

Original Research Article

COVID-19 immune history and post-PRP injection reactions in knee osteoarthritis

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ABSTRACT

Background: Intra-articular platelet-rich plasma (PRP) is a widely used orthobiologic treatment for knee osteoarthritis (OA). Whether COVID-19 vaccination history or prior SARS-CoV-2 infection influences local post-injection reactions has not been studied.

Methods: This exploratory retrospective cohort study included 57 patients who underwent 166 intra-articular PRP injection sessions for knee OA (March 2024–January 2026). Two per-patient outcomes were defined: pain rate (proportion of sessions with VAS pain > 0) and swelling rate (proportion of sessions with recorded swelling). Patients with a single injection and no follow-up were excluded. Four Spearman correlations between vaccination dose count, prior infection count, and both outcomes were computed with bootstrapped 95% BCa confidence intervals (1,000 samples) and Holm correction applied across the four p values. Subgroup analyses used the Kruskal-Wallis test. The analytical sample comprised 40 complete cases.

Results: All quantitative variables except age were non-normally distributed (Shapiro-Wilk $p < 0.001$). After Holm correction, none of the four primary correlations reached statistical significance. The strongest directional signal was an inverse association between prior infection count and swelling rate ($\rho = -0.339$, Holm-adjusted $p = 0.132$, BCa 95% CI $(-0.560, -0.064)$, $n = 40$). Post-injection pain (VAS > 0) occurred in 20 of 72 assessed sessions (27.8%); swelling in 8 of 75 (10.7%). No febrile reactions were documented.

Conclusions: Prior SARS-CoV-2 infection count showed a directional inverse association with post-PRP swelling rate that did not survive Holm correction for multiple comparisons. These findings are exploratory and hypothesis-generating only, and do not support clinical recommendations at this stage.

Keywords: Platelet-rich plasma, Knee osteoarthritis, COVID-19 vaccination, SARS-CoV-2 infection, Post-injection reactions, Regenerative medicine

INTRODUCTION

Knee osteoarthritis is a major cause of pain and disability worldwide.^{1,2} An analysis based on Global Burden of Disease 2021 data estimated that 374.7 million people had knee osteoarthritis in 2021, with the age-standardised prevalence rate increasing by 8.3% since 1990.³ Systematic reviews demonstrate that PRP may improve pain and function in knee OA.⁴ PRP cellular composition

was not reassessed in the present cohort, although platelet and leukocyte characteristics may influence clinical outcomes and local reactions.^{5,6} Post-injection adverse reactions are predominantly pain and swelling.^{6,7} SARS-CoV-2 infection and COVID-19 vaccination produce substantial immune responses. Rare inflammatory musculoskeletal events, including reactive arthritis and disease flares, have been described following COVID-19 vaccination in case reports, case series, and systematic

reviews.^{8–10} A nationwide cohort study found no overall increase in most autoimmune connective-tissue diseases, although small booster-associated signals were observed for several conditions.¹¹ These findings raise the question of whether vaccination-related immunological changes may affect the joint reaction to intra-articular PRP.

Additionally, repeated mRNA vaccination induces persistent epigenetic changes in monocyte-derived macrophages, including histone acetylation modifications that increase innate immune responsiveness.¹² This is part of the phenomenon known as trained immunity, where long-term reprogramming of innate immune cells increases their reactivity to secondary stimuli.¹³ A study of two consecutive BNT162b2 doses found greater short-term interferon-stimulated gene expression after the second dose than after the first, although these changes diminished within four weeks.¹⁴ Natural infection and vaccination generate partly different cellular immune profiles, including differences in antigenic breadth and T-cell responses.^{15,16} Responses of trained immunity may also differ based on the characteristics of the immunological stimuli.¹⁷

The aim of this study was to examine whether COVID-19 vaccination dose count and prior SARS-CoV-2 infection count were associated with post-injection pain and swelling in patients receiving PRP for knee OA, and to describe the frequency of these documented reactions.

METHODS

Study design

The study was designed as a single-centre retrospective observational cohort study, reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations. Clinical records were reviewed for the period March 2024 to January 2026. The study protocol was approved by the local ethics committee (registration number: 2022/EK/10078) and conducted according to the principles of the Declaration of Helsinki. All patient data were fully anonymised before analysis.

Participants

Patients were included if they received at least one intra-articular PRP injection into a knee joint for late-stage knee OA (Kellgren–Lawrence grades 3–4) and were on the waiting list for knee replacement and had COVID-19 vaccination and/or infection history recorded in their clinical notes. Patients treated in other joints such as ankle, Achilles tendon, or elbow were excluded to maintain a homogeneous treatment target.

PRP preparation and injection protocol

PRP was prepared by centrifuging 27 ml of citrated venous blood (S-Monovette) in a three-step process (3,200 rpm for

15 min; 1,500 rpm for 15 min; 3,200 rpm for 10 min) at room temperature.¹⁸ The lower plasma layer (3 ml) was isolated, shaken to resuspend platelets, and injected within 30 minutes, with all procedures conducted in a class II laminar flow cabinet.¹⁸ Platelet/leucocyte levels were not re-analysed, relying on previous characterisation.¹⁸ The PRP products were not activated before injection, as platelets are activated upon contact with collagen tissue. The injected volume was recorded per session and ranged from 2.6 to 3.4 ml (mean 3.02 ml, SD 0.13 ml). All intra-articular injections were performed by a single orthopaedic surgeon under aseptic conditions to ensure consistency. No corticosteroids were co-administered.

Data collection

For each injection session, the following variables were extracted from the clinical records: post-injection pain measured using a 0–10 visual analogue scale (VAS), post-injection swelling (present/absent), and fever when documented. Patient-level variables included COVID-19 vaccination dose count and the number of prior documented SARS-CoV-2 infections. Repeated injections were administered at seven-day intervals. Symptoms documented at visit *n*+1 were attributed to the injection administered at visit *n*, one week earlier. The outcome following the final injection in each treatment course was treated as missing when no subsequent assessment was available. Patients who received only one injection without a later follow-up contributed to the baseline cohort but not to the outcome analyses.

Two primary per-patient outcomes were defined: pain rate, the number of injection sessions followed by a pain-positive assessment (VAS > 0) divided by the number of injection sessions with available pain follow-up; and swelling rate, the number of injection sessions followed by recorded swelling divided by the number of injection sessions with available swelling follow-up. Missing follow-up was not treated as absence of a reaction. The proportion of patients who experienced at least one documented episode of post-injection pain or swelling was reported descriptively in Table 2.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics V. 32. Normality was assessed using the Shapiro–Wilk test. The analytical sample for correlation analyses comprised patients with complete data for vaccination dose count, prior infection count, pain rate, and swelling rate, totaling 40 patients. Four Spearman rank correlation coefficients (ρ) were computed between vaccination dose count, prior infection count, and the two primary outcomes, with bootstrapped unadjusted 95% bias-corrected and accelerated (BCa) confidence intervals (1,000 samples). To control for multiple comparisons, Holm correction was applied across the four primary correlations; both raw and Holm-adjusted *p*-values are reported. For subgroup analyses, pain rate was compared

across vaccination dose groups (0, 1–2, 3–4 doses) and swelling rate was compared across COVID-19 infection groups (0, 1, ≥ 2) using the Kruskal-Wallis test with Bonferroni-corrected pairwise comparisons. The Kruskal-Wallis analyses used all available cases for each specific comparison (pain rate $\times$ vaccination group: $n=40$; swelling rate $\times$ infection group: $n=41$). Outcome-specific sample sizes are reported for each analysis. Statistical significance was set at $\alpha=0.05$.

RESULTS

Patient and session characteristics

Of 57 enrolled patients, 40 had complete data for vaccination dose count, prior infection count, pain rate, and swelling rate and formed the analytical sample. Eight patients received only a single injection and had no follow-up visit; these were excluded from outcome analyses. Patient and session characteristics are shown in Table 1. The mean age was 60.5 years (SD 12.9, range 31–88). The sex distribution was 30 female (52.6%) and 27 male (47.4%). The mean number of injection sessions per patient was 2.91 (SD 1.60, range 1–9). Patients had a mean of 1.26 (SD 1.22) injection sessions with available pain follow-up and 1.32 (SD 1.30) with available swelling follow-up. Mean PRP volume per session was 3.02 ml (SD 0.13 ml, range 2.6–3.4 ml).

Vaccination data were available for 51 patients; six patients had no vaccination status documented in their clinical records and were excluded from vaccination analyses. The mean vaccination dose count was 2.16 (SD 1.19). Nine patients (17.6%) were unvaccinated, 13 (25.5%) had received 1–2 doses, and 29 (56.9%) had received 3–4 doses. COVID-19 infection data were available for 53 patients. The mean infection count was 1.11 (SD 0.99). Seventeen patients (32.1%) had no prior infection, 18 (34.0%) had one, and 18 (34.0%) had two or more.

Adverse reaction profile

Post-injection outcomes were attributable to 72 injection sessions for pain and 75 injection sessions for swelling, after applying the one-week alignment rule and excluding the final injection session in each patient's course. Fifteen patients had no eligible follow-up (8 single-session patients; 7 with no recorded outcome at any subsequent visit) and were excluded from outcome analyses; 42 patients contributed outcome data. Post-injection pain (VAS > 0) was recorded in 20 of 72 pain-assessed injection sessions (27.8%). Swelling was recorded in 8 of 75 swelling-assessed injection sessions (10.7%). No febrile reactions were documented in the available follow-up records. At the patient level, 18 of 42 patients with outcome data (42.9%) experienced at least one adverse reaction. The mean per-patient pain rate was 0.332 (SD 0.448, median 0.000) and the mean swelling rate was 0.131 (SD 0.316, median 0.000).

Spearman rank correlations

Four Spearman rank correlations were computed between vaccination dose count, prior COVID-19 infection count, and the two primary outcomes ($n=40$ complete cases for all pairs). After applying Holm correction across the four tests, none reached the corrected significance threshold. Vaccination dose count was not significantly correlated with pain rate ($\rho=0.161$, raw $p=0.320$, Holm-adjusted $p=0.640$, BCa 95% CI $(-0.115, +0.443)$) or swelling rate ($\rho=0.152$, raw $p=0.348$, Holm-adjusted $p=0.640$, BCa 95% CI $(-0.142, +0.398)$). Prior COVID-19 infection count was not significantly correlated with pain rate ($\rho=-0.221$, raw $p=0.170$, Holm-adjusted $p=0.510$, BCa 95% CI $(-0.483, +0.067)$). The strongest directional signal was an inverse association between prior infection count and swelling rate ($\rho=-0.339$, raw $p=0.033$, Holm-adjusted $p=0.132$, BCa 95% CI $(-0.560, -0.064)$), which did not remain statistically significant after Holm correction. Full results are shown in Table 3.

Subgroup analysis: Kruskal-Wallis test

Vaccination dose groups

The Kruskal-Wallis test comparing pain rate across vaccination dose groups did not reach statistical significance ($H=0.955$, $df=2$, $p=0.620$, $n=40$). All Bonferroni-corrected pairwise comparisons were non-significant (0 vs 1–2 doses: adj. $p=1.000$; 0 vs 3–4 doses: adj. $p=1.000$; 1–2 vs 3–4 doses: adj. $p=1.000$). Mean pain rates were 0.250 ($n=9$, 0 doses), 0.270 ($n=10$, 1–2 doses), and 0.429 ($n=21$, 3–4 doses). The directional pattern should not be interpreted as a dose-response effect in the absence of statistical significance.

COVID-19 infection groups

The Kruskal-Wallis test comparing swelling rate across infection groups did not reach statistical significance ($H=4.802$, $df=2$, $p=0.091$, $n=41$). All Bonferroni-corrected pairwise comparisons were non-significant (≥ 2 vs 1 infection: adj. $p=0.466$; ≥ 2 vs 0 infections: adj. $p=0.094$; 1 vs 0 infections: adj. $p=1.000$). Mean swelling rates were 0.269 ($n=13$, 0 infections), 0.143 ($n=14$, 1 infection), and 0.000 ($n=14$, ≥ 2 infections). The directional pattern is noted as a hypothesis-generating observation consistent with the Spearman correlation, but does not constitute a confirmed dose-response relationship. The within-cohort subgroup analyses used patients with no documented vaccination ($n=9$) and those with no prior infection ($n=17$) as lowest-exposure comparators rather than COVID-naïve controls, since exposure through the alternate route was present in the majority of each subgroup. Only three patients had no documented vaccination and no prior infection, precluding formal analysis of a fully COVID-naïve reference group. Future studies should prospectively recruit patients without any prior COVID-19 immune exposure as a dedicated comparator arm.

Table 1: Baseline patient and session characteristics.

Variables	Values	Details
Patients (knee OA)	57	—
Total injection sessions	166	Knee joints only
Injection sessions per patient, mean (SD)	2.91 (1.60)	Median 3, range 1–9
Sex, n (%)		
Female	30 (52.6%)	—
Male	27 (47.4%)	—
Age, mean (SD), years	60.5 (12.9)	Range 31–88
COVID-19 vaccination doses, mean (SD)	2.16 (1.19)	Range 0–4
0 doses (unvaccinated)	9 (17.6%)	
1–2 doses	13 (25.5%)	
3–4 doses	29 (56.9%)	Largest subgroup
Data missing	6 (10.5%)	Excluded from analysis
Prior COVID-19 infections, mean (SD)	1.11 (0.99)	Range 0–4
0 prior infections	17 (32.1%)	
1 prior infection	18 (34.0%)	
≥2 prior infections	18 (34.0%)	
Data missing	4 (7.0%)	Excluded from analysis
PRP volume, mean (SD), ml	3.02 (0.13)	Range 2.6–3.4 ml

Table 2: Post-injection adverse reaction profile.

Variables	N/%	Notes
Sessions evaluated for adverse reaction	72 (pain)/75 (swelling) of 166	Outcome-specific denominators
Post-injection pain >0/10	20 (27.8%)	of 72 pain-assessed sessions
Pain rate per patient, mean (SD)	0.332 (0.448)	Median 0.000
Swelling present	8 (10.7%)	of 75 swelling-assessed sessions
Fever	None documented	Not systematically assessed
Patients with any documented post-injection pain or swelling	18 / 42 (42.9%)	Patient-level
Swelling rate per patient, mean (SD)	0.131 (0.316)	Median 0.000

Table 3: Spearman rank correlations: primary outcomes (n=40 for all pairs).

Correlation pair	N	Spearman ρ	Raw p	Holm adj. p	BCa 95% CI
Vaccination doses→pain rate	40	0.161	0.320	0.640	−0.115, +0.443
Vaccination doses→swelling rate	40	0.152	0.348	0.640	−0.142, +0.398
COVID-19 infections→pain rate	40	−0.221	0.170	0.510	−0.483, +0.067
COVID-19 infections→swelling rate	40	−0.339	0.033	0.132	−0.560, −0.064

DISCUSSION

This exploratory retrospective cohort study found no statistically significant associations between COVID-19 immune history and post-injection reactions following intra-articular PRP for knee OA after Holm correction for multiple comparisons. The strongest directional signal was an inverse association between prior COVID-19 infection count and post-injection swelling rate ($\rho=-0.339$, Holm-adjusted $p=0.132$), which did not survive correction. To

our knowledge, this is the first cohort study to examine whether COVID-19 vaccination and prior infection history are associated with local reactions following intra-articular PRP for knee OA. A directional positive association was observed between vaccination-dose count and pain rate, although this did not remain statistically significant after Holm correction. Previously reported innate immune changes following mRNA vaccination provide a theoretical basis for further investigation; however, the present study did not assess immune mechanisms, and no

mechanistic inference can be drawn from the observed association.^{12–14} Natural infection and vaccination generate partly different cellular immune responses, providing a theoretical basis for investigating whether immune history influences local post-injection reactions.^{15,16} Trained-immunity responses and T-cell immunity profiles may also differ according to the nature of the immune stimulus.^{17,19} However, the present study did not include immune profiling, and the observed inverse association does not establish a causal or protective relationship. Whether immune history influences local vascular or inflammatory responses following intra-articular injection requires prospective investigation.

COVID-19 vaccination-related musculoskeletal reactions are documented in the literature. Wojturska et al reported reactive arthritis after both mRNA and adenoviral vector vaccines, which responded to NSAIDs and glucocorticoids.⁸ Chen et al identified new-onset inflammatory arthritis after vaccination, more commonly with BNT162b2 and ChAdOx1, and more frequent in older patients.⁹ Hoxha et al found post-vaccination joint flares in approximately 5–9% of patients with pre-existing inflammatory arthritis, though overall risk was not significantly elevated compared with controls.¹⁰ The present study did not establish a statistically significant association between vaccination history and post-PRP reactions in patients with OA.

The adverse event profile observed in this cohort, predominantly pain and swelling, is consistent with published data on intra-articular PRP safety.^{6,7} PRP volume was not formally analysed as a predictor of adverse reactions in this study.

This study has several important limitations. First, the retrospective design does not allow causal conclusions; confounding by unmeasured variables, including the exact Kellgren–Lawrence grade, baseline synovial inflammatory state, concurrent medications, and the timing of vaccination or infection relative to each injection, cannot be excluded. Second, outcomes were assessed at the subsequent weekly visit; therefore, final injections without later follow-up and single-injection patients contributed no outcome data. This reduced the number of assessable sessions and may have introduced selection bias. Third, eight patients received only a single injection and contributed no outcome data. Fourth, with 40 complete cases, statistical power was limited and all four primary Spearman correlations should be regarded as exploratory. Fifth, adverse reactions were documented in clinical notes rather than standardised patient-reported outcome instruments, introducing measurement variability. Sixth, six patients had no vaccination status documented in their clinical records, reducing the effective sample for vaccination analyses. Seventh, vaccine type and the timing of each vaccination or infection event relative to individual PRP sessions could not be systematically analysed. Eighth, no formally designated control group was included. The small number of patients

with no documented COVID-19 immune exposure of any kind—neither prior vaccination nor prior infection—(n=3) precluded the formation of a COVID-naïve reference group within this cohort.

In this exploratory retrospective cohort study of 57 patients receiving intra-articular PRP for knee OA, no association between COVID-19 immune history and post-injection reactions reached statistical significance after Holm correction across four primary Spearman correlations. The strongest directional signal was an inverse association between prior COVID-19 infection count and post-injection swelling rate ($\rho=-0.339$, Holm-adjusted $p=0.132$, BCa 95% CI $(-0.560, -0.064)$, $n=40$). A weak positive directional association was observed between vaccination dose count and pain rate ($\rho=0.161$, Holm-adjusted $p=0.640$), but this should be interpreted with caution given the absence of corrected significance.

CONCLUSION

Post-injection pain occurred in 20 of 72 pain-assessed injection sessions (27.8%) and swelling in 8 of 75 swelling-assessed injection sessions (10.7%); no febrile reactions were documented in the available follow-up records. These findings are exploratory and hypothesis-generating. Prospective studies with standardised outcome measures, immune profiling, and larger sample sizes are needed to determine whether COVID-19 immune history has a clinically meaningful influence on post-injection reactions following intra-articular PRP.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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