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Systemic inflammatory markers and psychophysical olfactory scores in coronavirus disease 2019 patients: is there any correlation?

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Main Article

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Abstract

Objective. To analyse the correlations between olfactory psychophysical scores and the serum levels of D-dimer, C-reactive protein, ferritin, lactate dehydrogenase, procalcitonin and neutrophil-to-lymphocyte ratio in coronavirus disease 2019 patients.

Methods. Patients underwent psychophysical olfactory assessment with the Connecticut Chemosensory Clinical Research Center test, and determination of blood serum levels of the inflammatory markers D-dimer, C-reactive protein, ferritin, lactate dehydrogenase, procalcitonin and neutrophil-to-lymphocyte ratio within 10 days of the clinical onset of coronavirus disease 2019 and 60 days after.

Results. Seventy-seven patients were included in this study. D-dimer, procalcitonin, ferritin and neutrophil-to-lymphocyte ratio correlated significantly with severe coronavirus disease 2019. No significant correlations were found between baseline and 60-day Connecticut Chemosensory Clinical Research Center test scores and the inflammatory markers assessed.

Conclusion. Olfactory disturbances appear to have little prognostic value in predicting the severity of coronavirus disease 2019 compared to D-dimer, ferritin, procalcitonin and neutrophil-to-lymphocyte ratio. The lack of correlation between the severity and duration of olfactory disturbances and serum levels of inflammatory markers seems to further suggest that the pathogenetic mechanisms underlying the loss of smell in coronavirus disease 2019 patients are related to local rather than systemic inflammatory factors.

Introduction

In recent months, the prognostic value of olfactory disturbances in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been widely debated.[1–6] Most authors report a higher prevalence of olfactory dysfunction in mild forms of coronavirus disease 2019 (Covid-19),[4–6] proposing that this is the result of an enhanced immune response in the upper respiratory tract.[7]

Recently, several studies have highlighted the prognostic value of some serum inflammatory markers, such as D-dimer,[8,9] C-reactive protein (CRP),[10] procalcitonin,[11] ferritin,[12] lactate dehydrogenase (LDH)[13] and neutrophil-to-lymphocyte ratio.[14,15] Specifically, D-dimer is elevated in the microangiopathy and hypercoagulability states of the most severe cases of Covid-19.[8,9] Lactate dehydrogenase, released by cells after damage to their membrane, has an immunosuppressive action and inhibits cytolytic cells, thus weakening the immune response against the virus.[13] Procalcitonin is a marker of bacterial superinfection that may contribute to complications of Covid-19. C-reactive protein, ferritin and neutrophil-to-lymphocyte ratio are instead markers of acute inflammation, and are particularly elevated during the cytokine storm typical of the most severe forms of Covid-19.[11,12,14,15] All of these markers have been associated with a higher rate of intensive care unit admission, acute respiratory distress syndrome and mortality.[8–15]

In order to determine the prognostic power of olfactory disturbances in Covid-19 patients, it would be useful to establish whether there are correlations between chemosensitive dysfunction, disease severity and these already validated serological markers. This study therefore aimed to analyse the correlations between the olfactory scores determined

by psychophysical tests and the serum levels of D-dimer, CRP, ferritin, LDH, procalcitonin and neutrophil-to-lymphocyte ratio in patients affected by Covid-19 and admitted to the coronavirus disease departments of the University Hospital of Sassari. The secondary objective was to establish whether any of these markers correlated with the persistence of olfactory dysfunction 60 days after onset.

Materials and methods

This cohort study was conducted in the coronavirus disease departments of the University Hospital of Sassari (namely the Infectious and Tropical Diseases, Pneumology, Onco-COVID and Neuro-COVID operative units).

The criteria for patient inclusion in the study were as follows: adults aged over 18 years, rhino-pharyngeal swab positive for SARS-CoV-2 infection, Covid-19 symptoms present for less than 10 days, and patient acceptance for participation in the study. The exclusion criteria were: uncooperative patients, assisted ventilation, psychiatric or neurological disorders, previous surgery or radiotherapy in the oral and nasal cavities, pre-existing self-reported smell and taste alterations, history of head trauma, allergic rhinitis, and chronic rhinosinusitis. Moreover, patients were excluded if they presented with underlying conditions that could alter serum levels of: procalcitonin (e.g. lung or thyroid cancer), CRP (e.g. known acute and chronic inflammatory conditions, Crohn's disease, acute myocardial infarction), ferritin (e.g. alcohol abuse, iron metabolism diseases, iron therapy), D-dimer (e.g. pregnancy, history of thromboembolism, severe liver failure), LDH (e.g. acute kidney, liver or pancreatic disease, haemolytic anaemia) or the neutrophil-to-lymphocyte ratio (e.g. haematological diseases with alteration of the granulocyte or lymphocyte line, advanced stage neoplasms).

The study was conducted in accordance with the ethical standards of the institutional research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The following clinical and epidemiological information was collected for all patients: age, gender and Covid-19 symptoms. All patients were followed up clinically until the rhino-pharyngeal swab results were negative. The overall clinical severity of Covid-19 was classified according to Tian *et al.*[16] as mild, moderate, severe or critical.

Psychophysical olfactory evaluation was performed with the Connecticut Chemosensory Clinical Research Center test. This test is a validated, widely used and easy-to-perform psychophysical test. The methodology, the scoring system and its application in Covid-19 patients have been extensively described in previous studies.[17–20] The test includes the assessment of the olfactory threshold using solutions with increasing concentrations of N-butyl acid and an identification task for common odorants. The olfactory score thus obtained allows a clinical classification of olfactory function according to five categories: normal function (scores of 90 or 100), mild hyposmia (scores of 70 or 80), moderate hyposmia (scores of 50 or 60), severe hyposmia (scores of 20, 30 or 40) or anosmia (scores of 0 or 10).

Within 24 hours before or after the olfactory test, plasma levels of D-dimer, CRP, ferritin, LDH, procalcitonin and neutrophil-to-lymphocyte ratio were determined from a peripheral blood sample taken from each patient. The olfactory function of each patient was re-evaluated with the Connecticut Chemosensory Clinical Research Center test 60 days after the first evaluation.

Statistical analyses were performed with SPSS 26.0 software (IBM, Armonk, New York, USA). Categorical variables are reported in numerals and percentages of the total. Descriptive statistics for quantitative variables are given as means ± standard deviations or medians (interquartile ranges). The Kruskal–Wallis test was performed to evaluate the statistical significance of differences in olfactory scores and assessed inflammatory markers between clinical severity subgroups. Post-hoc analysis with the Mann–Whitney U test was used to evaluate the significance of the differences between each subgroup of clinical severity of Covid-19 for those markers that presented significant *p*-values on the Kruskal–Wallis test. The correlations between olfactory scores and D-dimer, CRP, ferritin, LDH, procalcitonin and neutrophil-to-lymphocyte ratio levels were assessed with the Spearman rank correlation co-efficient. The level of statistical significance was set at $p > 0.05$, with a 95 per cent confidence interval.

Results

Following application of the inclusion and exclusion criteria, 77 patients were included in this study. Table 1 summarises the epidemiological and clinical features of the patients.

The severity of Covid-19 was classified as mild in 34 patients, moderate in 26 and severe in 17. On the psychophysical tests, 57 patients (74 per cent) presented with olfactory dysfunction, including 11 with mild hyposmia (14.3 per cent), 19 with moderate hyposmia (24.7 per cent), 13 with severe hyposmia (16.9 per cent), and 14 with anosmia (18.1 per cent) (Table 1). The median olfactory score was 60 (interquartile range, 30–90). No significant differences in olfactory scores between the Covid-19 severity subgroups were reported (Table 2). In contrast, D-dimer, procalcitonin, ferritin and neutrophil-to-lymphocyte ratio demonstrated significantly higher serum levels in patients with severe Covid-19 (Tables 2 and 3).

The correlations between baseline olfactory scores and serum levels of inflammatory markers were weak and non-significant for all the indexes evaluated (Table 4).

Seventy-three patients underwent an olfactory assessment with the Connecticut Chemosensory Clinical Research Center test 60 days after the first assessment. This second evaluation revealed a median olfactory score of 90 (interquartile range, 70–100). At this observation time, 65.8 per cent of patients had normal olfactory function. The remaining 34.2 per cent of patients had olfactory dysfunction, including 10 with mild hyposmia (13.7 per cent), 6 with moderate hyposmia (8.2 per cent), 6 with severe hyposmia (8.2 per cent) and 3 with anosmia (4.1 per cent) (Table 1).

There were no significant correlations between the markers assessed and the olfactory scores at two months (Table 4).

Discussion

To our knowledge, only two studies have previously analysed correlations between olfactory function and one or more serological markers of inflammation in Covid-19 patients,[21,22] and reported different results. Benkirane *et al.*[22] evaluated the correlations between self-reported olfactory loss and different clinical and laboratory markers in 108 Covid-19 patients. The authors found no significant correlations between loss of smell and serum levels of CRP, ferritin and LDH. Only D-dimer was significantly associated with the presence of olfactory dysfunction. In another study, by Talavera *et al.*,[21] performed with the same methodological setting, contrasting

Table 1. General and clinical features of study population

Parameter	Values
Gender (*n* (%)) (95% CI)	
– Male	48 (62.3) (50.6–73.1%)
– Female	29 (37.7) (26.9–49.4%)
Age (years) (mean ± SD)	63.7 ± 12.6 (60.9–66.5)
Days from Covid-19 symptoms onset (mean ± SD)	7.5 ± 3.2 (6.8–8.2)
Clinical stage (*n* (%)) (95% CI)	
– Mild	34 (44.2) (32.8–55.9%)
– Moderate	26 (33.8) (23.4–45.4%)
– Severe	17 (22.1) (13.4–32.9%)
– Critical	0 (0) (0–4.7%)
Laboratory findings (mean ± SD)	
– D-dimer (μg/ml) (NV = 0–0.5)	1.9 ± 4.2
– CRP (mg/dl) (NV = 0–0.5)	4.2 ± 4.9
– PCT (ng/ml) (NV = 0–0.05)	0.3 ± 0.68
– Ferritin (ng/ml) (NV = 20–120 for males, 20–200 for females)	779.9 ± 688.3
– LDH (U/l) (NV = 135–225)	308 ± 99.9
Baseline olfactory function assessment classification* (*n* (%)) (95% CI)	
– Normal	20 (26) (16.6–37.2%)
– Mild hyposmia	11 (14.3) (7.3–24.1%)
– Moderate hyposmia	19 (24.7) (15.6–35.8%)
– Severe hyposmia	13 (16.9) (9.3–27.1%)
– Anosmia	14 (18.1) (10.3–28.6%)
60-day olfactory function assessment classification† (*n* (%)) (95% CI)	
– Normal	48 (65.8) (53.7–76.5%)
– Mild hyposmia	10 (13.7) (6.8–23.7%)
– Moderate hyposmia	6 (8.2) (3.1–17%)
– Severe hyposmia	6 (8.2) (3.1–17%)
– Anosmia	3 (4.1) (0.9–11.5%)

*$n = 77$; †$n = 73$. CI = confidence interval; SD = standard deviation; Covid-19 = coronavirus disease 2019; NV = normative value; CRP = C-reactive protein; PCT = procalcitonin; LDH = lactate dehydrogenase

Table 2. Olfactory scores and inflammatory marker levels according to Covid-19 clinical severity[16]

	Covid-19 severity			
Parameter	Mild*	Moderate†	Severe‡	Kruskal–Wallis test *p*-value
CCCRC score	60 (30–70)	50 (32.5–85)	70 (32.5–90)	0.607
D-dimer (μg/ml)	0.94 (0.37–1.57)	0.7 (0.36–1.15)	2 (1–3.13)	0.021
CRP (mg/dl)	2.15 (1.12–2.7)	3.15 (1.14–7.37)	2.93 (1.33–6.7)	0.263
PCT (ng/ml)	0.03 (0.02–0.09)	0.05 (0.03–0.61)	0.17 (0.06–0.25)	0.017
Ferritin (ng/ml)	412 (276–568)	551 (250–963)	779 (693–1510)	0.007
LDH (U/l)	290 (241–326)	295.5 (246–349)	290.5 (260–378)	0.793
NLR	2.57 (1.77–5.03)	4.2 (2.78–5.39)	9.75 (7.05–12.93)	<0.001

Data represent medians (interquartile ranges), unless indicated otherwise. *$n = 34$; †$n = 26$; ‡$n = 17$. Covid-19 = coronavirus disease 2019; CCCRC = Connecticut Chemosensory Clinical Research Center test; CRP = C-reactive protein; PCT = procalcitonin; LDH = lactate dehydrogenase; NLR = neutrophil-to-lymphocyte ratio

results were found, with significant correlations detected between the absence of self-reported olfactory disturbance and high levels of CRP and D-dimer and, even if not significantly, with all the other negative prognostic markers. On the basis of these findings, the authors attributed a positive prognostic value to olfactory disturbances during Covid-19.

In another study, Elibol and Baran[23] analysed the relationship between D-dimer and ferritin and Covid-19 related

Table 3. Post-hoc analysis results

Parameter	Mann–Whitney U test *p*-value
D-dimer	
– Mild *vs* moderate Covid-19	0.267
– Moderate *vs* severe Covid-19	0.003
– Mild *vs* severe Covid-19	0.101
PCT	
– Mild *vs* moderate Covid-19	0.208
– Moderate *vs* severe Covid-19	0.136
– Mild *vs* severe Covid-19	0.004
Ferritin	
– Mild *vs* moderate Covid-19	0.213
– Moderate *vs* severe Covid-19	0.128
– Mild *vs* severe Covid-19	<0.001
NLR	
– Mild *vs* moderate Covid-19	0.066
– Moderate *vs* severe Covid-19	<0.001
– Mild *vs* severe Covid-19	<0.001

Covid-19 = coronavirus disease 2019; PCT = procalcitonin; NLR = neutrophil-to-lymphocyte ratio

Table 4. Correlation analysis results

Parameter	Spearman's correlation co-efficient	*P*-value
CCCRC scores at baseline		
– D-dimer	0.026	0.821
– CRP	0.017	0.883
– PCT	−0.124	0.282
– Ferritin	0.106	0.357
– LDH	0.046	0.689
– NLR	0.128	0.267
CCCRC scores at 60 days		
– D-dimer	0.115	0.332
– CRP	−0.027	0.822
– PCT	0.068	0.569
– Ferritin	0.149	0.207
– LDH	0.131	0.268
– NLR	0.143	0.226

CCCRC = Connecticut Chemosensory Clinical Research Center test; CRP = C-reactive protein; PCT = procalcitonin; LDH = lactate dehydrogenase; NLR = neutrophil-to-lymphocyte ratio

gustatory dysfunctions. As noted by Benkirane *et al.*[22] for olfactory disorders, the authors found a significant correlation between high levels of D-dimer and the presence of ageusia. It was not possible to find any study investigating correlations between systemic inflammatory markers and other post-viral olfactory dysfunctions.

The major limitation of the previously published studies is that the assessment of smell was not conducted using quantitative tests. It is now well known that self-reported smell loss alone significantly underestimates the real prevalence of Covid-19 related olfactory dysfunction in infected individuals.[24,25] Moreover, by reducing olfactory dysfunction to a dichotomous variable, it is not possible to perform a statistical analysis based on direct correlations between continuous variables, which is certainly more accurate. These limitations reduce the reliability of the results, and this possible bias is not acceptable if we think that these prognostic studies may influence people's behaviours or the implementation of public health measures.[26]

A further strength of our study is that the assessment of smell and laboratory markers occurred in the first 10 days of clinical onset, when the recovery of olfactory dysfunction has not generally yet begun and Covid-19 has not reached its maximum clinical severity.[27–30] The severity of Covid-19 was then monitored throughout the duration of the infection. In this way, it was possible to evaluate the prognostic power of all the variables taken into consideration. Regarding laboratory markers, D-dimer, procalcitonin, ferritin and neutrophil-to-lymphocyte ratio have shown a significant and directly proportional correlation with severe forms of Covid-19 (Tables 2 and 3). The prognostic value of these indices has been pointed out by other authors in recent months.[8,9,11,12,14,15,31]

Seventy-four per cent of the study patients had olfactory dysfunction at the time of evaluation. This high prevalence is influenced by the fact that the test was performed at a very early stage of the disease and is in line with findings at our centre for patients in the first wave of the pandemic.[17,18,20]

Olfactory scores proved unreliable as prognostic markers. In fact, there were no significant differences in the median scores between the subgroups of clinical severity of Covid-19, nor significant correlations with any of the laboratory indices analysed. This finding is evidently in contrast with that previously reported by Talavera *et al.*[21] and, as regards the D-dimer, by Benkirane *et al.*[22] This study conflicts with others which suggest that the development of olfactory loss may predict a less severe course of disease and the avoidance of hospitalisation.[4,32] It should be noted that, in contrast to the current study, all of these studies were performed retrospectively and relied on the self-reporting of olfactory loss. The findings are therefore subject to recall bias that likely differs according to disease severity: patients with severe disease may simply neglect transient olfactory dysfunction in the setting of severe respiratory compromise.

- Olfactory scores proved unreliable as prognostic markers
- There were no significant differences in median scores between the coronavirus disease 2019 (Covid-19) clinical severity subgroups
- In addition, there were no significant correlations with any of the laboratory indices analysed
- The correlations between olfactory scores and serum inflammatory markers were weak and non-significant at baseline and 60 days, for all indexes evaluated
- There were no correlations between the severity and duration of olfactory disturbance and serum levels of inflammatory markers
- This suggests that the pathogenetic mechanisms underlying smell loss in Covid-19 patients are related to local rather than systemic inflammatory factors

Furthermore, the levels of systemic inflammatory markers during the acute phase of infection were not correlated with the persistence of olfactory dysfunction at two months. The first 6- and 12-month follow-up studies are finding a significant prevalence of severe, long-lasting olfactory disturbances in Covid-19 patients.[27–30,33–35] This means that a large number

of patients will seek assistance for the treatment of this disabling long-term morbidity. In the near future, it will be crucial to identify whether there are epidemiological, clinical or laboratory risk factors for the development of persistent disorders. In this way, it would be possible to establish which patients should be subjected to specific therapy to prevent the persistence of olfactory dysfunction.[19,36,37]

Finally, the results of this study may provide some indication about the pathogenesis of Covid-19 related olfactory dysfunctions, which may be related to local rather than systemic inflammatory factors.[38–41] Future studies will be needed to determine if there are any correlations between the severity of olfactory dysfunction and the levels of inflammatory cytokines in the nasal mucus.

This study has several limitations. The number of patients is too small to draw definitive conclusions. However, the number of patients included was sufficient to show the prognostic value of D-dimer and other markers, suggesting that a type 2 statistical error is less likely. In addition, the 60-day follow up is still too short to detect some delayed functional recoveries that can occur even longer than 6 months after clinical onset.[27–30,33,34]

Conclusion

Olfactory disturbances appear to have a weak prognostic value in predicting the severity of Covid-19 compared to other markers such as D-dimer, ferritin, procalcitonin and neutrophil-to-lymphocyte ratio.

Competing interests. None declared

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