We support the hypothesis of a causal relation between worsening of neuralgic pain and Sars-Cov-2 infection considering in our cases:

1. The temporal correlation of the symptoms.
2. Exclusion of other obvious causes of sudden aggravation of CTS.
3. Pathophysiology of human coronaviruses infections. Myalgia, fever, and limb pain, indeed, may be explicated by a "cytokine avalanche" effect, which in some cases may reach the threshold to provoke a Cytokines Release Syndrome (CRS) [22,26,27].

The role of interleukins has been documented as precipitating and aggravating factors in peripheral nerve suffering [28-31]. A direct infusion of IL-2, furthermore, has been recognized as a provoking factor of CTS [28], and very recent studies have highlighted its role in COVID-19 pathogenesis [32]. In the same way, other molecules as CCL5 have a recognized role in both CTS and COVID-19 [23,33]. Peripheral nervous system findings in COVID-19 have been already described and should not be underestimated [3,24].

The lack of objective evaluation and exams such as electromyography and patient-reported outcomes measures in our report is an obvious limitation [34]. Further analyses on our two non-objectifiable cases are not possible at the moment [35]. Long-term implications for the neuralgic symptom need to be studied at follow. In the second patient, after the overt respiratory system involvement, median nerve pain lessened, but whether the neuralgic pain and motor symptoms are only transient or persistently worsened after acute illness resolution needs to be investigated. According to our hypothesis, a restitution to previous pain and impairment would be more likely after resolution of infection. A further concern on COVID-19 potential to cause peripheral nervous system damage has been

raised from Zhao et al., who reported a case of Guillain-Barré syndrome with a concomitant Sars-Cov-2 infection [4].

The available evidence suggests a potential association between COVID-19 infection and the development or exacerbation of CTS. However, the current literature is limited in terms of sample size, study design, and lack of control groups. Additional robust studies are needed to further investigate this relationship and understand the mechanisms involved. Healthcare providers should be aware of the potential association between COVID-19 and CTS and consider this possibility in patients presenting with hand and wrist symptoms during or after a Sars-Cov-2 infection.

### Conclusion.

Reviewing the literature, although limited, the available evidence suggests a potential link between COVID-19 and CTS. Healthcare providers should be vigilant in recognizing and managing CTS symptoms in COVID-19 patients. Further well-designed studies are required to validate and elucidate the underlying mechanisms of this association. Understanding the potential implications of COVID-19 on CTS can aid in early diagnosis, management, and appropriate referral of affected individuals [12,36].

We also presented a case series of worsening of the median nerve neuralgia, which presented among other symptoms of COVID-19 and a review of the literature on association between CTS and Sars-Cov-2. We conclude a causal relation may be relevant and needs to be further investigated and that the common external neurolysis performed for CTS not COVID-related could be an effective treatment for CTS Covid-related.

### Conflicts of Interest.

The authors report no conflicts of interest.

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### REFERENCES

1. Guan W-J, Ni Z-Y, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med.* 2020;382:1708-1720.
2. Gane SB, Kelly C, Hopkins C. Isolated sudden onset anosmia in COVID-19 infection. A novel syndrome? *Rhinology.* 2020;58:299-301.
3. Mao L, Jin H, Wang M, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol.* 2020;77:683-690.
4. Zhao H, Shen D, Zhou H, et al. Guillain-Barré syndrome associated with SARS-CoV-2 infection: causality or coincidence? Vol. 19, *The Lancet. Neurology.* England. 2020:383-384.
5. Passiatore M, Perna A, De Vitis R, et al. The Use of Alfa-Lipoic Acid-R (ALA-R) in Patients with Mild-Moderate Carpal Tunnel Syndrome: A Randomised Controlled Open Label Prospective Study. *Malaysian Orthop J.* 2020;14:1-6.
6. Passiatore M, Perna A, Taccardo G, et al. Pharmacological management of mild-moderate carpal tunnel syndrome: use of *Crocus sativus* L. combined with alpha-lipoic acid. *J Xiangya Med.* 2022;7.
7. D’Orio M, De Vitis R, Taccardo G, et al. Clinical usefulness of nutraceuticals with acetyl-L-carnitine,  $\alpha$ -lipoic acid, phosphatidylserine, curcumin, C, E and B-group vitamins in patients awaiting for carpal tunnel release during COVID-19 pandemic: a randomized controlled open label prospective st. *Acta Biomed.* 2023;94:e2023050.
8. Padua L, Lo Monaco M, Padua R, et al. Neurophysiological classification of carpal tunnel syndrome: assessment of 600 symptomatic hands. *Ital J Neurol Sci.* 1997;18:145-150.
9. Hanganu A-R, Constantin A, Moise E-S, et al. Peripheral nervous system involvement associated with COVID-19. A systematic review of literature. *PLoS One.* 2023;18:e0283827.
10. Horan E, Romeo P, Loch-Wilkinson A. Carpal tunnel syndrome caused by persistent median artery thrombosis with a possible link to COVID-19 vaccination: a case report. *Australas J Plast Surg.* 2023;6.
11. Fleischer M, Szepanowski F, Tovar M, et al. Post-COVID-19 Syndrome is Rarely Associated with Damage of the Nervous System: Findings from a Prospective Observational Cohort Study in 171 Patients. *Neurol Ther.* 2022;11:1637-1657.
12. Perozzo FAG, Punzi L, Costa AL, et al. Acute Calcium Pyrophosphate Crystal Arthritis of the Wrist Elicited by Anti-COVID-19 Vaccination After Carpal Tunnel Release. *Am J Case Rep.* 2022;23:e934833.
13. Ravella KC, Redondo ML, Mejia A, et al. Median Nerve Mononeuropathy and Meralgia Paresthetica After Prone Positioning in a Patient with COVID-19 ARDS: A Case Report. *JBJS case Connect.* 2021;11.
14. Roncati L, Gravina D, Marra C, et al. Cubital Tunnel Syndrome Temporally after COVID-19 Vaccination. *Tropical medicine, and infectious disease. Switzerland.* 2022:7.
15. Tullie S, Michell A, Reid AWN. Bilateral Carpal Tunnel Syndrome Following COVID-19 Vaccination: A Case Report. *J hand Surg Asian-Pacific Vol.* 2022;27:1035-1037.
16. Kardeş S, Erdem A, Gürdal H. Public interest in musculoskeletal symptoms and disorders during the COVID-19 pandemic : Infodemiology study. *Z Rheumatol.* 2022;81:247-252.
17. Kim J-H, Kwon MJ, Choi HG, et al. Changes in the mean incidence and variance of orthopedic diseases before and during the COVID-19 pandemic in Korea: a retrospective study. *BMC Musculoskelet Disord.* 2023;24:540.
18. Córdova-Martínez A, Caballero-García A, Pérez-Valdecantos D, et al. Peripheral Neuropathies Derived from COVID-19: New Perspectives for Treatment. *Biomedicines.* 2022;10.
19. Padua L, Cuccagna C, Giovannini S, et al. Carpal tunnel syndrome: updated evidence and new questions. *Lancet Neurol.* 2023;22:255-267.
20. Evangelista M, Cilli, De Vitis R, et al. Ultra-micronized Palmitoylethanolamide Effects on Sleep-wake Rhythm and Neuropathic Pain Phenotypes in Patients with Carpal Tunnel Syndrome: An Open-label, Randomized Controlled Study. *CNS Neurol Disord Drug Targets.* 2018;17:291-298.
21. De Vitis R, Passiatore M, Perna A, et al. COVID-19 contagion and contamination through hands of trauma patients: what risks and what precautions? *J Hosp Infect.* 2020;105:354-355.

22. Kim J, Thomsen T, Sell N, et al. Abdominal and testicular pain: An atypical presentation of COVID-19. *Am J Emerg Med.* 2020;38:1542.e1-1542.e3.
23. Li X, Geng M, Peng Y, et al. Molecular immune pathogenesis and diagnosis of COVID-19. *Journal of Pharmaceutical Analysis.* 2020.
24. Pleasure SJ, Green AJ, Josephson SA. The Spectrum of Neurologic Disease in the Severe Acute Respiratory Syndrome Coronavirus 2 Pandemic Infection: Neurologists Move to the Frontlines. *JAMA Neurol.* 2020;77:679-680.
25. Perna A, Passiatore M, Massaro A, et al. Skin manifestations in COVID-19 patients, state of the art. A systematic review. *Int J Dermatol.* 2021.
26. Favalli EG, Ingegnoli F, De Lucia O, et al. COVID-19 infection and rheumatoid arthritis: Faraway, so close! *Autoimmun Rev.* 2020;19:102523.
27. Zhang C, Wu Z, Li J-W, et al. The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce the mortality. *Int J Antimicrob Agents.* 2020;55:105954.
28. Puduvalli VK, Sella A, Austin SG, et al. Carpal tunnel syndrome associated with interleukin-2 therapy. *Cancer.* 1996;77:1189-1192.
29. Freeland AE, Tucci MA, Barbieri RA, et al. Biochemical evaluation of serum and flexor tenosynovium in carpal tunnel syndrome. *Microsurgery.* 2002;22:378-385.
30. Sikora SS, Samsonov ME, Dookeran KA, et al. Peripheral nerve entrapment: an unusual adverse event with high-dose interleukin-2 therapy. *Annals of oncology : official journal of the European Society for Medical Oncology.* England. 1996;7:535-536.
31. Heys SD, Mills KL, Eremin O. Bilateral carpal tunnel syndrome associated with interleukin 2 therapy. *Postgrad Med J.* 1992;68:587-588.
32. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet (London, England).* England. 2020;395:1033-1034.
33. Moalem-Taylor G, Baharuddin B, Bennett B, et al. Immune dysregulation in patients with carpal tunnel syndrome. *Sci Rep.* 2017;7:8218.
34. Passiatore M, De Vitis R, Cilli V, et al. The Italian version of the Michigan Hand Outcomes Questionnaire (MHQ): translation, cross-cultural adaptation and validation. *J Hand Surg Asian Pac Vol.* 2021;26:666-683.
35. Taccardo G, DE Vitis R, Parrone G, et al. Surgical treatment of trapeziometacarpal joint osteoarthritis. *Joints.* 2013;1:138-144.