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# Effectiveness of Platelet-Rich Plasma for COVID-19-Related Olfactory Dysfunction: A Controlled Study

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## Abstract

*Objective.* To investigate the effectiveness of platelet-rich plasma (PRP) injection into the olfactory clefts of coronavirus disease 2019 (COVID-19) patients with persistent olfactory dysfunction (OD).

*Study Design.* Controlled study.

*Setting.* Multicenter study.

*Methods.* From March 2022 to November 2022, COVID-19 patients with persistent OD were recruited from three European hospitals to undergo PRP injections into the olfactory clefts. Olfactory function was evaluated at baseline and 10 weeks postinjection with the Olfactory Disorder Questionnaire (ODQ) and threshold, discrimination, and identification (TDI) test. Data were compared with a control group of untreated patients.

*Results.* Eighty-one patients who underwent PRP injection and 78 controls were included. Sixty-five PRP patients (80.3%) experienced subjective smell improvement after a mean duration of 3.4 ± 1.9 weeks. The parosmia, life quality statement, and ODQ sub- and total scores significantly decreased from pre- to 10-week postinjection in the PRP group. The TDI sub- and total scores significantly increased 10 weeks postinjection. In controls, the ODQ score did not change over time, while the discrimination, identification, and total TDI scores significantly increase after 10 weeks of follow-up. The 10-week TDI and ODQ scores were significantly better in the PRP group compared with the controls.

*Conclusion.* Patients who underwent PRP injection reported better 10-week subjective and objective smell outcomes than controls. Future randomized-controlled studies using saline injection into the olfactory cleft of controls are needed to determine the superiority of PRP over placebo.

## Keywords

anosmia, COVID-19, hyposmia, olfactory, otolaryngology, platelet-rich plasma, recovery, rhinology, SARS-CoV-2, smell

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The prevalence of olfactory dysfunction (OD) is increasing in Western populations since the pandemic of coronavirus disease 2019 (COVID-19).[1] To date, studies reported that OD may reach 30% to 86% of COVID-19 patients according to variants.[2-4] Most individuals recover smell in a few weeks after the infection, but some patients report mid- to long-term OD, such as anosmia, hyposmia, phantosmia, or parosmia.[5] At 1-year postinfection, psychophysical olfactory evaluations suggested that 46% of patients had persistent OD,[6] while the prevalence of patient-reported OD ranged from 15% to 70%.[7,8] The management of persistent OD is challenging. Patients may adhere to an olfactory training protocol, which is, to date, the only approach with consistent results.[9-11] Yan et al[12] published

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a preliminary paper describing the injection of platelet-rich plasma (PRP) into the olfactory cleft of 7 individuals with persistent postviral OD. The findings of this preliminary study were consistent with the potential efficacy of this approach and the authors proposed PRP injection as a new in-office procedure to improve smell recovery.[12] Our team also conducted a preliminary uncontrolled study in 2022 demonstrating the safety of PRP injection into the olfactory cleft.[13] However, in this preliminary study, we did not have a control group, which limited the study of the efficacy of PRP in the olfactory cleft of COVID-19 patients with OD.

In the present controlled study, we investigated the effectiveness of PRP injection into the olfactory clefts of patients with OD related to COVID-19 and we compared the findings with a control group.

## Methods

### Setting and Patients

Patients with post-COVID-19 persistent OD were consecutively recruited from March 2022 to November 2022 in 4 European medical centers: Ear Nose and Throat Dour and/or Baudour Medical Center (Belgium), University Hospital of Sassari (Italy), University Hospital of Trieste (Italy), and La Conception University Hospital of Marseille (France). This study was a continuation of the preliminary uncontrolled study published in 2022.[13]

The COVID-19 etiology of OD was confirmed with reverse transcription-polymerase chain reaction and patients were followed over the postinfection time in ear, nose, and throat consultations. To be included in the present study, patients had to report persistent OD for more than 6 months and consisting of anosmia, hyposmia, phantosmia, or parosmia. Anosmia and hyposmia were defined with the Sniffin' Sticks threshold, discrimination, and identification test (TDI).[14] Anosmia consisted of a TDI score ≤ 16 points, while hyposmia was established as a TDI score of less than 30.75. TDI > 30.75 was considered normosmia.[14,15] Patients were included only if they had a TDI score below 30.75 or if they reported qualitative OD independently from the TDI score. Moreover, patients had no sinus or olfactory region abnormalities at the nasofibroscopy or imaging, for example, rhinosinusitis, olfactory, or nasal tumor. Patients with the following conditions were excluded: posttraumatic, neurological, idiopathic OD before the pandemic; chronic rhinosinusitis with or without nasal polyposis; nasal obstruction related to rhinitis; history of nasal chemo and/or radiation or functional endoscopic sinus surgery, severe neurological or psychiatric comorbidities. A control group of individuals with COVID-19 persistent OD and none of the above-mentioned exclusion criteria was formed. This group included individuals who refused PRP injection but agreed to participate in the follow-up study and patients who were not invited to benefit from PRP.

The study protocol was approved by ethics committees (Assistance Publique des Hopitaux de Marseille-AP-HM-2021-08, Cagliari-PG Institutional Review Board-2021/7118, Friuli Venezia Giulia Region [CEUR-OS156], and CHU Saint-Pierre-2102028 [initial study]) and was effective for all centers. Electronic informed consent was obtained for all patients.

### Demographic, Clinical, and Olfactory Outcomes

The following outcomes were collected through a standardized online questionnaire at the first evaluation: age; gender; comorbidities; allergy; tobacco consumption; previous adherence to an olfactory training protocol; and medication and/or dietary supplement intakes.

The patient-reported olfactory and gustatory evaluations were performed through the definitions of smell and taste component of the National Health and Nutrition Examination Survey,[16] and the Olfactory Disorder Questionnaire (ODQ). ODQ is a validated patient-reported outcome questionnaire including parosmia (/12), quality of life (/57), and sincerity (/18) scores (Supplemental Appendix 1, available online).[17] The questionnaire was available in Italian[18] and English[19] (Supplemental Appendix 2, available online). The ODQ total score ranges from 0 (no OD) to 87 (important impact of OD on quality of life). The psychophysical evaluations of patients were performed with TDI testing (Medisense).[14,15] Subjective and psychophysical olfactory evaluations were performed in PRP patients at baseline (prior injection) and 10 weeks postinjection. Individuals in the control group had similar evaluations at baseline and 10 weeks after the initial assessment.

### Injection Procedure and Outcomes

The PRP injection was proposed for patients with persistent OD and performed in Belgian Medical Center. There was only 1 practitioner that carried out the injection for European patients. The procedure was described in 2 recent papers,[13,20] and is reported in Supplemental Appendix 3, available online. In sum, the blood extraction was performed into a 20 mL tube with sodium citrate anticoagulant. The isolation of PRP was performed with a 10-min centrifugation at 4200 rpm. The supernatant was drawn up into a 10 mL syringe and the PRP was consecutively transferred into a 1 mL syringe. The injection was performed with a 27-G needle (10 cm). The nasal anesthesia was performed with Xylocaine 10% spray after the use of xylometazoline chlorhydrate drops. The injection was performed through a 0° rigid endoscope to guide the needle direction. In cases of septal deviation limiting the access to the olfactory cleft, the needle was bent and the physician used a 30° rigid optic. The practitioner performed bilateral 4 to 6 injections of 0.2 mL in the nasal septum of the olfactory cleft. An

additional injection of 0.2 mL was performed in the medial part of the middle turbinate consisting of the lateral wall of the olfactory cleft. The number of injections was determined by the access and the length of the olfactory cleft. When the olfactory cleft was hardly reachable (nasal deviation), the practitioner performed only 4 injections. Patients were observed for 15 minutes after the procedure for potential adverse events, and bleeding and were then discharged. At the end of the injection, patients were instructed to adhere to an olfactory training protocol for 3 months. Similar training was proposed for controls.

### *Statistical Analyses*

Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (SPSS, v23,0; IBM Corp). The evolution of subjective and psychophysical olfactory evaluations was investigated within each study group with the Wilcoxon rank test. The baseline and 10-week olfactory outcomes were compared between PRP patients and controls with the Mann-Whitney *U* test. The association between epidemiological, clinical, olfactory, and procedure outcomes was analyzed with the Spearman coefficient.

## Results

One hundred and fifty-nine patients completed the evaluations. Eighty-one patients underwent PRP injections into the olfactory clefts and 78 untreated individuals were followed up as controls (**Table 1**). Controls were followed in Dour and/or Baudour Medical Center (N = 19), La Conception Hospital (France, N = 24), and Sassari-Trieste Hospitals (Italy, N = 35). Fifty patients were excluded from the study because they did not complete the 10-week evaluations (28 in the PRP group and 22 in the control group). The mean age of patients was 45.2 ± 12.7 years old. There were no significant differences between groups regarding age and gender findings. The most common comorbidities included reflux disease, thyroid disorders, depression, asthma, and hypertension (**Table 1**). The proportions of allergic and smoker patients were 9% and 18%, respectively.

### *Baseline Olfactory Outcomes and Group Comparison*

The OD duration was 15.7 and 11.0 months in PRP and control patients, respectively ($p = .001$; **Table 2**). The PRP patients and controls adhered to a 12-week olfactory training protocol in 78% and 90% of cases prior to the study inclusion, respectively. There were no statistical differences in baseline means of ODQ scores between groups (**Table 2**). Only the sincerity subscore of ODQ was significantly lower in controls compared with PRP patients. The differences in baseline TDI scores were not significant between groups with the exception of the threshold subscore, which was higher in controls

**Table 1.** Demographic and Clinical Features of Patient Groups

| Outcomes | Patients (N = 81) | Controls (N = 78)[a] | N = 159 |
|---|---|---|---|
| Age (mean, range) | 43.5 ± 13.4 | 47.0 ± 11.1 | 45.2 ± 12.7 |
| Sex | | | |
| Male | 20 (25) | 26 (33) | 46 (29) |
| Female | 61 (75) | 52 (67) | 113 (71) |
| Comorbidities | | | |
| Reflux | 7 (9) | 11 (14) | 18 (11) |
| Thyroid disorder | 11 (14) | 6 (8) | 17 (11) |
| Depression | 5 (6) | 8 (10) | 13 (8) |
| Asthma | 4 (5) | 8 (10) | 12 (7) |
| Hypertension | 5 (6) | 6 (8) | 11 (7) |
| Diabetes | 6 (7) | 2 (3) | 8 (5) |
| Cardiologic affections | 1 (1) | 5 (6) | 6 (4) |
| Cancer history | 1 (1) | 3 (4) | 4 (2) |
| Respiratory insufficiency | 1 (1) | 2 (3) | 3 (2) |
| Renal insufficiency | 0 (0) | 3 (4) | 3 (2) |
| Hepatic insufficiency | 1 (1) | 1 (1) | 2 (1) |
| Immunodepression | 1 (1) | 1 (1) | 2 (1) |
| Allergy | 7 (9) | 8 (10) | 15 (9) |
| Tobacco consumption | 11 (14) | 18 (23) | 29 (18) |

Abbreviation: N, number.
[a]Controls were recruited from Belgium (N = 19), France (N = 24), and Italy (=35), whereas platelet-rich plasma patients were injected in Belgium.

(**Table 2**). According to TDI thresholds, the proportions of anosmic, hyposmic, and normosmic patients did not differ between groups. The prevalence of patient-reported parosmia reached 80% and 87% of individuals in the PRP and control group, respectively.

### *Evolution of Olfactory Outcomes and Predictors*

The 10-week endoscopic examination did not report synechia, mucosal alterations, or inflammation in patients and controls. The olfactory training was successfully completed in 81% of PRP patients and 90% of controls during the 10-week follow-up, respectively. In the PRP group, the parosmia, the life quality statement subscores, and the overall ODQ score significantly decreased (**Table 3**). Sixty-five patients (80.3%) reported a subjective improvement in smell sense. The first improvements were perceived by patients after a mean of 3.4 ± 1.9 weeks postinjection. The TDI subscores and total score significantly increased at 10 weeks postinjection (**Figure 1**).

There was no significant decrease in ODQ in the control group. The mean sincerity statement score significantly worsened. From a psychophysical standpoint, discrimination, identification, and total TDI scores significantly increased in controls (**Table 3**). Patients who underwent PRP injection reported significantly lower

**Table 2.** OD Features of Patients

| OD outcomes | Patients (N = 81) | Controls (N = 78) | *p* Value |
|---|---|---|---|
| Duration of OD, mo | 15.7 ± 7.5 | 11.0 ± 3.0 | .001 |
| Intervention preinjection | | | |
| Olfactory training (12 wk) | 63 (78) | 70 (90) | NS |
| Alpha lipoic acid | 16 (20) | 11 (14) | |
| Nasal corticosteroids | 42 (52) | 26 (33) | |
| Oral corticosteroids | 16 (20) | 14 (18) | |
| Vitamin B | 22 (27) | 16 (20) | |
| Vitamin A | 14 (17) | 7 (9) | |
| Zinc | 39 (48) | 36 (46) | |
| ODQ outcomes | | | |
| Parosmia statement | 7.6 ± 3.8 | 7.9 ± 3.7 | NS |
| Life quality statement | 34.1 ± 14.2 | 30.8 ± 10.7 | NS |
| Sincerity statement | 9.7 ± 4.5 | 6.0 ± 2.7 | .012 |
| ODQ total score | 51.3 ± 18.6 | 44.6 ± 12.5 | NS |
| Psychophysical evaluations | | | |
| Threshold | 3.6 ± 3.2 | 5.1 ± 2.7 | .001 |
| Discrimination | 8.3 ± 4.3 | 8.4 ± 3.4 | NS |
| Identification | 8.2 ± 4.1 | 8.0 ± 3.8 | NS |
| TDI total score | 19.8 ± 9.5 | 21.5 ± 8.4 | NS |
| OD types (TDI) | | | |
| Anosmia | 29 (35) | 26 (33) | NS |
| Hyposmia | 41 (51) | 38 (49) | NS |
| Normosmia with parosmia | 11 (14) | 14 (18) | NS |
| Patient-reported parosmia | 65 (80) | 68 (87) | NS |

The results consisted of mean ± standard deviation or number (%).
Abbreviations: NS, nonsignificant; OD, olfactory dysfunction; ODQ, Olfactory Disorder Questionnaire; TDI, threshold discrimination identification.

10-week sincerity statement and ODQ scores compared with controls. The discrimination and TDI total scores were significantly higher in the PRP group at 10 weeks compared with controls (**Table 3**).

There was a negative significant association between the age of the patient and the baseline ODQ ($r_s = -0.404$; $p = .002$), meaning that elderly patients reported a lower quality-of-life impact of OD than younger patients. The baseline TDI was a positive predictor of the 10-week TDI ($r_s = 0.710$; $p = .001$).

## Discussion

The recovery properties of PRP are known for a long time in several medical disciplines, including dermatology, sport medicine, orthopedic, plastic surgery,[21] or otolaryngology.[22-24] Precisely, in Otolaryngology–Head and Neck Surgery, PRP may be indicated in the management of vocal fold lesions,[22] neck fistula,[23] or tympanic membrane perforation.[24,25] To date, the injection of PRP into the olfactory clefts of patients with OD was attempted in a few small-cohort studies and reported safety[13] and promising findings.[12,26-28]

The primary finding of our study may suggest better significant improvements in both patient-reported outcome olfactory questionnaire and psychophysical evaluations in PRP patients compared with controls. In addition to the potential effectiveness of PRP in COVID-19 patients with OD, our preliminary[13] and current data supported that this procedure is safe and not associated with adverse events. The safety and tolerance of PRP injection into the olfactory clefts of OD patients were supported in our preliminary study,[13] and in the noncontrolled studies of Mavrogeni et al[28] and Yan et al[12] who did not report substantial adverse events or complications. In their preliminary study, Yan et al found a significant improvement of TDI in 5/7 patients with

**Table 3.** Evolution of Olfactory Outcomes

| Outcomes | PRP patients | | | Controls | | | Intergroup |
|---|---|---|---|---|---|---|---|
| | Baseline | 10 wk | *p* Value | Baseline | 10 wk | *p* Value | *p* Value |
| Parosmia score | 7.6 ± 3.8 | 6.9 ± 3.3 | .047 | 7.9 ± 3.7 | 7.4 ± 3.4 | NS | NS |
| Life quality statement score | 34.1 ± 14.2 | 24.2 ± 9.2 | .001 | 30.8 ± 10.7 | 27.1 ± 10.6 | NS | NS |
| Sincerity Statement score | 9.7 ± 4.5 | 7.5 ± 3.4 | NS | 6.0 ± 2.7 | 11.1 ± 3.9 | .033 | .003 |
| Fr-ODQ total score | 51.3 ± 18.6 | 38.6 ± 11.7 | .001 | 44.6 ± 12.5 | 45.5 ± 13.3 | NS | .020 |
| Threshold | 3.6 ± 3.2 | 6.6 ± 4.1 | .001 | 5.1 ± 2.7 | 5.5 ± 2.6 | NS | NS |
| Discrimination | 8.3 ± 4.3 | 11.5 ± 2.9 | .001 | 8.4 ± 3.4 | 10.0 ± 3.0 | .001 | .001 |
| Identification | 8.2 ± 4.1 | 10.8 ± 3.6 | .001 | 8.0 ± 3.8 | 9.9 ± 3.4 | .001 | NS |
| TDI total score | 19.8 ± 9.5 | 28.5 ± 9.1 | .001 | 21.5 ± 8.4 | 25.4 ± 7.7 | .001 | .011 |

The intergroup analysis compared the 10-week values (Mann-Whitney *U* test).
Abbreviations: Fr-ODQ, French version Olfactory Disorder Questionnaire; NS, nonsignificant; PRP, platelet-rich plasma; TDI, threshold discrimination identification; wk, weeks.

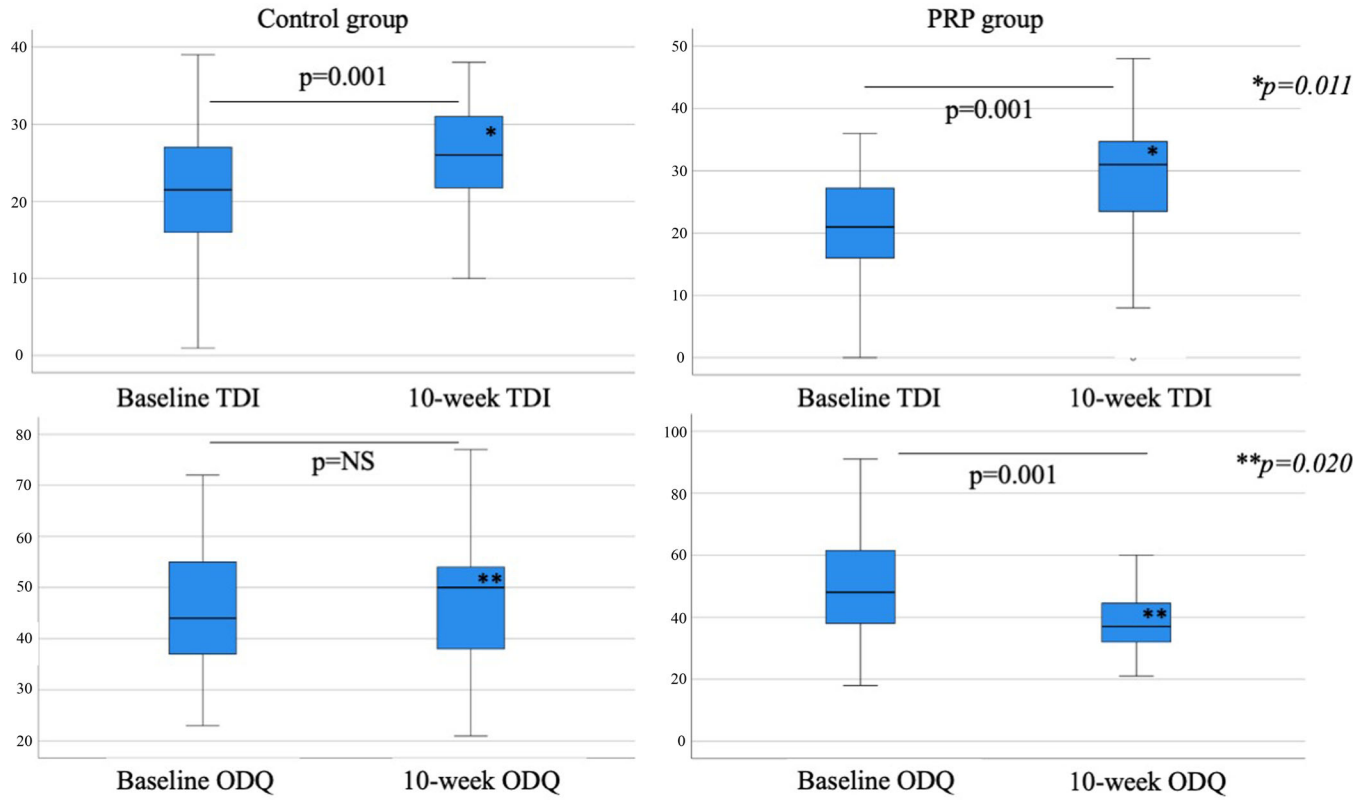


**Figure 1.** Evolution of psychophysical evaluations and Olfactory Disorder Questionnaire (ODQ). NS, nonsignificant; PRP, platelet-rich plasma; TDI, threshold discrimination identification

postviral anosmia or hyposmia, while all patients reported subjective improvement of their perceived smell sense.[12] Recently, Steffens et al investigated the effectiveness of PRP injection in COVID-19 patients with persistent (>1 year) hyposmia or anosmia at the TDI score.[26] In this preliminary controlled study, authors reported that the 1-month increase of TDI scores was higher in PRP patients compared with controls but both the low number of patients and the lack of follow-up at 3 months postinjection limited the draw of clear conclusion. The usefulness of PRP injection into the olfactory cleft was supported by Goljanian et al[27] who observed that patients benefiting from functional endoscopic sinus surgery and PRP injection reported better postoperative smell testing than those who were operated without PRP injection. However, the authors focused on patients with chronic rhinosinusitis with nasal polyposis, which is a different condition from ours.

In the present study, patients recovered subjective smell sense 3 weeks after the injection, which may corroborate the current knowledge of the clinical[29] and animal[30] studies. In an anosmia-induced mice model, Yasak et al observed the first signs of PRP effectiveness at 1, 2, and 3 weeks.[30] Interestingly, these authors observed that the neuroepithelium injuries were significantly lower in mice treated with PRP compared with mice receiving plasma injection.[30] From a physiological standpoint, the injected PRP pockets into the neuroepithelium progressively release anti-inflammatory and proregenerative factors leading to the upregulation of some factors by olfactory cells, such as growth and transforming factors, vascular endothelial growth molecules, epidermal growth factor, and insulin-like growth factor.[21,29] In addition, PRP was found to promote axon regeneration and neuroregeneration, which could be an important mechanism of recovery in cases of patients with OD related to mucosa injuries.[21] The anti-inflammatory effects of PRP are particularly relevant according to a recent study where authors supported that OD patients have a persistent virus, chronic inflammatory reaction in the olfactory neuroepithelium, and related prolonged or relapsing loss of smell.[31] Theoretically, the potential anti-inflammatory effect of PRP should reduce chronic inflammation and cell-related injuries, which should promote the regeneration of the olfactory tissues. Theoretically, the PRP effect appears to be maximized when there is an ongoing inflammatory process. To date, it is unclear if the inflammatory process of the neuroepithelium is still present after 6 months of OD and, consequently, the effectiveness of PRP in smell recovery may be underestimated in the present study. Other points that require future studies are the best timing of PRP injection in the clinical course of the disease and the number of injections.

An important question in olfactory investigation is whether results may reflect clinically meaningful benefits

of a procedure. The minimal clinically important difference (MCID) of the TDI and the ODQ has been reported to be 5.5 and 5.2, respectively.[32] Our primary observations between TDI of PRP and control groups did not reach the 5.5 cutoff, while those for ODQ did. However, more patients in the PRP group had improvements in the TDI that exceeded the MCID compared to patients in the control group. Because patients of the control group also had a higher baseline threshold score than patients of the PRP group, it is unclear if this difference reduced the possibility of achieving an MCID of improvement, since we know that it is harder to achieve improvement in less severe disease (control group).

The present investigation is the largest controlled cohort study reporting evolutions of patient-reported outcome questionnaires and psychophysical evaluations after PRP injections. The large recruitment was possible according to the prevalence of COVID-19-related OD in the population and the development of specific consultations dedicated to the PRP injection with trained nurses and practitioners. Our results support those of Yan et al in their randomized controlled study including 26 COVID-19 loss of smell.[33] Authors observed that PRP treatment resulted in greater improvement in olfaction compared with a placebo group at 3 months and a higher response rate (57.1% vs 8.3%, odds ratio: 12.5).

The primary strengths of the study are the use of validated patient-reported outcome questionnaires and psychophysical evaluations in a large number of patients. In the present study, patients from the control group reported baseline better sincerity statement scores and threshold evaluations than patients of the PRP group. This difference may consist of a comparison bias, especially regarding the MCID analysis. The primary weaknesses are the lack of saline solution injection in the control group, and the lack of use of parosmia-psychophysical evaluations and training, which are more indicated for patients with parosmia.[34] Indeed, in practice, the TDI score may be biased in parosmic patients who recognized some odors of the sniffing sticks because they memorized the significance of these related modified odors. Moreover, some patients reported that the disappearance of parosmia led to anosmia, which was associated with worsening of the TDI score but subjective patient-reported improvement. Thus, the usefulness of PRP injection into the olfactory clefts of COVID-19 patients needs future large-cohort randomized controlled studies considering these several profiles of OD patients through adapted clinical instruments. The lack of statistical power analysis for the calculation of the adequate sample size is another limitation of the study.

## Conclusion

The present investigation is the largest controlled cohort study reporting evolutions of patient-reported outcome questionnaires and psychophysical evaluations after olfactory cleft PRP injection. Patients who benefited from olfactory cleft PRP injection reported better 10-week subjective and objective smell outcome evolutions than controls. Future large-cohort randomized controlled studies using saline solution injection into the olfactory cleft of controls are needed to determine the superiority of PRP injection over placebo.

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## Author Contributions

**Jerome R. Lechien**, design, acquisition of data, data analysis and interpretation, drafting, final approval, and accountability for the work, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; **Sven Saussez**, design, acquisition of data, data analysis and interpretation, drafting, final approval, and accountability for the work, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; **Luigi A. Vaira**, design, acquisition of data, data analysis and interpretation, drafting, final approval, and accountability for the work, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; **Giacomo De Riu**, design, acquisition of data, data analysis and interpretation, drafting, final approval, and accountability for the work, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; **Paolo Boscolo-Rizzo**, design, acquisition of data, data analysis and interpretation, drafting, final approval, and accountability for the work, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; **Giancarlo Tirelli**, design, acquisition of data, data analysis and interpretation, drafting, final approval, and accountability for the work, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; **Justin Michel**, design, acquisition of data, data analysis and interpretation, drafting, final approval, and accountability for the work, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; **Thomas Radulesco**, design, acquisition of data, data analysis and interpretation, drafting, final approval, and accountability for the work, final approval of the version to be

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## Supplemental Material

Additional supporting information is available in the online version of the article.

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