

Platelet-Rich Plasma for Treating COVID-19-Related Anosmia, Hyposmia, and Parosmia: A Controlled Longitudinal 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 anosmia, hyposmia, and parosmia.

Study Design. Controlled study.

Setting. Multicenter study.

Methods. From March 2022 to July 2024, 514 COVID-19 patients undergoing PRP injection and olfactory training versus olfactory training (controls) for a persistent olfactory dysfunction (OD) were consecutively recruited from two medical centers. Subjects were evaluated from pre- to 3 months post-injection with the olfactory disorder questionnaire (ODQ) and the threshold, discrimination, and identification (TDI) test. Olfactory outcomes were compared between controls and patients considering the type of OD (anosmia, hyposmia, and parosmia).

Results. The PRP group was composed of 416 patients with anosmia (N = 111; 26.7%), hyposmia (N = 160; 38.5%), and parosmia (N = 145; 34.9%). The baseline ODQ of patients with parosmia was significantly higher than those of the other groups ($P = .001$). The increase in TDI subscores and total score was significantly higher in all PRP subgroups compared to controls ($P = 0.001$). The ODQ significantly reduced from pre- to post-PRP injection in hyposmia and parosmia groups ($P = 0.001$). Patients with parosmia showed a significantly greater reduction in ODQ scores compared to the control group. The 3-month TDI score was negatively influenced by the age of patients ($r_s = -0.263$; $P = 0.001$) and the duration of OD ($r_s = -0.213$; $P = .001$).

Conclusion. Patients with parosmia experienced a stronger impact of OD on quality of life (QoL), and showed greater QoL improvement following PRP injections compared to other groups.

Keywords

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

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Population-based cross-sectional studies showed a prevalence of olfactory disorders (OD) ranging from 2.7% to 24.5% in the populations of the Western countries.¹ The prevalence of OD has significantly increased in Western populations since the pandemic of coronavirus disease 2019 (COVID-19).² To date, studies that evaluated patient-reported outcome questionnaires and psychophysical olfactory tests showed that 5.2% to 30% of COVID-19 patients had persistent OD at 2 and 3 years post-infection (eg, anosmia, hyposmia, or parosmia),^{2–4} which represents 45 to 90 million patients worldwide.² The injection of platelet-rich plasma (PRP) has been found as a potential procedure for accelerating the recovery of smell sense in patients with long-lasting OD.^{5–8} The few studies investigating the effectiveness of PRP were conducted on small cohorts and, consequently, were limited in analyzing the effectiveness of PRP among subgroups of OD patients, such as patients with anosmia, hyposmia, and parosmia.^{5–8} However, anosmia, hyposmia, and parosmia can share different pathophysiological mechanisms, recovery outcomes, and impact on quality of life.^{9,10}

The present controlled study investigated the effectiveness of PRP injections into the olfactory clefts of patients

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with OD related to COVID-19 according to the type of OD (anosmia, hyposmia, and parosmia).

Methods

Setting and Patients

Patients with a self-reported persistent OD related to COVID-19 were consecutively recruited from March 2022 to July 2024 in the Ear Nose and Throat Dour Medical Center and the Baudour Hospital (Belgium). This study is a continuation of a previously published preliminary study.⁸ Patients were included if they reported persistent COVID-19-related OD for more than 6 months, which consist of anosmia, hyposmia, or parosmia. Anosmia and hyposmia were defined according to the Sniffin' Sticks threshold, discrimination, and identification test (TDI).¹¹ Normative studies reported that anosmia was defined as a TDI score ≤ 16 points and hyposmia was defined as a TDI ≤ 30.75 . TDI > 30.75 was considered normosmia.^{11,12} Patients were included only if they had a TDI score below 30.75 or if they reported qualitative OD independent of the TDI score consisting of parosmia. The parosmia group was composed of patients with parosmia findings on a validated structured questionnaire on parosmia,¹³ and a $> 8/12$ parosmia score at the olfactory disorder questionnaire (ODQ).¹⁴ Moreover, they needed to report that their parosmia symptoms were more severe than potential anosmia/hyposmia complaints. The score ranges from 0 (*no parosmia*) to 12 (*severe parosmia*). A control group was composed from the recruited patients, including individuals who refused PRP injection but agreed to participate in the follow-up study; patients who cannot have PRP injection due to distance from their home to the medical office (located in Belgium) or the PRP cost. To date, PRP is authorized in a few European countries (eg, Belgium, Spain, Luxemburg), leading some patients from other countries to require an international consultation. The control group was designed to reflect the typical population of patients suffering from persistent COVID-19-related olfactory dysfunction, encompassing individuals with anosmia, hyposmia, or parosmia. We did not create separate control subgroups based on specific olfactory dysfunctions (ie, parosmia, anosmia, or hyposmia). This approach prevented us from determining which particular type of olfactory dysfunction might be most responsive to PRP treatment when compared to the broader population of COVID-19-related olfactory dysfunction patients.

Patients had no sinus or olfactory region abnormalities on nasofibroscopy or imaging, rhinosinusitis with or without nasal polyps, olfactory or nasal tumor. Consistent with previous research,⁸ patients with following disorders were excluded: post-traumatic, neurological, idiopathic OD before the pandemic; chronic rhinosinusitis with or without nasal polyposis; nasal obstruction related to rhinitis; history of nasal chemo/radiation or functional endoscopic sinus surgery, severe neurological or psychiatric comorbidities.

Importantly, only patients completing the pre- to post-injection evaluations (PRP group) or follow-up (controls) were included.

The study protocol was approved by the ethics committee (CHU Saint-Pierre Hospital-2102028). Electronic informed consent was obtained for all patients.

Demographic, Clinical, and Olfactory Evaluations

The age, gender, comorbidities, allergies, and tobacco consumption were collected at baseline. At the same time, patients were invited to detail their previous adherence to an olfactory training protocol of 12 weeks,¹⁵ or medication or dietary supplement intakes, alpha lipoic acid, vitamins A, B₁₂, zinc, nasal and oral corticosteroids.

Patient-reported olfactory function and quality of life were assessed using the validated French version of the ODQ.¹⁴ The ODQ is a validated patient-reported outcome questionnaire that includes subscores for parosmia (0-12 points), quality of life (0-57 points), and sincerity (0-18 points) (Supplemental Appendix 1, available online).¹⁴ The questionnaire evaluates the impact of OD on the patient's quality of life, with total scores ranging from 0 (no OD) to 87 (severe impact of OD on quality of life).¹⁴ Psychophysical evaluations were conducted using the threshold, discrimination, and identification (TDI) test (Medisense, Groningen, Netherlands) for both patients and controls.^{11,12} Based on normative data, olfactory function was classified as anosmia (TDI ≤ 16 points), hyposmia (TDI < 30.75), or normosmia (TDI > 30.75).¹² Both subjective and psychophysical olfactory outcomes were evaluated before injection and at 3 months post-injection. Controls underwent ODQ and TDI assessments following the same timeline.

Injection Procedure and Outcomes

The PRP injections were carried out by the same practitioner (J.R.L.). The olfactory cleft endoscopic scale¹⁶ was used to rate the findings of olfactory clefts before injection. The procedure has been described in recent papers.^{8,17} In summary, the blood was extracted into a 20 mL tube with sodium citrate anticoagulant, and the isolation of the PRP was performed with a 10-minute centrifugation at 4200 RPM. The supernatant was drawn up into a 10 mL syringe. The PRP was consecutively transferred into a 1 mL syringe. The nasal anesthesia was performed with Xylocaine 10% spray after the use of xylometazoline hydrochloride drops. The injection was performed with a bent 27-G needle (10 cm) to have better access to the olfactory cleft in case of septum deviation. In contrast to previous studies, the practitioner used a 30° rigid endoscope to guide the needle direction and not a 0° optic as previously described.⁸ Bilateral four to six injections of 0.2 mL were performed in the nasal septum of the olfactory cleft. The access and the length of the olfactory cleft determined the number of injections. In contrast with previous studies, the injection of > 1 mL of

PRP was carried out contralaterally in case of nasal septum deviation limiting the injection to one side. Patients were monitored for 15 minutes post-procedure for potential adverse events and bleeding before discharge. Patients received only one injection for this study. At the end of the injection, all patients were instructed to adhere to an olfactory training protocol for 3 months despite a potential history of unsuccessful olfactory training before injection. Similar training was proposed for controls. Following the Oleszkiewicz et al¹⁵ guidelines, olfactory training was performed at least twice per day using common household odors (soap, coffee, fruit, fragrances) and aromatic compounds.

Statistical Analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (SPSS, v30.0; IBM Corp). Demographics, comorbidities, baseline, and 3-month olfactory outcomes were compared between groups with the Kruskal-Wallis, Mann-Whitney *U* tests, and χ^2 . The evolution of subjective and psychophysical olfactory outcomes was investigated within each study group with the Wilcoxon Rank test. The differences in 3-month ODQ and TDI changes have been investigated with the Kruskal-Wallis test for comparing score differences (*Z*) between PRP and control groups; and between subgroups of PRP (anosmia, hyposmia, parosmia) and controls. The study of associations between epidemiological, clinical, olfactory, and procedure outcomes was analyzed with the Spearman coefficient. A *P* value of <.05 has been considered significant.

Results

Five hundred and fourteen patients completed the evaluations. Of them, 423 underwent PRP injections into the olfactory clefts and post-PRP olfactory training, and 91 were included in the control group (olfactory training only). Seven PRP patients were excluded for a second COVID-19 infection during the follow-up (**Figure 1**). Of the 416 patients, patients had anosmia (*N* = 111; 26.7%), hyposmia (*N* = 160; 38.5%), and parosmia (*N* = 145; 34.9%) (**Table 1**). In the parosmia group, there were 16 (11.0%) patients with anosmia, and 81 (55.9%) with hyposmia at the TDI, respectively. The mean age across groups ranged from 45.7 ± 15.0 to 52.8 ± 15.9 years. The proportion of female patients was significantly higher in the parosmia group compared to the hyposmia and anosmia groups (*P* = .037; **Table 1**). Patient and control comorbidities are detailed in **Table 1**. The anosmia group showed a significantly higher prevalence of hypercholesterolemia compared to other groups. The control group included patients with anosmia (*N* = 30; 33.0%), hyposmia (*N* = 34; 37.4%), and parosmia (*N* = 27; 29.6%). The pre-injection interventions are detailed in **Table 2**. Most patients completed an olfactory training after the onset of OD. The use of dietary

supplements or medication did not differ between groups. However, patients in the parosmia group had attempted significantly more therapeutic interventions compared to those in the anosmia and hyposmia groups (**Table 2**). In the PRP treatment group (*n* = 416), adverse events were documented in 11 patients (2.6%), consisting of 10 vasovagal episodes and one case of sustained epistaxis requiring nasal packing, occurring two days post-injection in a hypertensive patient.

Baseline Olfactory Evaluations

The mean duration of OD was 21.6 ± 11.5 months overall, with group-specific durations ranging from 23.2 ± 16.4 to 28.1 ± 15.0 months, showing no significant between-group differences. At baseline, PRP patients and controls had comparable ODQ scores. Among PRP subgroups, parosmia patients showed significantly higher ODQ-parosmia scores than other groups (**Table 2**), while anosmia patients demonstrated significantly lower TDI scores compared to hyposmia and parosmia groups. No significant differences were observed in ODQ scores between anosmic and hyposmic patients, or in olfactory cleft endoscopic scale scores across groups.

Evolution of Olfactory Outcomes

Changes in TDI and ODQ scores over the study period for PRP patients (*n* = 416) and controls (*n* = 91) are presented in **Table 3**. There were no significant differences between the 3-month ODQ of controls and PRP patients, and anosmic and controls (**Table 4**). In the hyposmia group, the 3-month life quality statement ODQ of patients was significantly lower compared to controls (**Table 5**). The parosmia subgroup showed significantly greater improvements than controls in parosmia score, quality-of-life statement, and ODQ total score (**Table 6**). The minimal clinically important difference (MCID) of ODQ (5.2)⁸ was only achieved in the parosmia group.

All PRP groups demonstrated significant improvements in TDI scores, with anosmia and parosmia groups exceeding the MCID of 5.5 points.⁸ Compared to controls, the anosmia group showed greater improvements in T, D, and total TDI scores (**Table 4**), the parosmia group showed similar improvements (**Table 6**), and the hyposmia group demonstrated greater improvements in T, I, and total TDI scores (**Table 5**). Among PRP groups, parosmia and hyposmia patients achieved greater improvements in threshold scores compared to anosmia patients.

Associations and Predictors

The baseline ODQ was negatively associated with the duration of the OD ($r_s = -0.140$; *P* = .006).

The 3-month TDI score was negatively influenced by the age of patients ($r_s = -0.263$; *P* = .001) and the duration of OD ($r_s = -0.213$; *P* = .001).

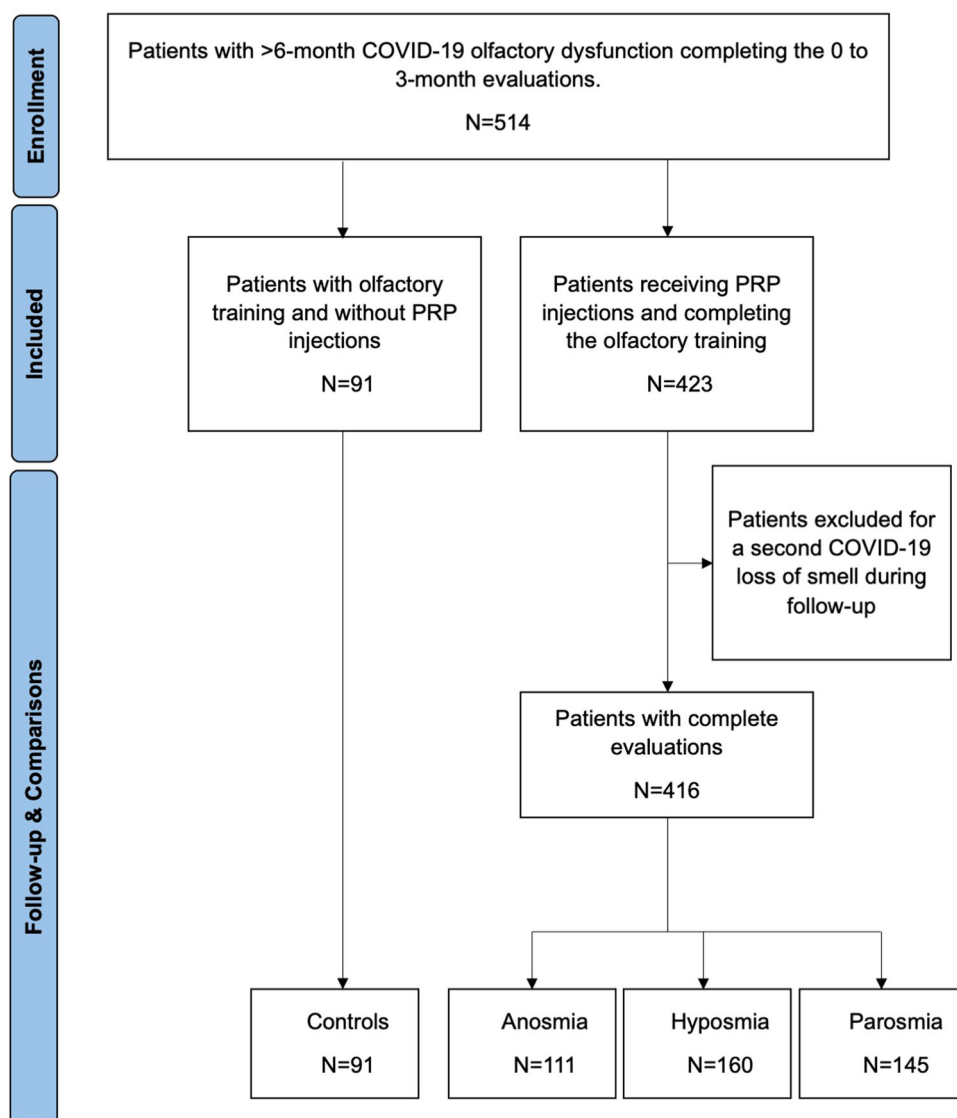


Figure 1. Chart flow. PRP, platelet-rich plasma.

Discussion

The management of OD related to COVID-19 is challenging given the significant impact on QoL. To date, the studies investigating the effectiveness of PRP on COVID-19-related OD reported promising results,^{6,8,18-21} but none stratified patients according to the type of OD.

In this study, our observations confirm the effectiveness of PRP injections into the olfactory clefts of the COVID-19-related OD patients, which corroborates the findings of preliminary placebo randomized controlled trials,⁶ and controlled studies.^{8,19,21}

The subgroup analysis reported that patients with parosmia had attempted a significantly higher number of treatments in the months/years before the injection compared to others. Moreover, this group of patients reported significantly higher quality of life scores (ODQ) at baseline compared to others. Qualitative olfactory dysfunction (parosmia or phantosmia) affects approximately 40% to 50% of individuals who experience decreased olfactory

sensitivity during or after COVID-19 infection.^{22,23} Previous studies have demonstrated that parosmia typically has a more severe negative impact on quality of life than quantitative dysfunctions alone,²⁴⁻²⁶ which explains the higher treatment-seeking behavior observed in our parosmia group. Our findings align with Winter et al,²⁴ who reported that COVID-19 patients with parosmia experienced greater quality-of-life impairment compared to those with hyposmia or anosmia.

In this study, the MCID of TDI was reached in the anosmia and parosmia groups. Moreover, these two groups of patients experienced greater improvement in TDI after PRP injection compared to controls who only adhered to the olfactory training protocol. While the MCID of TDI was not reached in the hyposmia group, hyposmic patients reported greater improvement compared to controls. The TDI findings do not suggest a potentially better effect of PRP on parosmia versus anosmia or hyposmia. However, it should be noted that

Table 1. Demographics and Epidemiological Features

Outcomes	Patients (N = 416)			P value	Controls (N = 91)	Patients vs Controls P value
	Anosmia N = 111	Hyposmia N = 160	Parosmia N = 145			
Age (mean, range)	52.8 ± 15.9	51.2 ± 14.8	45.7 ± 15.0	.001	48.0 ± 11.3	.218
Sex						
Male	39 (35.1)	63 (39.4)	34 (23.4)	.037	30 (33.0)	.068
Female	72 (64.9)	97 (60.6)	111 (76.6)		61 (67.0)	
Comorbidities						
Reflux	17 (15.3)	24 (15.0)	20 (13.8)	.194	11 (12.1)	.583
Thyroid disorder	17 (15.3)	20 (12.5)	19 (13.1)	.488	6 (6.6)	.081
Hypercholesterolemia	20 (18.0)	22 (13.8)	18 (12.4)	.038	2 (2.2)	.220
Hypertension	12 (10.8)	26 (16.3)	25 (17.2)	.855	7 (7.7)	.072
Depression	6 (5.4)	7 (4.4)	13 (9.0)	.405	8 (8.8)	.335
Asthma	4 (3.6)	6 (3.8)	10 (6.9)	.656	8 (8.8)	.139
Mellitus diabetes	9 (8.1)	4 (2.5)	9 (6.2)	.068	2 (2.2)	.225
Cardiologic affections	5 (4.5)	5 (3.1)	4 (2.8)	.527	5 (5.5)	.301
Cancer history	4 (3.6)	4 (2.5)	5 (3.4)	.761	3 (3.3)	.892
Respiratory insufficiency	4 (3.6)	2 (1.3)	6 (4.1)	.379	2 (2.2)	.749
Renal insufficiency	2 (1.8)	2 (1.3)	2 (1.4)	.880	3 (3.3)	.206
Hepatic insufficiency	3 (2.7)	4 (2.5)	3 (2.1)	.818	1 (1.1)	.458
Allergy	11 (9.9)	13 (8.1)	7 (4.8)	.160	8 (8.8)	.603
Tobacco consumption	8 (7.2)	9 (5.6)	12 (8.3)	.668	18 (19.8)	.090

The gender proportion and the proportion of patients with/without comorbidities were evaluated with the χ^2 .

Abbreviations: N, number; NS, non-significant.

Table 2. Olfactory Dysfunction Features of Patients and Controls

Olfactory dysfunction outcomes	Patients			P value	Controls	P value
	Anosmia	Hyposmia	Parosmia			
<i>Intervention pre-injection</i>						
Olfactory training (12 weeks) ^a	87 (78.4)	127 (79.4)	105 (72.4)	0.281	80 (87.0)	.440
At least one medical treatment	56 (50.5)	97 (60.6)	112 (77.2)	0.001	70 (76.9)	.525
Alpha lipoic acid	7 (6.3)	15 (9.4)	14 (9.7)	0.924	13 (14.3)	.636
Nasal corticosteroids	32 (28.8)	53 (33.1)	65 (44.8)	0.416	30 (32.9)	.381
Oral corticosteroids	13 (11.7)	14 (8.8)	27 (18.6)	0.162	16 (17.6)	.156
Vitamin B ₁₂	16 (14.4)	40 (25.0)	42 (29.0)	0.350	19 (20.8)	.125
Vitamin A	7 (6.3)	18 (11.3)	19 (13.1)	0.732	8 (8.8)	.648
Zinc	27 (24.3)	57 (35.6)	60 (41.4)	0.504	41 (45.1)	.660
<i>ODQ outcomes</i>						
Parosmia statement	3.7 ± 2.5	5.0 ± 2.4	10.1 ± 1.4	0.001	3.6 ± 3.0	.006
Life quality statement	26.5 ± 9.8	23.8 ± 10.4	30.1 ± 10.2	0.001	27.1 ± 11.6	.996
Sincerity statement	4.5 ± 2.4	4.7 ± 3.0	5.8 ± 3.0	0.001	7.5 ± 5.1	.079
ODQ total score	34.7 ± 11.5	33.4 ± 12.7	45.9 ± 12.2	0.001	38.3 ± 16.8	.624
<i>Psychophysical evaluations</i>						
Threshold	1.2 ± 0.7	3.9 ± 2.8	4.9 ± 5.1	0.001	5.0 ± 3.2	.001 ^b
Discrimination	3.5 ± 3.2	9.9 ± 2.0	9.5 ± 3.0	0.001	8.3 ± 3.5	.906
Identification	2.3 ± 2.9	9.8 ± 2.5	9.2 ± 3.2	0.001	7.9 ± 3.8	.851
TDI total score	8.0 ± 5.6	23.5 ± 4.1	23.2 ± 7.6	0.001	21.1 ± 8.5	.096
Olfactory Cleft Endoscopic Scale	0.1 ± 0.1	0.1 ± 0.2	0.1 ± 0.3	0.719	0.1 ± 0.2	.545

Abbreviations: NS, non-significant; ODQ, olfactory disorder questionnaire; TDI, threshold discrimination identification.

^aThe olfactory training was completed in the months/years before the injection of PRP.

^bDifferences related to the inclusion criteria with anosmia and hyposmia defined through the TDI.

Table 3. Evolution of Olfactory Outcomes in PRP Patients Versus Controls

Outcomes	All PRP patients				Controls				Intergroup (Z) P value
	Baseline	3 months	Z	P value	Baseline	3 months	Z	P value	
Parosmia score	6.7 ± 3.5	5.8 ± 3.3	0.9	.001	3.6 ± 3.0	4.0 ± 3.8	−0.4	.886	.306
Life Quality Statement score	26.9 ± 10.5	22.7 ± 11.0	4.2	.001	27.1 ± 11.6	26.6 ± 14.4	0.5	.789	.116
Sincerity Statement score	5.1 ± 2.9	5.7 ± 3.0	−0.6	.001	7.5 ± 5.1	6.9 ± 4.8	0.6	.474	.103
ODQ total score	38.6 ± 13.5	34.2 ± 14.0	4.3	.001	38.3 ± 16.8	37.5 ± 20.4	0.8	.878	.255
Threshold	3.4 ± 3.7	5.4 ± 4.0	2.0	.001	5.0 ± 3.2	5.1 ± 2.8	0.1	.166	.001
Discrimination	7.9 ± 3.9	10.0 ± 3.8	2.1	.001	8.3 ± 3.5	9.7 ± 3.1	1.4	.001	.037
Identification	7.0 ± 4.0	9.1 ± 3.9	1.4	.001	7.9 ± 3.8	9.4 ± 3.7	1.5	.001	.758
TDI total score	18.9 ± 9.1	24.4 ± 9.4	5.5	.001	21.1 ± 8.5	24.2 ± 8.3	3.1	.001	.001

The evolution of olfactory outcomes through the 3-month follow-up was assessed with the Wilcoxon Rank test. The changes of PRP and control groups (Z) were compared with the Mann-Whitney *U* test.

Abbreviations: NS, non-significant; ODQ, olfactory disorder questionnaire; PRP, platelet-rich plasma; TDI, threshold discrimination identification.

Table 4. Evolution of Olfactory Outcomes in Anosmia Patients Versus Controls

Outcomes	Anosmia patients				Controls				Intergroup (Z) P value
	Baseline	3 months	Z	P value	Baseline	3 months	Z	P value	
Parosmia score	3.7 ± 2.5	3.8 ± 2.4	−0.4	.278	3.6 ± 3.0	4.0 ± 3.8	−0.4	.886	.621
Life Quality Statement score	26.5 ± 9.8	22.8 ± 11.3	2.5	.003	27.1 ± 11.6	26.6 ± 14.4	0.5	.789	.199
Sincerity Statement score	4.6 ± 2.4	5.4 ± 2.8	−0.8	.470	7.5 ± 5.1	6.9 ± 4.8	0.6	.474	.124
ODQ total score	34.7 ± 11.5	32.1 ± 13.5	1.3	.225	38.3 ± 16.8	37.5 ± 20.4	0.8	.878	.698
Threshold	1.2 ± 0.7	2.8 ± 3.1	1.6	.001	5.0 ± 3.2	5.1 ± 2.8	0.1	.166	.001
Discrimination	3.5 ± 3.2	6.5 ± 4.1	2.8	.001	8.3 ± 3.5	9.7 ± 3.1	1.4	.001	.002
Identification	2.3 ± 2.9	5.6 ± 3.7	2.2	.001	7.9 ± 3.8	9.4 ± 3.7	1.5	.001	.178
TDI total score	8.0 ± 5.6	14.9 ± 8.8	6.6	.001	21.1 ± 8.5	24.2 ± 8.3	3.1	.001	.001

The evolution of olfactory outcomes through the 3-month follow-up was assessed with the Wilcoxon Rank test. The changes of PRP and control groups (Z) were compared with the Mann-Whitney *U* test.

Abbreviations: NS, non-significant; ODQ, olfactory disorder questionnaire; PRP, platelet-rich plasma; TDI, threshold discrimination identification.

Table 5. Evolution of Olfactory Outcomes in Hyposmic Patients Versus Controls

Outcomes	Hyposmia patients				Controls				Intergroup P value
	Baseline	3 months	Z	P value	Baseline	3 months	Z	P value	
Parosmia score	5.0 ± 2.4	4.5 ± 2.6	0.4	.114	3.6 ± 3.0	4.0 ± 3.8	−0.4	.886	.714
Life Quality Statement score	23.8 ± 10.4	20.7 ± 10.5	3.5	.001	27.1 ± 11.6	26.6 ± 14.4	0.5	.789	.358
Sincerity Statement score	4.7 ± 3.0	5.4 ± 3.4	−0.7	.070	7.5 ± 5.1	6.9 ± 4.8	0.6	.474	.048
ODQ total score	33.4 ± 12.7	31.0 ± 13.0	3.3	.016	38.3 ± 16.8	37.5 ± 20.4	0.8	.878	.620
Threshold	3.9 ± 2.8	5.9 ± 3.5	2.1	.001	5.0 ± 3.2	5.1 ± 2.8	0.1	.166	.001
Discrimination	9.9 ± 2.0	11.3 ± 2.5	1.6	.001	8.3 ± 3.5	9.7 ± 3.1	1.4	.001	.328
Identification	9.8 ± 2.5	10.5 ± 2.9	0.8	.001	7.9 ± 3.8	9.4 ± 3.7	1.5	.001	.019
TDI total score	23.5 ± 4.1	27.6 ± 5.8	4.5	.001	21.1 ± 8.5	24.2 ± 8.3	3.1	.001	.030

The evolution of olfactory outcomes through the 3-month follow-up was assessed with the Wilcoxon Rank test. The changes of PRP and control groups (Z) were compared with the Mann-Whitney *U* test.

Abbreviations: NS, non-significant; ODQ, olfactory disorder questionnaire; PRP, platelet-rich plasma; TDI, threshold discrimination identification.

the TDI was primarily developed for quantitative rather than qualitative OD.

Differential PRP effects on quality of life were observed among groups, with the parosmia group showing greater ODQ improvement compared to

anosmia and hyposmia groups. Only the parosmia group achieved the minimal clinically important difference in ODQ scores (5.2).²⁶ Comparison with current literature is limited due to the scarcity of similar studies in research databases. The pathophysiology of parosmia remains

Table 6. Evolution of Olfactory Outcomes in Parosmic Patients Versus Controls

Outcomes	Parosmia patients				Controls				Intergroup P value
	Baseline	3 months	Z	P value	Baseline	3 months	Z	P value	
Parosmia score	10.1 ± 1.4	8.1 ± 2.9	2.0	.001	3.6 ± 3.0	4.0 ± 3.8	−0.4	.886	.003
Life Quality Statement score	30.1 ± 10.2	24.4 ± 11.1	5.8	.001	27.1 ± 11.6	26.6 ± 14.4	0.5	.789	.029
Sincerity Statement score	5.8 ± 3.0	5.9 ± 2.7	−0.5	.370	7.5 ± 5.1	6.9 ± 4.8	0.6	.474	.138
ODQ total score	45.9 ± 12.2	38.5 ± 14.3	7.3	.001	38.3 ± 16.8	37.5 ± 20.4	0.8	.878	.034
Threshold	4.9 ± 5.1	7.1 ± 4.1	2.4	.001	5.0 ± 3.2	5.1 ± 2.8	0.1	.166	.001
Discrimination	9.5 ± 3.0	11.4 ± 2.8	2.0	.001	8.3 ± 3.5	9.7 ± 3.1	1.4	.001	.059
Identification	9.2 ± 3.2	10.5 ± 3.1	1.4	.001	7.9 ± 3.8	9.4 ± 3.7	1.5	.001	.920
TDI total score	23.2 ± 7.6	28.6 ± 7.9	5.8	.001	21.1 ± 8.5	24.2 ± 8.3	3.1	.001	.001

The evolution of olfactory outcomes through the 3-month follow-up was assessed with the Wilcoxon Rank test. The changes of PRP and control groups (Z) were compared with the Mann-Whitney U test.

Abbreviations: NS, non-significant; ODQ, olfactory disorder questionnaire; PRP, platelet-rich plasma; TDI, threshold discrimination identification.

incompletely understood. Some hypotheses support that distortions are related to central (brain) abnormalities in the brain area dedicated to odor identification,^{27,28} while others proposed that distortions are related to significant modifications in the odor receptors and neuron connection in the neuroepithelium.²⁷ PRP facilitates tissue recovery by releasing various growth factors (eg, Platelet-Derived Growth Factor [PDGF], Transforming Growth Factor- β [TGF- β], Vascular Endothelial Growth Factor [VEGF], Epidermal Growth Factor [EGF], Fibroblast Growth Factor [FGF]) and plasma proteins, which help reduce chronic inflammatory responses in long-lasting OD.^{29,30} Several studies suggested that the long-lasting OD should be due to the persistence of transcriptomes or virus antigens in the mucosa/neuroepithelium during the recovery process leading to a reactivation of the immune system and an early apoptosis of stem cells in the process of differentiation.^{31,32} Yasak et al demonstrated that PRP injection into the olfactory region in a murine model of chronic OD resulted in superior olfactory recovery and epithelial healing compared to saline solution controls.³³ While our current study cannot definitively support either central or peripheral pathophysiological hypotheses, the localized action of PRP in the neuroepithelium suggests a peripheral mechanism may be involved in the observed improvements, particularly in parosmia patients. This peripheral hypothesis warrants further investigation through targeted experimental studies. Correlation analyses revealed a negative association between OD duration and ODQ scores, likely reflecting patients' development of coping mechanisms and habituation to their olfactory deficits over time.³⁴ Additionally, the negative correlation between age and 3-month TDI scores indicates diminished olfactory recovery in elderly patients, consistent with established age-related olfactory decline patterns documented in previous studies.^{35,36}

In this consecutive patient series, we observed a significantly higher proportion of females in the parosmia group compared to anosmia and hyposmia groups. Sex-based differences in both OD development and recovery

patterns have been documented in multiple studies.^{37,38} Our demographic findings align with a large-scale population survey, where authors demonstrated higher parosmia prevalence among females.³⁹

This represents the largest cohort study of PRP treatment for COVID-19-related OD in current literature. The study design incorporated a heterogeneous control group of COVID-19-related OD patients, allowing comparison of olfactory outcomes between standard olfactory training and PRP injection across specific patient populations (anosmia, hyposmia, and parosmia). This approach addresses a critical clinical need, as treatment effectiveness for specific OD subtypes has remained undefined until now. The lack of a placebo group and the lack of use of specific parosmia-psychophysical evaluations are the primary limitations of the study. Indeed, the conventional TDI evaluation can be biased in parosmic patients who can recognize some odors of the sniffing sticks because they memorize the signification of these related modified odors. As similarly observed in preliminary studies,⁸ some patients reported that the disappearance of parosmia led to anosmia, which led to the worsening of the TDI score in some parosmia patients.

Conclusion

The present study represents the largest controlled cohort study evaluating PRP effectiveness in both quantitative and qualitative olfactory disorders. Our findings demonstrate that PRP injection into the olfactory cleft significantly improves psychophysical olfactory measures across all OD subtypes (anosmia, hyposmia, and parosmia). Notably, while parosmia patients experienced greater quality-of-life impairment at baseline, they achieved superior quality-of-life improvements following PRP treatment compared to anosmia and hyposmia groups.

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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.

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Supplemental Material

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

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