Persistent Gustatory Dysfunction in COVID-19 Survivors: A Narrative Literature Review

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Author’s contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

ABSTRACT

Patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exhibit a diverse spectrum of clinical manifestations, some of which last for a long time, making a great impact on the healthcare of patients who recovered from coronavirus disease 2019 (COVID-19). Although taste disorders have been well-recognized to be closely associated with COVID-19, understanding of gustatory sequelae is relatively poor compared with oral symptoms in the early phase of COVID-19. The aim of this study was to characterize gustatory dysfunction in COVID-19 survivors by a narrative literature review of follow-up studies and to speculate the pathogenic mechanisms underlying such a persistent symptom. Scientific articles were retrieved by searching PubMed, LitCovid, ProQuest, medRxiv and bioRxiv from 1 April 2020 with a cut-off date of 10 September 2021. The follow-up time periods of the relevant 49 studies ranged from 4 weeks to 12 months. Results of the literature search indicated that ageusia, hypogeusia and/or dysgeusia persist in up to 45.0% of COVID-19 survivors and that the prevalence of these taste impairments varies depending on ethnicity, age, gender and disease severity of patients. Gustatory dysfunction can be detected at high frequency even one year after symptom onset. Persistence of gustatory dysfunction is pathogenically related to expression of SARS-CoV-2 cellular entry-relevant
receptors in taste cells and neural cells, decreased saliva secretion, zinc deficiency, disturbed nervous system and inflammation associated with persistent SARS-CoV-2 infection. Given the long-term persistence of gustatory dysfunction in COVID-19 survivors, their discharge from hospital is not the end of disease. Careful attention should be continuously paid to taste perception of post-COVID-19 patients to recover the health-relating quality of life, which is required for health providers, especially dental professionals who not only may experience COVID-19 survivors but also can easily become aware of their taste abnormalities.

Keywords: COVID-19 survivor; persistent gustatory dysfunction; speculative pathogenesis.

1. INTRODUCTION

Since the first emergence of coronavirus disease 2019 (COVID-19) in late 2019, infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) quickly spread worldwide, causing 234,888,941 COVID-19 cases confirmed as of 4 October 2021 with over 4.8 million deaths according to the Johns Hopkins University & Medicine Coronavirus Research Center (https://coronavirus.jhu.edu/map.html). With an ongoing global pandemic of SARS-CoV-2 infection, it became evident that COVID-19 patients develop a wide range of clinical manifestations [1]. Oral symptoms are closely associated with COVID-19 as well as other typical respiratory, neurological and cardiovascular symptoms [2]. Among them, gustatory dysfunction has been well-known to occur with great frequency in the early phase of COVID-19 or during disease and referred to as one of predominant symptoms with a predictive value for SARS-CoV-2 infection [3]. Such gustatory dysfunction includes ageusia (complete loss of taste), hypogeusia (reduced taste sensation) and dysgeusia (altered or distorted taste perception).

Infectious diseases generally progress from the initial or acute phase to the prolonged or post-acute phase. An adverse impact of SARS-CoV-2 infection is not confined to acute manifestations but extends to long-term sequelae. It is increasingly recognized that COVID-19 involves long-term sequelae [4]. In a follow-up study after 2 months from symptom onset, 87.4% of COVID-19 recovered patients reported at least one symptom such as fatigue, dyspnea, cough and joint/chest pain, and 55% of them had three or more symptoms [5]. In addition to these sequelae, prolonged chemosensory disorders are becoming a matter of concern to the health-related quality of life of COVID-19 survivors [6]. However, understanding of gustatory sequelae is relatively poor compared with oral symptoms in the early phase of COVID-19. Taste disorders lasting after recovery from COVID-19 have not been comprehensively verified. Nor has been elucidated the pathogenesis of persistent gustatory dysfunction despite that its elucidation should contribute to therapeutic and rehabilitation measures for COVID-19 survivors.

The aim of this study was to characterize gustatory dysfunction as one of oral sequelae in COVID-19 survivors by a narrative literature review of follow-up studies and to speculate the pathogenic mechanisms underlying persistent gustatory dysfunction. There is neither generally accepted time period to follow up COVID-19 patients nor established terminology for lingering manifestations. Greenhalgh et al. [7] defined post-acute COVID-19 as extending beyond 3 weeks from symptom onset and chronic COVID-19 as extending beyond 12 weeks. Given the recovery of replication-competent virus and the duration of reverse transcription polymerase chain reaction (RT-PCR) positivity, it is considered necessary for persistent symptom assessment to follow up COVID-19 patients at least 3 weeks after disease onset [8]. A considerable number of COVID-19 patients recover from acute chemosensory disorders within 3 weeks [9]. The mean duration of early gustatory dysfunction has been suggested to be 16 days for symptomatic COVID-19 patients [10]. The present study focused on follow-ups of longer than 4 weeks from symptom or disease onset by referring to the post-COVID-19 symptoms [8, 11].

2. MATERIALS AND METHODS

Scientific articles were retrieved by searching PubMed, LitCovid and ProQuest from 1 April 2020 with a cut-off date of 10 September 2021. Given the rapid world-wide spread of SARS-CoV-2 infection and the ever-progressing COVID-19 studies, the preprint data bases medRxiv and bioRxiv were also used to retrieve latest information. The search was conducted by using the following terms or combinations
thereof: “COVID-19”, “SARS-CoV-2”, “gustatory dysfunction”, “taste disorder”, “ageusia”, “hypogeusia”, “dysgeusia”, “persistent symptom”, “sequelae” and “post-COVID-19”. A literature review was limited to papers published in English. The exclusion criteria were case reports and studies that lacked demographic data and did not specify the diagnostic methods to confirm SARS-CoV-2 infection or COVID-19 (such as RT-PCR test and serological antibody test). The studies of COVID-19 survivors who received therapeutic drugs that could potentially influence prevalence and persistence of gustatory dysfunction were excluded as far as they were specified. Limited review articles were used to improve understanding of SARS-CoV-2 infection and taste perception, and to deepen discussion about the pathogenesis of gustatory dysfunction. Cited papers in the retrieved articles were further searched for additional references. Collected articles were reviewed by title, abstract and text for relevance.

3. RESULTS AND DISCUSSION

Results of the literature search indicated that gustatory dysfunction persists in up to 45.0% of COVID-19 survivors for months. Moraschini et al. [12] demonstrated that 14.1% of test subjects developed ageusia at a mean 67-day follow-up by analyzing 8 observational studies to verify the long-term effects of COVID-19. Table 1 shows a total of 49 relevant studies in increasing order of follow-up time after disease and symptom onset or hospital discharge. They include prospective and retrospective cohort studies that recruited patients who had been confirmed to be infected with SARS-CoV-2 and recovered from COVID-19. Although impaired taste and smell are collectively expressed by chemosensory disorders, gustatory dysfunction is referred to as a symptom independent of olfactory dysfunction and in some cases, gustatory dysfunction occurs more frequently than olfactory dysfunction in the early phase of COVID-19 [12,60]. COVID-19 patients were reported to present with gustatory dysfunction not accompanied by rhinorrhea and nasal obstruction [61]. Since it is difficult to discriminate pure gustatory dysfunction from the simultaneously occurring olfactory dysfunction, 16 of 50 retrieved studies described taste disorders as ageusia/anosmia, dysgeusia/anosmia, taste or smell alteration, taste/smell disorder, and taste and smell disorder or dysfunction.

3.1 Symptom Characterization

The prevalence ranges of oral symptoms in the early phase of COVID-19 are related to differences in ethnicity, age, gender, and disease severity [62,63]. Therefore, persistence of gustatory dysfunction in COVID-19 survivors or post-COVID-19 patients may also be influenced by their demographic and symptomatic features. Characterization of persistent gustatory dysfunction by comparing with the early symptoms would provide an insight into understanding of gustatory sequelae of COVID-19.

3.1.1 Ethnicity

In the early phase of COVID-19, gustatory dysfunction occurs more frequently in Caucasians than in East Asians as 70-90% of European and American COVID-19 patients report taste disorders, but 3.4-15% of Chinese and South Korean patients [2]. In a systematic review of 27,687 COVID-19 cases in 23 countries also indicates persistence of gustatory dysfunction as the early symptom is 48% for total Europe including Belgium (88.8%), France (45.1%), Germany (48.2%), Italy (62.7%), Poland (47.5%), Spain (39.3%) and UK (64.7%), and 67.8% for total America including USA (63.1%), Canada (61.6%) and Brazil (76.2%), whereas 13.1% for East Asia including China (17.8%) and North Korea (12.2%) [3]. In a geographical variation of 38 studies, gustatory dysfunction shows prevalence of 5.1% in Asian cohorts, but 52.3% in Western and Middle Eastern cohorts [64]. A meta-analysis of 29,349 COVID-19 cases in 23 countries also indicates that taste disorders are observed in 55.2%, 61.0%, 27.1%, 29.5% and 25.0% of European, North American, Asian, South American, and Australian patients, respectively [60].

When Chinese COVID-19 patients were followed up, 3.6 % of 55 patients with mild to severe disease [40] and 7.3% of 1733 discharged patients [52] complained of hypogeusia after 3 months from hospital discharge and 6 months from symptom onset, respectively. In a cohort of mostly Japanese, 4.8% and 1.6% of 63 patients reported ongoing dysgeusia 60 and 120 days after symptom onset, respectively [43]. On the other hand, at 3-6 months follow-ups of Italian COVID-19 patients, 42% of 122 hospitalized patients [42], 5.0% of 238 patients with severe disease [45] and 18.0% of 183 outpatients [48]
## Table 1. Persistent gustatory dysfunction in COVID-19 survivors

<table>
<thead>
<tr>
<th>Patients or disease severity</th>
<th>Country or ethnicity</th>
<th>Number of patients</th>
<th>Age (year), mean or median (range or ±SD)</th>
<th>Female (%)</th>
<th>Specified, mean or median follow-up time (range)</th>
<th>Symptom</th>
<th>Prevalence (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Italy</td>
<td>187</td>
<td>56 (20-89)</td>
<td>55.1</td>
<td>4 weeks after symptom onset</td>
<td>Taste or smell alteration</td>
<td>36.9</td>
<td>*Boscolo-Rizzo et al. [13]</td>
</tr>
<tr>
<td>Mild to moderate</td>
<td>USA</td>
<td>423</td>
<td>41 (18-93)</td>
<td>55.6</td>
<td>28 days after disease diagnosis</td>
<td>Ageusia/ dysgeusia</td>
<td>10.2</td>
<td>*Blair et al. [14]</td>
</tr>
<tr>
<td>Asymptomatic (35.5%) and mild (64.5%)</td>
<td>India</td>
<td>225</td>
<td>35 (5-65)</td>
<td>28.4</td>
<td>28 days after hospital admission</td>
<td>Dysgeusia</td>
<td>3.3</td>
<td>Panda et al. [15]</td>
</tr>
<tr>
<td>Patients with ICU stay (25.0%) and without ICU stay (75.0%)</td>
<td>Switzerland</td>
<td>196</td>
<td>70 (60-80)</td>
<td>39.3</td>
<td>30 days after symptom onset</td>
<td>Dysgeusia/ anosmia</td>
<td>10</td>
<td>Pellaud et al. [16]</td>
</tr>
<tr>
<td>Mild (66.2%), moderate (31.5%) and severe (2.4%)</td>
<td>USA</td>
<td>337</td>
<td>45.7 (44.6-57.9: mild-severe)</td>
<td>68.0</td>
<td>30 days after symptom onset</td>
<td>Ageusia/ anosmia</td>
<td>5</td>
<td>O'Keefe et al. [17]</td>
</tr>
<tr>
<td>Home-quarantined</td>
<td>Italy</td>
<td>151</td>
<td>45 (18-70)</td>
<td>62.9</td>
<td>30 days after symptom onset</td>
<td>Gustatory dysfunction</td>
<td>11.1</td>
<td>*Paderno et al. [18]</td>
</tr>
<tr>
<td>Mild (59.0%), severe (36.7%) and critical (4.3%)</td>
<td>France</td>
<td>139</td>
<td>48.5 (±15.3)</td>
<td>62.6</td>
<td>30-35 days after symptom (fever and dyspnea) disappearance</td>
<td>Ageusia</td>
<td>11.5</td>
<td>*Poncet-Megemont et al. [19]</td>
</tr>
<tr>
<td>Outpatients</td>
<td>Belgium</td>
<td>72</td>
<td>38.9 (±12.4)</td>
<td>68.1</td>
<td>37 days after symptom onset</td>
<td>Hypogeusia/ Ageusia</td>
<td>5.6</td>
<td>*Le Bon et al. [20]</td>
</tr>
<tr>
<td>Mild to moderate</td>
<td>Italy</td>
<td>121</td>
<td>46.7 (NR)</td>
<td>59.5</td>
<td>38.2 days after disease diagnosis</td>
<td>Ageusia</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Hospitalized (non-ICU ward)</td>
<td>Italy (Caucasian)</td>
<td>100</td>
<td>65 (29-94)</td>
<td>40.0</td>
<td>1 month after hospital discharge</td>
<td>Gustatory dysfunction</td>
<td>9.9</td>
<td></td>
</tr>
</tbody>
</table>

* indicates references with more comprehensive data.
Table 1. Continued

<table>
<thead>
<tr>
<th>Patients or disease severity</th>
<th>Country or ethnicity</th>
<th>Number of patients</th>
<th>Age (year), mean or median (range or ±SD)</th>
<th>Female (%)</th>
<th>Specified, mean or median follow-up time (range)</th>
<th>Symptom</th>
<th>Prevalence (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatients</td>
<td>France</td>
<td>214</td>
<td>39 (29-51)</td>
<td>60.1</td>
<td>6 weeks after disease diagnosis</td>
<td>Ageusia</td>
<td>5.1</td>
<td>*Armange et al. [22]</td>
</tr>
<tr>
<td>Hospitalized in emergency room</td>
<td>Spain</td>
<td>130</td>
<td>50.6 (±15.3)</td>
<td>50.8</td>
<td>6 weeks after hospital admission</td>
<td>Ageusia/anosmia</td>
<td>45.0</td>
<td>Caronna et al. [23]</td>
</tr>
<tr>
<td>Hospitalized</td>
<td>Belgium</td>
<td>93</td>
<td>42 (±12)</td>
<td>71.0</td>
<td>6 weeks after symptom onset</td>
<td>Hypogeusia (subjectively reported)</td>
<td>22.6</td>
<td>*Le Bon et al. [24]</td>
</tr>
<tr>
<td>Outpatients</td>
<td>USA</td>
<td>26</td>
<td>47.5 (23-78)</td>
<td>76.9</td>
<td>6 weeks after symptom onset</td>
<td>Taste alteration</td>
<td>3.8</td>
<td>Cellai &amp; O'Keefe [25]</td>
</tr>
<tr>
<td>Mild to moderate</td>
<td>White 81.6%, Asian 15.8%</td>
<td>114</td>
<td>38 (29.5-48)</td>
<td>75.4</td>
<td>51.5 days after symptom onset</td>
<td>Hypogeusia</td>
<td>43.7</td>
<td>*Andrews et al. [26]</td>
</tr>
<tr>
<td>Mild</td>
<td>Italy</td>
<td>183</td>
<td>56 (45-67)</td>
<td>52.0</td>
<td>4 and 8 weeks after symptom onset</td>
<td>Ageusia</td>
<td>9.2</td>
<td>*Boscolo-Rizzo et al. [27]</td>
</tr>
<tr>
<td>Mild to moderate (74.4%) and severe (25.6%)</td>
<td>France</td>
<td>150</td>
<td>&lt;30 to ≥70</td>
<td>56.0</td>
<td>32.7 and 59.7 days after symptom onset</td>
<td>Ageusia/anosmia</td>
<td>30-day: 26.7 60-day: 22.3</td>
<td>*Carvalho-Schneider et al. [28]</td>
</tr>
<tr>
<td>Severe</td>
<td>Germany</td>
<td>33</td>
<td>64 (±3)</td>
<td>33.3</td>
<td>56 (48-71) days after hospital discharge</td>
<td>Ageusia</td>
<td>9.1</td>
<td>*Daher et al. [29]</td>
</tr>
<tr>
<td>Hospitalized</td>
<td>Italy</td>
<td>138</td>
<td>51.2 (±8.8)</td>
<td>50.7</td>
<td>60 days after symptom onset</td>
<td>Hypogeusia and ageusia</td>
<td>4.3</td>
<td>*Vaira et al. [30]</td>
</tr>
<tr>
<td>Outpatients</td>
<td>Italy</td>
<td>143</td>
<td>56.5 (±14.6)</td>
<td>37.1</td>
<td>60.3 days after symptom onset</td>
<td>Dysgeusia</td>
<td>&lt;10</td>
<td>*Carfi et al. [5]</td>
</tr>
</tbody>
</table>
**Table 1. Continued**

<table>
<thead>
<tr>
<th>Patients or disease severity</th>
<th>Country or ethnicity</th>
<th>Number of patients</th>
<th>Age (year), mean or median (range or ±SD)</th>
<th>Female (%)</th>
<th>Specified, mean or median follow-up time (range)</th>
<th>Symptom</th>
<th>Prevalence (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>NR</td>
<td>Italy</td>
<td>111</td>
<td>44.5 (18-77)</td>
<td>46.8</td>
<td>62.9 (28-165) days after viral infection</td>
<td>Gustatory dysfunction</td>
<td>6.5</td>
<td>*Niklassen et al. [31]</td>
</tr>
<tr>
<td>Outpatients and inpatients</td>
<td>Germany</td>
<td>701</td>
<td>40 (18-78)</td>
<td>67.2</td>
<td>63 (60-76) days after the first survey</td>
<td>Gustatory dysfunction</td>
<td>9.4</td>
<td>*Chiesa-Estomba et al. [32]</td>
</tr>
<tr>
<td>Non-hospitalized</td>
<td>USA, Arizona</td>
<td>303</td>
<td>44 (12-82)</td>
<td>70.0</td>
<td>61 (30-250) days after disease diagnosis</td>
<td>Taste or smell alteration</td>
<td>≥30 days: 26.4</td>
<td>Bell et al. [33]</td>
</tr>
<tr>
<td></td>
<td>(Non-Hispanic white 67.7%, Hispanic 22.8%, Others 6.3%)</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalized</td>
<td>USA</td>
<td>1250</td>
<td>62 (50-72)</td>
<td>48.2</td>
<td>60 days after hospital discharge</td>
<td>Ageusia and/or anosmia in 488 follow-ups</td>
<td>13.1</td>
<td>Chopra et al. [34]</td>
</tr>
<tr>
<td></td>
<td>(Black 51.6%, White 37.3%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Admitted to ICU</td>
<td>Italy</td>
<td>39</td>
<td>56 (±10.5)</td>
<td>10.3</td>
<td>61 days after ICU discharge</td>
<td>Taste alteration</td>
<td>20.5</td>
<td>Monti et al. [35]</td>
</tr>
<tr>
<td>Non-hospitalized</td>
<td>Netherlands</td>
<td>2113</td>
<td>47.0 (39-54)</td>
<td>85.3</td>
<td>79 days after symptom onset</td>
<td>Ageusia</td>
<td>11</td>
<td>*Goërtz et al. [36]</td>
</tr>
<tr>
<td>(94.7%) and hospitalized</td>
<td>Belgium</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild to critical</td>
<td>Italy</td>
<td>100</td>
<td>67.5 (56-78.5)</td>
<td>41.0</td>
<td>82 (70-101) days after symptom onset</td>
<td>Dysgeusia</td>
<td>15.0</td>
<td>*Spinicci et al. [37]</td>
</tr>
<tr>
<td>Outpatients</td>
<td>Australia</td>
<td>102</td>
<td>45 (17-87)</td>
<td>60</td>
<td>83 days after disease diagnosis</td>
<td>Hypogeusia</td>
<td>28</td>
<td>*Horvath et al. [38]</td>
</tr>
<tr>
<td>Mild to severe</td>
<td>Spain</td>
<td>277</td>
<td>56 (42-67.5)</td>
<td>47.3</td>
<td>8-12 weeks after disease onset</td>
<td>Dysgeusia-anosmia</td>
<td>21.4</td>
<td>*Moreno-Pérez et al. [39]</td>
</tr>
<tr>
<td>Mild to severe</td>
<td>China</td>
<td>55</td>
<td>47.7 (±15.5)</td>
<td>41.8</td>
<td>3 months after hospital discharge</td>
<td>Hypogeusia</td>
<td>3.6</td>
<td>*Zhao et al. [40]</td>
</tr>
</tbody>
</table>
Table 1. Continued

<table>
<thead>
<tr>
<th>Patients or disease severity</th>
<th>Country or ethnicity</th>
<th>Number of patients</th>
<th>Age (year), mean or median (range or ±SD)</th>
<th>Female (%)</th>
<th>Specified, mean or median follow-up time (range)</th>
<th>Symptom</th>
<th>Prevalence (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalized (ward 80.0% and ICU 20.0%)</td>
<td>France</td>
<td>120</td>
<td>Total: 63.2 (±15.7) Ward: 64.1 (±16.1) ICU: 59.6 (±13.7)</td>
<td>Total: 37.5 Ward: 41.7</td>
<td>110.9 days after hospital admission</td>
<td>Ageusia</td>
<td>Total: 10.8 Ward: 9.4 ICU: 16.7</td>
<td>*Garrigues et al. [41]</td>
</tr>
<tr>
<td>Hospitalized</td>
<td>Italy</td>
<td>122</td>
<td>62.5 (53.9-74.1)</td>
<td></td>
<td>104 (95-132) days after hospital discharge</td>
<td>Taste alteration</td>
<td>approx. 42</td>
<td>*Gherlone et al. [42]</td>
</tr>
<tr>
<td>Hospitalized</td>
<td>Japan (Japanese 88.9%, Chinese 4.8%, Vietnamese 1.6%, Bangladeshi 1.6%, Others 3.2%)</td>
<td>63</td>
<td>48.1 (±18.5)</td>
<td>33.3</td>
<td>60 and 120 days after symptom onset</td>
<td>Dysgeusia</td>
<td>60-day: 4.8 120-day: 1.6</td>
<td>*Miyazato et al. [43]</td>
</tr>
<tr>
<td>Hospitalized</td>
<td>Italy</td>
<td>91</td>
<td>NR</td>
<td>NR</td>
<td>4 months after hospital discharge</td>
<td>Dysgeusia</td>
<td>14.3</td>
<td>*Boari et al. [44]</td>
</tr>
<tr>
<td>Severe</td>
<td>Italy</td>
<td>238</td>
<td>61 (50-71)</td>
<td>40.3</td>
<td>4 months after hospital discharge</td>
<td>Ageusia</td>
<td>5.0</td>
<td>*Bellan et al. [45]</td>
</tr>
<tr>
<td>Outpatients (84.7%), inpatients (9.0%) and asymptomatic patients (6.2%)</td>
<td>USA (White 76.3%, Hispanic/Latin 4.0%, Black 1.7%, Others 17.5%)</td>
<td>177</td>
<td>48.0 (±15.2)</td>
<td>57.1</td>
<td>169 (31-300) days after disease onset</td>
<td>Ageusia/anosmia</td>
<td>13.6</td>
<td>*Logue et al. [46]</td>
</tr>
<tr>
<td>Home-isolated</td>
<td>Norway</td>
<td>247</td>
<td>43 (27-55)</td>
<td>53.0</td>
<td>6 months after disease onset</td>
<td>Taste/smell disorder</td>
<td>27.1</td>
<td>*Blomberg et al. [47]</td>
</tr>
</tbody>
</table>
Table 1. Continued

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<thead>
<tr>
<th>Patients or disease severity</th>
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<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild to moderate</td>
<td>Italy</td>
<td>183</td>
<td>55 (21-84)</td>
<td>55.2</td>
<td>6 months after disease diagnosis</td>
<td>Taste or smell alteration</td>
<td>18.0</td>
<td>*Boscolo-Rizzo et al. [48]</td>
</tr>
<tr>
<td>Hospitalized (ward and ICU)</td>
<td>France 75.3%, African 9.6%, Arabian 8.5%, Asian 1.4%</td>
<td>1137</td>
<td>61 (50-71)</td>
<td>37.3</td>
<td>6 months after hospital admission</td>
<td>Ageusia</td>
<td>7.0</td>
<td>*Ghosn et al. [49]</td>
</tr>
<tr>
<td>Mild</td>
<td>Israel</td>
<td>103</td>
<td>35 (±12)</td>
<td>37.9</td>
<td>6 months after the first survey</td>
<td>Taste alteration</td>
<td>7.8</td>
<td>*Klein et al. [50]</td>
</tr>
<tr>
<td>Mild to moderate</td>
<td>Italy</td>
<td>300</td>
<td>43.6 (33-53)</td>
<td>75</td>
<td>6 months after disease onset</td>
<td>Gustatory dysfunction</td>
<td>10</td>
<td>*Petrocelli et al. [51]</td>
</tr>
<tr>
<td>Discharged patients</td>
<td>China</td>
<td>1733</td>
<td>57 (47-65)</td>
<td>48.2</td>
<td>186 (175-199) days after symptom onset</td>
<td>Ageusia in 11.1 month: 6.8-month</td>
<td>7.3</td>
<td>*Huang et al. [52]</td>
</tr>
<tr>
<td>(recovered from severe to critical disease)</td>
<td>Asymptomatic (9.2%), mild (68.6%), moderate (15.6%), severe (4.0%) and critical (2.5%)</td>
<td>Italy Italian 91.4%</td>
<td>599</td>
<td>53 (18-94)</td>
<td>53.4</td>
<td>187 days after disease onset</td>
<td>Dysgeusia/anosmia</td>
<td>10.4</td>
</tr>
<tr>
<td>Mild (97.1%), moderate (2.2%) and severe (0.7%)</td>
<td>Germany</td>
<td>958</td>
<td>43 (31-54)</td>
<td>53.5</td>
<td>131 and 207 days after symptom onset</td>
<td>Ageusia in 442 follow-ups Ageusia in 353 follow-ups</td>
<td>Ageusia in 11.1 month: 6.8-month</td>
<td>*Augustin et al. [54]</td>
</tr>
<tr>
<td>Severe to critical</td>
<td>UK</td>
<td>200</td>
<td>56.5 (±13.2)</td>
<td>37.5</td>
<td>4-7 months after disease onset</td>
<td>Ageusia</td>
<td>6.3</td>
<td>*Gautam et al. [55]</td>
</tr>
<tr>
<td>Patients or disease severity</td>
<td>Country or ethnicity</td>
<td>Number of patients</td>
<td>Age (year), mean or median (range or ±SD)</td>
<td>Female (%)</td>
<td>Specified, mean or median follow-up time (range)</td>
<td>Symptom</td>
<td>Prevalence (%)</td>
<td>Reference</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>---------------------</td>
<td>--------------------</td>
<td>------------------------------------------</td>
<td>------------</td>
<td>------------------------------------------------</td>
<td>---------</td>
<td>---------------</td>
<td>----------</td>
</tr>
<tr>
<td>Hospitalized</td>
<td>France</td>
<td>125</td>
<td>36 (16-85)</td>
<td>55.2</td>
<td>221.7 days after symptom onset</td>
<td>Ageusia</td>
<td>Taste and smell disorder</td>
<td>11.5</td>
</tr>
<tr>
<td>Non-hospitalized</td>
<td>Israel</td>
<td>97</td>
<td>37.5 (19-74)</td>
<td>55.7</td>
<td>229 (191-253) days after RT-PCR test negativity</td>
<td>Gustatory dysfunction</td>
<td>Taste and smell disorder</td>
<td>25.8</td>
</tr>
<tr>
<td>Mild to moderate</td>
<td>Italy</td>
<td>268</td>
<td>48 (38-56)</td>
<td>61.9</td>
<td>1 year after symptom onset</td>
<td>Taste or smell impairment</td>
<td>Taste disorder</td>
<td>12.7</td>
</tr>
<tr>
<td>Mild to moderate</td>
<td>Italy</td>
<td>304</td>
<td>47 (18-76)</td>
<td>60.9</td>
<td>12 months after symptom onset</td>
<td>Taste or smell impairment</td>
<td>22.0</td>
<td>*Boscolo-Rizzo et al. [59]</td>
</tr>
</tbody>
</table>

* Asterisks indicate the studies used in discussion. Demographic data and patients' characteristics at baseline. NR: not reported.
reported taste alteration, ageusia, and taste or smell alteration, respectively. Follow-up studies conducted in France showed that ageusia persisted in 10.8% and 11.5% of hospitalized patients 110 days after hospital admission [41] and 220 days after symptom onset [56], respectively. At 5.6–6.8 months follow-ups after disease/symptom onset, ageusia was detected in 13.6% of American patients [46] and 11.0% of German patients [54].

At 3-7 months follow-ups of COVID-19 patients, ageusia, dysgeusia and hypogeusia persisted in 1.6-7.3% of Chinese and Japanese patients [40,43,52], but in 5.0-42% of French, Italian, American, Norwegian, Israeli, German, and British patients [41,42,44-51,53-55]. For longer follow-up time (to 12 months), gustatory (and olfactory) dysfunction was observed in 25.8% of Israeli patients [57], 12.7% of Italian patients [58] and 22.0% of Italian patients [59]. Persistent gustatory dysfunction is likely to be less prevalent in Asian patients compared with patients in other countries, suggesting that ethnicity may be a risk factor to prolong gustatory dysfunction in COVID-19 survivors. To verify a relation between ethnicity and gustatory dysfunction, Andrew et al. [26] followed up 114 patients with mild to moderate COVID-19 52 days after symptom onset. While their patients consisted of white (81.6%), Asian (15.8%), black/African/Caribbean (1.3%), mixed/multiple ethnic (1.3%) and unknown, ethnicity (being white) positively influenced the recovery time of taste \((P = 0.022)\). An ethnic difference in persistence of gustatory dysfunction is attributable to a genetic variation. Angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) play critical roles in the entry of SARS-CoV-2 into host cells as described in the section of pathogenic mechanisms. Genes encoding these proteins are variable depending on ethnicity as comparative genetic analyses indicate a significant difference of ACE2 and TMPRSS2 expression between Asian and European populations [2].

3.1.2 Age

When comparing in the early phase of COVID-19, children show significantly lower prevalence of gustatory dysfunction than adults in French and Israeli cohorts, whereas younger patients more frequently report taste/smell disorders in South Korean, Spanish, Italian and Turkish cohorts [2]. Moreno-Pérez et al. [39] assessed symptoms after 8-12 weeks from disease onset by following up 277 Spanish patients aged 42-67.5 years with mild to severe COVID-19. Prevalence of dysgeusia-anosmia was 24.9% for patients of < 65 years but 13.5% for patients of > 65 years (< 65 years vs > 65 years, \(P = 0.03\)). In a 12-month follow-up study of 304 Italian patients with mild to moderate COVID-19, the risk of symptom persistence was significantly higher in subjects aged between 40 and 54 years (odds ratio (OR) = 1.92; 95% confidence interval (CI), 1.07-3.44; \(P = 0.029\)) [59]. These results suggest that persistence of gustatory dysfunction may be associated with the relatively young age. However, when symptoms of 187 Italian patients aged 20-89 years with mild COVID-19 were assessed after 4 weeks from symptom onset, the rate of recovery from taste and smell disorders was similar in 51.7% for patients younger than 55 years and 45.5% for patients older than 55 years (Cohen \(d = 0.13\); 95% CI, -0.24-0.49) [13]. An objective and prospective study of 138 Italian patients showed no significant relations between age and persistent ageusia/hypogeusia at a 60-day follow-up after symptom onset [30]. It remains inconclusive whether the age of COVID-19 survivors is a determinant of gustatory sequelae.

Old age per se is associated with impairments of the gustatory and olfactory system. Systematic reviews and meta-analysis studies previously addressed the effects of age on chemosensory disorders such as lower symptom prevalence with increasing age [63], although they are largely confined to the early phase of COVID-19. While appetite and food intake are generally reduced with aging, no studies have examined persistence of gustatory dysfunction in relation to malnutrition of COVID-19 patients.

3.1.3 Gender

With respect to the early symptoms in mild to moderate COVID-19 cases, a European multicenter epidemiologic study indicates that gustatory dysfunction occurs in females more frequently than in males [61]. Ageusia, dysgeusia and taste/smell disorder of female patients are more prevalent than those of male patients in Italian, South Korean, French, Polish and Turkish cohorts [2], while the assessment of impaired tastes using the taste substance solutions shows no significant relations between gender of patients and chemosensory disorders at acute COVID-19 [65].
At a 1-month follow-up of Italian patients, females needed longer time to recover gustatory function than males [10,18]. A survey of 114 Italian patients with mild to moderate COVID-19 after 52 days from symptom onset demonstrated that female gender negatively influenced the recovery from gustatory dysfunction [26]. When mostly non-hospitalized 353 German COVID-19 patients were followed up 6.8 months after symptom onset, ageusia was reported by 7.9% of females (13.9% in 202 females) and 3.1% of males (7.3% in 151 males) [54]. Male gender was associated with a lower risk of symptom persistence (OR = 0.49; 95% CI, 0.31-0.77). In a follow-up study of 125 French COVID-19 patients after 7 months from symptom onset, females complained of ageusia and anosmia with prevalence of 17.6%, but males with prevalence of 6.4% [56]. Gender (being female) is considered to affect persistence of gustatory dysfunction as a risk factor in COVID-19 survivors, while some follow-up studies for months suggested no significant relations between gender and long-term taste impairments [30,39]. Since expression of ACE2 and TMPRSS2 responsible for the cellular entry of SARS-CoV-2 is not different between females and males, a gender difference in prevalence of gustatory sequelae may be due to that in taste responsiveness and the number of taste buds [2].

3.1.4 Disease severity

In the early phase of COVID-19, taste perception is more frequently impaired in mildly symptomatic and non-severe COVID-19 cases compared with severe to critical cases, and ageusia is reported in decreasing order of prevalence by asymptomatic, mild, moderate, severe, and critical COVID-19 patients [2].

Patients with mild to severe COVID-19 complained of ageusia/anosmia depending on hospital admission at 30- and 60-day follow-ups after symptom onset (at 60-day: OR = 1.6; 95% CI, 0.8-3.4) [28]. Huang et al. [52] symptomatically assessed 6-month consequences of 1733 Chinese COVID-19 patients discharged from hospital. At a 186-day follow-up after symptom onset, gustatory dysfunction persisted in 8.7% of patients who had not required supplemental oxygen (S1), in 6.7% of patients who had required supplemental oxygen (S2) and in 6.8% of patients who had required high-flow nasal cannula for oxygen therapy, non-invasive ventilation, or invasive mechanical ventilation (S3) (S1 vs S2: OR = 0.84; 95% CI, 0.54-1.30 and S1 vs S3: OR = 0.80; 95% CI, 0.32-2.02). Peghin et al. [53] followed up 599 hospitalized and non-hospitalized COVID-19 patients for 6 months after disease onset and suggested the possibility that chemosensory disorders might persist depending on disease severity. In their results, prevalence of persistent dysgeusia/anosmia was 13.9% in patients with mild disease (more prevalent in mild COVID-19 patients, P < 0.001), whereas 4.3% with moderate, 4.2% with severe and 0% with critical disease. Boscolo-Rizzo et al. [27] also reported that long-lasting taste disorders were more prevalent in mild to moderate COVID-19 patients followed up for months after symptom onset. Similar to the early symptoms, the severity of COVID-19 at baseline is associated with persistence of gustatory dysfunction in COVID-19 survivors. The occurrence of gustatory sequelae is not limited to non-severe COVID-19 cases. Garrigues et al. [41] compared gustatory dysfunction of hospitalized COVID-19 patients between ward group and intensive care unit (ICU) group by following up 110 days after hospital admission. Even after hospital discharge, ageusia persisted in 16.7% of ICU patients as well as ward patients.

On the other hand, a follow-up study of Spinicci et al. [37] indicated that symptom persistence after 60 days from hospital discharge was not related to disease severity (83% in mild/moderate vs 85% in severe/critical, P = 0.807) and ICU admission (84% in ICU vs 84% in non-ICU, P = 0.981). Gautam et al. [55] followed up COVID-19 patients admitted to hospital ward and intensive treatment unit (ITU) for 4-7 months from disease onset. They did not find significant differences in persistent symptoms between ward and ITU groups. Nor did a meta-analysis of Moraschini et al. [12] any differences between the severity of COVID-19 and the duration of impaired taste.

3.1.5 Quantitative and qualitative dysfunction

Gustatory dysfunction is quantitatively classified into ageusia, hypogeusia and dysgeusia. Hypogeusia is further divided into mild, moderate and severe hypogeusia. In a meta-analysis of the early symptoms in 29,349 COVID-19 cases, dysgeusia shows the highest prevalence of 41.3%, followed by hypogeusia of 33.5% and ageusia of 28.0% [60]. In the early phase of COVID-19 or during disease, prevalence of mild
hypogeusia, moderate hypogeusia, severe hypogeusia and ageusia ranges from 22.2 to 24.2%, from 12.1 to 15.3%, from 9.1 to 9.7% and from 1.4 to 6.1%, respectively [2].

Andrew et al. [26] followed up 114 patients with mild to moderate COVID-19 and demonstrated that hypogeusia and ageusia persisted in 43.7% and 9.2% of patients, respectively, after 52 days from symptom onset. When COVID-19 cohorts other than East Asians were followed up for 1-7 months, hypogeusia was reported by 22.6-28% patients [24,38], but ageusia by 5.0-11.5% [19,22,29,36,41,45,46,55,56]. Gustatory sequelae are quantitatively characterized, that is, hypogeusia is more likely to persist in COVID-19 survivors compared with ageusia.

Depending on which basic taste is affected, gustatory dysfunction is qualitatively characterized by sweet, sour, salty, bitter and/or umami taste impairment. In the early phase of mild COVID-19, prevalence of sweet, salty, and sour taste loss is 47.7%, 42.2% and 41.4%, respectively [66]. With respect to the early gustatory symptoms, 48% and 11% of COVID-19 patients present with impairments of two or more tastes and of a single taste, in which salty, sweet, bitter, sour and umami taste is impaired in 44.9%, 44.8%, 39.2%, 37.9% and 29.3% of laboratory-tested patients, respectively [67].

Huart et al. [68] assessed the ability of 10 COVID-19 patients to perceive four tastes by gustatory scoring with taste strips after 2 weeks from SARS-CoV-2 infection. Although the follow-up time was relatively short and the sample number was small, they found that sweet and bitter tastes were more significantly impaired than salty and sour tastes. Chaaban et al. [69] comparatively studied perception of four tastes in 102 Danish COVID-19 patients during the post-acute phase defined as the phase in which patients had not fully recovered and were suffering from lingering effects of COVID-19. Hypogeusia and ageusia of sweet, salty, sour and bitter taste were subjectively reported by 62.5%, 61.3%, 58.0% and 59.9% of the recruited patients, respectively. Interestingly, enhanced taste perception (hypergeusia) of sweet, bitter, salty and sour taste was also reported by 16%, 12%, 5% and 5%, respectively. Niklasson et al. [31] assessed gustatory function of COVID-19 survivors 2 months after SARS-CoV-2 infection by a taste strips gustatory test, in which filter paper strips impregnated with different concentrations of tastants of four basic taste qualities (sweet, salty, bitter and sour) were subjected to taste identification by patients and the number of correctly identified tastes was scored, indicating that the smaller the score is, the more significant the gustatory dysfunction is. They found that bitter and sour taste scores decreased differently from other tastes. Their results suggest that COVID-19 survivors may develop the dysfunction of specific taste qualities, giving insights into the pathophysiology of gustatory sequelae.

### 3.1.6 Duration and recovery

Blair et al. [14] followed up 187 American patients with mild to moderate COVID-19 for 1, 2, 3 and 4 weeks after disease diagnosis. Ageusia/dysgeusia prevalence of 28.2% peaked in 2 weeks, thereafter gradually reducing to 16.1% and 10.2% in the next 1 and 2 weeks. In a longer follow-up study of Poncet-Megemont et al. [19], ageusia persisted in 11.5% of French patients 1 month after symptom disappearance of fever and dyspnea. Boscolo-Rizzo et al. [27] assessed symptoms of mild COVID-19 patients for up to 8 weeks after symptom onset and revealed that prevalence of taste or smell alteration was 60.1% at baseline, 36.6% at a 4-week follow-up and 18.6% at an 8-week follow-up. In an objective and prospective study of Vaira et al. [30], the number of Italian patients presenting with hypogeusia and ageusia decreased by 60.7% and 80.9% of baseline 10 days and 20 days after symptom onset, respectively, but gustatory dysfunction persisted in 4.3% of patients after 60 days. Chiesa-Estomba et al. [32] revealed that 68.8% of COVID-19 outpatients and inpatients complained of gustatory dysfunction in the first survey. Although 90.6% of such patients reported the complete recovery of taste with a mean dysfunctional duration of 11 days, 9.4% still suffered from gustatory dysfunction after 2 months. Boscolo-Rizzo et al. [48] followed up 183 Italian home-quarantined patients with COVID-19 and demonstrated that prevalence of taste or smell alteration was 60.1%, 36.6%, 18.6% and 18.0% at baseline, 4-week, 8-week and 6-month follow-up after diagnosis, respectively. Ghosn et al. [49] assessed persistent symptoms of French COVID-19 patients 3 and 6 months after hospital admission. In their results, one-fourth of the patients complained of three or more symptoms and ageusia persisted in 7.0% of COVID-19 survivors even at a 6-month follow-up. These results indicate that the duration of gustatory dysfunction
can be at least 6 months following recovery from COVID-19.

Lee et al. [9] conducted a prospective study of 3191 South Korean patients with asymptomatic to mild COVID-19. While ageusia or anosmia was observed in 15.3% of patients in the early phase, most patients recovered from such chemosensory disorders within 3 weeks with a median recovery time of 7 days. Of 200 Indian patients with mild to moderate COVID-19, 7.0% and 4.0% complained of ageusia and both ageusia and anosmia, respectively, but the patients completely recovered from ageusia within 14 days and from both disorders within 21 days [70]. In a prospective French cohort study, 9.9% of non-severe COCID-19 patients reported ageusia after 6 weeks from disease diagnosis, whereas the other patients showed a median recovery time of 2 weeks [22]. A European multicenter study indicated that at least 25.5% of mild to moderate COVID-19 patients recovered gustatory and olfactory functions 2 weeks after the resolution of general symptoms [61]. However, different studies indicated that gustatory dysfunction was not completely recovered even after more than 6 months from symptom or disease onset so that 7.3-25.8% of COVID-19 survivors presented with ageusia or taste disorders [52-57]. At a 7.6-month follow-up after the second negative PCR test, 38.5% of non-hospitalized COVID-19 patients who had developed gustatory dysfunction in the early phase reported only the partial recovery of normal taste [57]. Based on intensity ratings of perception of four basic tastes, Konstantinidis et al. [71] indicated that 27.8% of 79 Greek patients with mild or moderate COVID-19 complained of ageusia during disease but returned to normal taste within 4 weeks in most cases. They found two types of recovery, that is, the rapid almost complete recovery group of 63.3% showed significantly better taste scores than the slow partial recovery group of 36.6%.

3.1.7 Assessment

Prevalence of gustatory dysfunction may be influenced by the methods used for assessment of taste disorders. Although the pooled prevalence of taste disorders in the early phase of COVID-19 is 48.1% in a meta-analysis of 59 cases, the objective assessment shows prevalence of 59.2% that is larger than prevalence of 47.3% of the subjective assessment [60]. Higher prevalence of early chemosensory disorders in COVID-19 patients has been indicated in objective assessment methods compared with subjective methods [63]. Persistent gustatory dysfunction of COVID-19 has been commonly assessed by subjectively-reported impressions of patients on taste impairment or alteration, whereas psychophysical tests using the solutions of taste substances were employed by several studies [20,24,30,31,51]. When 93 hospitalized COVID-19 patients were followed up 6 weeks after symptom onset, prevalence of hypogeusia was 4.3% in objective evaluation by taste strips gustatory tests but 22.6% in subjective evaluation by self-reporting questionnaires [24]. Psychophysical evaluation of 72 COVID-19 outpatients 5 weeks after symptom onset also showed prevalence of 5.6% for hypogeusia and 1.4% for ageusia [20]. When comparing the prevalence of gustatory dysfunction at 1-2 months follow-ups, the objective assessment indicated that hypogeusia and ageusia persisted in 4.3-7.0% of COVID-19 survivors [20,30,31], whereas the subjective assessment, in 21.5-52.9% [21,26]. Persistence of gustatory dysfunction may be relatively overestimated by assessing subjectively.

3.2 Speculative Pathogenesis

Gherlone et al. [42] followed up COVID-19 patients whose SARS-CoV-2 clearance had been confirmed by two consecutive negative results of nasopharyngeal swab RT-PCR tests. After 3 months from hospital discharge, 83.6% of COVID-19 survivors presented with oral symptoms including taste disorders. Boscolo-Rizzo et al. [13] repeated PCR tests with nasopharyngeal and throat swabs in 163 Italian patients COVID-19, and consequently revealed that 31.9% of patients were still PCR-positive during the fourth week after the first swab. In the following study, they indicated that a longer duration of PCR test positivity could be an increasing risk of persistent gustatory dysfunction by a one-year prospective study of patients with mild to moderate COVID-19 [58]. These results suggest that gustatory sequelae may be induced by the direct and long-lasting cytopathic effects of persistent SARS-CoV-2.

Yagi et al. [72] pathogenically classified taste disorders into three categories: (1) external damage to lingual papillae and taste buds caused by dry mouth, tongue problem, toxin exposure, iatrogenic disease, etc., (2) internal damage to lingual papillae and taste buds...
caused by aging, deficient zinc, medication, diabetes mellitus, etc., and (3) disturbance of taste sensation neural pathway resulting from peripheral and central nerve damage. By referring to these categories, the pathogenic mechanisms underlying gustatory sequelae can be discussed by relating taste disorders to viral cellular entry-responsible receptors, decreased saliva secretion, zinc deficiency, disturbed nervous system and inflammation associated with persistent viral infection. Considering that different pathophysiology is presumable, taste abnormalities of COVID-19 survivors may result from multiple causes. Cooper et al. [73] reported an excellent review paper on mechanistic hypotheses for chemosensory disorders. Mahmoud et al. [74] also recently reviewed the possible pathogenesis of dysgeusia as an early or acute COVID-19 symptom.

### 3.2.1 ACE2 receptor

The entry of SARS-CoV-2 into host cells is mediated by binding of viral spike proteins to ACE2 receptors and the subsequent protein priming by TMPRSS2. Since these membrane proteins are widely expressed in the human body, many tissues have the potential to undergo acute and chronic damages during the viral cellular entering process. Interestingly, ACE2 is expressed in oral mucosae and highly enriched in epithelial cells of the tongue [75]. ACE2 and TMPRSS2 are also expressed in human cultured fungiform papillae taste cells as well as in human taste buds [76]. Distribution in the tongue of ACE2-positive cells correlates to that of taste-relating gene marked cells with the property to respond to specific taste stimuli [2]. A possible role of ACE2 in modulating taste perception was suggested by ACE inhibition and angiotensin II receptor blocking [77]. ACE inhibitor perindopril and selective angiotensin II receptor antagonist losartan induced taste disturbance in healthy human volunteers [78]. ACE inhibitors (enalapril, perindopril, lisinopril, ramipril and trandolapril) affected taste sensitivity or caused taste alteration in patients with primary hypertension [79]. SARS-CoV-2 would directly exhibit cytopathic effects on ACE2- and TMPRSS2-expressing cells responsible for taste perception, thereby inducing gustatory dysfunction with the subsequent dysfunctional persistence.

ACE1 and ACE2 are the key enzymes of renin-angiotensin system (RAS) with the antagonistic effects. SARS-CoV-2 can disrupt ACE1/ACE2 balance and activate the RAS, eventually leading to disease progression. RAS produces angiotensin II with the ability to suppress the taste response to salt and enhance the taste response to sweeteners, whereas ACE2 converts angiotensin II to angiotensin-(1-7) with the property opposite to angiotensin II. Three RAS components (renin, angiotensinogen and ACE1) are present in the taste buds of fungiform and circumvallate papillae of mice as well as ACE2 [80]. ACE2 and angiotensin II are considered to play critical roles in taste perception and modulation. ACE2 receptor can not only mediate the virus-causing damage to taste buds but also dysregulate the local RAS in taste organs, affecting gustatory functions in the acute phase and the post-acute phase of COVID-19.

The human tongue has 4 types of papillae: fungiform papillae covering the anterior two-thirds of the tongue surface, foliate papillae locating in both lateral edges of the posterior tongue, circumvallate papillae situated in the border between oral and pharyngeal tongue, and filiform papillae being the most common of lingual papillae. Taste buds reside in fungiform, foliate and circumvallate papillae, although filiform papillae do not contain taste buds but provide the tongue with rough texture and touch sensation. In contrast to previous studies [75,76], Wang et al. [81] reported that ACE2 was enriched in a subpopulation of mouse tongue epithelial cells in filiform papillae but not in other papillae. Their finding that non-gustatory papillary cells are the primary target of SARS-CoV-2 conflicts with the pathogenic mechanism that gustatory dysfunction is caused by the direct interaction between SARS-CoV-2 and ACE2 in taste bud cells.

Signal transduction of five basic tastes (sweet, bitter, umami, sour and salty) is triggered by distinct taste receptor cells. Each taste bud comprises 50-100 taste receptor cells embedded in the epithelia of tongue, palate, and epiglottis, which are categorized into three cell types according to the morphological and functional features [73]. Type I cells are glia-like supporting cells, type II cells are G-protein coupled receptors (GPCRs) that function as sweet taste receptors (taste receptor type 1 member 2: T1R2 and T1R3), bitter taste receptors (T2Rs) and umami taste receptors (T1R1 + T1R3), and type III cells are ion channels to transduce sour taste, although salty taste stimuli appear to be detected by as-yet-undetermined cells [82]. By using an in situ hybridization probe and an antibody specific
to ACE2, Doyle et al. [83] revealed that ACE2 was expressed in taste bud Type II cells but not co-expressed with Types I and III cell markers. They also found that replicating SARS-CoV-2 was present in type II cells of fungiform papillae biopsied from COVID-19 patients presenting with gustatory dysfunction. The expression of ACE2 in taste bud cells and the viral replication in taste receptor type II cells pathogenically meet the occurrence of gustatory dysfunction, being consistent with sweet and bitter taste disorders lingering for weeks [68,69]. Damaged taste bud cells require weeks to proliferate and recover their taste perception ability, possibly causing persistence of gustatory dysfunction in COVID-19 survivors.

3.2.2 G-protein coupled receptor

With respect to the qualitative gustatory dysfunction, COVID-19 survivors reported the relatively prevalent impairments of sweet and bitter tastes [31,68,69]. Sweet and bitter tastes are transduced by type II taste receptor cells T1R2, T1R3 and T2Rs that belong to a class of GPCRs, whereas sour and salty tastes are presumed to be mediated by channel-type receptors, type III ionotropic taste receptor cells and epithelial sodium channels (ENaCs), respectively. Singh et al. [84] suggested that GPCRs expressed on lung epithelial cells may be involved in the cellular entry mechanism of SARS-CoV-2.

GPCRs function as angiotensin II type 1 receptor (AT1R) and angiotensin II type 2 receptor (AT2R). Angiotensin II modulates sweet and salty taste sensitivities in mice by enhancing nerve responses to sweeteners or suppressing nerve responses to salt, and these effects are blocked by an AT1R antagonist [85]. RAS components to produce angiotensin II are present in taste buds and co-expressed with sweet taste receptor component T1R3 or salty taste transduction-relevant ENaC [80]. Since AT2R has a higher binding affinity for SARS-CoV-2 spike proteins than ACE2, this receptor is referred to as one of possible key genes for the viral cellular entry into human cells [86].

SARS-CoV-2 would target GPCR-constituting taste receptors and angiotensin II receptors to affect their taste transduction functions during the interaction between virus and receptor, inducing gustatory dysfunction. If such an interaction lasts for a long time, the resultant gustatory dysfunction could persist in COVID-19 survivors.

3.2.3 Decreased saliva secretion

Saliva plays an important role not only in dissolution of taste substances as a solvent and their transportation to taste receptors but also in protection of taste buds. Altered saliva secretion would adversely affect taste perception as observed in patients with Sjögren’s syndrome who exhibit taste abnormality simultaneously with dry mouth. With respect to oral symptoms in the early phase of COVID-19, gustatory dysfunction is the most common symptom with prevalence of 59.5% followed by xerostomia with prevalence of 45.8%, and COVID-19 patients mostly develop dry mouth that was accompanied by taste disorders [87]. Decreasing changes of saliva secretion result in dry mouth, xerostomia (subjective complaint of oral dryness) and hyposalivation (objective reduction of salivary flow rate).

At a median 104-day follow-up after hospital discharge, 24.6% and 42% of 122 Italian COVID-19 survivors presented with dry mouth and taste alteration, respectively [42]. Biadsee et al. [57] assessed gustatory symptoms in 97 Israeli COVID-19 cases and showed that xerostomia was reported by 61.9% of patients at the time of the first survey. At a 7.6-month follow-up after the negative RT-PCR results, they also found that xerostomia persisted in 14.4% of survivors simultaneously with gustatory dysfunction in 25.8%. The co-occurrence of long-term xerostomia and gustatory dysfunction suggest that decreased saliva secretion may be pathogenically associated with gustatory sequelae.

Song et al. [88] evaluated the expression of ACE2 and TMPRSS2 in salivary glands of a healthy population by using genotypetype-tissue expression dataset and analyzing the single-cell sequencing data for submandibular salivary gland and parotid gland of mice. Their results indicated that these proteins responsible for the cellular entry of SARS-CoV-2 were present in salivary glands. Usami et al. [89] immunohistochemically investigated the expression and localization of ACE2 in human salivary glands. They described that ACE2 was expressed in the cell membrane of duct components including interlobular excretory ducts and interlobular ducts of minor salivary glands and in the cell membrane/brush border of the main ducts, interlobular excretory ducts and interlobular ducts of submandibular glands. SARS-CoV-2 would target ACE2-localizing
salivary glands and disturb their secretion functions, resulting in a decrease of saliva secretion with the subsequent impairment of taste. If the viral effects on salivary glands are prolonged, gustatory dysfunction could persist in COVID-19 survivors.

### 3.2.4 Zinc deficiency

Zinc is an essential element for transmission of tastes, regeneration of taste buds and maintenance of gustatory functions. While zinc-metalloenzyme carbonic anhydrase is localized in taste buds of rats, inhibitors of this enzyme induce dysgeusia [72]. Zinc also has the potential to affect ACE2 receptors responsible for the viral cellular entry because ACE2 is one of zinc-metalloenzymes to require zinc for the activity. In addition, zinc exhibits anti-inflammatory and immunomodulatory activities, and exerts an antiviral effect on SARS-CoV-2 by interacting with viral RNA-dependent RNA-polymerase. Recent evidence suggests a pathophysiological link between zinc and COVID-19. When rats were fed zinc-deficient or low zinc diets, the induced long-term zinc deficiency decreased taste sensitivity [90]. Ikeda et al. [91] histologically compared the expression and localization of T2Rs and ENaCs in vallate papillae obtained from rats that were fed zinc-deficient or normal diets. They found that the number of T2R-positive cells was markedly smaller in zinc-deficient diet rats than in normal diet rats, suggesting that zinc deficiency may affect bitter taste receptor cells. Zinc deficiency also causes the degeneration of taste buds in rat soft palate [72].

Jothishani et al. [92] measured zinc in serum of COVID-19 patients at hospitalization. They demonstrated that zinc concentrations of the patients were significantly lower than those of healthy controls and that zinc-deficient patients showed prolonged hospital stay and increased mortality. Gonçalves et al. [93] determined serum zinc levels of COVID-19 patients who were admitted to ICU and required invasive mechanical ventilation. They revealed that prevalence of zinc deficiency defined as being < 70 µg dL⁻¹ was 79.6% at ICU admission. Yasui et al. [94] verified the possible relation between serum zinc level and COVID-19 severity by measuring zinc in serum at the time of blood sampling on the first day of hospitalization and 2-3 days later. Zinc deficiency (< 70 µg dL⁻¹) was observed in 85.7% of patients with severe disease, but in 13.6% of patients with mild to moderate disease. They also followed up time-dependent zinc levels of 4 patients who were administered to ICU, treated with enteral nutrition delivered from the tube inserted through the nose and finally discharged from hospital. The test subjects showed prolonged hypozincemia, that is, serum zinc concentrations maintained below or near the cut-off concentration of zinc deficiency for 4 weeks after disease onset, suggesting the possibility that zinc deficiency may be responsible for persistent gustatory dysfunction.

Nutritionally inadequate zinc intake causes hypogeusia with a significant alteration of sweet taste, and rats fed zinc-deficient diets show a decrease of bitter taste gene marker-positive cells in taste buds of circumvallate (or vallate) papillae [91]. Zinc deficiency may be linked to sweet and bitter taste impairments that were observed in qualitative gustatory dysfunction of COVID-19 survivors. During zinc deficiency, the zinc concentration in taste buds would be lowered to affect their regeneration and proliferation, and the low zinc content in taste buds could inhibit the activity of carbonic anhydrase, resulting in gustatory dysfunction. Lingering deficiency of in vivo zinc is presumed to be one of pathogenic mechanisms of persistent gustatory dysfunction. Decreasing zinc is favorable for the interaction between ACE2 and SARS-CoV-2 spike protein, whereas increasing zinc inhibits ACE2 expression [92]. In addition, zinc stimulates the secretion of unstimulated and stimulated whole saliva in humans, therefore zinc deficiency may conversely induce gustatory dysfunction through saliva secretion inhibition.

### 3.2.5 Disturbed nervous system

Neurological manifestations of COVID-19 are attributable to disturbance of the central nervous system (CNS) and/or the peripheral nervous system. Neurotropic viruses possibly enter the CNS through two direct routes: hematogenous dissemination or neuronal retrograde dissemination [95]. In the former route, SARS-CoV-2 that has spread throughout the body via bloodstream can enter the brain by crossing the blood-brain barrier (BBB). Zhou et al. [96] speculated that SARS-CoV-2 possibly binds to ACE2 expressed in the capillary endothelium of the BBB to gain access to the CNS. SARS-CoV-2 can also use the axonal transport machinery to gain access from the periphery to the CNS [97]. Cranial nerves involved in taste signal
transmission may be damaged during the viral neuro-invasion process. Lingual taste buds are innervated by sensory afferents from the facial nerve (the 7th cranial nerve, CN VII) and the glossopharyngeal nerve (the 9th cranial nerve, CN IX). Among cranial nerves, CN VII that is damaged through SARS-CoV-2 infection is more responsible for gustatory dysfunction associated with COVID-19 [73].

Given the widespread expression of ACE2 receptors in the brain, SARS-CoV-2 has the potential to infect neurons and glial cells throughout the CNS [95]. Positron emission tomography (PET), using fluorine-18 fluorodeoxyglucose (\(^{18}\text{F-FDG}\)), \(^{18}\text{F-FDG}\) brain PET, is a molecular imaging technique that has been used to investigate regional cerebral glucose metabolism and neuronal activity changes. Guedj et al. [98] analyzed \(^{18}\text{F-FDG}\) brain PET of patients with long COVID-19 and compared the PET abnormalities with patients' characteristics and functional complaints. They revealed that the patients exhibited hypometabolic clusters in various brain regions such as the bilateral rectal/orbital gyrus (including the olfactory gyrus), the right temporal lobe (including the amygdala and the hippocampus extending to the right thalamus), the bilateral pons/medulla brainstem and the bilateral cerebellums. The brain hypometabolism may be related to gustatory dysfunction because medullar, pontine, midbrain, thalamic and cerebellar lesions appear to cause quantitative taste disorders [99]. If such brain disturbance persists, COVID-19 survivors could develop gustatory sequelae.

### 3.2.6 Persistent viral infection and associated inflammation

Whether SARS-CoV-2 directly damages papillae, taste buds and taste receptors or indirectly affects the physiological function of taste perception, the long-term in vivo presence of viruses and the prolonged adverse effects of viruses are the prerequisite for persistence of gustatory dysfunction.

ACE2-expressing neurons and glial cells are potential targets for SARS-CoV-2 and the olfactory nerve can serve as a shortcut for the viral entry into the CNS [96]. Although neuropilin-1 (NRP1) was found to potentiate the cellular entry and infectivity of SARS-CoV-2, the exact route for viruses to enter into the CNS still remains unclear. Cantuti-Castelvetri et al. [100] pathologically analyzed olfactory epithelial cells obtained from human COVID-19 autopsies and revealed that SARS-CoV-2 infected NRP1-positive cells facing the nasal cavity. De Melo et al. [101] conducted a virologic, molecular and cellular study of COVID-19 patients presenting with anosmia. They produced evidence that the olfactory neuroepithelium was the major site of SARS-CoV-2 infection and the viral replication in such a tissue was associated with local inflammation. They also demonstrated that SARS-CoV-2 caused anosmia and ageusia in golden Syrian hamsters, which lasted as long as the viruses remained in olfactory epithelium and bulb. Furthermore, they found that viral transcripts and SARS-CoV-2-infected cells were present in olfactory mucosae of COVID-19 patients suffering from persistent anosmia together with long-lasting inflammation. Persistent SARS-CoV-2 infection and the associated inflammation could account for relapsing chemosensory symptoms of COVID-19.

Superantigens are a class of antigens that nonspecifically activate T-cells, resulting in polyclonal T cell activation and massive cytokine release. Unlike normal antigens, superantigens can activate up to 25% of T cells and overproduce proinflammatory cytokines such as interleukin (IL)-2, IL-6 and tumor necrosis factor-α (TNF-α) [102]. SARS-CoV-2 spike protein was suggested to have a superantigenic character [103]. Jacobs [104] hypothesized that viral superantigens could overstimulate anti-virus immune responses, inducing the negative immunological feedback loop that allows SARS-CoV-2 to reproduce and persist in the body, especially where the immune response is relatively weak. Inflammation lasting for several weeks after SARS-CoV-2 infection might cause long-term symptoms in COVID-19 survivors. Local inflammation induced by persistent viral infection disrupts taste bud homeostasis [81]. Inflammatory cytokines also trigger apoptotic cell death to cause the abnormal turnover of taste buds, leading to gustatory dysfunction.

### 3.3 Possible Therapy

Le Bon et al. [105] verified the efficacy of oral corticosteroids in management of persistent olfactory dysfunction of COVID-19 patients. The patients presenting with anosmia or hyposmia after 5 weeks from symptom onset were received a 10-day course of 32 mg methylprednisolone once daily combined with olfactory training. Their
olfactory function was evaluated by a sniffin’ sticks battery test in which odors were delivered by felt-tip pens carrying a tampon soaked with liquid odorants and the sum of correctly identified pens was determined as the total score. After 10 weeks, they showed significantly increased olfactory scores with the subjective smell improvement. In a multicenter randomized case-control study of Vaira et al. [106], COVID-19 survivors who had anosmia or hyposmia for more than 30 days were prescribed systemic prednisone and nasal irrigation with betamethasone, ambroxol and rinazine for 15 days. After 20 and 40 days from the first evaluation, olfactory dysfunction was significantly improved compared with baseline.

In contrast to these corticosteroid treatments used for olfactory dysfunction, there are only limited clinical trials for gustatory dysfunction of COVID-19 survivors. Abdelmaksoud et al. [107] compared the recovery of chemosensory disorders of 105 patients with mild to critical COVID-19 between zinc therapy and control group. The patients received zinc sulfate of 220 mg (corresponding to 50 mg zinc) twice daily and were followed up until the results of RT-PCR test with pharyngeal swabs were negative. The recovery time of gustatory and/or olfactory function was significantly shorter in the zinc therapy group than the control group, although the time for complete recovery from COVID-19 was not significantly different between two groups. Elalfy et al. [108] evaluated the effects of antiviral drugs and zinc supplementation on patients with mild to severe COVID-19 by comparing with age- and gender-matched patients who were subjected to the routine supportive treatment. The patients received combined antivirals (ivermectin, nitazoxanide and ribavirin) plus zinc supplement of 50 mg twice daily for 2 weeks. Prevalence of taste/smell loss was 4.8% in the combined drug group but 17.6% in the supportive treatment group.

Cellular intake of zinc is possibly enhanced by using ionophores. Rather than supplementation of zinc alone, combination with zinc ionophores such as chloroquine, hydroxychloroquine, and phytochemical bioflavonoid quercetin or (-) epigallocatechin-3-gallate could be a more effective therapy for gustatory dysfunction of COVID-19 survivors [109].

4. CONCLUSION

In addition to fatigue, dyspnea, cough, joint/chest pain, cognitive and attention deficits (brain fog), hair loss and anosmia, gustatory dysfunction is considered as one of long-term sequelae of COVID-19. In the literature, a substantial number of COVID-19 survivors complain of ageusia, hypogeusia and dysgeusia even after one year from symptom onset. Persistence of such taste disorders is likely to vary depending on ethnicity, age, gender and disease severity of patients. Long-lasting taste impairment can occur in outpatients or patients with mild COVID-19 at baseline, possibly affecting more COVID-19 survivors than expected. However, it is still unclear why gustatory dysfunction persists after recovery from COVID-19 or how long abnormal taste lasts in COVID-19 survivors. It is an urgent issue to elucidate the pathogenic mechanisms underlying gustatory sequelae together with developing the effective therapy.

The potential mutability of SARS-CoV-2 brought about the emergence of variants, causing major epidemics in UK, Brazil, and South Africa. Since first detected in India, SARS-CoV-2 delta variant with higher infectivity has globally spread very quickly to be the dominant strain worldwide. The delta variant could provoke different symptoms from the prototype Wuhan strain and other variants. Further COVID-19 symptom studies are needed to determine whether SARS-CoV-2 variants show different characteristics of long-term sequelae including gustatory dysfunction.

Although gustatory dysfunction may not be life-threatening, its persistence causes not only discomfort but also appetite loss and eating-habit alteration, adversely affecting overall quality of life. The intake of food with dominant sweet, salty, sour and bitter taste can significantly change in COVID-19 patients with taste disorders. A follow-up is essential for COVID-19 convalescent or recovered patients to get normal taste back and improve the quality of life. Given the long-term persistence of gustatory dysfunction in COVID-19 survivors, their discharge from hospital is not the end of disease. Careful attention should be continuously paid to taste perception of post-COVID-19 patients to recover their health-relating quality of life, which is required for health providers, especially dental professionals who not only may experience COVID-19 survivors but also can easily become aware of their taste abnormality.

CONSENT

It is not applicable.
ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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