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Review

A German AWMF’s S2e/realist synthesis and meta-narrative snapshot of craniomaxillofacial manifestations in COVID-19 patients: Rapid living update on 1 January 2021

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A B S T R A C T

Purpose: To execute a review answering the following question: “Among novel coronavirus disease (COVID19) patients, what are craniomaxillofacial (CMF) manifestations?” based on the RAMESES and the German Association of Scientific Medical Societies (AWMF)’s S2e guidelines.

Methods: We performed a realist synthesis and meta-narrative review extracting data in English, French, German and Thai from PubMed/Medline, Embase, Biomed Central, Cochrane Library, and Thai Journals Online, until 1 January 2021. The primary outcome variable was CMF manifestations grouped into 5 categories: (1) mouth and throat, (2) nose, paranasal sinus, and skull base (3) ocular/orbital and periorbital tissue, (4) ear, and (5) craniofacial skin. Appropriate statistics was computed.

Results: Thirty-seven original articles meeting the inclusion criteria were analysed; all were in English and indexed in PubMed/Medline. Hand searches of their references yielded a total of 101 articles for the review. Most data were in low level of evidence and focused on smell and taste disturbances and non-specific orofacial lesions. Iatrogenic complications may occur in this body region. Conservative measures remained effective and were usually enough for patient care.

Conclusion: Because SARS-CoV-2 infection is new and becomes the stringent worldwide pandemic within a short time period, most of the data on CMF symptoms are of low level evidence. Apart from taste and smell dysfunctions, non-specific CMF lesions can be found and treated conservatively. Treatment complications are possible. Dentists and CMF surgeons are privileged to examine the orofacial region and work closely with colleagues in other specialities to combat this pandemic.

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1. Introduction

In early 2020, the World Health Organization (WHO) announced the ongoing coronavirus disease (COVID-19) pandemic due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Anecdotal evidences of COVID-19 manifestations in the oral and craniofacial region have been incrementally reported. Until now,
there is no comprehensive review integrating these data from diverse specialities: craniomaxillofacial (CMF) surgery, dentistry, otolaryngology, facial plastic surgery, ophthalmic plastic and reconstructive surgery, and (facial) dermatology. Previously published papers often focused mainly on a limited aspect of head and neck symptomatology and treatments, e.g. oral lesions only.

The purpose of this study was to perform a concise but comprehensive overview designed to answer the following research question: “Among COVID-19 patients, what are CMF manifestations?”

2. Materials and methods

2.1. Study design and samples

Using a literature review design, we searched the PubMed/Medline (https://pubmed.ncbi.nlm.nih.gov), Embase (https://www.embase.com), Biomed Central (https://www.biomedcentral.com/), Cochrane Library (https://www.cochranelibrary.com), and Thai Journals Online (https://www.tci-thaijo.org/) from inceptions until 1 January 2021, to identify literature in English, French, German and Thai. The search terms were “COVID-19” OR “Coronavirus” OR “SARS-CoV-2” AND “oral” or “mouth” or “taste” or “gustatory” or “face” OR “nose” OR “smelling” OR “sinos” OR “eye” OR “ear” OR “hearing” OR “skin”. Only studies or reports on CMF manifestations were included. No restrictions with regard to samples were applied, and expert opinions, editorials and small case series (n < 20) were excluded. References of the selected papers were searched for relevant studies to include in the analyses, including papers in Evidence Level 4–5, if relevant. When a systematic review with/without meta-analysis existed, its references were not included to prevent duplication. Because this was a meta-narrative review, no attempt was made to identify unpublished studies, or literature in languages other than English, French, German and Thai, or to contact researchers for unpublished data, or to perform a meta-analysis.

Because of neither patient nor animal contacts in this study, the ethical approval was not required. However, the World Medical Association’s Declaration of Helsinki Version 2008 (https://www.wma.net/wp-content/uploads/2018/07/DH-Oct2008.pdf) was followed throughout the study. The review and data synthesis were adhered to the German Association of Scientific Medical Societies (German: “Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V.”; AWMF)’s S2e (i.e. guideline based on evidence) [1] and the RAMESES guideline for the realist and meta-narrative evidence synthesis (http://www.ramesesproject.org).

2.2. Study variables

The primary predictor variable was COVID-19 infection. The primary outcome variable was CMF manifestations. Other variables included demographic, clinical, investigative, and therapeutic parameters.

2.3. Data collection and analysis

We reviewed each report and abstracted data regarding the following variables: author, country of origin, study design, Level of Evidence according to the Oxford’s Centre for Evidence-Based Medicine (CEBM: https://www.cebm.ox.ac.uk/resources/levels-of-evidence/oxford-centre-for-evidence-based-medicine-levels-of-evidence-march-2009), sample size, sign and/or symptom, further investigation, treatment. Descriptive, uni- and/or bivariate statisti-
and non-specific stomatitis, which often combine with aphthae in the oral cavity (Level of Evidence 5) [4,6–10]. Compared with aphthae in young adults with mild infection, aphthous-like lesions in older patients with immunosuppression and severe SARS-CoV-2 infection frequently contain necrosis and haemorrhagic crusts. Anyhow, most aphthae heal within 5–15 days, and often regress faster on systemic improvement (Level of Evidence 3a) [5]. Other oral lesions, e.g. candidiasis, herpetic lesions, appear secondary to the patient’s weakened systemic condition or immunity impairment, or adverse reactions of medications against COVID-19. Most of them heal within 3–21 days spontaneously, or through topical treatments, or oral hygiene measures (Level of Evidence 2a) [2].

Paramyxovirus (mumps virus), influenza A, parainfluenza virus, and human immunodeficiency virus (HIV) can infect salivary glands. Similarly, acute nonsuppurative sialadenitis is another initial manifestation of SARS-CoV-2 infection. Viral transmission into the salivary glands frequently occurs through haematogenous spread, or retrograde ductal migration, particularly in dehydrated patients, and the salivary glands become potential reservoirs for the virus (Level of Evidence 5) [11,12].

Periodontal pockets collect many pathogens, including viruses amid bacteriophages in dental plaque, e.g. Herpes simplex virus, Epstein-Barr virus, Human Cytomegalovirus and SARS-CoV-2. The COVID-19 virus is released from infected periodontal cells or by terminal capillary complexes in periodontal tissues after viraemia (Level of Evidence 5) [13]. Sirin and Ozcelik [14] reported the pertinent results linking the COVID-9 severity and radiological dental damages, which comprised the number of dental caries, root canal treatments, tooth fillings, dental implants, prosthetic crowns, and missing teeth (Level of Evidence 2b). This finding may suggest that patients with severe COVID-19 infections tend to suffer from severe dental diseases. On the other hand, patients with neglected/poor oral hygiene may be at risk of COVID-19 infection with complications. Indeed, SARS-CoV-2 targets and depletes TPMRSS2 and ACE2 of the inflamed dental pulp, worsening treatment outcomes of pulpitis, similar to in pneumonia and inflammatory bowel disease due to COVID-19 (Level of Evidence 5) [3]. The increased pulpitis virulence due to SARS-CoV-2 requires meticulous collaboration between primary dental and inpatient services; i.e. dental generalists and CMF surgeons, especially during lockdown periods because of limited hospital capacity for

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**Fig. 1.** Flow chart of the literature search.
### Table 1: Summary of reviewed articles after excluding single-case reports, small case series, and any duplicated reference studies (all are laboratory-confirmed cases).

| Authors (country) | Study design (Level of Evidence) | Patients/sample size | Manifestations | Patient investigations | Treatments |
|-------------------|----------------------------------|----------------------|----------------|------------------------|------------|
| Abalo-Lojo et al. [79] (Spain) | Retrospective study (2b) | 131 | Taste dysfunction only (1.5%) Anosmia only (3.8%) Both taste and smell dysfunctions (55%) | History, physical exam | ? |
| Aggarwal et al. [49] (India, Singapore, USA) | Systemic review of retrospective studies and better studies (2a) | 2347 | Ocular pain (31.2%) Ocular discharge (19.2%) Ocular redness (10.8%) Follicular conjunctivitis (7.7%) | History, physical exam, self-report survey | Most resolved fully |
| Amorim Dos Santos et al. [2] (Brazil) | Systemic review of retrospective studies and better studies (2a) | 10,220 | Dysgeusia (38%) Hypogeusia (35%) Others: white and erythematous plaques, irregular ulcers, blisters, petechiae, desquamative gingivitis (?) | History, physical exam | Most resolved fully |
| Avci et al. [80] (Turkey) | Retrospective study (2b) | 1197 | Anosmia (44.2%) | History, physical exam | ? |
| Bernabei et al. [81] (Italy) | Systemic review of retrospective studies and better studies (2a) | 2176 | Ocular surface symptoms (3.2%) | History, physical exam, self-report survey | Most resolved fully |
| Bianco et al. [82] (Italy) | Prospective Study (1b) | 50 | Olfactory/taste dysfunctions (52%) | History, physical exam, self-report survey | ? |
| Bostanci Ceran and Ozates [83] (Turkey) | Retrospective study (2b) | 93 | Ocular hyperaemia (21.5%) Photophobia (16.1%) Epiphora (9.7%) Follicular conjunctivitis (8.6%) Visual change (4.8%) Chemosis (3.2%) Episcleritis (2.2%) | History, physical exam, self-report survey | ? |
| Cao et al. [84] (China, USA) | Systemic review of retrospective studies and better studies (2a) | 1930 | Increased secretion (10%) Eye itching (9%) Foreign body sensation (6%) | History, physical exam, self-report survey | Most resolved fully |
| Cavalleri et al. [85] (Italy) | Retrospective study (2b) | 172 | Conjunctival hyperaemia (15.1%) Epiphora (13.4%) Foreign body sensation (9.9%) Itching (7%) Lid swelling (2.9%) Mucopurulent discharge (2.3%) | History, physical exam | ? |
| Chen et al. [86] (China) | Retrospective study (2b) | 535 | Conjunctival congestion (5%) Conjonctivitis (6.2%) Xerophthalmia (4.5%) Keratitis (2.6%) | History, physical exam, self-report survey | ? |
| Conforti et al. [42] (Italy, Romania) | Systemic review of case series and better studies (3a) | 7 (655 with skin lesions) | Facial urticaria only (0.2%, or 1/655) Facial oedema with fever (0.5% or 3/655) Conjunctivitis only (1.7%, or 11/655) Eyelid dermatitis only (0.3%, or 2/655) Conjunctivitis with eyelid dermatitis (0.2%, or 1/655) Nonblanching periorbital dyschromia (0.3%, or 2/655) Conjunctivitis as a part of Kawasaki disease-like disease (0.8%, or 5/655) | History, physical exam, self-report survey | Conservative ocular/orbital care, antihistamine |
| El-Anwar et al. [87] (Egypt) | Systemic review of case series and better studies (3a) | 1773 | Sore throat (11.3%) Pharyngeal erythema (5.3%) Nasal congestion (4.1%) Rhinorrhea (2.1%) Upper respiratory tract infection (1.9%) Tonsil enlargement (1.3%) | History, physical exam | ? |
| Fantozzi et al. [88] (Italy) | Retrospective study (2b) | 326 | Taste dysfunction (59.5%) Xerostomia (45.9%) Smell dysfunction (41.4%) | History, physical exam, self-report survey | Most resolved fully |
| Freni et al. [89] (Italy) | Retrospective study (2b) | 50 | Olfactory dysfunction (92%) Taste dysfunction (70%) | History, physical exam, self-report survey | Most resolved fully |
| Gambini et al. [44] (Italy) | Retrospective study (2b) | 64 | Ocular surface symptoms during infection (60.9%) Ocular surface symptoms postinfection (43.8%) | History, physical exam, self-report survey | ? |
| Gözên et al. [90] (Turkey) | Case-controlled study (3b) | 59 | Olfactory dysfunction (52.5%) Taste dysfunction (42.5%) | Self-report survey | ? |
| Gorzkowski et al. [91] (France) | Retrospective study (2b) | 261 | Olfactory dysfunction (70.3%) | Self-report survey/telephone interview | Most resolved fully |
| Horváth et al. [92] (Australia) | Retrospective study (2b) | 102 | Either smell or taste disturbance or both (74%) Post-recovery: ongoing hyposmia (34%), hypogeusia or ageusia (28%), anosmia (2%) | Self-report survey/telephone interview | Most resolved fully |
Table 1 (Continued)

| Authors (county) | Study design (Level of Evidence) | Patients/sample size | Manifestations | Patient investigations | Treatments |
|------------------|----------------------------------|---------------------|----------------|-----------------------|------------|
| Inomata et al. [48] (Japan, USA)³ | Systemic review of case series and better studies (3a) | 1533 | Ocular symptoms (11.2%) | History, physical exam | Conservative, antihistamine/antivirus/antibacterials |
| Irmannesh et al. [5] (Iran)³ | Systemic review of case series and better studies (3a) | 91 | Oral mucosal lesions at tongue (38%), labial mucosa (26%), palate (22%), gingiva (8%), buccal mucosa (5%), oropharynx (4%), and tonsil (1%) | History, physical exam | Most resolved fully |
| Katz and Yue [4] (USA) | Retrospective study (2b) | 889 | Recurrent aphthous stomatitis (0.67%) | History, physical exam | ? |
| Kavaz et al. [93] (Turkey) | Retrospective study (2b) | 53 | Olfactory/taste dysfunctions (60.4%), Sore throat (13.2%), Nasal congestion (11.3%) | History, physical exam, self-report survey | Most resolved fully |
| Lechner et al. [94] (UK) | Retrospective study (2b) | 208 | Olfactory or taste dysfunctions (89.9%) | Self-report survey | 51.4% recovered fully |
| Lovato and Filippis [95] (Italy)³ | Systemic review of retrospective studies and better studies (2a) | 1556 | Pharyngodynia (12.4%), Nasal congestion (3.7%) | History, physical exam | ? |
| Luers et al. [96] (Germany) | Retrospective study (2b) | 72 | Olfactory dysfunction (74%), Taste dysfunction (69%) | History, physical exam, self-report survey | No treatment |
| Luo et al. [97] (China) | Retrospective study (2b) | 60 | Xerostomia (29.1%), Olfactory dysfunction (12.7%) | History, physical exam, self-report survey |? |
| Ma et al. [43] (China) | Retrospective study (2b) | 216 (paediatric patients only) | Nasal discharge (3.2%), Nasal congestion (2.8%), Conjunctival discharge (2.3%), Conjunctival congestion (1.9%), Blephritis (37.9%), Conjunctival hyperaemia and/or chemosis (24.1%), Eye burning (13.8%), Foreign body sensation (10.3%), Epiphora (10.3%) | History, physical exam, self-report survey | Conservative, antihistamine/antivirus/antibacterials |
| Meduri et al. [45] (Italy) | Case series (3b) | 29 | Olfactory dysfunction (41%), Taste dysfunction (41%), Olfactory dysfunction (29%), Glottis abnormalities (93.8%), Tracheal abnormalities (43.8%), Supraglottic abnormalities (37.5%), Subglottic abnormalities (18.8%) | History, physical exam, self-report survey | ? |
| Meini et al. [98] (Italy) | Case series (3b) | 100 | Taste dysfunction (41%), Olfactory dysfunction (29%), Glottis abnormalities (93.8%), Tracheal abnormalities (43.8%), Supraglottic abnormalities (37.5%), Subglottic abnormalities (18.8%) | Telephone interview | Self-limiting in 2 – 3 weeks |
| Naunheim et al. [18] (USA) | Case series (3b) | 20 | Taste dysfunction (41%), Olfactory dysfunction (29%), Glottis abnormalities (93.8%), Tracheal abnormalities (43.8%), Supraglottic abnormalities (37.5%), Subglottic abnormalities (18.8%) | History, physical exam | Diverse laryngological procedures |
| Panda et al. [99] (India) | Prospective study (1b) | 225 | Anosmia (12.8%), Olfactory dysfunction (17.3%), Taste dysfunction (41%), Combined smell and taste disturbance (9.3%), Foreign body sensation (10.3%), Epiphora (10.3%) | History, physical exam, self-report survey | Self-limiting in 1 – 29 days |
| Piraigla et al. [100] (Italy) | Prospective study (1b) | 43 (COVID-19 with pneumonia) | Bilateral conjunctivitis (7%), Unilateral posterior choriorretinitis (2.3%), Olfactory dysfunction (51.2%), Taste dysfunction (47.1%), Olfactory dysfunction (47.9%) | History, physical exam | ? |
| Sakalli et al. [101] (Turkey) | Retrospective study (2b) | 175 | Olfactory dysfunction (51.2%), Taste dysfunction (47.1%), Olfactory dysfunction (47.9%) | Self-report survey/telephone interview | Self-limiting in 20 days |
| Saniasiaya et al. [28] (Malaysia)³ | Systemic review of retrospective studies and better studies (2a) | 27,492 | Olfactory dysfunction (40.4%), Taste dysfunction (36.5%) | History, physical exam, self-report survey/telephone interview | Most resolved fully |
| Sayin et al. [102] (Turkey) | Retrospective study (2b) | 52 | Olfactory dysfunction (40.4%), Taste dysfunction (36.5%) | History, physical exam, self-report survey/telephone interview | Most resolved fully |
| Shemer et al. [47] (Israel) | Case series (3b) | 48 | Foreign body sensation (31.3%), Eye redness (25%), Acute conjunctival injection (19%), Smell dysfunction (52.7), Taste dysfunction (43.9) | History, physical exam, self-report survey | Most resolved fully |
| Tong et al. [25] (USA)³ | Systemic review of case-control and better studies (3a) | 1627 | | History, physical exam, self-report survey | Most resolved fully |

Note: ³ - secondary data; ? - not mentioned; N/A - not applicable.

Cervicofacial odontogenic infection patients (Level of Evidence 2b) [15].

Another particular concern with regard to prolonged prone position in COVID-19 patients is acute macroglossia. The first-line treatments are corticosteroids and use of bite blocks. A tracheostomy is indicated in refractory cases to minimise external compression and preserve airway patency (Level of Evidence 4) [16]. After prolonged intubation, laryngological endoscopic examination is recommended to examine iatrogenic injuries, including dysphagia (Level of Evidence 3b) [17,18].

Oncologic patient care related to COVID-19 infections is another hot issue. SARS-CoV-2 depletes ACE2 and extracellular matrix metalloproteinase inducer (EMMPRIN; BASIGIN/CD147), perhaps becoming a protective mechanism against oral squamous cell carcinoma (OSCC). Overexpression of ACE2, EMMPRIN and IL-6 is associated with OSCC progression and worse prognosis. Ang II promotes angiogenesis and migration of OSCC cells (Level of Evidence 5) [8,19–21]. Meanwhile, IL-6 was found to be a fatality predictor in COVID-19 patients. IL-6 blockade may mitigate radiation-induced DNA damage in OSCC patients (i.e. adding
tocilizumab to radiotherapy), and mortality in acute respiratory distress syndrome (ARDS) due to COVID-19. Hence, tocilizumab as an IL-6 blocker could synergistically be beneficial in OSCC patients with COVID-19 (Level of Evidence 5) [19,22]. However, these preclinical data warrant future investigations. Despite healthcare resource constraints during the COVID-19 pandemic, primary radiotherapy or chemoradiation for resectable OSCC cannot preclude the surgery-first approach (stage I-II: hazard ratio [HR] 2.39, 95% CI, 1.56–3.67; stage III–IV: HR 1.98; 95% CI, 0.85–4.64) (Level of Evidence 2a) [23].

4.2. Nose, paranasal sinus and skull base

The sinonasal passage is a major target of COVID-19 infection and SARS-CoV-2 transmission. Similar to oral, salivary glandular, pulmonary epithelial cells, overexpression of ACE2 receptors in ciliated epithelial and goblet cells of the nasal mucosa make viral loads in the nasal cavity high (Level of Evidence 3a) [24,25]. Epithelial tropism of the virus is important for viral transmission via oral, salivary, and nasal secretions (Level of Evidence 5) [7]. Sinoantral aerosol-generating procedures, including electrocautery, in COVID-19 patients thereby require the use of at least N95 (FFP2) (Level of Evidence 5) [24]. It is also important to note that nasal pathologies, e.g. septal deviation, or polyps, may hinder accurate nasal swab sampling and causes a false-negative result (Level of Evidence 5) [24]. Prevalence of rhinosinusitis is not different between COVID-19 and non-COVID-19 patients (Level of Evidence 2b) [26]. However, patients with pre-existing atopy or chronic rhinosinusitis tend to have long SARS-CoV-2 RNA spreading (real-time polymerase chain reaction positivity on nasopharyngeal samples ≥28 days) and require a longer quarantine (Level of Evidence 3b) [27].

Hyposmia/anosmia is a prominent COVID-19 symptom with prevalence of 47.9% (95% CI, 41.20–54.50) (Level of Evidence 2a) [28]. The US Center for Disease Control and Prevention (CDC) added “the newly encountered loss of taste or smell in the absence of other sinonasal symptoms” to the symptom list of COVID-19. It may appear 2–14 days after exposure to COVID-19, i.e. possible prodromal or before other symptoms [25], or even before the reinfection (Level of Evidence 5) [29]. Smell disturbance as an initial COVID-19 symptom is linked to low IL-6 levels prior to the cytokine storm with high IL-6 levels (Level of Evidence 2b) [30]. Microscopically, microsialin/CD68+ inflammatory cells infiltrate the hypoxic/anosmic nose in COVID-19 patients (Level of Evidence 2a) [31], indicating innate and adaptive immunity response to the virus.

Recently, the British Rhinological Society (BRS) launched its guideline on smell disturbances in COVID-19 patients. An MRI scan of the brain should be performed in patients with loss of smell ≥4–6 weeks with neurological or persistent nasal symptoms, regardless of COVID-19 test results. Treatment modalities include olfactory training and support, intranasal sprays (optional: drops or rinses), and omega-3 supplements (Level of Evidence 5) [32]. There are significant associations between COVID-19, and a reversible obstruction of the olfactory cleft on MRI and a reduced metabolic activity in the orbitofrontal cortex. It is possible that the olfactory obstruction results from the interaction between the SARS-CoV-2 and ACE2 protein expressed by the olfactory epithelium, and prevents odour molecules from reaching the olfactory epithelium, similar to in patients with chronic rhinosinusitis and sinonasal polyposis (Level of Evidence 3b) [33].

One or more of these 3 pathways aid in viral spread intracranially: (1) transcriibional route: the virus crosses the cribriform plate of the ethmoid bone, where olfactory nerve axons transverse. The nerve sheath comprises dura and pia arachnoid matter, and contains spaces communicating with the intracranial cerebrospinal fluid. Smell disturbance can originate from SARS-CoV-2-induced olfactory mucositis, or damage to olfactory mucosa/bulb, cerebellum and frontal lobe. This finding may partly explain accompanying neurological deficits, e.g. ataxia and agitated states without encephalopathy or meningitis, in hypoxic/anomasic patients; (2) retrograde trigeminal neural route to the trigeminal bulb via ACE2-expressing target cells in the oral cavity; and (3) retrograde phrenic nerve route to the respiration regulatory centres in brainstem (Level of Evidence 5) [34].

Once infected, immune dysfunction predisposes the patients to rapidly progressive infections. Maan et al. [35] recently reported a case with oribito-nasal-antral infections with meningitis due to nasal vestibulitis and subsequent extensive nasal septal abscesses. Timely and appropriate management of any infections in COVID-19 patients is indicated, but also depends on patient’s general conditions.

4.3. Ocular/orbital and periorbital tissue

Given high viral load and expression of ACE2 and TMPRSS2 in the nasal cavity, sinuses and nasolacrimal system, viral spreading from the sinonasal cavity and nasolacrimal duct (and perhaps from ocular surface) is an important transmission route. To reduce the risk of COVID-19 transmission, oral, sinonasal, and orbital surgery should be limited to urgent cases during the pandemic, and the use of povidone-iodine solution before and during surgery and minimally invasive approaches, e.g. transconjunctival or retro-caruncular incisions, can better reduce disease transmission (Level of Evidence 5) [36,37].

Sporadic reports demonstrated orbital infections in immunocompromised COVID-19 patients. These include bacterial cellulitis, acute invasive rhino-oral mucormycosis and aspergillosis. The pre-existing risk factors are diabetes mellitus, HIV, neutropenia, and use of broad-spectrum antibiotics, immunosuppressants or corticosteroids. Nasal congestion from COVID-19 compromises mucociliary clearance, obstructs the maxillary sinus, and initiates an orbital infection. Moreover, dysregulated immune in COVID-19 patients, e.g. reduced numbers of CD4 + T, and CD8 + T cells, makes an environment hospitable for fungal coinfections. Orbital compartment syndrome (OCS), oculomotor nerve palsy, cavernous sinus thrombosis, and necrotising haemorrhagic encephalopathy develop secondary to orbital infections per se and/or COVID-19 coagulopathy or neurotropic damage (Level of Evidence 4) [22,38–41].

A meta-analysis by Conforti et al. [42] revealed local ocular/orbital/periorbital inflammation in only 3.8% of patients with cutaneous manifestations (Table 1) (Level of evidence 3a). However, early data from China explicated that ocular complications in COVID-19 adult patients were common: xerophthalmia (20.9%), blurred vision (13.9%), foreign body sensation (11.8%), ophthalmalgia (4.1%), conjunctival congestion (18.4–31.6%) or hypersecretions (18.4%) (Level of Evidence 2b) [40], and in paediatric patients (22.7%) (Level of Evidence 2b) [43]. Dry eye in COVID-19 patients significantly increases, regardless of days of intensive care and oxygen therapy (Level of Evidence 2b) [44]. An Italian series by Meduri et al. [45] linked the correlations between conjunctival hyperaemia and COVID-19 severity (P = 0.002), and between blepharitis symptoms and COVID-19 duration (P = 0.003) (Level of Evidence 3b). Conjunctivitis may be isolated or a part of Kawasaki syndrome-like symptoms in paediatric patients, or toxic shock syndrome (Level of Evidence 5) [46], and significantly increases in taste- and smell-disturbed patients (Level of Evidence 3b) [47], as well as 12.8% of conjunctivitis are a prodromal symptom (Level of Evidence 3a) [48]. Overall, ocular/orbital
manifestations increase in COVID-19 patients with severe pneumonia (6.91%; 95% CI: 1.75 to 15.58) (Level of Evidence 2a) [49]. Acute-onset neuroophthalmic diseases can be found in COVID-19 patients, for example, optic neuritis, cranial nerve palsy, Miller Fisher/Guillain–Barré syndrome, and vision loss. The mechanisms seem to be related to virus spread haematogenously, by infecting choroid plexus or meninges, or via olfactory nerves and later spread to the thalamus and brainstem. Moreover, Miller Fisher/Guillain–Barré syndrome and optic neuritis in COVID-19 patients may indicate the viral potential to stimulate autoantibody production and subsequently cause an immune-mediated injury. Diplopia, bulbus pain with movements, vision changes, difficulty in walking, or other neurologic symptoms should therefore be investigated when the COVID-19 infection is suspected (Level of Evidence 5) [50]. Thus, it
is possible that ophthalmological outcome may become more difficult in patients with SARS-CoV-2.

Some ocular/orbital pathologies are iatrogenic, e.g. retinal toxicity due to hydroxychloroquine and chloroquine therapy [51]. Pressure from wearing an FFP2/N95 mask can accidentally rupture venous vessels or an anomalous arteriovenous communication, producing self-limiting conjunctival haemorrhage. The risk factors include ageing, hypertension, hyperlipidaemia, and taking antiplatelet and/or anticoagulant agents. (Level of Evidence 4) [52]. Spontaneous orbital emphysema may develop in relation to high positive end-expiratory pressure (PEEP) ventilation (Level of Evidence 4) [53–55], in a similar manner with our previous report on periorbital emphysema after nose blowing [56]. Ocular complications related to prone patient positioning >16 h a day comprise exposure keratopathy, bacterial keratitis (often by Pseudomonas aeruginosa, Acinetobacter spp. and Staphylococcus epidermidis), acute angle closure, vascular occlusions, ischaemic optic neuropathy, OCS, and conjunctival chemosis (“ventilator eye”) (Level of Evidence 5) [57].

Striking prevalence of ocular/orbital injuries after complete lockdown in the Middle East and South Asia countries may relate to household violence due to emotional stress during the quarantine and/or culture in this world region (Level of Evidence 4) [58,59]. Guidelines for ocular/orbital trauma surgery related to COVID-19 were proposed by Natarajan et al. [59] and Wong et al. [60].

4.4. Ear (acoustic and vestibular system)

The ear is often less damaged than other craniofacial organs. However, sporadic reports showed some otological diseases in COVID-19 patients, e.g. sudden sensorineural hearing loss (SSNHL: mostly unilateral), intralabyrinthine haemorrhage, isolated tinnitus, acquired nystagmus. The cause of SSNHL may be due to direct viral invasion of the labyrinth or cochlear nerve (or later in the auditory centre in the temporal lobe), reactivation of a latent virus within strial vasculatures or spiral ganglion, and immune-mediated mechanism against the viral infection. Intralabyrinthine haemorrhage might arise from coagulopathy within the cochlear microcirculation due to the virus. Clinically, COVID-19 patients often have significantly low-frequency pure tone audiometry thresholds and transient evoked otoacoustic emissions (TEOAE) and distortion product otoacoustic emissions (DPOAE) low-frequency amplitudes, indicating damage to the cochlear outer hair cells. Poor prognosis of SSNHL with incomplete recovery includes female gender, age >60 years, severe hearing loss, poor vocal discrimination, and audiometry with a flat curve (Level of Evidence 5) [61–65].

Dizziness can be found in ca. 20% of the cases, and associated with cranial neuropathies: i.e. anoma and ophthalmoparesis. It is therefore possible that SARS-CoV-2 could cause labyrinthitis or vestibular neuritis as same as other herpes viruses do (Level of Evidence 5) [61,63].

4.5. Craniofacial skin

Based on early Spanish evidence (n = 375), skin lesions can be grouped into 5 subtypes: (1) pityriasis rosea-like perifollicular maculopapules (47%), (2) asymmetrical erythema-oedema with vesicles or pustules (“pseudo-chilblain”) (19%), (3) urticarial-like lesions (19%), (4) monomorphic haemorrhagic vesicles (9%), and (5) livedo or necrosis due to occlusive vascular disease (6%). Most of the skin lesions were found on the trunk and limbs (Level of Evidence 2b) [66].

In the molecular level, C5b-9, C4d, and MASp2 complement complex mediators damage the epithelial cells and activate coagulation factors to induce disseminated intravascular coagulation (DIC) (Level of Evidence 5) [7]. Until now, only one lip necrosis and one necrotising periodontitis in COVID-19 patients were reported in the literature (Level of Evidence 3a) [5,67]. This finding may indicate that orofacial tissue could well escape from the arterial occlusive disease associated with COVID-19.

5. Conclusions

Most of the data on CMF symptoms rely on low level evidence. Adding multiple databases to PubMed/Medline and languages other than English did not affect the results of this review. In addition to taste and smell dysfunctions, non-specific CMF lesions, e.g. aphtha, erythema/pestechiae, fungal superinfections, conjunctivitis, necrosis, can be seen, but often treated conservatively. Complications, for example, extensive infections during corticosteroid therapy, acute macroglia ossing to prolonged prone position, OCS due to long-lasting ventilator dependency, may encounter patient care. Dentists and CMF surgeons, together with otolaryngological colleagues, play an important role in orofacial examination and close collaboration with other speciality colleagues to combat this pandemic. Fig. 2 summarises CMF manifestations in COVID-19 patients. We also refer interested readers to extensive reviews on natural history, pathogenesis, clinical manifestations and treatments by other authors [68–78].

Authorship disclosure

Conception and study design: P.P., J.-P.M., N.S., K.S., P.O.-C., S.S., P.A., R.M.-P., A.N.

Acquisition and analysis/interpretation of data: P.P., N.S., K.S., A.I., P.A., R.M.-P., A.N.

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Conflicts of interest

The authors indicate full freedom of investigation and manuscript preparation. There was no potential conflict of interest as regards this study.

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