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

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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),1–6 proposing that this is the result of an enhanced immune response in the upper respiratory tract.5

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 chemosensitivie 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. 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. 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. Moreover, the olfactory scores at two months (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, and reported different results. Benkirane et al. 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., performed with the same methodological setting, contrasting

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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 Baran23 analysed the relationship between D-dimer and ferritin and Covid-19 related
gustatory dysfunctions. As noted by Benkirane et al. 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. 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.

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 yet generally begun and Covid-19 has not reached its maximum clinical severity. 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.

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.

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. and, as regards the D-dimer, by Benkirane et al. 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. 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 across individuals. 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.

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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. This means that a large number of
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.17–30,33,34

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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