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RESEARCH NOTE

Analysis of the correlations between the severity of lung involvement and olfactory psychophysical scores in coronavirus disease 2019 (COVID-19) patients

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KEYWORDS
anosmia, chest CT, coronavirus, COVID-19, hyposmia, olfactory, pneumonia, recovery, SARS-CoV-2, smell

INTRODUCTION

The prognostic value of olfactory dysfunction (OD) in coronavirus disease 2019 (COVID-19) remains controversial, with conflicting reports of the association between OD and COVID-19 severity.[1] Many of the prognostic studies published so far have important drawbacks that limit the reliability of the results; most are anamnestic studies that do not formally evaluate olfactory function with risk of recall bias, and use "need for hospitalization" alone to determine COVID-19 severity.

Interstitial pneumonia is an important complication of COVID-19 and a reliable negative prognostic factor.[2] This study aimed to analyze the correlation between olfactory psychophysical scores and severity of lung involvement detected by chest computed tomography (CT) in COVID-19 patients suspected of having interstitial pneumonia. We also evaluated whether severity of respiratory disease predicted recovery of OD.

PATIENTS AND METHODS

This prospective study was undertaken at the University Hospital of Sassari (ethical approval PG/2021/5471) and included consecutive patients with polymerase chain reaction (PCR)-confirmed severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection who underwent high-resolution chest CT scan. Exclusions were as follows: COVID-19 diagnosis >10 days earlier, psychiatric or neurological diseases, previous trauma, surgery or radiotherapy in the oral and nasal cavities, preexisting OD, allergic rhinitis, chronic rhinosinusitis, and lung disease; nonconsenting patients were also excluded.

Chest CT imaging was performed using a 16-detector CT scanner (Emotion; Siemens Medical Solutions USA, Inc., Malvern, PA, USA) on admission to the Emergency Department. Images were acquired supine during a single inspiratory breath-hold, with the following parameters; x-ray tube 120 kVp, 350 mAs; rotation time 8.10 s; rotation time 0.8 s; pitch 1.5; slice thickness 1 mm; window lung. Lung involvement was staged by the chest CT severity score (CT-SS) proposed by Yang et al.,[3] ranging from 0 (no pneumonia) to 40 points. Each case was independently assessed by three blinded, experienced radiologists. The median CT-SS was considered.

Psychophysical olfactory evaluation was performed with the Connecticut Chemosensory Clinical Research Center test (CCCRC) within 48 h of the CT and repeated 60 days later by the same researcher, blinded to the CT-SS results. The test methodology and scoring system have been described in previous studies.[4]

The statistical analysis was performed with SPSS 26.0 (IBM, Armonk, NY, USA). The correlation between olfactory scores and CT-SS was assessed using Pearson's correlation coefficient (statistical significance: $p < 0.05$ with a 95% confidence interval [CI]).

RESULTS

Forty-six COVID-19 patients were recruited and completed baseline evaluation. Patient demographics and clinical features are reported in Table 1. At baseline, 35 patients (76.1%) had OD: 12 cases of anosmia (26.1%), severe hyposmia in 10 (21.7%), and moderate hyposmia in 13 cases (28.3%). The mean CT-SS was 15.2 ± 10.7. No radiological signs of interstitial pneumonia were detected in nine patients. Correlation between CCCRC scores and CT-SS at baseline was weak and not significant ($r_s = 0.183$; $p = 0.222$) (Figure 1).

Forty-two subjects completed 60-day assessment (two patients died and two were lost to follow-up). At this endpoint, 47.6% of patients had normal olfactory function, mild hyposmia was found in 26.2% whereas moderate or severe dysfunction persisted in 26.1% (Table 1). A significant directly proportional correlation was found between the CCCRC scores at 60 days and the CT-SS at baseline ($r_s = 0.531$; $p < 0.001$) (Figure 1).

DISCUSSION

The study of the correlations between olfactory scores and the severity of lung involvement, using a standardized and objective clinical outcome such as the CT-SS, may help to determine the prognostic value of olfactory disorders in predicting the severity of COVID-19. The correlation between CCCRC scores at baseline and CT-SS was weak and not significant. This finding is in contrast with previous studies that found an inverse correlation between severity of COVID-19 and self-reported olfactory loss.[1] These may have been influenced by the subjective and retrospective nature of evaluation and by utilization of nonstandardized outcomes such as "need for hospitalization".

An interesting finding is the significant directly proportional correlation between severity of the interstitial pneumonia at baseline and olfactory scores at 60 days. Better olfactory outcomes in more severe cases may be related to treatments prescribed, because most patients with severe respiratory disease were treated with dexamethasone. Preliminary trials of local and systemic corticosteroids suggest benefit in COVID-19–related anosmia,[5] although further studies are required before these can be widely recommended.[6] However, a post hoc correlation analysis based on whether (25 patients, 59.5%) or not (17 patients, 40.5%) patients were treated with corticosteroids found nonsignificant correlations between CCCRC scores at 60 days and CT-SS for both subgroups (treated group: $r_s = 0.318$, $p = 0.121$; not treated group: $r_s = 0.237$, $p = 0.361$). Potential selection bias should therefore be considered a limitation of the present study.

It could be hypothesized that cytokine storm associated with the severity of pneumonitis might be associated with greater severity and persistence of OD, due to an increase in nasal inflammatory cytokine. A statistically significant directly proportional correlation between the

TABLE 1 General and clinical features of the study population

Parameter	Value	CI
Gender, *n* (%)		
Male	27 (58.7)	95% CI, 43.2–73
Female	19 (41.3)	95% CI, 27–56.8
Age (years), mean ± SD	64.5 ± 12	95% CI, 61–68
Days from COVID-19 symptoms onset, mean ± SD	6.9 ± 2.2	95% CI, 6.3–7.5
CT-SS, mean ± SD	15.2 ± 10.7	95% CI, 12.1–18.3
Clinical findings, *n* (%)		
Fever	38 (82.6)	95% CI, 68.5–92.2
Asthenia	41 (89.1)	95% CI, 76.4–96.4
Cough	28 (60.9)	95% CI, 45.3–74.9
Chest pain	3 (6.5)	95% CI, 1.4–17.9
Appetite loss	39 (84.8)	95% CI, 71.1–93.7
Joint pain	41 (89.1)	95% CI, 76.4–96.4
Muscle pain	40 (87)	95% CI, 73.7–95.1
Headache	35 (76.1)	95% CI, 61.2–87.4
Diarrhoea	6 (13)	95% CI, 4.9–26.3
Abdominal pain	8 (17.4)	95% CI, 7.8–31.4
Nausea	8 (17.4)	95% CI, 7.8–31.4
Conjunctivitis	1 (2.2)	95% CI, 0.05–11.5
Urticaria	0 (0)	97.5% CI, 0–7.7
Sticky throat mucus	16 (35)	95% CI, 21.3–50.2
Nasal obstruction	19 (41.3)	95% CI, 27–56.8
Rhinorrhoea	21 (45.6)	95% CI, 30.9–61
Nasal burning	17 (37)	95% CI, 23–51
Throat pain	12 (26.1)	95% CI, 13.4–38.9
Ear pain	3 (6.5)	95% CI, 1.4–17.9
Face pain	1 (2.2)	95% CI, 0.05–11.5
Swallowing difficulties	17 (37)	95% CI, 23–51
Voice issues	3 (6.5)	95% CI, 1.4–17.9
Mouth burning	3 (6.5)	95% CI, 1.4–17.9
Taste loss	31 (67.4)	95% CI, 52–80.5
Baseline psychophysical olfactory function assessment, *n* (%)		
Normal	11 (23.9)	95% CI, 12.6–38.8
Mild hyposmia	0 (0)	97.5% CI, 0–0.8
Moderate hyposmia	13 (28.3)	95% CI, 16–43.5
Severe hyposmia	10 (21.7)	95% CI, 10.9–36.4
Anosmia	12 (26.1)	95% CI, 14.3–41.1
Baseline self-reported olfactory function assessment, *n* (%)		
Normal	15 (32.6)	95% CI, 19.5–48
Partial loss	18 (39.1)	95% CI, 25.1–54.6
Total loss	13 (28.3)	95% CI, 16–43.5
60-Day psychophysical olfactory function assessment ($n = 42$), *n* (%)		
Normal	20 (47.6)	95% CI, 32–63.6
Mild hyposmia	11 (26.2)	95% CI, 13.9–42
Moderate hyposmia	5 (11.9)	95% CI, 4–25.6
Severe hyposmia	3 (7.1)	95% CI, 1.5–19.5

(Continues)

TABLE 1 (Continued)

Parameter	Value	CI
Anosmia	3 (7.1)	95% CI, 1.5–19.5
60-Day self-reported olfactory function assessment, *n* (%)		
Normal	32 (76.2)	95% CI, 60.6–87.9
Partial loss	8 (19)	95% CI, 8.6–34.1
Total loss	2 (4.8)	95% CI, 0.6–16.2

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; CT-SS, computed tomography severity score; SD, standard deviation.

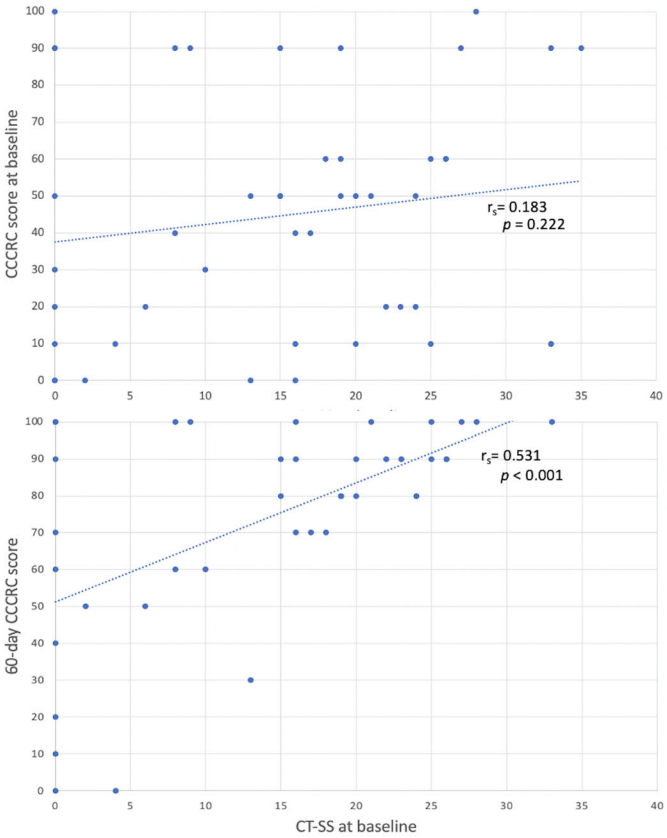

FIGURE 1 Correlation analysis between CCCRC scores at baseline and 60 days, and CT-SS at baseline. Abbreviations: CCCRC, Connecticut Chemosensory Clinical Research Center; CT-SS, computer tomography severity score

severity of chronic ODs and serum levels of interleukin 6 (IL-6), released as part of the COVID-19 cytokine storm has been reported.[7] In contrast, we found that patients with more severe lung disease, in whom levels of serum inflammatory cytokines would expect to be elevated, had better olfactory recovery. The initial injury to the olfactory epithelium is borne largely by sustentacular supporting cells that express highest levels of angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) receptors.[8] Perhaps, higher circulating pro-inflammatory cytokines initiate apoptosis of the infected cells and more effective viral clearance, followed by recovery and return of olfactory function. Given the severity of respiratory and other symptoms, transient loss of smell is then neglected by patients in retrospective anamnestic studies. In the absence of severe disease, the virus may persist,[9] allowing ongoing mild inflammation that appears to be associated with downregulation of the expression of olfactory sensory neuron (OSN) receptors[10] or may even allow direct infection of OSNs or indirect secondary damage. This may also represent a mechanism of potential benefit from corticosteroids.

This study recruited relatively small numbers of patients and it is likely that only more severely symptomatic patients underwent radiological investigations. Furthermore, different treatments were given, in part based on severity, which limits interpretation of the long-term outcomes. Further research should look to include larger numbers of patients receiving standardized medical therapies and a wider range of markers of severity including inflammatory cytokine levels.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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