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Results from psychophysical tests of smell and taste during the course of SARS-CoV-2 infection: a review

Risultati dei test psicofisici olfattivi e gustativi durante l'infezione COVID-19: revisione della letteratura

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SUMMARY

Only a few studies have assessed smell and taste in Coronavirus Disease 2019 (COVID-19) patients with psychophysical tests, while the majority performed self-rating evaluations. Given the heterogeneity of the published literature, the aim of this review was to systematically analyse the articles on this topic with a focus on psychophysical testing. A search on PubMed and Web of Science from December 2019, to November 2021, with cross-references, was executed. The main eligibility criteria were English-language articles, investigating the clinical features of olfaction and gustation in COVID-19 patients using self-rating assessment, psychophysical testing and imaging techniques. A total of 638 articles were identified and 66 were included. Self-rating assessment was performed in 31 studies, while psychophysical testing in 30 and imaging techniques in 5. The prevalence of chemosensory dysfunction was the most investigated topic, followed by the recovery time. About the psychophysical assessment, the extended version of the Sniffin' Sticks was used in 11 articles and the Connecticut Chemosensory Clinical Research Center test in another 11. The olfactory threshold performance was the most impacted compared to the discrimination and identification capacities in accordance with the hypothesis of a tropism of SARS-CoV-2 for the olfactory mucosa. The timing significantly influenced the results of the psychophysical testing with 20% of patients presenting olfactory dysfunction at one month after infection.

KEY WORDS: smell, olfaction disorders, taste, anosmia, rhinology, COVID-19, infections

RIASSUNTO

La maggioranza degli studi ha valutato la capacità olfattiva e gustativa nei pazienti COVID-19 con questionari e autovalutazione. Data l'eterogeneità della letteratura pubblicata, lo scopo di questa 'review' è stato quello di analizzare gli articoli sull'argomento, focalizzando l'attenzione sui test psicofisici. È stata eseguita una ricerca su PubMed e Web of Science da dicembre 2019 a novembre 2021. I principali criteri di inclusione sono stati articoli in lingua inglese, che studiavano le caratteristiche cliniche dell'olfatto e del gusto nei pazienti COVID-19 utilizzando test soggettivi, psicofisici e 'imaging' radiologico. In totale sono stati identificati 638 articoli e di questi ne sono stati inclusi 66. In 31 studi è stata eseguita una valutazione soggettiva, mentre in 30 sono stati utilizzati test psicofisici e in 5 tecniche di 'imaging' radiologico. La prevalenza della disfunzione chemosensoriale è stata l'argomento più studiato, seguita dal tempo di recupero. Per quanto riguarda la valutazione psicofisica, gli Sniffin' Sticks sono stati utilizzati in 11 articoli e il test del Connecticut Chemosensory Clinical Research Center in altri 11. La performance della soglia olfattiva è stata la più intaccata rispetto alle capacità di discriminazione e identificazione in linea con l'ipotesi di un tropismo del virus COVID-19 per la mucosa olfattoria. La tempistica ha influenzato significativamente i risultati del test psicofisico con solo il 20% dei pazienti affetti da disfunzione olfattiva dopo un mese dall'infezione.

PAROLE CHIAVE: *olfatto, disturbi olfattivi, gusto, anosmia, COVID-19, infezioni*

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Introduction

Chemosensory dysfunction due to upper respiratory tract infection (URTI) can be caused by many common cold viruses, namely rhinovirus, adenovirus, influenza virus and coronavirus, including Coronavirus Disease 2019 (COVID-19), firstly detected in December 2019 in Central China, in the city of Wuhan [1]. After China, Italy was the first European country to experience a large-scale outbreak in February 2020 with 4,757,231 confirmed cases and 132,004 deaths as of October 2021 according to the World Health Organization (WHO). Since the beginning of this pandemic, otolaryngologists have had a key role in the treatment of many symptoms of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, such as fever, cough, sore throat and smell and taste disorders, which suddenly became known to everyone thanks to media attention and massive release of publications about this topic [2]. However, quantity does not always imply quality, and COVID-19 articles in the field of otolaryngology have been often related to poorer evidence levels than non-COVID-19 and pre-COVID-19 articles [3,4]. This is even truer in the case of publications about smell and taste dysfunction which were often based on subjective findings [5] and case reports/small case series [6], with most of the studies using self-administered tests or screening tests of olfactory function, especially in the first wave of pandemic because of the cancellation of hospital visits and elective procedures [7]. Conversely, only a few studies have evaluated smell and taste in COVID-19 patients with psychophysical tests [8,9].
Given the high heterogeneity of the published literature and the increasing interest in olfaction and taste before, during and after SARS-CoV-2 infection, the aim of this review was to systematically analyse the articles on this topic with a focus on publications where smell and taste in COVID-19 patients has been assessed with psychophysical tests.

Materials and methods

This systematic review was conceived according to the Primary Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Guidelines [10,11].

Search strategy and article selection process

The National Library of Medicine through PubMed and Web of Science were searched for the following keywords: *"Smell"* OR *"Olfaction"* OR *"Taste"* OR *"Gustation"* OR *"Olfaction disorders"* OR *"Anosmia"* OR *"Rhinology"* AND *"COVID-19"* OR *"SARS-CoV-2 infection"*. The first author collected articles published between December 2019, and November 2021. Also, references of the collected articles were considered potentially eligible for this systematic review, as well as records identified through websites and other organizations.
The main eligibility criteria were English-language articles, randomised and controlled trials in humans investigating the clinical features of olfaction and gustation in COVID-19 patients using self-rating assessment, psychophysical testing and/or imaging techniques. Articles using psychophysical tests of any type (i.e., Sniffin' Sticks extended test, 16-item Sniffin' Sticks identification test, Connecticut Chemosensory Clinical Research Center - CCCRC, University of Pennsylvania Smell Identification Test - UPSIT) and quality, including validated screening tests, were assessed for eligibility. Literature reviews, technical notes, letters to the editor, case reports, case series or trials including less than 12 participants, instructional courses and conference papers were excluded from this systematic review. Papers not focusing on smell and taste in COVID-19 patients, and where the methodology was inconsistent, were also excluded.

Data extraction and quality assessment

Two authors (E.M.C.T., M.C.) independently screened the full-text version of each publication, conducted data extraction and excluded those whose content was judged not to be relevant for the purpose of this review. When agreement could not be reached, another author from the group (M.G.) was consulted, and another (F.L.) was asked for data extraction and quality assessment.
Publications were classified according to the olfactory/gustatory assessment in self-rating evaluation, psychophysical testing, and imaging techniques. Articles where psychophysical testing was used were further analysed according to the threshold, discrimination and identification olfactory performance.
Among these three groups, topics of interest, such as recovery from chemosensory dysfunction, treatment outcomes and recovery time, were identified.
The general features of each article (i.e., journal, first author, country, year of publication, population, methods, prevalence, topic of the paper, and study quality) were recorded in a spreadsheet. The quality of the included studies was assessed using "The Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) Statement with a score interval from 0 to 22, with a higher score indicating a better study quality [12]. To mitigate the risks of bias, papers of all quality were included in this systematic review.

Results

Seventy-eight articles were identified through other methods (i.e., websites, organisations, citation searching), and

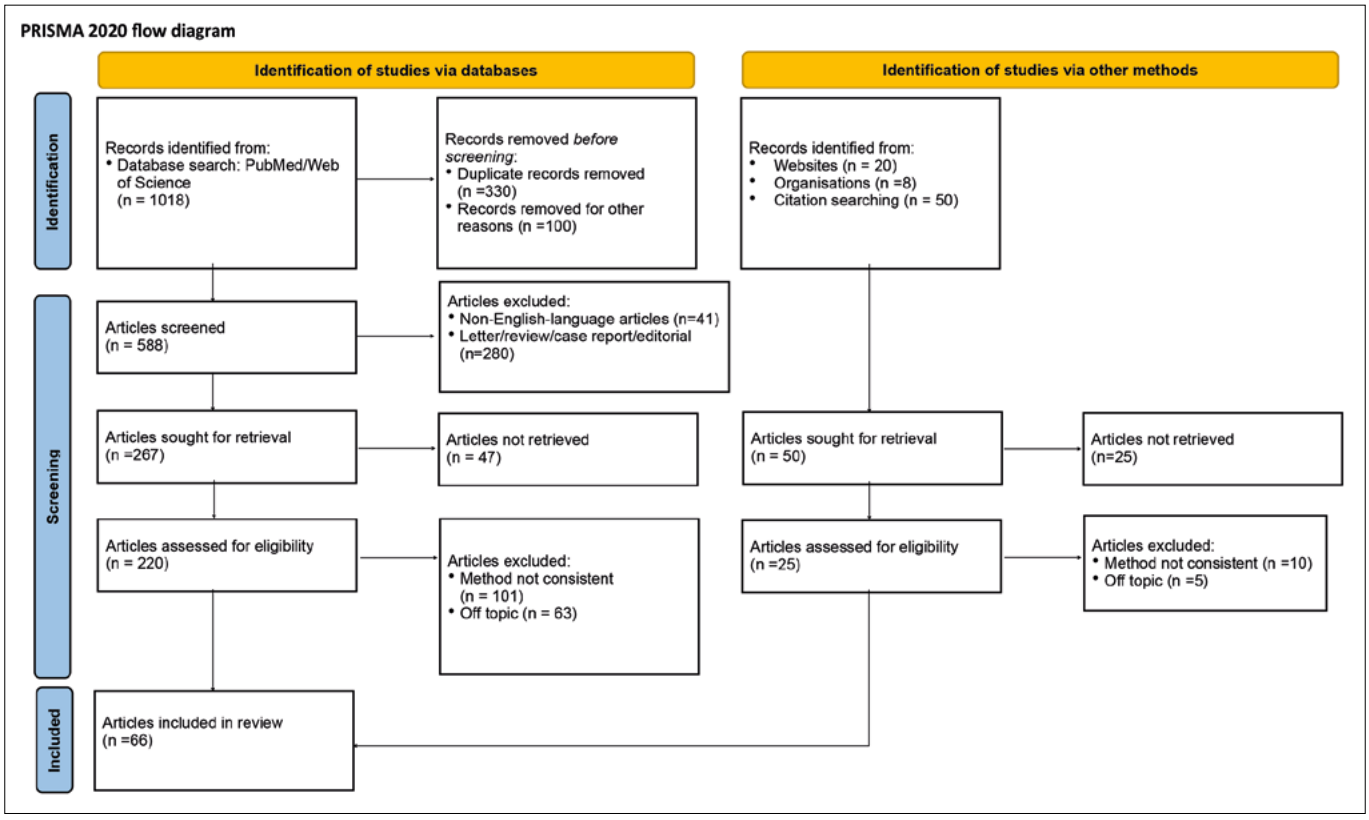

Figure 1. PRISMA (Primary Reporting Items for Systematic Reviews and Meta-analyses) flow diagram.

1018 via databases (i.e., PubMed, Web of Science). After excluding duplicates, 638 articles were considered potentially eligible for screening. Out of these, 72 publications were not retrieved and 500 were eliminated for the following reasons (Fig. 1): written in languages other than English (n = 41); other than original articles (i.e., reviews, editorials, case reports etc.: n = 280); not being directly relevant to the topic (n = 68) and methodology inconsistent (n = 111). After these exclusions, 66 papers were included for final analysis.

Regarding the olfactory/gustatory testing used, self-rating assessment was used in 31 studies [13-42] (Tab. I), and psychophysical testing in 30 [9,43-70] (Tab. II). Lastly, imaging techniques were used in 5 articles [71-75] (Tab. III).

About the olfactory assessment, the extended version of the Sniffin' Sticks test was used in 11 articles [9,44,46,48,50,51,67,68,72-74], Connecticut Chemosensory Clinical Research Center (CCCRC) olfactory test in 11 [43,57,61-67,69,70], the 16-item Sniffin' Sticks identification test in 7 [31,32,49,52-54,60], University of Pennsylvania Smell Identification Test (UPSIT) in 3 [45,47,55], a new validated psychophysical self-administered test in 3 [57,69,70], 12-item Brief Smell Identification Test (BSIT) in 2 [58,59], an olfactory and gustatory home test in one [28] and evaluation of the ethyl alcohol olfactory threshold and discriminative function for six common household odorants in one [56].

Concerning gustatory assessment, taste strips were used in 3 articles [46,49,51] and taste sprays in 3 [9,56,57].

Results from psychophysical tests of smell during SARS-CoV-2 infection (Tab. IV) showed that the olfactory threshold score was more impacted than the odour discrimination and identification scores in the studies using the extended version of the Sniffin' Sticks test. In fact, this group of articles presented an overall threshold, discrimination and identification (TDI) score of 22.5 ± 7.8 indicating moderate hyposmia, while the threshold score was 5.2 ± 1.3 and the discrimination and identification, respectively, were 10.8 ± 0.9 and 10.7 ± 1.0. Similarly, the CCCRC and the UPSIT global scores were, respectively, 40.8 ± 14.7 and 25.2 ± 2.5, indicating moderate hyposmia. With screening tests, scores from the 12-item BSIT were 8.5 ± 0.5 (hyposmia: ≤ 9) [76] and 11.6 ± 0.8 from the 16-item Sniffin' Sticks identification (normosmia: ≥ 12) [77].

The prevalence of chemosensory dysfunction was the most investigated topic in half of articles (n = 33), followed by recovery time in 8 articles (Fig. 2). Other topics of

Table I. Features of the studies using self-rating assessment.

Source		Year	Country	Study population	Methods	Prevalence	Recovery time	Topic	STROBE score*
1	Altundag A [13]	2021	Turkey, USA	135 COVID-19 patients	Structured questionnaire	OD: 59.3%; Mean recovery: 7.8 days	N/A	Prevalence and recovery of chemosensory dysfunction	20
2	Bagheri SH [14]	2020	Iran	10 069 COVID-19 patients	Structured questionnaire	OD: anosmia 60.9%, 80.4% combined dysfunction	N/A	Prevalence of chemosensory dysfunction	20
3	Barillari MR [15]	2020	Italy	294 COVID-19 patients	Validated questionnaires	OD: 70.4%; GD: 59.2%	N/A	Prevalence of chemosensory dysfunction	21
4	Boscolo Rizzo P [16]	2021	Multicentric	268 COVID-19 patients	Validated questionnaires	Combined chemosensory dysfunction: 81.3%; OD: 10.2%; GD 8.6%	N/A	Prevalence of chemosensory dysfunction	22
5	Boscolo-Rizzo P [18]	2020	Italy, UK	187 COVID-19 patients	Validated questionnaires	Baseline: - OD or GD: 60.4%; 4 weeks: - complete resolution or improvement: 89%	N/A	Prevalence of chemosensory dysfunction and recovery time	21
6	Boscolo-Rizzo P [17]	2020	Italy	296 household contacts of home-isolated COVID-19 patients	Structured questionnaire	OD or GD: 25%	N/A	Prevalence of chemosensory dysfunction	21
7	Chapurin N [19]	2021	USA	1003 COVID-19 patients	Validated questionnaires	OD and GD: 73%	19.7 days	Prevalence of chemosensory dysfunction	20
8	Chiesa-Estomba CM [20]	2020	Multicentric	751 COVID-19 patients	Validated questionnaires	OD: 82.7%; anosmia 83%, hyposmia 17%	N/A	Prevalence and recovery of chemosensory dysfunction	22
9	Cho RHW [21]	2020	Hong Kong	83 COVID-19 patients; 60 controls	Structured questionnaire	OD: 47%; GD: 43.4%	OD: 10.3 days; GD: 9.5 days	Correlation between olfactory dysfunction and viral load	22
10	Gerkin RC [22]	2021	Multicentric	4148 COVID-19 patients	Validated questionnaires; VAS	N/A	N/A	Predictive value of olfactory loss in COVID-19	22
11	Gorzkowski V [23]	2020	France	229 COVID-19 patients	Structured questionnaire	OD: 70.3%	11.6 days	Prevalence of chemosensory dysfunction and recovery time	22
12	Haehner A [24]	2020	Germany	500 patients suspected for COVID-19: 34 confirmed cases	Structured questionnaire; VAS for OD/GD	Smell and/or taste loss: 13.8%	N/A	Predictive value of olfactory loss in COVID-19	19
13	Hopkins C [25]	2021	Multicentric	434 responders; 114 COVID-19 patients	Structured questionnaire	6 months: 40.9% patients normosmic; 97.2% normogeusic	N/A	Prevalence of chemosensory dysfunction	20
14	Iravani B [26]	2020	Multicentric	2440 patients	Data collection website smelltracker.org	Relationship between the COVID-19 prediction model and odour intensity ratings over time, $\rho = -0.83$, $P < 0.001$	N/A	Predictive value of olfactory loss in COVID-19	21

▶

Table I. Features of the studies using self-rating assessment *(follows).*

Source		Year	Country	Study population	Methods	Prevalence	Recovery time	Topic	STROBE score*
15	Jalessi M [27]	2021	Iran, UK	243 COVID-19 patients	Validated questionnaires	OD: 88.5% anosmia at the onset.	N/A	Prevalence of chemosensory dysfunction	20
16	Konstantinidis I [28]	2020	Greece	79 COVID-19 patients	VAS; olfactory and gustatory home test	OD: 36.7%; GD: 27.8%	N/A	Prevalence of chemosensory dysfunction	22
17	Lal P [83]	2021	India	435 COVID-19 patients	Structured questionnaire	OD and/or GD: 10.8%	- OD 12.1 days; - GD 10.8 days	Recovery time	15
18	Lechien JR [29]	2020	Multicentric	417 COVID-19 patients	Validated questionnaires	OD: 85.6%. GD: 88.0%	N/A	Prevalence of chemosensory dysfunction	21
19	Lechien JR [32]	2021	Multicentric	2581 COVID-19 patients	Validated questionnaires; Sniffin' sticks identification test (233 patients)	OD: 85.9% (mild forms) moderate-to-critical forms (4.5-6.9%). Psychophysical testing: 54.7% hyposmia/anosmia	- OD 21.6 days	Prevalence and recovery of chemosensory dysfunction	20
20	Lechien JR [31]	2021	Multicentric	2579 COVID-19 patients	Validated questionnaires; Sniffin' sticks identification test (231 patients)	OD: 73.7%. GD: 46.8%. Psychophysical testing: 23.5% anosmia; 18.6% hyposmia	N/A	Prevalence of chemosensory dysfunction	20
21	Lechien JR [30]	2020	Multicentric European	1420 COVID-19 patients	Validated questionnaires	OD: 70.2%; GD: 54.2%	N/A	Prevalence of chemosensory dysfunction	20
22	Locatello LG [33]	2021	Italy	101 COVID-19 patients	Validated questionnaires	Chemosensory dysfunction; - One month: 44%; -Three months: 37%	N/A	Treatment outcomes	21
23	Lucidi D [34]	2020	Italy	110 COVID-19 patients	Validated questionnaires	N/A	Complete recovery: 7-14 days in 63% patients. Partial recovery: 1-3 months in 22% patients	Prevalence of chemosensory dysfunction	20
24	Maiorano E [35]	2021	Italy	170 COVID-19 patients	Structured questionnaire; VAS for OD/GD	OD and GD: 96%	N/A	Prevalence of chemosensory dysfunction	19
25	Paderno A [36]	2020	Italy	508 COVID-19 patients	Structured questionnaire	OD: 56%; GD: 63%	N/A	Prevalence of chemosensory dysfunction	22
26	Parma V [37]	2020	Multicentric	4039 COVID-19 patients	Validated questionnaires	Mean reduction of smell: -79.7%; taste: -69.0%; chemestetic: -37.3%	N/A	Prevalence of chemosensory dysfunction	22
27	Qiu C [38]	2020	Multicentric	394 COVID-19 patients	Validated questionnaires, VAS	Olfactory and/or gustatory dysfunction: 41%	N/A	Prevalence of chemosensory dysfunction	22

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Table I. Features of the studies using self-rating assessment *(follows).*

Source		Year	Country	Study population	Methods	Prevalence	Recovery time	Topic	STROBE score*
28	Raad N [39]	2021	Iran	1299 COVID-19 patients	Validated questionnaires	Parosmia: 10.8%	N/A	Prevalence of parosmia	20
29	Spinato G [40]	2021	Italy	230 COVID-19 patients; 230 controls	Validated questionnaires	N/A	N/A	Validation of a questionnaire	21
30	Vaira LA [41]	2021	Multicentric	153 COVID-19 patients after vaccination	Validated questionnaires	OD: 62.3%. GD: 53.6%	N/A	Prevalence of chemosensory dysfunction in COVID-19 cases after vaccination	21
31	Yan CH [42]	2020	USA	128 COVID-19 patients	Structured questionnaire	OD: -hospitalized 26.9%, outpatients 66.7%; GD: -hospitalized 23.1%, outpatients 62.7%	N/A	Predictive value of olfactory loss in COVID-19	19

OD: indicates olfactory dysfunction; GD: gustatory dysfunction; N/A: not applicable; VAS: visual analogue scale.
** Scores interval from 0 to 22, with higher scores showing better study quality [12].*

Table II. Features of the studies using psychophysical testing.

Source		Year	Country	Study population	Methods	Prevalence	Recovery time	Topic	STROBE score*
1	Amadu AM [43]	2021	Multicentric	46 COVID-19 patients	CCCRC	OD: 76.1%; anosmia 26.1%, severe hyposmia 21.7%, moderate hyposmia 28.3%	N/A	Correlation between olfactory dysfunction and lung involvement	21
2	Bordin A [44]	2021	Italy	101 COVID-19 patients	Sniffin' sticks; validated questionnaires	6 months: - OD: 55.6%	N/A	Prevalence of chemosensory dysfunction and recovery time	21
3	Boscolo Rizzo P [45]	2021	Multicentric	145 COVID-19 patients	UPSIT	6 months: -OD 60%, anosmia 6.9%, severe hyposmia 4.8%	N/A	Recovery time	21
4	Boscolo-Rizzo P [46]	2021	Multicentric	100 COVID-19 patients	Sniffin' sticks, taste strips, screening for intranasal trigeminal dysfunction (visual analogue scale)	Orthonasal smell in COVID-19 patients: OD 46% (7% anosmic). Gustatory function in COVID-19 patients: GD 27%. Nasal trigeminal sensitivity significantly lower in COVID-19 patients	N/A	Prevalence of chemosensory dysfunction	22
5	González C [47]	2021	Chile, USA	100 COVID-19 patients; 63 controls	UPSIT	OD: -Baseline 75%; -One month: 41%	N/A	Prevalence of chemosensory dysfunction	21
6	Iannuzzi L [48]	2020	Italy	30 COVID-19 patients	Sniffin' sticks; validated questionnaires (VAS, Hyposmia rating scale)	10% anosmia, > 50% hyposmia	1 month	Recovery time	21

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Table II. Features of the studies using psychophysical testing *(follows)*.

Source		Year	Country	Study population	Methods	Prevalence	Recovery time	Topic	STROBE score*
7	Le Bon SD [51]	2021	Multicentric	72 COVID-19 patients	Sniffin' sticks, taste strips, screening for intranasal trigeminal dysfunction (identification of menthol)	OD: anosmia 8%, hyposmia 29%, normosmia 63%	N/A	Prevalence of chemosensory dysfunction	22
8	Le Bon SD [49]	2021	Multicentric	93 COVID-19 patients	Sniffin'sticks (identification test); taste strips	OD: 18% hyposmic, 3% anosmic. GD: 12% hypogeusic, no ageusic patients	N/A	Prevalence of chemosensory dysfunction	20
9	Le Bon SD [50]	2021	Belgium	27 COVID-19 patients	Sniffin' sticks	Improvement in the group oral corticosteroids + olfactory training: 7.7 points; olfactory training: 2.1 points	N/A	Treatment outcomes	21
10	Lechien JR [54]	2020	Multicentric	78 COVID-19 patients	Validated questionnaires; Sniffin' sticks identification test (46 patients)	OD: 11% anosmia; 24% hyposmia	N/A	Prevalence of chemosensory dysfunction	20
11	Lechien JR [53]	2020	Multicentric	88 COVID-19 patients	Sniffin' sticks (identification test); validated questionnaires	OD: 44.6%. Recovery at 2 months: 79.5%	N/A	Recovery time	20
12	Lechien JR [52]	2020	Multicentric	47 COVID-19 patients	Sniffin'sticks (identification test); validated questionnaires	OD: 8.5% anosmia, 19.1% hyposmia	N/A	Prevalence of chemosensory dysfunction	19
13	Moein ST [55]	2020	Iran	100 COVID-19 patients	UPSIT	OD: -Baseline: 96%; -after 5 weeks: 63%	N/A	Prevalence of chemosensory dysfunction and recovery time	22
14	Niklassen AS [9]	2021	Multicentric	111 COVID-19 patients	Sniffin' sticks, taste sprays	OD: 21% anosmia; 49% hyposmia; GD: 26%	28 days	Prevalence of chemosensory dysfunction and recovery time	22
15	Petrocelli M [56]	2021	Multicentric	300 COVID-19 patients	Evaluation of the ethyl alcohol olfactory threshold and the discriminative function for six groups of common household odorants. Taste sprays	Baseline: anosmia 47%, ageusia 38%; 6 months: anosmia 5%, ageusia 1%	N/A	Recovery time	19
16	Petrocelli M [94]	2020	Italy	300 COVID-19 patients	Validated psychophysical self-administered test	OD and/or GD: 70%; anosmia 47%, ageusia 38%	N/A	Prevalence of chemosensory dysfunction	19
17	Prajapati DP [58]	2020	USA	81 COVID-19 patients	12-item BSIT; VAS	OD: 66.6%	N/A	Prevalence of chemosensory dysfunction	21

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Table II. Features of the studies using psychophysical testing *(follows)*.

Source		Year	Country	Study population	Methods	Prevalence	Recovery time	Topic	STROBE score*
18	Prajapati DP [59]	2021	USA	52 COVID-19 patients	12-item BSIT; VAS	OD: 63%	12 days	Prevalence of chemosensory dysfunction and recovery time	21
19	Saussez S [60]	2021	Multicentric	288 COVID-19 patients	Validated questionnaires; Sniffin' sticks identification test	Baseline: anosmia 39.2%, hyposmia 13.2%; 60 days: anosmia 9.4%, hyposmia 16%	N/A	Recovery time	20
20	Vaira LA [68]	2021	Multicentric	170 COVID-19 patients; 170 controls	Sniffin' sticks	COVID-19 patients: anosmia in 4.7%, hyposmia in 21.8% cases. Controls: hyposmia in 3.5% cases	N/A	Prevalence of chemosensory dysfunction	22
21	Vaira LA [63]	2021	Multicentric	60 COVID-19 patients	CCCRC	Prevalence of OD = 76.7%; anosmia 20%, severe hyposmia 18.3%, moderate hyposmia 18.3%, mild hyposmia 16.7%	N/A	Correlation between olfactory dysfunction and viral load	22
22	Vaira LA [62]	2021	Multicentric	77 COVID-19 patients	CCCRC	Prevalence of OD= 74%; anosmia 18.1%, severe hyposmia 16.9%, moderate hyposmia 24.7%, mild hyposmia 14.3%	N/A	Correlation between olfactory dysfunction and inflammatory markers	21
23	Vaira LA [61]	2021	Multicentric	74 COVID-19 patients	CCCRC	OD: mild hyposmia 14.9%, moderate hyposmia 24.3%, severe hyposmia 16.2, anosmia 18.9%	N/A	Correlation between olfactory dysfunction and inflammatory markers	21
24	Vaira LA [67]	2021	Multicentric	774 COVID-19 patients	Sniffin-Sticks test, CCCRC	OD = 62.1%: hyposmic 36.2%, anosmic 25.9%	N/A	Prevalence of chemosensory dysfunction	21
25	Vaira LA [66]	2021	Multicentric	18 COVID-19 patients	CCCRC	Median olfactory score: -Baseline: treatment group 10; controls 20	N/A	Treatment outcomes	22
26	Vaira LA [65]	2020	Multicentric	138 COVID-19 patients	CCCRC	Chemosensory dysfunction: baseline 84.8%; 2 months 7.2%	N/A	Recovery time	19
27	Vaira LA [64]	2020	Multicentric	106 COVID-19 patients	CCCRC	Baseline: OD 67%, GD 65.6%	N/A	Prognostic value of olfactory dysfunction	19
28	Vaira LA [69]	2020	Italy	345 COVID-19 patients	Validated psychophysical self-administered test; CCCRC	OD: mild disease 66.6%; moderate 67%; severe 69.2% GD: mild 70.2%, moderate 71.3%, severe 65.4%.	N/A	Prevalence of chemosensory dysfunction	20

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Table II. Features of the studies using psychophysical testing *(follows)*.

Source		Year	Country	Study population	Methods	Prevalence	Recovery time	Topic	STROBE score*
29	Vaira LA [70]	2020	Italy	33 COVID-19 patients	Validated psychophysical self-administered test; CCCRC	N/A	N/A	Validation of a self-administered olfactory and gustatory test	21
30	Vaira LA [57]	2020	Italy	72 COVID-19 patients	CCCRC, taste sprays	OD: anosmia 2.8%, hyposmia 80.6%. GD: ageusia 1.4%, hypogeusia 47.2%	N/A	Prevalence of chemosensory dysfunction	22

Abbreviations: CCCRC: indicates Connecticut Chemosensory Clinical Research Center test; OD: olfactory dysfunction; GD: gustatory dysfunction; UPSIT: University of Pennsylvania Smell Identification test; VAS: Visual Analogue Scale; BSIT: Brief Smell Identification Test.
**Scores interval from 0 to 22, with higher scores showing better study quality [12].*

Table III. Features of the studies using imaging techniques.

Source		Year	Country	Study population	Methods	Prevalence	Recovery time	Topic	STROBE score*
1	Altundag A [71]	2020	Turkey, USA	91 cases: 24 cases COVID-19 patients, 38 patients with PIOD, and a control group of 29 patients	CT scan, MRI	COVID-19 patients: 100% anosmic	N/A	Radiological study	22
2	Kandemirli SG [72]	2021	Turkey, USA	23 COVID-19 patients	Sniffin' sticks, CT scan, MRI	COVID-19 patients: 100% anosmic	N/A	Radiological study	20
3	Lechien JR [73]	2020	Multicentric	16 COVID-19 patients	Validated questionnaire, Sniffin' sticks, olfactory cleft examination, CT scan	COVID-19 patients: 100% anosmic	N/A	Radiological study	22
4	Tekcan Sanli DE [74]	2021	Turkey, USA	50 COVID-19 patients	Sniffin' sticks, CT scan.	N/A	N/A	Radiological study	21
5	Yildirim D [75]	2021	Turkey, USA	31 COVID-19 patients, 97 patients with PIOD	Olfactory bulb MRI, DTI, and olfactory fMRI	COVID-19 patients: 100% anosmic; PIOD patients: 18.6% hyposmic, 81.4% anosmic	N/A	Radiological study	21

PIOD: indicates post-infectious olfactory disorder; CT: computed tomography; MRI: magnetic resonance imaging; N/A: not applicable.
**Scores interval from 0 to 22, with higher scores showing better study quality [12].*

interest were studies using imaging techniques (n = 5), the predictive value of olfactory loss in COVID-19 (n = 5), miscellaneous (n = 5) and studies investigating both the prevalence of chemosensory dysfunction and recovery time (n = 5). Less explored themes were treatment outcomes (n = 3) and validation of new tests (n = 2).

About the recovery time (Fig. 3), results from psychophysical tests (i.e., Sniffin' Sticks extended test, CCCRC) showed a prevalence of olfactory dysfunction about the 70% during SARS-CoV-2 infection, with only 20% of patients still presenting impairment after one month.

Within the included articles, 32 (48.5%) were multicentric.

Discussion

The results of this review demonstrate that the prevalence of olfactory and gustatory dysfunction in COVID-19 patients is highly variable in the current literature and depends on the methodology used. In fact, the prevalence of olfactory dysfunction ranges from 14 to 89% in case of assessments based on self-ratings (Tab. I), while it ranges from 21 to 96% in case of psychophysical assessment (Tab. II). Regarding taste impairment, although generally less present [78], we found rates of 9 to 88% based on self-ratings (Tab. I) and of 12 to 66% based on psychophysical testing. This discrepancy

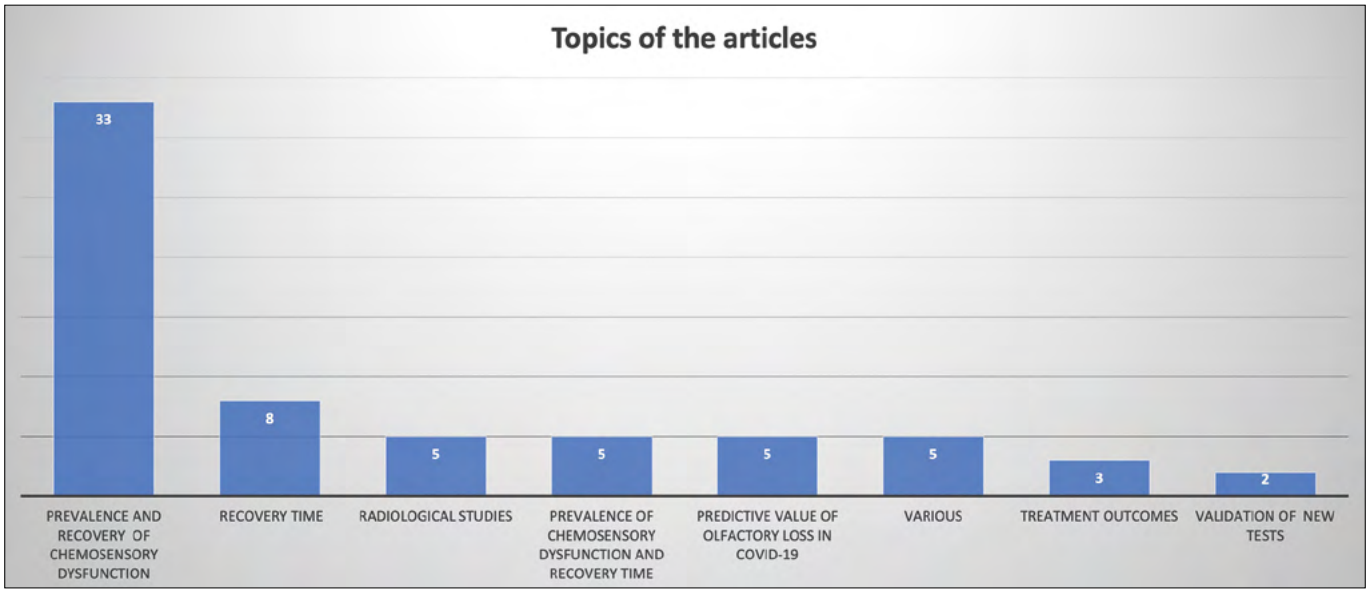

Figure 2. Topics of included articles about COVID-19 chemosensory dysfunction from December 2019 to November 2021. Prevalence of chemosensory dysfunction was the most investigated topic.

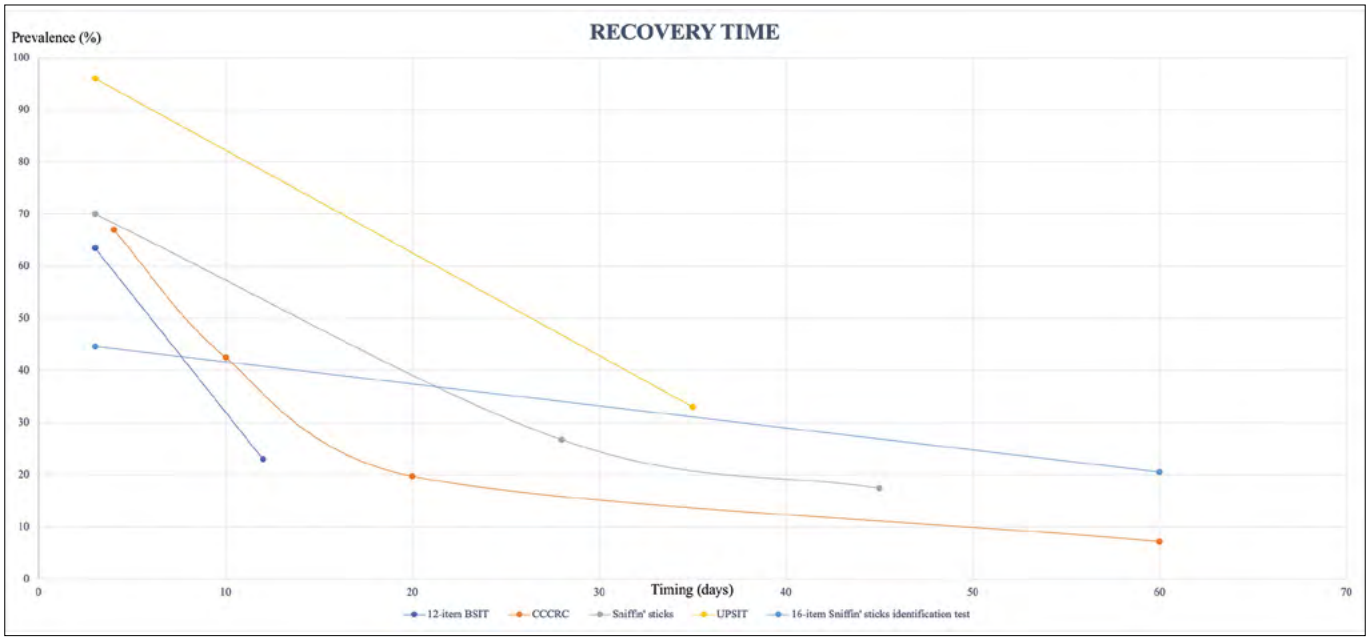

Figure 3. Recovery time of olfactory dysfunction evaluated using psychophysical testing. The figure shows the prevalence of patients suffering from olfactory dysfunction according to the timing of SARS-CoV-2 infection.

is partly due to the fact that the importance attributed to smell, taste and flavour varies among the general population according to sex, age and sociocultural factors, which is a major bias in response behaviour [79-82]. In fact, many studies adopted visual analogue scales (VAS) to rate olfactory/gustatory dysfunction [28,35], as well as ad hoc questions [83]. Other studies used only the responses to taste or smell-related questions of certain patient response outcome measures, like the Sinonasal Outcome test 22 (SNOT-22) [16,19]. Only a few studies used validated questionnaires specifically investigating smell impairment such as the Questionnaire of Olfactory Dysfunction (QOD) [38] or the short version of the

Questionnaire of Olfactory Disorders-Negative Statements (sQOD-NS) [29]. However, the prevalence of olfactory/gustatory dysfunction varies remarkably among the studies (Tabs. II, IV) where psychophysical assessment was conducted with a wide range of tests that highly differ from each other (i.e., Sniffin' Sticks extended version, CCCRC olfactory test, UPSIT, BSIT, home self-administered test, taste sprays, taste strips). Many research groups used only screening tests to assess olfactory function, such as the 12-item BSIT [58,59] or the 16-item smell identification test of the Sniffin' Sticks battery [53,60]. However, the Sniffin' Sticks test in its full version consists of three subtests aiming at thorough evaluation of the olfactory capacity of individuals. The test results in a comprehensive TDI score [1-48] with scores > 30.5 indicating normosmia [84]. Conversely, other olfactory tests are less difficult, less expensive and less time-consuming, but they do not provide such an extensive assessment as the Sniffin' sticks. In fact, the UPSIT [85] is a smell identification test and the CCCRC [86] includes only the smell detection threshold (using the method of ascending limits) and smell identification assessment. Similarly, for gustatory assessment, the taste sprays used in many of the studies included can be considered just as a screening test. Conversely, the taste strips allow to collect more accurate data about the primary taste which is impacted (i.e., sweet, salty, bitter, and sour) and to classify taste capacity of patients in normogeusia and hypogeusia [87].

Interestingly, results from psychophysical tests of olfactory function presented in Table IV showed that the threshold score was significantly more impacted than the discrimination and identification performances in the studies using the extended version of the Sniffin' Sticks test (T: 5.2 ± 1.3; D: 10.8 ± 0.9; I: 10.7 ± 1.0). This also appears to be valid in publications using the CCCRC (T: 18.8 *versus* I: 47.6), although this test does not evaluate the discrimination capacity as the Sniffin' Sticks. Therefore, the results of psychophysical tests suggest that COVID-19 olfactory dysfunction impacts less the more complex cognitive processing of olfactory information. The SARS-CoV-2 virus has a major tropism for the nasal structures, such as the olfactory epithelium, which may partly explain the stronger effect on odour thresholds than odour identification. For further analysis of global olfactory function, a comprehensive evaluation using the extended version of the Sniffin' Sticks test is preferable to an odour identification test alone, whenever possible.

The recovery time was the second most investigated parameter with eight articles focusing on this topic [9,45,48,53,56,60,65,83] and another five studying both the prevalence of chemosensory dysfunction and recovery time [18,23,44,55,59]. The recovery time was on average 14.3 days for olfactory function and 10.2 days for gustatory function according to the studies included in Table I in which self-ratings of smell function were performed. Similarly, it was 23.3 days for olfaction according to the articles included in Table II in which psychophysical testing was executed. Studies investigating the long-term outcomes of olfactory dysfunction showed chemosensory dysfunction in 7% of patients at 2 months [65] with the 80% of COVID-19 patients reporting olfactory recovery [53]. Using the UPSIT another article suggested severe microsmia in 2% and anosmia in 5% of COVID-19 patients after 6-month follow-up [45]. Hence, the timing of the evaluation during and after SARS-CoV-2 infection significantly influences the results of the psychophysical tests. This is important as patients who show persistent dysfunction after 15-20 days should be referred to an otolaryngologist to be tested and to start timely treatment that includes safety counselling (e.g., maintain smoke and gas detectors, monitor spoiled food), olfactory training and possible adjuvant medication (e.g., intranasal vitamin A, systemic omega 3) [88]. Regarding treatment, a pilot study in a small sample of patients included in Table II of this review using the Sniffin' sticks test reported that a 10-day treatment of oral corticosteroids associated with olfactory training led to significant improvement of the olfactory score compared to olfactory training alone [50].

Table IV. Results from psychophysical tests of smell during SARS-CoV-2 infection. Results are presented as mean plus standard deviation.

Test	Threshold	Discrimination	Identification	TDI score	CCCRC score
Sniffin' sticks extended test	5.2 ± 1.3	10.8 ± 0.9	10.7 ± 1.0	22.5 ± 7.8	N/A
CCCRC	18.8*	N/A	47.6*	N/A	40.8 ± 14.7
UPSIT	N/A	N/A	25.2 ± 2.5	N/A	N/A
16-item Sniffin' stick identification test	N/A	N/A	11.6 ± 0.8	N/A	N/A
12-item brief BSIT	N/A	N/A	8.5 ± 0.5	N/A	N/A

BSIT: indicates Brief Smell Identification Test; N/A: not applicable; CCCRC: Connecticut Chemosensory Clinical Research Center test; UPSIT: The University of Pennsylvania Smell Identification test; TDI score: threshold discrimination identification score.

** Results of CCCRC score according to threshold and identification scores were presented only in the article "Objective evaluation of anosmia and ageusia in COVID-19 patients: Single-center experience on 72 cases". By Vaira LA et al. [57].*

However, there is skepticism in the current literature about the use of systemic corticosteroids to treat COVID-19 olfactory impairment as documented in an international consensus article [89]. In fact, the experts have called for caution against the use of oral corticosteroids because of the lack of solid scientific evidence and the potential side effects (i.e., glaucoma, hip fractures). Moreover, COVID-19-related olfactory impairment tends to spontaneously recover in one month. Additionally, conventional intranasal administration of topical steroids does not appear to be an effective therapeutic option since steroid sprays do not appropriately reach the olfactory cleft [90].

The debate concerning the pathogenesis of SARS-CoV-2 chemosensory dysfunction is still open and some studies have postulated that the viral-associated damage might be extended not only to the olfactory epithelium, but also to the olfactory bulb and the central nervous system [8]. Five studies [71-75] included in Table III used imaging techniques (i.e., computed tomography-CT scan, magnetic resonance imaging-MRI) to investigate chemosensory dysfunction in COVID-19 patients and contributed to the understanding of the mechanisms underlying smell and taste impairment. In these radiological studies, abnormalities such as higher olfactory cleft width and volume [71,74] and decreased white matter tract integrity of olfactory regions were detected in COVID-19 patients [75]. In contrast, a post-mortem study on 85 COVID-19 deceased patients demonstrated that sustentacular cells are the main target in the olfactory mucosa, while olfactory sensory neurons and parenchyma of the olfactory bulb are not affected [91]. Another recent review of animal and human studies also suggested that infections of the olfactory epithelium in COVID-19 patients rarely result in a brain infection because of the lack of entry protein expression in olfactory neurons that creates a barrier [92]. Therefore, the neurotrophic action of COVID-19 is still uncertain, and this is in accordance with the results of the psychophysical tests of this review showing that olfactory threshold performance is more impacted than discrimination and identification capacities (Tab. IV).

Olfactory dysfunction is now globally recognised as a key symptom of SARS-CoV-2 infection, while its positive prognostic value is still debated. Five studies investigated the predictive value of olfactory loss in the diagnosis and course of COVID-19 [22,24,26,42,64]. It was found that sudden olfactory loss presents a high specificity of 97% and a sensitivity of 65%, while it has a positive predictive value of 63% and negative predictive value of 97% for SARS-CoV-2 infection [24]. Interestingly, the use of olfactory loss as an indicator of COVID-19 in the general population could have important clinical applications in underserved areas with limited access to COVID-19 testing [26]. Another four publications studied the correlation between olfactory dysfunction and inflammatory markers [61,62] as well as lung involvement [43] and viral load [21]. For inflammatory markers, the level of interleukin 6 (IL-6), which is known to be a proinflammatory cytokine secreted by COVID-19 infected cells, was found to be significantly correlated with the severity of SARS-CoV-2 infection with a directly proportional association, but the correlation between IL-6 plasma concentrations and olfactory performance was not significant [61]. Additionally, smell dysfunction seems to have poorer prognostic value in predicting the severity of COVID-19 compared to other systemic inflammatory markers (i.e., D-dimer, ferritin, procalcitonin and neutrophil-to-lymphocyte ratio). These findings could suggest that the pathogenesis of COVID-19 chemosensory dysfunction is more likely due to intranasal local factors rather than to systemic inflammation [62]. Lung involvement detected by CT in COVID-19 patients did not exhibit a significant correlation with olfactory performance measured by CCCRC [43].

Finally, new tools were developed and validated to overcome many limitations that arose during various lockdown measures and hospital reorganisation due to the COVID-19 pandemic [7]. It is worth mentioning the COVID-19 Questionnaire (COVID-Q) [40], a novel symptom questionnaire specific for COVID-19 to identify patients who are likely to suffer from SARS-CoV-2 infection, and the validation of a self-administered olfactory and gustatory test for the remote evaluation of COVID-19 patients [70]. Precisely, the COVID-Q [40] was tested on 230 non-hospitalised COVID-19 patients and 230 controls enrolled at Treviso Hospital. The questionnaire included 27 items in its final version, which relate to "asthenia", "gastrointestinal symptoms", "ear and nose symptoms", "breathing issues", "throat symptoms", "anosmia/ageusia" and "muscle pain". Interestingly, "anosmia/ageusia" items were significantly correlated with rates of positive COVID-19 test positivity. Concerning the self-administered olfactory and gustatory tests for remote evaluation of COVID-19 patients [70], these have been assessed in 33 home-quarantined COVID-19 patients and the results compared with those obtained from the CCCRC and an operator-administered gustatory screening test. The novel self-administered test comprised an olfactory threshold test plus an odour discrimination test and a gustatory screening test with four solutions corresponding to the primary tastes. Although the cohort was made up only of infected health personnel and is not representative of the general population, the preliminary findings appear promising as there were no significant differences between the results of the tests for either smell ($p = 0.201$) or taste ($p = 0.180$). Pilot data were later confirmed by another study on 300 COVID-19 patients belonging to the healthcare staff of the Bellaria-Maggiore Hospital in Bologna [94].

Conclusions

The results of this review confirm that smell and taste impairments are key symptoms of SARS-CoV-2 infection, even in asymptomatic and mildly symptomatic patients [29,93], and that the timing significantly influenced the results of the psychophysical testing with a consistent improvement at one month after infection. The olfactory threshold performance was the most impacted compared to odour discrimination and odour identification capacities in accordance with the findings of a major tropism of SARS-CoV-2 for the olfactory mucosa [91,92]. Finally, COVID-19 chemosensory dysfunction brought to the attention of the scientific community the central role of the otolaryngologists in the management of chemosensory dysfunction and the importance of performing psychophysical testing to offer smell rehabilitation and valid treatment options to patients with persistent sensory impairment [9].

Conflict of interest statement

The authors declare no conflict of interest.

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Authors' contributions

All authors meet the International Commitee of Medical Journal Editors (ICMJE) criteria:
1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work (EMCT, MC, FL, MG); 2) Drafting the work or revising it critically for important intellectual content (EMCT, TH); 3) Final approval of the version to be published (EMCT, MC, FL, PP, CM, TH, MG); 4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved (EMCT, PP, CM). EMCT and MG were specifically responsible for the data collection.

Ethical consideration

This systematic review was exempted from institutional ethical committee approval.

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