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Latest discoveries related to taste and smell disorders in patients with post-COVID-19 and other neuroviruses – a systematic literature review

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Abstract: Introduction: The SARS CoV-2 infection, responsible for COVID-19, has spread worldwide starting with the end of 2019, with major impact in the years 2020 and 2021, especially through the alpha, beta, and delta strains respectively. These strains have also been associated with the development of symptoms of anosmia and ageusia, even after overcoming the acute form of the disease, as part of the post-COVID-19 sequalae that make up the so-called "long-Covid". [1] The purpose of this systematic literature review was to study these disabling symptoms in the context of long-COVID syndrome.
Material and methods: In order to accomplish this review, we used the method Preferred Reporting Items for Systematic Reviews and Meta-Analyses (acronym - PRISMA) to filter and select the articles of interest that appeared in the period 1/01/2021-31/12/2022, in the international medical databases: Elsevier, NCBI/ PubMed,NCBI/ PMC and PEDro (= Physiotherapy Evidence Database classification), as well as ISI Web of Knowledge (Institute for Scientific Information - ex Thomson Reuters - Clarivate Analytics). We used the keywords for the selection: "COVID-19" / "viral neuroinfections" + "smell" /"olphactory" + "taste" /"gustatory"+ "anosmia" + 'ageusia' +'recovery'+'rehabilitation'.
Results and discussion: After applying indirect and then direct quantitative and qualitative filtering, 25 articles remained that met the selection criteria (noted in order of relevance in table 1, at the end of the article). We also added a number of freely identified papers, considered relevant to our topic. We studied aspects of the "long-COVID" syndrome, mainly related to neuro-psychiatric symptoms - especially taste and smell disorders (anosmia/ageusia), risk factors, predictors for this status, pathophysiology, their intricate mechanism of action, frequency of symptoms, neuroanatomy imaging correlated with clinical aspects, effect of anosmia and ageusia on quality of life, recovery from such sequelae, favorable/unfavorable prognostic factors in this regard.
Conclusions: Smell and taste are more than just simple sensations/perceptions and anosmia/ ageusia does not always recover spontaneously. The category of patients who are left with such permanent qualitative/quantitative alterations requires in-depth study in order to establish standardized and more effective methods of diagnosis, evaluation and treatment and recovery, than those available at the moment. The chosen topic represents a partially studied niche in the current well of knowledge, which will allow us, following the theoretical and practical deepening of the subject, some possible elements of future contribution.

Keywords: viral neuroinfections, COVID-19, anosmia, ageusia, olphactory, gustatory, taste, smell, recovery, rehabilitation (used in our search of medical databases)

Introduction

SARS CoV-2 infection, responsible for **COVID-19**, has been spreading globally since late 2019, with major impact in the 2020s and 2021s through alpha and beta strains. Despite serial vaccination efforts, SARS CoV2 has affected over 1.1 million individuals in the US alone, with new waves of infection, in part due to viral mutations in newer, more easily transmissible strains (e.g. delta strain). [3] There was also a percentage of patients who became reinfected with the virus despite vaccination efforts, raising concerns about its effectiveness. [4] Although we observed significant mortality and morbidity especially in the elderly population, once vaccination of this vulnerable group was achieved, there remained a significant viral transmission in the young, unvaccinated population. [5] [6] Virtually any individual could develop the infection during this study period and the persistent symptoms of interest for the current paper - anosmia and ageusia. [7] In January, 2021 - when the cited study was created, there were >90 million confirmed cases and 2 million deaths worldwide. The global spread was rapid and irreversible, under the cover of the fact that many patients were asymptomatic/ with mild forms of the disease. [8] It also invariably affected the world population who, by adhering to a lockdown lifestyle, promoted a series of unhealthy life choices, including dietary changes and increased body weight, low physical activity. [9] [10]

SARS-CoV2, known as acute respiratory syndrome virus, belongs to the coronavirus family. Like other viruses in this family, it is responsible for both acute and post-infectious disease, along with MERS (Middle East Respiratory Syndrome) and SARS (Severe Acute Respiratory Syndrome) [11] . What makes this virus so dangerous, however, is its surprisingly severe course in patients of very different ages and associated comorbidities. [12] Moreover, even recovery from the acute form of the disease can lead to multi-systemic post-COVID-19 sequelae, two of these persistent symptoms being the subject of the current paper (anosmia and ageusia), as part of what has been termed by many researchers as "long-COVID" syndrome. [8] [1]

Long-COVID is an umbrella term, initially used by patients and later adopted by researchers and clinicians [11], that encompasses a multisystemic entity with a cluster of signs and symptoms that can have an ever changing evolution, affecting virtually any organ/tissue (e.g. lung, nasal mucosa, brain, heart, etc.) [13], through mechanism of pathological inflammation (e.g. viral persistence, immune dysregulation, autoimmunity). [14] [6]

We also identified a series of risk factors [15] [16] associated with developing post-COVID syndrome [17], which are female gender, obesity, age, initial severe COVID-19 form, with 5+ initial, early symptoms (including early dyspnea, abnormal lung auscultation, initial psychiatric disorders), presence of specific biomarkers (D-dimer, CRP, elevated lymphocytes) – although still in study [18], smoking/vaping, acute hospitalization/working in medical/paramedical field. [19]

A number of **predictive factors** for disease progression could also be identified, their presence during the acute phase being correlated with developing the post-COVID status, namely diarrhea, anosmia, dyspnea, pleurisy, increased skin sensitivity, A2 blood group [20]; low IgG at acute presentation were found as a predictor for the development of anosmia and post-COVID 19 ageusia [21]. Interestingly, the severity of COVID-19 symptoms in the acute phase did NOT correlate with the severity of post-COVID symptoms, except for the neuropsychiatric disorders (anxiety, depression, PTSD, memory and attention disorders). [22] We also found predictive factors for the development of severe pneumonia (with associated dyspnea and persistent coughing), namely pulmonary surface opacities on chest X-ray > 50% and high AV at presentation. [23]

Methods:

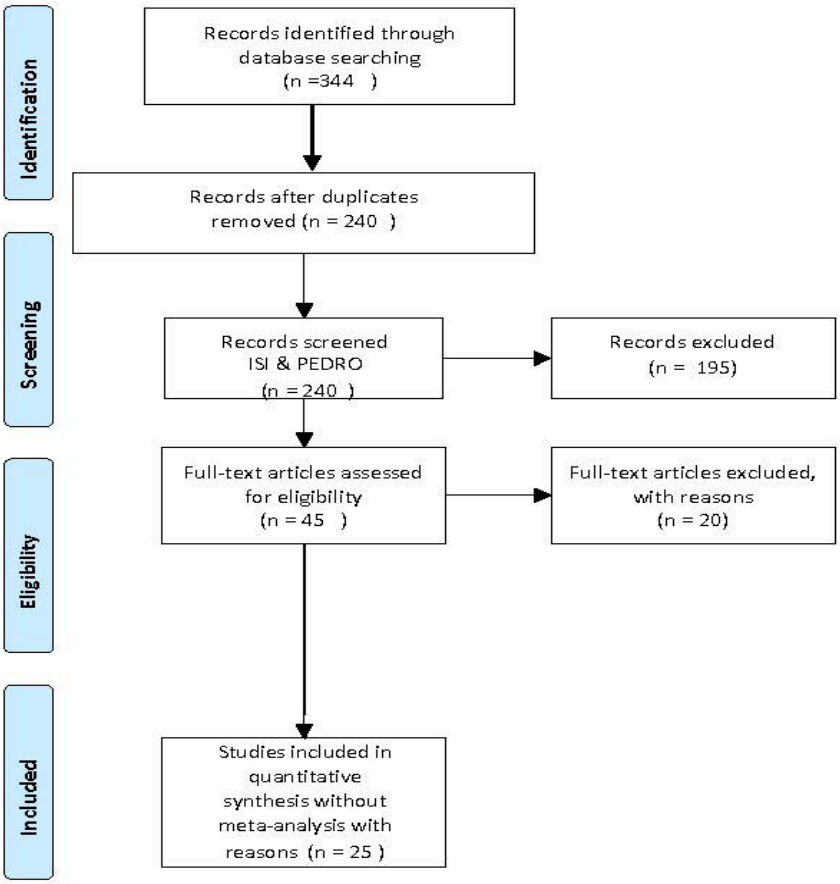
To conduct this literature review in a rigorous manner, we followed the internationally accepted **PRISMA** method for searching, filtering, selecting articles ("Preferred International Reporting Items for Systematic Reviews and Meta-Analyzes). [24]
We **included** open access articles, published in English, during the period 1/01/2021-31/12/2022 (period that coincided with the prevalence of alpha and beta strains and, implicitly, symptoms of anosmia and ageusia [3]), from internationally recognized and **ISI** indexed databases [25]: **Elsevier** [26], **NCBI/ PubMed**, **NCBI/ PMC** [27], as well as **PEDro** [28].

Keywords	Elsevier	PubMed	PMC	PEDro	Total
"COVID-19" + "smell" + "taste" + "anosmia" + "ageusia" + "recovery " + "rehabilitation"	0	0	236	0	236
"viral neuroinfections" + "smell" + "taste" + "anosmia" + "ageusia" + "recovery " + "rehabilitation"	0	0	0	0	0
"COVID-19" + "olphactory" + "taste" + "anosmia" + "ageusia" + "recovery " + "rehabilitation"	0	0	0	0	0
"viral neuroinfections" + "olphactory" + "taste" + "anosmia" + "ageusia" + "recovery " + "rehabilitation"	0	0	0	0	0
"COVID-19" + "smell" + "gustatory" + "anosmia" + "ageusia" + "recovery " + "rehabilitation"	0	0	108	0	108
"viral neuroinfections" + "smell" + "gustatory" + "anosmia" + "ageusia" + "recovery " + "rehabilitation"	0	0	0	0	0
"COVID-19" + "olphactory" + "gustatory" + "anosmia" + "ageusia" + "recovery " + "rehabilitation"	0	0	0	0	0
"viral neuroinfections" + "olphactory" + "gustatory" + "anosmia" + "ageusia" + "recovery " + "rehabilitation"	0	0	0	0	0
Total	0	0	344	0	344

Figure 1: Keywords combinations using for search of medical databases

Data selection involved 5 stages described in the PRISMA flow chart (excluding meta-analysis in the last stage). In the first stage, we selected studies using keywords in contextual queries - combinations/syntaxes of search keywords (Table 1), resulting in 344 articles selected from the 4 international databases mentioned. Secondly, duplicate articles (same articles found in different queried databases) were removed, leaving 240 total articles. In the third stage, the indirect qualitative filtering process was performed by checking the publication of the selected articles in ISI indexed journals and then by applying an adapted version of the PEDro. This meant that the basic criteria for was a weighted calculation of the number of citations per year [29]. This resulted in a custom weighting between the number of citations and the year of publication, on a scale: 0-10 points. This also meant keeping articles of quality in terms of PEDro score of at least 4 points ("fair quality"). 195 articles were thus removed and 45 articles remained.
In the fourth stage, the full-text verification of the 45 articles (belonging to the area of interest of our research) was carried out and 20 of them were removed because they did not represent relevant information regarding the research topic.
The remaining 25 articles formed the research foundation on which we built this article (Table 1- noted in order of relevance at the end of this article) and were subjected to qualitative analysis and synthesis (without meta-analysis). To this base, we also added a number of freely identified papers, considered relevant to our topic.

Figure 2: Flux type PRISMA diagram in different phases of our systematic literature review



Results and discussions:

The **most common symptoms during acute COVID-19** infection appear to be fatigability, fever, dyspnea, dry cough, myalgia, paresthesia, ageusia and anosmia (the latter present even in mild forms of the disease). [30] We emphasize the important prevalence of ageusia and anosmia among these symptoms, considered major diagnostic criteria and estimated to occur in 56.5-85.9% of patients with mild forms of acute SARS-COV2 infection. [31]

The **most common long-COVID symptoms** - which can last from months to years after acute infection - are: dyspnea and fatigue, cognitive/mental disorders, chest and joint pain, palpitations, myalgia, taste and smell disturbances, cough, headache, gastrointestinal and cardiac disorders. [17]. However, we note that there is no clear consensus on the exact frequency of these post-COVID symptoms, report vary from centre to centre and study to study, but those listed above are, in average, most commonly noted. [30] [32]

Regarding the **correlation between the acute form of the disease and long-COVID,** the cited meta-analysis estimates that 80% of patients with the acute form of COVID-19 involving at least one symptom develop long-term clinical sequelae and paraclinical changes (biological, imaging), with a significant proportion neuropsychiatric symptoms and sequelae. [33] What is of concern is that many of the patients involved in a 3-month study of patients with mild-to-moderate forms of COVID-19 at baseline developed neurological lesions in tandem with persistent symptoms, thus demonstrating that even such seemingly harmless forms can induce persistent brain effects. [34]

Regarding the evolution of the patient with acute symptoms of COVID-19 toward long-COVID, even in situations where there is substantial pulmonary improvement - visible on radiological and functional investigations (e.g. spirometry) - symptoms of long-COVID may persist. [35] This is explained pathophysiologically by the involvement of

multisystemic lesions, with multifactorial mechanisms of production (e.g. dyspnea), with major impact on the quality of life of affected individuals. [36]

The **most common post-COVID-19 neuropsychiatric symptoms** identified in the literature are taste and smell disturbances, fatigue, muscle weakness, sleep disturbances, myalgia, headache, vertigo, cognitive disturbances - including "brain fog" phenomena (a mild form of cognitive impairment: disturbance of concentration, attention, confusion, slowing of thinking, memory impairment) [37], slurred speech, executive dysfunction, psychiatric depression, anxiety, PTSD, insomnia. [38] Another study showed a significant prevalence of neurological symptoms among persistent complaints in patients reassessed by post-COVID teleconsultation (about a third from total complaints). [39] However, a cohort study related to COVID-19 induced brain diseases (which included severe pathology: ischaemic and haemorrhagic strokes, encephalopathies), concluded that the initial severity of COVID-19 infection plays little role in predicting the prognosis of these brain diseases. [40]

Regarding **anosmia and ageusia**, the focus of the current literature review, in the context of long-COVID status, the cited article listed them as among the most disabling symptoms on the subjective scale completed by various patient groups. Their frequency in long-COVID appears to be somewhere around 13% for anosmia/ dysosmia and around 11% for ageusia/ dysgeusia. [41]

Anosmia/ Hyposmia/ Dysosmia is a total/partial loss/ impairment of olfactory ability, frequently associated with COVID-19, especially in the acute phase of SARS-CoV2 infection, but also persisting in chronic phases. [42] [43] [44] There appears to be a spontaneous "wearing-off" over time of this symptom. [45] [46] The pathophysiology is not completely known, but it is certain that as the virus enters the nasal cavity via the ACE-2 receptor, the olfactory neuroepithelium is damaged in the process. [47] [48]

Ageusia/ Hypogeusia/ Dysgeusia is a total/partial loss/ impairment of gustatory ability, frequently associated with COVID-19, especially in the acute phases of COVID (arguably more so than even anosmia [49]), with "wearing-off" over time, spontaneously, similar to anosmia [31] [46]. Pathophysiology is uncertain: the underlying mechanism seems to be invasion of oral/ lingual mucosa directly/ retrograde via the nasopharynx, with ACE2 expression at this level. [50]

In addition, loss of both senses appears to involve **brain lesions** (including the taste and smell centers) - especially in the post-COVID phases of the disease, through direct viral invasion (via the blood-brain barrier/olfactory nerves), endothelial dysfunction, systemic inflammation, vegetative storm, cerebrovascular changes (including hypercoagulability), hypoxia - all probably in combination. [50] The olfactory and gustatory "sense library" suffers as a result of this encephalitis. Post-mortem brain autopsies have revealed brain-related genomic changes in both the taste and smell centers. [48] Because the senses are so closely linked, there is evidence that the loss of one sense contributes strongly to the loss of the other. [51] Another pathophysiological theory supports the persistence of certain post-COVID symptoms (such as anosmia and ageusia) is due to the persistence of small amounts of virus in different organs and tissues. This remaining initial virus stagnates in the mentioned sites, where it undergoes genetic mutation and leads to new species of viral strains with different genetic background. Thus the individual in question is prone to viral reinfection/reactivation (as with HIV infection) [52]

We observed the inclusion of anosmia/ageusia in many articles in the **domain of neuroscience**. [13] This consideration is partly due to the fact that even though smell and taste rely on the integrity of the ENT system, the effect of SARS CoV2 has been numerously cited on cranial nerves I (olfactory) for smell and VII (facial), IX (glossopharyngeal) and X (vagus) for taste. Basically, anosmia and ageusia are due to a combination of lesions to the peripheral nervous system (cranial nerves - including VII, IX, X, which function as

peripheral nerves - equivalents of cranial spinal nerves) and CNS (nerves I and II being considered both externalized portions of the brain, along with inflamed cerebral gustatory and olfactory centers). [53]

Dysosmia can be characterized by **parosmia** (altered smell), a qualitative disorder, defined as distorted olfactory perception in the presence of a stimulus [54], a frequently encountered phenomenon in long-COVID. [55] The pathophysiological mechanism of parosmia in COVID-19 seems to be, similarly to that caused by other viruses, related to a preponderance of immature neurons during reinnervation, occurring during the regeneration phase of the olfactory nerves. [54] **Troposmia** is another form of dysosmia, represented by the unpleasant perception of odorants. It may follow post-COVID-induced anosmia and persist for months. [56]

Smell and taste have an **interdependent relationship**, which led us to study and discuss them together. However, in vivo, individuals experience them independently. Researchers cited have noted that the perception of the organoleptic characteristics of food and drink reflects the information gathered by multiple gustatory and olfactory sensory afferents, that is integrated at cortical level, maintaining a specificity of each individual sensory modality. Despite the capacity for differentiation, the way we perceive the taste and smell of food and drink, their aroma, is also achieved in an integrative, unitary way: different brain sensory areas are 'anatomically distinct but functionally linked'. [51]

Another notion that has long been studied is the way in which humans have the ability to integrate the olfactory and gustatory senses into a mix that makes up **flavor** - one effect that has been observed (and is frequently used by commercial juice/sweets manufacturers), is the ability of an odor to enhance the intensity of a taste. For example, the use of artificially created strawberry/vanilla scents to enhance the intensity of the sweet sensation in ice cream/ juice. [57] This phenomenon resembles synesthesia, defined as the perception of one stimulus that attracts the perception of another synchronous stimulus, but studies demonstrate a much stronger, almost ubiquitous association in the taste-smell relationship. [51]

In this process there is no chemical interaction per se between the smelled/tasted substances, as this phenomenon ceases once the odorant is blocked from reaching the olfactory receptors (e.g. pressure on the nostrils) and it has been shown that the odorant itself has no taste. At the basis seems to be a multimodal functional activity of the perception of the quality of an odor. [51]

A real **bidirectional mechanism** of inference is thus emerging - it seems that molecules released during mastication can eliminate faintly perceptible odor vapours, which reach the retronasal olfactory epithelium; but also a vice versa mechanism: odor announces in advance the possible quality of the food to be ingested. [58]

Unlike other senses, taste and smell form a strong **connection with the limbic and paralimbic system** - so their interpretation is related to processing at a much earlier ontogenetic level (and is closely related to emotion and affect). Proximity to the hippocampus induces an association of taste and smell with early experiences, so important in the formation of an individual. [59] we also found mentioned a summation effect of these senses - their repetition increases their intensity of perception. This explains the difficulty in breaking a harmful eating habit. Thus we discover a true "library of associations" – a concept that is based on the congruence of tastes and smells, coupled together in terms of their quality (leading to expressions such as "the sweet smell of honey, the sour smell of vinegar") [60]

We also found promising data regarding the connections between **smell and memory**, and its role in the screening of dementia/ neurocognitive decline. It has long been hypothised that loss of smell is a predictive factor for both Parkinson's disease and Alzheimer disease. This has been proven to be right: one of the most important sources of pluripotent stem

cells capable of neurological differentiation inside our body can be found in the olfactory bulb. Even more importantly, positive biopsy of the olphactory bulb (in a patient with anosmia) has capable predictive power for neurodegeneration. [61]

There are still uncertainties about typical **brain imaging** findings in patients with long-COVID, anosmia and aguezia. Some researchers consider relevant correlations between neurological symptoms in tandem with brain MRI images [34] [41], respectively in regions associated with memory and smell impairment [41], namely atrophy and degeneration of the olfactory bulb [62] [63]; however, other researchers have cautioned in misdiagnosing anosmia on account of olfactory bulb changes, which can also occur in healthy patients. [64]

As mentioned previously, COVID-19 infection has been associated with structural and metabolic brain abnormalities congruent with persistent neurological deficits anexed to these areas. We found the following areas (highlighted as hypometabolism on **PET-CT** [65]) as being more frequently affected during/ post-COVID: oribital gyrus, olfactory, temporal lobe, amygdala, hippocampus, thalamus, pons, bulb, cerebellum. [66] These areas correlate highly with the symptoms of anosmia, brain fog, insomnia, as part of the neurological symptoms of long-COVID. [67] Other researchers have named this brain area responsible for smell (+- taste) as the "**chemosensory aroma network**". [68]

Multiple articles have used subjective scales to assess the impact on **quality of life (QOL)** of various post-COVID symptoms in the study population. [15] [69] [70] [71] Approximately two thirds of hospitalized patients experienced a significant decrease in quality of life (QOL) - quantified as diminished daily satisfaction related to smell, taste, and perception of food aromas. [69] [70] This was quantified by a specific scale (QOD) = olfactory-related QOL - used in selective centers for both acute COVID and post-COVID patients.[69] [71] The cited study applied this scale to 149 patients, all of whom experienced symptoms in the sphere of taste, smell, appetite [71]. A significant impairment was observed in the acute group followed by "wearing-off" in the intensity of QOL impairment in the post-COVID group. [46] [70] [71] However, there was an important and resilient category of patients who were still affected by the lack of these extremely important senses. [15] [71]

We would also like to emphasize the **safety hazard** that can be associated with removing the ability to smell (or in extreme cases, taste) potential dangers – corrosive gases, vapors, poisons - we come in contact with. In the moment of contact, chemical airway (or digestive) exposures are detected by the olfactory, gustatory and nociceptive sensory systems, that initiate protective physiological and behavioral responses. In anosmia/ ageusia afflicted patients, these important defenses are lacking, predisposing these category of patients to potentially fatal intoxication. [72]

We found multiple studies who researched **rehabilitation** from the most common symptoms of long-COVID - namely **dyspnea and fatigue**, but with no major breakthroughs regarding anosmia and ageusia. [73] [74]. This rehabilitation includes exercise and psychotherapy individualized on the patient (due to the variable clinical and pathophysiological impairment in post-COVID patients), based also on his personal capacity for exertion/psychological hardship respectively. Moreover, the association of the two had statistically valid results for improving anxiety associated with the disease, but not depression. [75] [76] These exercises do not have an effect on all forms of long-COVID, only mild or moderate ones - severely affected respiratory, cardiac forms (frequently with neurological deficits) are associated with risk: lesions built up at these levels lead to recurrence of symptoms despite rehabilitation attempts. [77] Other researchers have studied the impact of occupational therapy and found potentially beneficial effects on moderate-severe post-COVID fatigue, improving the overall activities of daily living in the selected patients. [78] It's worth mentioning that lockdown lifestyle has gravely affected rehabilitation of the aforementioned symptoms. [9] [10] Not only this, but researchers

proved an increased risk of sarcopenia and nutrition related complaints, with poor nutritional status, in COVID-19 patients during and after hospital admission. [10]

Non-pharmacological **rehabilitation** from **anosmia and ageusia** is rarely cited in the literature. In principle, the studies we found recommend that patients with persistence over 2 months of anosmia and ageusia should be referred to a specialized olfactory/taste training center. Their rehabilitation involves exposure to different and refined smells and tastes on a daily basis for 3 months. This is made possible through a series of approved, statistically endorsed tests. These recovery methods also serve diagnostic purposes and to assess the persistence/improvement of symptoms. Certainly, this area of study, which is lacking current literature, represents a niche for further research. [50]

Positive outcome factors for the recovery of taste and smell are still a topic of debate in several articles. [47] A study on a large group of patients, who were evaluated by a subjective questionnaire related to the recovery of taste and smell, demonstrated total spontaneous recovery in a proportion of 75% at 2 months and 95% at 6 months, respectively. Other researchers have shown a significant initial frequency of anosmia and ageusia in a population with mild COVID-19 (59.1% ageusia, 54.3% anosmia at onset), with significant spontaneuos gradual decline in these symptoms' frequency at 4 months (12.4% anosmia, 11.1% ageusia) and 7 months (14.7% anosmia, 11.0% ageusia), but with an important decline in the addressability of patients enrolled for reassessment by teleconsultation. [21] The cited study also calculated **negative outcome factors:** patient with high initial severity of anosmia and ageusia and hospitalization in the acute phase of COVID-19 infection were found to have worse prognosis for taste and smell recovery.

At the end of this literature review, we observed a significant worldwide interest in SARS CoV-2, with impact on both the general population and within the ranks of scientists and physicians. [79] A huge number of articles have been published targeting symptoms, pathophysiological mechanisms and theories, therapeutic targets, risk and predictive factors, hospital and case management plans, quality of life of affected patients [13], but less have approached the rehabilitation of specific symptoms occurring in long-COVID. [80] [75]

A secondary aim of this study has been that of comparing the sequelae arising post-COVID-19 with those caused by other post-infectious statuses, specifically neuroinfections. The cited article compared sequelae after hospitalization for COVID-19 with those after influenza viral infection, and after sepsis, respectively. They observed an increase in the risk of venous thromboembolic events in about 1 year after COVID-19 infection, but with comparable preponderance of other medical and mental conditions occurring in survivors of all these infections. This study also demonstrated that the greatest cost to the health care system, including unforeseen future repercussions, is evidently correlated with the initial severity of the infection. [81]

Conclusions:

The COVID-19 pandemic has had an unprecedented impact on the whole world from multiple points of view - medical, scientific, economic, socio-cultural - a fact also demonstrated by the significant number of articles and theories that have been released in 2019 – 2022, that was the period on which this paper focused. However, anosmia and ageusia, highly disabling symptoms, occurring as part of post-COVID status, represent an area still incompletely elucidated.

Smell and taste are much more than mere sensations. They represent our interface with proper nutrition and digestion [10], the hazard filter for potential noxious substances [72], an important source of satisfaction in the work-life balance and an important factor in ensuring quality of life.[71]

Anosmia/dysosmia, ageusia/dysguesia do not always recover spontaneously and the category of patients who are left with permanent qualitative/quantitative alterations

requires a thorough study in order to establish an effective and standardized method of diagnosis, evaluation and treatment.

At the moment, in Romania, the subject of the whole doctoral study, including its clinical component - of which this article is an expression of the documentation necessary to ensure an adequate knowledge base - has never been approached at this level so that, in conjunction with the necessary and adequate extraction and analysis of data resulting of data from international experiences, can contribute to achieving the objective set: improving the effectiveness of the approach and rehabilitation of post-COVID-19 sequelae taste and smell disorders - an objective we plan to add to further personal contribution in the near future.

Bibliography

Table 1: The 25 PRISMA-selected articles, link, year of publication, number of citations, PEDro score (full citation in extended bibliography)

No.	Name of article	Article link	Pub. year	Citation count	PEDro score
1	**Assessment of the Frequency and Variety of Persistent Symptoms Among Patients With COVID-19: A Systematic Review** [41]	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8155823/	2021	121	10
2	**Confronting COVID-19-associated cough and the post-COVID syndrome: role of viral neurotropism, neuroinflammation, and neuroimmune responses** [6]	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8041436/	2021	9	10
3	**Post-COVID-19 Syndrome: The Persistent Symptoms at the Post-viral Stage of the Disease. A Systematic Review of the Current Data** [21]	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8129035/	2021	42	10
4	**Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments** [17]	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8146298/	2021	11	10
5	**Long COVID, a comprehensive systematic scoping review** [80]	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8317481/	2021	29	10
6	**Post-acute COVID-19 syndrome** [36]	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8924706/	2022	26	10

7	More than 50 long-term effects of COVID-19: a systematic review and meta-analysis [33]	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8352980/	2021	10	10
8	Post-COVID syndrome in non-hospitalised patients with COVID-19: a longitudinal prospective cohort study [22]	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8129613/	2021	11	10
9	Long-term complications of COVID-19 [32]	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8721906/	2022	24	10
10	Persistent COVID-19 symptoms in a community study of 606,434 people in England [19]	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9005552/	2022	20	10
11	Characterizing Long COVID: Deep Phenotype of a Complex Condition [79]	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8613500/	2021	11	10
12	Unraveling the Mystery Surrounding Post-Acute Sequelae of COVID-19 [1]	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8278217/	2021	12	10
13	Post-COVID syndrome. A case series and comprehensive review [30]	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8428988/	2021	32	9
14	Long Covid-19: Proposed Primary Care Clinical Guidelines for Diagnosis and Disease Management [14]	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8073248/	2021	28	8
15	Long-Term Outcomes of Patients with Coronavirus Disease 2019 at One Year after Hospital Discharge [46]	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8269002/	2021	30	8

16	**Epidemiology and organ specific sequelae of post-acute COVID19: A narrative review** [15]	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8118709/	2021	30	8
17	**COVID-19 sequelae in adults aged less than 50 years: A systematic review** [5]	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7898978/	2021	29	8
18	**Nutrition in the Actual COVID-19 Pandemic. A Narrative Review** [9]	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8228835/	2021	24	7
19	**The Conundrum of 'Long-COVID-19': A Narrative Review** [2]	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8214209/	2021	26.5	7
20	**ESCMID rapid guidelines for assessment and management of long COVID** [75]	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8849856/	2022	22	6
21	**Poor nutritional status, risk of sarcopenia and nutrition related complaints are prevalent in COVID-19 patients during and after hospital admission** [10]	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8056328/	2021	19.5	5
22	**Molecular Imaging Findings on Acute and Long-Term Effects of COVID-19 on the Brain: A Systematic Review** [65]	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9258567/	2022	17	5
23	**Reinfection in patients with COVID-19: a systematic review** [4]	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9051013/	2022	19	5
24	**More Than 100 Persistent Symptoms of SARS-CoV-2 (Long COVID): A Scoping Review** [13]	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8591053/	2021	19	5

25	**Age, Sex and Previous Comorbidities as Risk Factors Not Associated with SARS-CoV-2 Infection for Long COVID-19: A Systematic Review and Meta-Analysis**	**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9787827/**	**2022**	**17**	**5**

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