Platelet-rich plasma for the treatment of COVID-19 related olfactory dysfunction: a systematic review*

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Abstract

Introduction: Olfactory Dysfunction (OD) is a prevalent issue with a significant number of cases attributed to COVID-19. This systematic review aimed to evaluate the effectiveness of platelet-rich plasma (PRP) in the treatment of COVID-19 related OD, including anosmia, hyposmia, and parosmia.

Methods: A comprehensive literature search was conducted using Medline, Scopus, Directory of Open Access Journals (DOAJ), and Google Scholar from inception until December 22, 2022. The eligibility criteria were confirmed COVID-19 patients with OD, whether it was measured objectively and/or subjectively, who received PRP treatment. The study followed a pre-specified protocol registered in PROSPERO (ID: CRD42023386803) and adhered to PRISMA guidelines.

Results: Four studies that enrolled 233 patients were included. The degree of improvement was assessed using threshold-discrimination-identification (TDI) scores at baseline and 1 and 2 months after PRP injection. Parosmia was assessed using the Visual Analog Scale (VAS) scores. Treatment of OD with PRP injections resulted in variable degrees of improvement. However, PRP injections can be considered safe, effective, and promising therapeutic options, as revealed by pooled studies.

Conclusions: This systematic review indicated that PRP may be an effective treatment for COVID-19 related OD. However, additional large-scale studies are required to further investigate PRP efficacy in the treatment of OD following COVID-19.

Key words: olfactory dysfunction, COVID-19, platelet-rich plasma, ansomia

Introduction

Olfactory Dysfunction (OD) is defined as a loss of, decrease, or distortion in the ability to smell. It has a prevalence of 5-15% in the general population [1,2]. There are several suggested causes of OD, including head trauma, upper tract infection, or Coronavirus Disease-19 (COVID-19) [3,4]. A substantial proportion of patients with COVID-19 might develop long lasting change in their sense of smell or taste [5]. The prognosis is worsened by a longer duration of OD [6,7]. Possible therapeutic options for post COVID-19 related OD have shown variable efficacy. Nonetheless, the treatment of COVID-19 related OD through olfactory training has shown the best outcome [8–10]. The use of topical intranasal medications, oral anti-inflammatory, and neuroprotective agents has shown some efficacy since the pre pandemic era [11-13].

Promising emerging therapy for COVID-19 related OD is Platelet-Rich Plasma (PRP), which is an autologous biological product made from fresh whole blood that contains a high concentration of platelets. In OD patients, the olfactory neuroepithelium and olfactory filae, which traverse the cribriform plate, are regenerative and can thus be targeted therapeutically. PRP has been shown to have regenerative and anti-inflammatory properties and it upregulates growth factors such as TGF, EGF, VEGF,

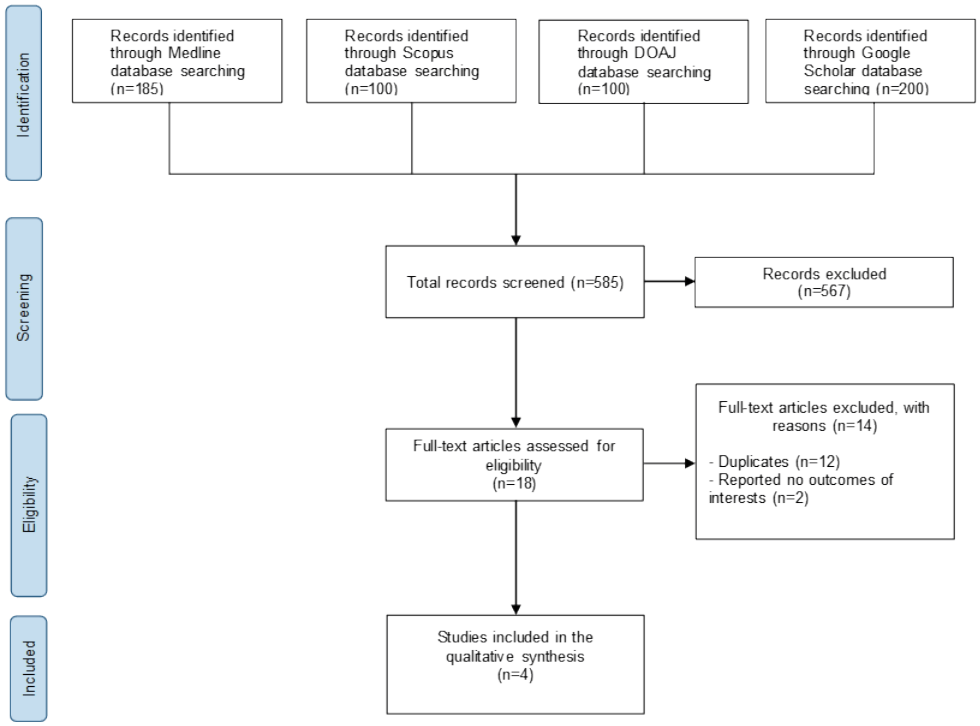

Figure 1. An overview of the study selection process based on PRISMA.

and insulin-like growth factor [14]. In addition, PRP can promote axon and nerve regeneration [15]. Growth factors have demonstrated the ability to treat anosmia and regenerate the olfactory neuroepithelium [16,17]. A pilot study on the use of PRP in patients with hyposmia found subjective improvements in 5 patients [18]. Additionally, the safety of PRP in OD has been discussed in several studies [18–20].

This systematic review aimed to assess the effectiveness of PRP in the treatment of COVID-19 related OD. This review would provide significant insights that can help otolaryngologists worldwide to help patients suffering from anosmia, hyposmia, and parosmia following COVID-19 infection.

Materials and methods

Study registration

This study utilized a pre-specified protocol registered in PROSPERO (ID: CRD42023386803) and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [21].

Information sources and search strategy

A systematic search of the literature was performed using Medline, Scopus, Directory of Open Access Journals (DOAJ), and Google Scholar from inception until December 22, 2022. The search terms included "COVID-19 OR coronavirus" and "Platelet-rich plasma OR platelet-rich plasma injection OR PRP" and "Olfactory dysfunction OR anosmia OR hyposmia OR parosmia." We complemented our computerized search with a manual search by reviewing the reference lists of all included studies.

Eligibility criteria

This systematic review included all confirmed COVID-19 patients who had OD (i.e., anosmia, hyposmia, and parosmia) during or after their infection and who received PRP either during or after their infection. Inclusion criteria were met if the studies reported outcomes of interest for adult patients treated with PRP. Studies without time limits were included. Randomized controlled trials (RCTs) and observational studies were included. Studies in which patients developed OD before the COVID-19 infection were excluded. We excluded review articles such as meta-analyses, systematic reviews, and narrative reviews. We also excluded studies that did not report the outcomes of interest or were published in languages other than English. Two independent reviewers screened the titles and abstracts of the included articles (OA, HA), and a third reviewer resolved disagreements (BAR).

Data extraction

Reviewers (OA, HA) independently identified and screened full-text articles. Any disagreements were resolved by a third reviewer (BAR). Study characteristics such as author name, country, study design, journal name, and sample size were extracted. We extracted the patients' demographic characteristics such as mean age and sex. We extracted the type of OD and its duration, Threshold-Discrimination-Identification (TDI) at baseline and one month, and the degree of improvement following admi-

Table 1. Included studies' characteristics.

Study, year	Country	Study design	Journal	Sample size	Mean age (in years)	Gender
Steffens et al. 2022	Belgium	Prospective	European Archives of Oto-Rhino-Laryngology	PRP group = 30 No PRP group = 26	PRP group = 39 ± 12 No PRP group = 44 ± 11	Male = 20, female = 36
Lechien et al. 2022	Belgium	Prospective	European Archives of Oto-Rhino-Laryngology	87	41.6 ± 14.6	Male = 25, female = 62
El Naga et al. 2022	Egypt	Pilot study	The Egyptian Journal of Otolaryngology	PRP group = 30 No PRP group = 30	PRP group = 28.9 No PRP group = 30.07	Male = 20, female = 40
Yan et al. 2022	United States	RCT	International Forum of Allergy Rhinology	PRP group = 18 No PRP group = 12	PRP group = 44.6 No PRP group = 43.4	Male = 15, female = 15

RCT: randomized controlled trial, PRP: platelet-rich plasma

nistration of PRP. Data on pre-PRP interventions, olfactory cleft injection, local anesthesia time, Visual Analog Scale (VAS) score, and clinical recommendations were also extracted. We extracted all relevant statistical variables such as percentages, hazard ratios, odds ratios, and p-values, when available.

Risk of bias assessment

Three investigators (BAR, OA, and HA) used the Critical Appraisal Skills Programme (CASP) tools for randomized control trials and cohort studies to assess the risk of bias and evaluate the quality of the studies included in this systematic review. The CASP tools address several components of the included studies, such as the appropriateness of the study design, validity of the study methodology, accuracy and precision of the reported results, and applicability of the study results to the local population.

Statistical analysis

Owing to the heterogeneity of the included studies, a meta-analysis was not possible. Alternatively, a descriptive analysis of the included studies was conducted to report the results comprehensively.

Results

Study selection

A total of 585 records were obtained after searching Medline, Scopus, DOAJ, and Google Scholar. Of these, 567 records did not meet the inclusion criteria. The remaining 18 studies underwent a full-text assessment, resulting in the exclusion of 14 studies. Figure 1. provides an overview of the study selection process. Overall, four studies were included in this systematic review [20,22–24]. One of the four selected studies was a randomized controlled trial (RCT) followed by two prospective studies and one pilot study [20,22-24].

Study characteristics

The total number of participants was 233, of whom 68 were not treated with PRP. The studies predominantly consisted of females, accounting for 153 of the sample size, and males, accounting for 80. The mean age of participants ranged from 28.9 to 55. Table 1. summarizes the characteristics of the included studies. Prior to PRP injections, most studies included olfactory training, vitamin B, B12, and A, omega, zinc, and corticosteroid (nasal, oral, and topical) administration as a treatment for OD. OD was characterized by any anosmia, hyposmia, or parosmia. Most studies used nasal endoscopy to guide 1 ml of PRP injection into the olfactory cleft. The degree of improvement was assessed using TDI at baseline and one-month post-PRP injection. At baseline mean TDI ranged between 21.3 to 24.3 in PRP patients and 24.5 – 26 in non-PRP patients. TDI at one month follow up was then assessed, yielding a significant improvement in all four studies, as shown in Table 2.

Risk of bias within studies

All included studies had a clearly focused research question. Half of the studies randomized the intervention to participants. Three studies included all participants who entered the study for their conclusions. It was not clearly stated in all the studies whether all participants, investigators, and people analyzing the outcomes were blinded. All the studies had similar groups at the start of the study. All studies reported that the intervention and placebo groups were treated equally, and that all results were reported comprehensively. However, three studies did not report an estimate of the treatment effect (i.e., confidence interval). All studies reported that the benefits of the intervention outweighed the harms and costs, and that the results can be applied to any other population. All studies reported that the experimental intervention would provide greater value to people with OD than any existing intervention. The details are presented in Table 3.

Measurement of smell loss and parosmia

The included studies had some differences in the measurements of smell loss and parosmia. Steffens et al. evaluated OD objectively using the Sniffing Stick test via TDI scores and subjectively

Table 2. Included articles discussing the effectivity of platelet-rich plasma for the treatment of COVID-19 related olfactory dysfunction.

Study	Type of olfactory dysfunction	Duration of olfactory dysfunction (months)	Degree of improvement based on objective (quantitative) measurement		Degree of improvement based on subjective (qualitative) measurement	Clinical recommendations
			TDI at Baseline (mean ± SD)*	TDI at one month (mean ± SD)**		
Steffens et al. 2022	Chronic olfactory dysfunction: 56 patients	PRP: 7–16 Control: 6–17	PRP: 21.3 ± 7.4 Control: 24.5 ± 7.4	PRP: 28.0 ± 5.0 Control: 25.0 ± 7.7	The mean self-assessment of improvement in smell function was 1.8 (mild-to-moderate) in the PRP group, which was significantly higher than the score (0.3) in the control group ($p < 0.001$). No adverse effects were reported throughout the study	PRP in the olfactory cleft can increase the olfactory threshold one month after the injection. Timing of treatment may be an important factor and PRP is a safe treatment because no adverse effects were reported throughout the study
Lechien et al. 2022	Anosmia: 30 patients Hyposmia: 40 patients Parosmia: 17 patients	PRP: 14.1–17.3	PRP: 20.3 ± 10.5 Control: NA	PRP: 26.0 ± 11.2 Control: NA	Eight patients (22%) did not report subjective improvement of olfactory dysfunction, while 20 (54%) and 9 patients (24%) reported substantial improvement in anosmia/hyposmia or parosmia, respectively. According to patient experience, a significant improvement in olfaction occurred after a mean of 3.6 ± 1.9 weeks	The injection of PRP into the olfactory clefts is safe and associated with adequate patient-reported outcomes. The findings of this preliminary study suggest possible efficacy on subjective and psychophysical evaluations, but future randomized controlled studies are needed to determine the superiority of PRP injection over placebo
El Naga et al. 2022	Parosmia: 60 patients	NR	NR	NR	There was a highly significant improvement in VAS for parosmia ($p <0.00001$) in the PRP group and a significant improvement in VAS for parosmia in the control group ($p=P=0.00148$). There was a significant difference between the two groups regarding the degree of improvement, favoring the case group ($p=0.002$)	Platelet-rich plasma injection in the olfactory cleft offers a therapeutic option for treating patients with post-COVID-19 olfactory parosmia who failed to respond to traditional conservative treatment

PRP: platelet-rich plasma, TDI: threshold-discrimination-identification, SD: standard deviation, VAS: visual analog scale, CI: confidence interval, NR: not reported NA: not applicable.

*Functional anosmia is defined as TDI score ≤ 16.5, hyposmia is defined as TDI score ≤ 30.5, and normosmia is defined as TDI score > 30.5.

**Lechien et al. 2022 has reported the TDI at two months.

Table continues on next page

Study	Type of olfactory dysfunction	Duration of olfactory dysfunction (months)	Degree of improvement based on objective (quantitative) measurement		Degree of improvement based on subjective (qualitative) measurement	Clinical recommendations
			TDI at Baseline (mean ± SD)*	TDI at one month (mean ± SD)**		
Yan et al. 2022	Did not specify: 35 patients	PRP: 8.9 Placebo: 8.6 Six months' duration was used as a cutoff to ensure that the majority of patients known to spontaneously improve after COVID-19–induced smell loss would not confound the improvement from the intervention. One year duration was used as a cutoff as we know the duration of loss of smell often predicts recovery prognosis.	PRP: 24.3 Placebo: 26	PRP: 28.61 ± 8.62 Placebo: 27.17 ± 2.33	When assessing subjective changes in smell function, both the PRP and placebo group showed significant improvement in VAS scores at one and three months compared to baseline. However, no significant difference was found in the change in subjective olfaction scores using VAS at either one or three months between the PRP and placebo groups	Olfactory function following COVID-19 can improve spontaneously after 6 months and can improve to a greater extent with PRP injection. These data build on the promise of PRP to be a safe potential treatment option for patients with COVID-19-related smell loss, and larger-powered studies will help further assess its efficacy

using a Likert scale ranging from zero (no sense of smell) to three (strong sense of smell). They evaluated the OD at baseline and one month after the last PRP injection [20]. Similarly, Lechien et al. evaluated OD objectively using the Sniffing Stick test via the TDI scores and subjectively using the Olfactory Disorder Questionnaire (ODQ) score, which ranged from zero (no OD) to 87 (significant impact of OD on quality of life). They evaluated the OD at baseline and two months after the last PRP injection [22]. In contrast, El Naga et al. evaluated parosmia only subjectively using the VAS score, which ranges from zero to ten, and they considered reaching from zero to one complete improvement. They evaluated parosmia at baseline and one month after the last PRP injection [23]. Finally, Yan et al. evaluated OD objectively using the Sniffing Stick test via TDI scores and subjectively using the VAS, which ranged from zero (no smell) to ten (perfect smell). They evaluated the OD at baseline and at one and three months after the last PRP injection [24].

Effects of intervention

Most patients who were treated for post COVID-19 olfactory parosmia failed to respond to conservative therapies such as olfactory training and steroid irrigation. Additionally, the paucity of definitive treatment options has made PRP injection a proposed therapy for treating patients with post COVID-19 OD. As reported by all the included studies, the treatment of OD with PRP injections resulted in variable degrees of improvement, as shown in Table 2. While PRP injections showed an increase in TDI scores, which were used as an objective measurement tool for OD and an increase in subjective measurement tools such as self-assessment and questionnaires, as revealed by the pooled studies, the improvement following PRP therapy is still subjective, and patients need to be aware that the results carry a range of variability based on individual factors.

Objective (quantitative) outcomes

The effect of PRP was measured using both objective and subjective measurements of smell loss in most of the included studies. Steffen et al. reported that the mean TDI score changed from 21.3 at baseline to 28 after one month of administering PRP injections to the intervention group, which was higher than that of the control group, where the mean TDI score changed from 24.5 at baseline to 25 after one month without administering PRP injections [20]. Similarly, Lechien et al. reported a mean TDI score change from 20.3 at baseline to 26 after two months of administering PRP injections [22]. Additionally, Yan et al. reported that the mean TDI score changed from 24.3 at baseline to 28.61 one month after administering PRP injections compared with the placebo group, which had a mean TDI score of 26 at baseline and 27.17 after one month [24].

Subjective (qualitative) outcomes

To ensure that PRP injections are measured comprehensively, most studies have used subjective tools to measure the OD, such as self-assessment forms and questionnaires. Steffen et al. used a Likert scale that ranged from zero (no smell) to three (strong smell) and reported that the mean self-assessment of improvement in smell function was 1.8 in the PRP group, which was significantly higher than the score in the control group which was 0.3 [20]. Similarly, Lechien et al. used the OD Questionnaire, which ranged from zero (no OD) to 87 (significant impact of OD on quality of life) and reported that 20 (54%) and nine patients (24%) reported substantial improvement in anosmia/

Table 3. Risk of bias among the included studies.

First Author	1	2	3	4	5	6	7	8	9	10	11
Steffens et al. 2022	Y	N	Y	CT	Y	Y	Y	N	Y	Y	CT
Lechien et al. 2022	Y	N	CT	CT	Y	Y	Y	N	Y	Y	Y
El naga et al. 2022	Y	Y	Y	CT	Y	Y	Y	N	Y	Y	CT
Yan et al. 2022	Y	Y	Y	CT	Y	Y	Y	Y	Y	Y	Y

Y: Yes, N: No, and CT: Cannot Tell.

1: Did the study address a clearly focused research question?
2: Was the assignment of participants to interventions randomised?
3: Were all participants who entered the study accounted for at its conclusion?
4: Were the participants, investigators, and people analyzing the outcome blinded?
5: Were the study groups similar at the start of the study?
6: Apart from the experimental intervention, did each study group receive the same level of care (that is, were they treated equally)?
7: Were the effects of intervention reported comprehensively?
8: Was the precision of the estimate of the intervention or treatment effect reported?
9: Do the benefits of the experimental intervention outweigh the harms and costs?
10: Can the results be applied to your local population/in your context?
11: Would the experimental intervention provide greater value to the people in your care than any of the existing interventions?

hyposmia or parosmia, respectively compared to eight patients (22%) who did not report subjective improvement of OD following PRP injections [22]. According to patient experience, a significant improvement in olfaction occurred after a mean of 3.6 ± 1.9 weeks [22].

Furthermore, El Naga et al. was the only study that relied on the subjective measurement of OD alone without an objective measurement tool to measure olfactory function and used the VAS score [23]. They reported that there was a highly significant improvement in the VAS score for parosmia ($p < 0.00001$) in the PRP group and a significant improvement in the VAS score for parosmia in the control group ($p=0.00148$). There was a significant difference between the two groups regarding the degree of improvement, favoring the case group ($p=0.002$) [23]. Similarly, Yan et al. used the VAS score to subjectively assess OD [24]. The VAS scores ranged from zero (no smell) to ten (perfect smell). They reported that when assessing subjective changes in smell function, both the PRP and placebo groups showed significant improvements in VAS scores at one and three months compared to baseline. However, no significant difference was found in the change in subjective olfaction scores using VAS at either one or three months between the PRP and placebo groups.

Adverse events

In all the included studies, only Lechien et al. reported acute and delayed adverse events [22]. Post-injection transient epistaxis was the major acute adverse event reported in 31 patients, 10 patients had transient parosmia because of using xylocaine spray as a local anesthetic, and 4 patients had vasovagal episodes that resulted in coagulation of two PRP syringes. Panic attack was the least common acute adverse event reported by two patients. On the other hand, the only two delayed adverse events that occurred on the post-injection days were postnasal drip sensation (N = 5) and nausea (N = 2).

Discussion

This systematic review aimed to evaluate the effectiveness and safety of PRP injections as treatment for COVID-19 related OD. This review included 233 participants, predominantly female, who experienced anosmia, hyposmia, or parosmia. While PRP injections appear to be a promising therapy for COVID-19 related OD, the available evidence assessing olfactory function using TDI scores and subjective measurement tools at various follow-up dates still lacks the ability to make definitive statistically significant conclusions. Nevertheless, PRP injections following COVID-19 related OD had shown some subjective improvement that vary based on individual factors. These results suggest that PRP injections could be a potential treatment option for post COVID-19 OD.

In this review, most of the included studies reported a noticeable increase in mean TDI scores after PRP injections. The Sniffing Test uses TDI scores to objectively assess olfactory function, where functional anosmia is defined as TDI score ≤ 16.5, hyposmia is defined as TDI score ≤ 30.5, and normosmia is

Table 4. Included articles discussing pre-PRP interventions, PRP injections, and Visual Analogue Scale (VAS).

Study	Intervention pre-platelet-rich plasma injections	Olfactory cleft injection	Local Anesthesia Time (min)	Visual Analog Scale (VAS)
Steffens et al. 2022	NR	1ml of PRP in each olfactory cleft via nasal endoscopy	NR	NR
Lechien et al. 2022	Olfactory training: 58 Alpha lipoic acid: 16 Nasal corticosteroids: 39 Oral corticosteroids: 37 Vitamin B: 26 Vitamin A: 14 Omega 3: 12 Zinc: 37	NR	1.1 ± 0.3	According to the visual analog scale ranging from 0 (ineffective) to 3 (fully effective), the mean score of the local anesthesia effectiveness was 2.1 ± 0.9. The local anesthesia was evaluated as optimal, adequate, moderately adequate, and ineffective in 33 (38%), 33 (38%), 18 (21%), and 3 (3%) patients, respectively.
El naga et al. 2022	Olfactory training Topical corticosteroids Omega 3 Vitamin B12 Zinc supplementation	PRP is injected into the olfactory region approximately every 1 cm2 using a 1ml syringe and 30-G needle	30	PRP group: Pretreatment VAS: 9.13 ± 0.73 Post treatment VAS: 3.33±3.29 Control group: Pretreatment VAS: 9.27±0.78 Post treatment VAS: 7.43±2.84 There was a highly significant improvement in VAS for parosmia ($p < 0.00001$) in the PRP group and a significant improvement in VAS for parosmia in the control group ($p = 0.00148$). There was a significant difference between both groups regarding the degree of improvement favoring the PRP group ($p = 0.002$).
Yan et al. 2022	Olfactory training Topical budesonide nasal irrigations	1ml of PRP, 0.5ml in each cleft	NR	Placebo VAS score at 1-month: 1.2 (CI: 0.05–2.35, $p = 0.040$) Placebo VAS score at 3-months: 1.25 (CI: 0.27–2.23, $p = 0.014$) PRP VAS score at 1-month: 1.5 (CI: 0.51–2.49, $p = 0.004$) PRP VAS score at 3 months: 2.13 (CI:1.33–2.93, $p < 0.0001$) Additional secondary end points were the change in individual TDI component scores from baseline, and subjective olfaction via 0- to 10-point visual analog scale (VAS, 0 = no smell, 10 = perfect smell.

PRP: platelet-rich plasma, VAS: visual analog scale, TDI: threshold-discrimination-identification.

defined as TDI score > 30.5. PRP injections seemed to have a moderate to significant increase in olfactory function, as observed in the pooled studies. This may be because PRP injections stimulate olfactory receptors, which leads to the stimulation of neurotrophic factors. In contrast, several tools have been used to subjectively assess olfactory function. Self-assessment and questionnaires can be used, but their results are variable. All the included studies reported that most of the PRP groups reported improvement, especially in patients with anosmia and hyposmia. Two studies that assessed olfactory function using the VAS score reported that even the control groups improved, but the difference between the PRP and control groups was significant, favoring the PRP group in one study and not significant in the other study [23,24]. This is possibly due to the variability of the included participants and differences in the subjective measurement tools. There is no standardized international subjective tool to assess olfactory function; thus, researchers use different tools. Two studies used the VAS scoring system; therefore, future researchers may opt to use it to provide more studies leading to robust clinical conclusions.

The therapeutic use of PRP for post-COVID-19 related OD looks promising [18,23]. El Naga et al. conducted a study with 60 patients suffering from post-COVID-19 parosmia to evaluate the degree of improvement in parosmia severity, as measured by the VAS, before and after three weekly PRP olfactory cleft injections [23]. The study demonstrated highly significant improvement following the intervention. Another study by Mavrogeni et al. assessed the efficacy of PRP in treating five patients with anosmia, with four patients reporting complete recovery of their sense of smell and the remaining patient experiencing partial improvement [18].

Yan et al. conducted a pilot study to examine the effectiveness of PRP in treating OD persisting for more than 6 months but less than 12 months in 7 patients [19]. The Sniffing Sticks test criteria

of TDI were used to measure changes at the beginning of the study, as well as at one month and three-month follow-ups after a single intranasal PRP injection. All patients reported subjective improvements in their sense of smell at the one-month follow-up, which plateaued by the three-month follow-up. At this point, 60% of the patients with hyposmia achieved normosmia [19]. The previous study did not include participants with COVID-19 related OD thus, we did not include it in this systematic review.

In a randomized controlled trial by the same authors, Yan et al. studied 26 patients with COVID-19-related olfactory loss with the University of Pennsylvania Smell Identification Test (UPSIT) score ≤ 33 [24]. They found greater improvement in olfaction than in the placebo group at one-month and three-month follow-ups, with smell discrimination showing the most significant improvement. However, when evaluating subjective changes in olfactory function, there was no significant difference between the placebo and intervention groups' improvements in the VAS scores [24]. The authors suggested that this finding might be due to an underpowered study sample that did not account for spontaneous recovery or placebo effect.

Steffens et al. conducted a similar study on the effectiveness of PRP for persistent OD related to COVID-19, comparing 30 participants receiving PRP injections to a control group of 26 participants undergoing basic olfactory training for one month [20]. Significant improvements in both mean TDI and self-assessment scores were observed [20]. In contrast to Yan et al.'s randomized controlled trial, Steffens et al.'s study had a shorter follow period [20,24]. These factors, along with the effect of spontaneous resolution, may explain the differences in olfactory improvement between the control groups in the two studies.

Furthermore, Lechien et al. investigated the efficacy of PRP in COVID-19 patients with persistent OD and observed improvements in hyposmia, anosmia, and parosmia at two-month follow-up after PRP injection [22]. The study also reported acute adverse events such as transient epistaxis, vasovagal episodes, and parosmia during local anesthesia as well as delayed adverse events such as postnasal drip sensation and nausea [22]. These adverse events were not reported in the randomized controlled trial by Yan et al. or Steffens et al. [20,24]. Despite these events, the authors concluded that PRP injections in COVID-19 patients are a safe approach associated with satisfactory patient-reported outcomes [22].

In the study done by Ahmet et al. that aimed to investigate the effectiveness of PRP injections in treating anosmia, anosmia-induced mice were subjected to PRP lavage after 3-MI injection [25]. The results showed a significant improvement in the Food-Finding Test (FFT) and histopathological examination after PRP lavage compared with the saline group. The study suggests that PRP, which contains various growth and neurotrophic factors, has regenerative and therapeutic effects on neuroepithelial cells in the olfactory system [25]. The use of PRP in anosmia treatment is promising but requires further research with objective methods and a larger number of subjects for clinical use.

A study by McWilliams et al., which aimed to investigate the long-term patterns of recovery and non-recovery in individuals experiencing smell loss associated with COVID-19, revealed that while most individuals recover their sense of smell within three months of COVID-19-associated smell loss, a significant percentage experienced prolonged or no recovery [26]. Of the participants, 38.7% reported complete recovery, 51.0% reported partial recovery, and 10.3% showed no improvement. Notably, individuals under 40 years of age had higher rates of complete recovery than older individuals [26]. The study suggests that spontaneous long-term recovery can occur regardless of when smell loss occurs during the pandemic, highlighting the need for ongoing support and research to understand the mechanisms underlying variable recovery outcomes in post-COVID-19 smell loss.

The current study summarized all relevant literature assessing the efficacy and safety of PRP in patients with OD. However, all included studies have some limitations that need to be addressed to cautiously interpret our findings. Steffens et al study lacked randomization, had low number of participants, and a short follow-up time of one month [20]. Lechien et al study lacked a control group and had a low number of participants but used validated and objective tools to assess olfactory function such as ODQ and TDI scores [22]. El Naga et al. study lacked an objective assessment tool to measure OD and used the VAS score [23]. Yan et al study had a low number of participants, their analysis did not account for the spontaneous recovery in the control group, and they did not have prior data to identify the optimal concentration of PRP injections for OD patients [24].

Future studies should include RCTs with larger sample sizes, longer follow-up periods lasting more than six months, and sufficient control groups. They should also include validated and objective tools to assess olfactory function and consider other confounding factors, such as spontaneous recovery, placebo effect, other ongoing treatment, or previous treatment. In addition, assessment of unilateral injections of PRP can enable an internal control group comparison and identify its effect on both nostrils. Understanding the mechanism of action of PRP treatment in post-viral OD can help to identify the optimal concentration at which PRP injections can be beneficial to OD patients.

Limitations

This systematic review has some limitations that impact the validity and generalizability of our findings. First, the small number of available studies restricts our ability to draw robust conclusions because the limited data may not provide an accurate representation of the phenomenon under investigation. Second, the heterogeneity of the included studies prevented us from conducting a meta-analysis, which further limited the comprehensiveness of our review. Additionally, some variables in the studies were unavailable or inconsistently reported, hampering our ability to compare and synthesize the findings. Lastly, our review did not incorporate unpublished articles, potentially leading to a publication bias that may skew our understanding of the existing literature. These limitations warrant cautious interpretation of our results and highlight the need for further research to address the gaps in the current body of knowledge.

Conclusion

The results of this systematic review indicate that while PRP injections appear to be a promising therapy for COVID-19 related OD, the available evidence lacks the ability to make definitive conclusions. Nevertheless, PRP injections following COVID-19 related OD have shown some subjective improvements that vary based on individual factors. Although the degree of improvement may be subjective and influenced by individual factors, PRP injections could be considered a potential treatment option for post-COVID-19 olfactory dysfunction. The presence of minor acute and delayed adverse events in some studies does not negate the overall safety of PRP injections. Further studies with larger sample sizes, longer follow-up periods, and more rigorous controls for spontaneous recovery and placebo effects are required to strengthen the evidence for PRP as an effective treatment option for post-COVID-19 OD.

Authorship contribution

BAR is the main author of this publication and contributed to the research idea, submitting the study proposal to PROSPERO, screening the studies, data extraction, creating the tables, and writing the manuscript. OA contributed to screening the studies, data extraction, risk of bias assessment, and writing the manuscript. AA contributed to screening the studies and writing the manuscript. HA contributed to data extraction, risk of bias assessment, and writing the manuscript. YA contributed to writing the manuscript. BAL reviewed and supervised the manuscript. All authors have read and approved the final manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

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