

## Main Article

Dr J Saniasiaya takes responsibility for the integrity of the content of the paper

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## Abstract

**Objective.** To outline the impact on quality of life in coronavirus disease 2019 patients with olfactory dysfunction.

**Methods.** Five databases were searched for articles referring to the impact on quality of life in coronavirus disease 2019 patients with olfactory dysfunction. The search was conducted for the period from November 2019 to April 2021. The search was conducted over one month (May 2021).

**Results.** Four studies that met the objective were included. Altogether, there were 1045 patients. Various questionnaires were used to assess quality of life. Overall, the quality of life deficit affected 67.7 per cent of patients. Quality of life domains investigated include overall quality of life (four studies), food and taste dysfunction (two studies), mental health (two studies), cognitive function (one study), functional outcome (one study) and safety domains (one study).

**Conclusion.** Quality of life deficit was reported to be 67.7 per cent among coronavirus disease 2019 patients with olfactory dysfunction. The high prevalence of persistent olfactory dysfunction prompts more serious research, as the long-standing consequences of olfactory dysfunction are detrimental.

## Introduction

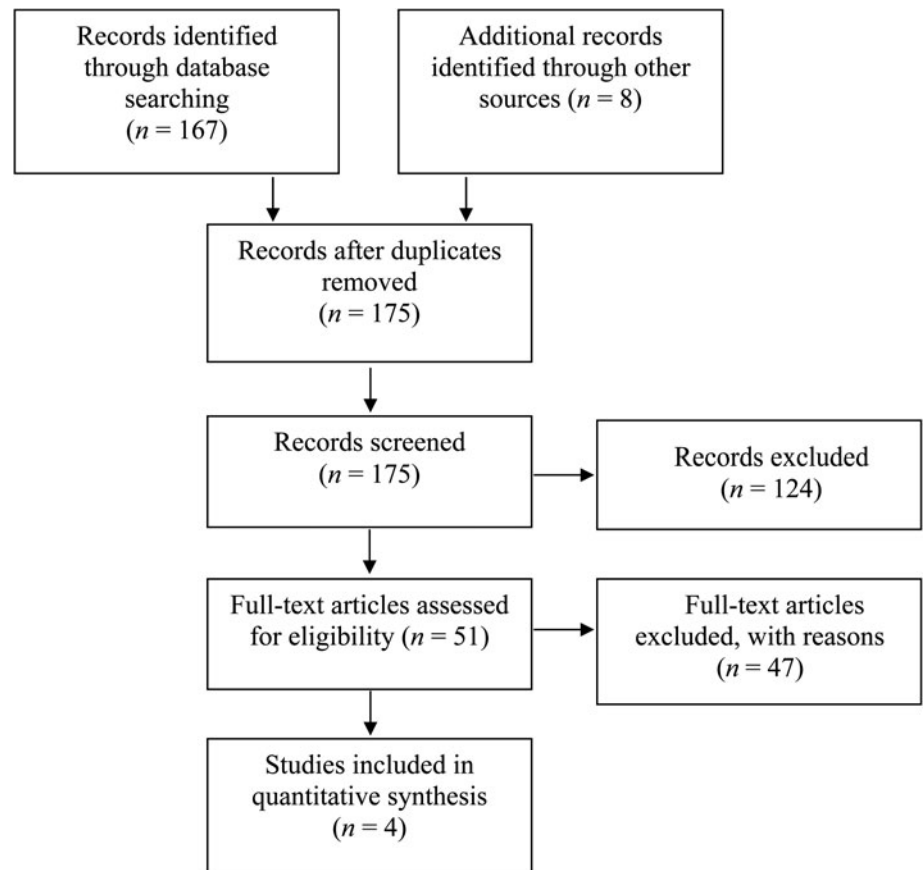
Whilst most of us have adapted to the new norms of social distancing and handwashing, as a result of the coronavirus disease 2019 (Covid-19) pandemic, survivors of Covid-19 with persistent loss of smell or olfactory dysfunction are now having to battle a new norm of being 'scentless'. Many may not be aware that a scentless life may be a consequence of surviving Covid-19. Albeit reported to afflict only a small number of patients, persistent olfactory dysfunction can severely impair quality of life (QoL), and it poses a life-threatening situation to the patient and their family members.

From the initial anecdotal report on the association between new-onset olfactory dysfunction and Covid-19 in early March 2020, olfactory dysfunction has been regarded as a key manifestation of Covid-19. Myriad studies and research on olfactory dysfunction in Covid-19 have emerged over the past year, with a prevalence of 47.85 per cent.<sup>1</sup> Nearly 15–20 per cent of the afflicted population have reported persistent olfactory dysfunction.<sup>2</sup> Yet, this is starkly different from the findings of a six-month psychophysical olfactory assessment study, in which 60 per cent of the cohort were found to have persistent olfactory dysfunction, whilst only 18 per cent of this group self-reported on altered smell.<sup>3</sup> Parallel to that, the prevalence of, as well as recovery from, olfactory dysfunction in Covid-19 patients may be underreported, as most study findings are based on self-reports.<sup>4</sup>

Whilst great attention is being paid to curbing the ongoing pandemic, with vaccination programmes being carried out globally, the fate of Covid-19 survivors with olfactory dysfunction remains a conundrum. Many may not be aware of the crippling effect of olfactory dysfunction amongst Covid-19 survivors. Recently published studies have focused on the prevalence and outcome of olfactory dysfunction amongst Covid-19 patients. Yet, the question is how olfactory dysfunction affects the QoL of these patients, as the road to recovery remains an enigma. This systematic review aimed to cover the current literature available on the impact of olfactory dysfunction on QoL in Covid-19 patients.

## Methods

We conducted a systematic review of the literature, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses ('PRISMA') guidelines, to identify studies that investigated the impact of olfactory dysfunction on QoL in Covid-19 patients. This systematic review used a population, intervention, comparison and outcome framework, to identify studies: involving patients with persistent Covid-19-related olfactory dysfunction (population), through either subjective or objective assessment (intervention), whereby the impact of QoL specific to olfactory dysfunction is assessed (outcome).



**Fig. 1.** Flow diagram of Preferred Reporting Items for Systematic Reviews and Meta-Analyses ('PRISMA') for the systematic literature search.

The review was specifically designed to: (1) clarify the QoL of Covid-19 patients with persistent olfactory dysfunction; (2) identify gaps in the literature; and (3) help guide the direction of future research.

### Data sources

PubMed, Embase and Scopus databases were searched to identify studies published from 1 November 2019 to 30 April 2021. The following key terms were searched: 'olfactory dysfunction', 'loss of smell', 'quality of life', 'Covid-19', 'Covid19' and 'SARS-CoV-2'. Complete details of the search strategy are shown in Figure 1. In order to ensure a robust search procedure, references of the included studies were also searched. Duplicate studies were excluded using EndNote™ X10 reference management software.

The search was conducted over a period of one month (May 2021), in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines<sup>5</sup> and the Cochrane Handbook for Systematic Reviews of Interventions<sup>6</sup> when appropriate.

After being scrutinised by the panel members, four original clinical research articles were selected based on our objective and selection criteria. The selected articles were appraised using the Quality Assessment Tool for Case Series studies from the National Heart, Lung and Blood Institute guideline.<sup>7</sup>

### Study selection

Articles of interest were screened, based on the title and abstract, to identify eligible studies. This was followed by independent reading of the full text by two authors (JS and NP). Any disagreements regarding the inclusion of articles were discussed and resolved by consensus.

### Data extraction and quality assessment

Data extraction was performed independently by two authors (JS and NP). We extracted the following information from each eligible study and entered it into a predefined Excel® spreadsheet: first author's last name; study design; country of the participants; total number of patients; age; gender; duration of olfactory dysfunction; type of olfactory dysfunction; olfactory dysfunction assessment tool; QoL assessment tool; and QoL outcome.

### Outcome measures

The primary outcome was defined as QoL deficit resulting from olfactory dysfunction. Secondary outcomes were other related outcomes resulting from persistent olfactory dysfunction. Studies that did not report on QoL outcomes were excluded.

### Ethical considerations

The study was performed in accordance with ethical standards.

### Results

A total of four studies, initially published online during the study period, that fulfilled the selection criteria were included in the review.<sup>8-11</sup> All four studies were considered to have a level of evidence of 3 (prospective, observational, cross-section studies). Altogether, there were 1045 patients. Gender predominance and mean age were not determined, as these variables were not mentioned in two studies.<sup>8,11</sup> The studies included in this review are summarised in Table 1. A meta-analysis was considered inappropriate in our study because of the heterogeneity issue. Hence, meaningful interpretation of the

**Table 1.** Summary of QoL findings for Covid-19 patients with persistent olfactory dysfunction

Study, country	Study type	Total patients (n)	Age (mean $\pm$ SD; years)	Gender (n)	Duration of olfactory dysfunction assessment	Olfactory dysfunction type/ test used	QoL assessment tool	QoL outcome	Specific treatment
AlShakhs <i>et al.</i> , <sup>8</sup> Saudi Arabia	Prospective cross-section	179	NR	NR	NR	NR / NR	Online questionnaire: short version of QOD-NS	Of patients, 37.6% had problems taking part in daily activities, 42% felt isolated, 68.1% had a change in appetite, 51.4% were stressed, 28.2% had increased anger, & 44.5% were worried about struggle adapting to changes in sense of smell	NR
Coelho <i>et al.</i> , <sup>9</sup> USA	Prospective cross-section	322	41.57	258 F, 63 M	6 months	NR / NR	Online questionnaire: survey questions on QoL & safety	Of patients, 96% had 1 QoL deficit & 75% had 3+ QoL deficits. 87% had reduced food & taste, 43% had depression, 57% had safety-related concerns, & 45% were unable to smell smoke	NR
Elkholi <i>et al.</i> , <sup>10</sup> Egypt	Prospective cross-section	487	31.4 $\pm$ 9.7	370 F, 117 M	NR	Anosmia / NR	Online questionnaire: socio-demographics, multi-clinic smell & taste questionnaire, & General Well-Being Schedule	Of patients, 76% had QoL deficit, 73.3% suffered negative effects, 84.6% had diminished ability to taste or enjoy food, and 66.5% had loss of appetite	NR
Rass <i>et al.</i> , <sup>11</sup> Austria	Prospective cross-section	57/127	NR	NR	3 months	Hyposmia or anosmia / 16-item Sniffin' Sticks test	Assessment of: health-related QoL (36-SFv2), mental health (MoCA) & functional outcome	Of patients, 31% had QoL deficit & 23% had cognitive deficit. Regarding functional outcome, all patients were living independently after 3 months	NR

QoL = quality of life; Covid-19 = coronavirus disease 2019; SD = standard deviation; NR = not reported; QOD-NS = Questionnaire of Olfactory Disorders – Negative Statements; F = female; M = male; SF-36v2 = 36-item Short Form Health Survey, version 2; MoCA = Montreal Cognitive Assessment

outcomes in the studies needed expert discussion and clinical judgment by us.

We found that in three studies, QoL assessment was obtained through an online platform. Various questionnaires were used to assess the QoL, including the short version of the Questionnaire of Olfactory Disorders – Negative Statements,<sup>8</sup> the Multi-Clinic Smell and Taste Questionnaire,<sup>10</sup> the General Well-Being Schedule<sup>10</sup> and the 36-item Short Form Health Survey.<sup>11</sup> In one study, standard questions were used during clinical evaluations at the Virginia Commonwealth University of Smell and Taste Center.<sup>10</sup>

The QoL domains investigated included overall QoL,<sup>8–11</sup> mental health,<sup>8,9</sup> taste dysfunction,<sup>9,10</sup> cognitive function,<sup>11</sup> functional outcome<sup>11</sup> and safety issues.<sup>9</sup> Overall, the QoL deficit affected 67.7 per cent of the included population. Olfactory dysfunction was assessed objectively in one study using the 16-item Sniffin' Sticks odour identification test.<sup>11</sup> Eighty-six per cent of the subjects tested had a reduced ability to taste food.<sup>9,10</sup> Loss of appetite was reported in two studies, affecting 67.3 per cent of subjects.<sup>8,10</sup>

Mental health status was described in two studies.<sup>8,9</sup> AlShakhs *et al.* revealed that 42 per cent of Covid-19 patients with olfactory dysfunction mentioned feeling isolated,<sup>8</sup> whereas depression was reported to be present in 43 per cent by Coelho *et al.*<sup>9</sup> AlShakhs *et al.* revealed stress in 51.4 per cent of their cohort.<sup>8</sup> Safety-related concerns were reported in one study, and affected 57 per cent of patients.<sup>9</sup> None of the studies described any methods of olfactory dysfunction treatment. The quality assessment of the results of the selected articles is summarised in Table 2.

## Discussion

Persistent olfactory dysfunction has a detrimental effect on the population, resulting in a major impact on a person's social skills, relationship, wellbeing and QoL. Our review revealed four studies reporting on the impact of QoL in Covid-19 patients with olfactory dysfunction,<sup>8–11</sup> involving various QoL domains, including overall QoL, and mental, physical, social functioning and safety domains. Results from this review echo findings from previous studies on the QoL impact of various conditions causing olfactory dysfunction.<sup>12</sup>

### Food, taste and appetite

Olfactory dysfunction has been reported to gravely impair the QoL of the affected individual because of numerous day-to-day activity limitations. The most noticeable change is the decrease in flavour perception from impaired retronasal olfaction, which leads to reduced food pleasure, found in approximately 69 per cent of individuals, based on a study by Nordin *et al.*<sup>13</sup> The ramifications from diminished food enjoyment result in a grievous situation, as food is a significant part of one's life.

Previous studies have revealed that permanent olfactory dysfunction reduces appetite in almost 56 per cent of patients, although nearly 20 per cent of patients consume more food.<sup>14</sup> In the same vein, these patients have demonstrated difficulties with cooking and preparing food, as well as detecting rotten food. In our review, reduced ability to taste food was present in 86 per cent of cases.<sup>9,10</sup> Loss of appetite was reported in two studies, affecting 67.3 per cent of cases.<sup>8,10</sup>

**Table 2.** Quality assessment of all four study reports

Study	Research of objectives clearly stated	Study population clearly specified	Cases were consecutive	Subjects were comparable	Intervention was clearly described	Outcome measures were clearly defined	Adequate follow-up length	Statistical methods were well described	Results were well described
AlShakhs <i>et al.</i> <sup>8</sup>	Yes	Yes	NR	No	Yes	Yes	No	Yes	Yes
Coelho <i>et al.</i> <sup>9</sup>	Yes	Yes	NR	No	Yes	Yes	No	Yes	Yes
Elkholi <i>et al.</i> <sup>10</sup>	Yes	Yes	NR	No	Yes	Yes	No	Yes	Yes
Rass <i>et al.</i> <sup>11</sup>	Yes	Yes	NR	No	Yes	Yes	No	Yes	Yes

NR = not reported

### Safety issues

Odours serve as the first warning signal, alerting one to various harmful conditions such as smoke or fire, spoiled food, or hygiene-related issues. Patients with olfactory dysfunction may not be aware of life-threatening situations associated with the inability to detect harmful odorants such as fire, gas leaks and smoke, which has been demonstrated to afflict 61 per cent of such patients, as described by Nordin *et al.*<sup>13</sup> Safety-related concern was reported in one study in our review, involving 57 per cent of their cohort. Croy *et al.* revealed that patients with olfactory dysfunction are involved in more household accidents as compared with normosmic individuals.<sup>15</sup> Patients with olfactory dysfunction tend to be more insecure and constantly worry about safety issues.<sup>16</sup>

### Personal hygiene

Individuals with olfactory dysfunction are affected by hygiene-related concerns, as they are unable to detect their own body odour. This leads to further insecurity, and could result in isolation and damage to self-esteem. None of the patients included in this review reported on hygiene impairment.

### Occupation issues

Intact olfactory function is crucial in many olfaction-reliant occupational groups, notably chefs, gas fitters, firefighters, perfumers, sommeliers, coffee- and tea-tasters, grocers, chemical industry workers, and domestic helpers.<sup>17</sup> Loss of smell is also regarded as a criterion for the discharge of US military and reservists, as well as coastguard employees.<sup>18</sup> These groups of affected individuals are among millions who may have to find a new source of income and relocate, as olfaction is a central part of their job. None of the included studies mentioned job-related concerns associated with olfactory dysfunction. This may be attributed to the fact that the outcome of olfactory dysfunction in Covid-19 remains elusive.

### Mental health

Olfactory dysfunction has been traditionally linked to depression.<sup>19</sup> Interestingly, olfactory function has been regarded as a marker for depression.<sup>12</sup> AlShakhs *et al.*<sup>8</sup> found that 42 per cent of Covid-19 patients with olfactory dysfunction felt isolated, and a study by Coelho *et al.*<sup>9</sup> revealed that depression affected 43 per cent of such patients. Although the link between olfactory dysfunction and depression remains unexplained, an overlap between the brain areas implicated in both depression and the olfactory process has been postulated, notably the orbitofrontal cortex, anterior and posterior cingulate cortices, insula, amygdala, hippocampus and thalamus.<sup>20</sup> In the same vein, odours are known to have a profound effect on the emotions, mood and behaviour, which could explain depression amongst these patients.<sup>21</sup>

### What is next for 'scentless' survivors?

It is salutary to note that although spontaneous recovery from olfactory dysfunction has been linked to post-infectious olfactory dysfunction, we are yet to unravel the outcome of olfactory dysfunction post-Covid-19. Currently, olfactory dysfunction following Covid-19 is possibly underreported in the available data, as most studies are based on self-reports rather than a

more objective assessment. The implications of long-standing olfactory dysfunction in terms of the economic burden have been reported in previous studies.

To date, no validated medication exists specifically to treat post-infectious olfactory dysfunction, although numerous trials involving systemic and topical steroids, vitamin B, caroverine, acupuncture and alpha-lipoic acid have been attempted, with varying results.<sup>22</sup> None of the included studies proposed a treatment regimen.

Olfactory retraining therapy has gained popularity recently because of the rising numbers of patients afflicted with olfactory dysfunction post-Covid-19. This non-invasive intervention, directed at the rehabilitation of olfactory dysfunction, has demonstrated promising outcomes in relation to olfactory dysfunction from various causes.<sup>23,24</sup> As well as being easy to administer, olfactory retraining therapy has been reported to decrease depressive episodes amongst patients.<sup>25</sup> The concept behind olfactory retraining therapy is based on daily repeated exposure to selected odorants. Four odours are traditionally incorporated, based on the odour prism proposed by Henning, of rose, eucalyptus, lemon and clove,<sup>26</sup> which correspond to one from each category: fruity, flowery, resinous and spicy.<sup>27</sup> Olfactory retraining therapy is believed to strengthen the olfactory nerve through repeated exercise. The only drawback of olfactory retraining therapy is the need to repeat the training exercise for months, which may be tiresome to most patients. Nonetheless, favourable results have been demonstrated amongst Covid-19 patients with olfactory dysfunction, whereby early olfactory retraining therapy corresponds to a better olfactory outcome.<sup>28</sup>

- New-onset olfactory dysfunction is a known manifestation of coronavirus disease 2019, with a prevalence of nearly 50 per cent worldwide
- Objective assessment of olfactory dysfunction revealed that olfactory dysfunction prevalence has been underestimated
- Nearly 15–20 per cent of the afflicted population has persistent olfactory dysfunction
- Persistent olfactory dysfunction has detrimental effects on quality of life (well-being, safety, taste, mental health, cognitive impairment, social functioning)
- Early implementation of coping and safety strategies is advised

Several coping strategies directed to managing olfactory dysfunction from various causes have been carried out successfully over the past decade. These include safety measures such as installing gas or smoke detectors.<sup>16</sup> Olfactory dysfunction patients tend to rely on family members to test food or check perfume usage. Family members and close friends need to play an important role in supporting these Covid-19 survivors, as they may be vulnerable and fearful of having permanent smell loss. Dysregulated appetite can be addressed by scheduled eating hours.<sup>16</sup> Strict adherence to manufacturing dates on food and drink is required to avoid food poisoning. Additionally, there are numerous social support groups that can play an important role in targeting emotional adaptation.<sup>13</sup> Currently, the ongoing pandemic has witnessed charity-based support groups such as Fifth Sense and AbSent coming forward to help afflicted patients. Online patient support groups enable patients newly affected with olfactory dysfunction to share their struggle with others who have managed olfactory dysfunction from other causes. Finally, the patients themselves need to come to terms with and gain emotional acceptance of the deficit to allow adaptive adjustment to the disease.

## Conclusion

A QoL deficit is found in 67.7 per cent of Covid-19 patients with olfactory dysfunction. Yet, the numbers may be even higher, as olfactory dysfunction has been underreported following a lack of proper assessment. Research involving Covid-19 survivors with persistent olfactory dysfunction needs to be carried out hand-in-hand with curbing the pandemic, as persistent olfactory dysfunction will lead to a global health burden in addition to detrimental socio-economic effects.

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**Competing interests.** None declared

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