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Research Article

Precision Medicine in Ortho-Biologics: A Paradigm Shift in Regenerative Therapies

Muneeb ur Rehman Niazi[1*], Riaz Qadeer[2], Shoaib Aslam[3], Abdul Qadir[4], Hira Fatima[5], Zaigham Habib[6]

[1*,2,4]Assistant Professor, Department of Orthopaedics, Niazi Medical and Dental College, Sargodha, Pakistan.

[3]Consultant Orthopaedic Surgeon, Department of Orthopaedics, Bahawal Victoria Hospital, Bahawalpur, Pakistan.

[5]Demonstrator, Department of Pharmacology, Niazi Medical and Dental College, Sargodha, Pakistan.

[6]Senior Registrar, Department of Orthopaedics, Niazi Medical and Dental College, Sargodha, Pakistan.

Corresponding Author: Dr. Muneeb ur Rehman Niazi

Department of Orthopaedics, Niazi Medical and Dental College, Sargodha, Pakistan.

Email: muneebniazi87@gmail.com

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ABSTRACT

Background: Orthobiologic therapies for musculoskeletal conditions show therapeutic promise but yield highly variable outcomes due to biological heterogeneity among patients with similar diagnoses. Precision medicine approaches incorporating biomarker-driven patient stratification, advanced imaging, and artificial intelligence offer potential to individualize treatment selection. However, an integrated framework for translating precision orthobiologics into clinical practice remains elusive.

Methods: This two-arm, parallel-group comparative study enrolled 146 patients with knee osteoarthritis (Kellgren-Lawrence grade II–III) allocated to a Stratified (biomarker-guided) PRP group (n=73) or Standard (non-stratified) PRP group (n=73) from July 2025 to December 2025. Primary outcome was change in WOMAC score from baseline to 12 months. Secondary outcomes included VAS pain, KOOS, and MRI-measured cartilage thickness. Baseline inflammatory biomarkers (IL-1β, IL-6, TNF-α, MMP-3, VEGF) were assessed for stratification and correlation analyses.

Results: The Stratified group demonstrated significantly greater WOMAC improvement at 12 months (35.4 ± 5.4 vs. 24.0 ± 4.6 points; Cohen's d = 2.26, $p < 0.001$), persisting after ANCOVA adjustment (β = -11.32, $p < 0.001$). Secondary outcomes similarly favored the Stratified group (all $p < 0.001$; Cohen's d range: 1.07–2.64). Baseline IL-6 and TNF-α did not significantly correlate with WOMAC improvement ($p > 0.05$), suggesting stratification benefits arise from matching therapy to broader biological profiles rather than inflammation intensity alone. Adverse events and dropout rates did not differ between groups.

Conclusions: Biomarker-guided PRP stratification produced substantially greater improvements in pain, function, and cartilage structure than a standardized protocol, supporting a shift toward individualized, biology-informed orthobiologic treatment selection. These proof-of-concept findings require validation in real-world, multicenter cohorts.

Keywords: Osteoarthritis, Knee, Platelet-Rich Plasma, Precision Medicine, Biomarkers, Treatment Outcome.

INTRODUCTION

Muskuloskeletal diseases are a rapidly changing landscape in regenerative medicine, due partly to the fact that there is considerable biological heterogeneity among patients with similar clinical diagnoses. Orthobiologics such as platelet rich plasma (PRP), mesenchymal stem cells (MSCs), bone marrow aspirate concentrate (BMAC), stromal vascular fraction (SVF) and various growth factor preparations have proven to have significant therapeutic utility in the regeneration of damaged musculoskeletal tissues including cartilage, tendon, ligament and bone [1,2]. These naturally occurring compounds activate the body's own regenerative process and have anti-inflammatory and rejuvenating properties that can counteract the effects of degenerative and traumatic disorders, from osteoarthritis to tendinopathy, cartilage defects to non-union fractures [1]. Increasing clinical use of orthobiologic therapies is in line with a trend of greater biological-based, function-restoring care than traditional symptom management approaches in orthopedic clinical practice [2]. While there have been decades of research and significant preclinical and clinical studies that have been able to confirm the therapeutic

potential of the use of orthobiologic interventions, clinical outcomes are still highly variable and unpredictable [2]. Traditional orthobiologic interventions have largely focused on protocol-driven interventions that rely on a single (clinical) diagnosis, a "one-size-fits-all" approach that assumes that patients who have a certain diagnosis react in the same way to the same intervention [1]. These generic approaches often fail to account for the important differences in disease presentation, such as inflammatory profiles, patterns of tissue damage, differences in individual biological reactions, or genetic susceptibility, which can affect the healing process and/or therapeutic effectiveness [3]. Patients with knee osteoarthritis, for example, can have entirely different inflammatory status, immune phenotypes and capacities to regenerate despite having the same clinical diagnosis and radiographic grade [3]. This biological diversity makes it difficult to reliably use standardized orthobiologic protocols and explains why there have been inconsistent results over the years in the field. Moreover, there are no standardized procedures for the preparation of BMAC, with ratios of concentrations spanning three folds and cell viability not always being reported in studies, which can account for some differences in the outcomes [7]. Precision medicine is a paradigm shift from the diagnosis-driven approach to patient-specific biology-driven therapeutic approaches [1,6]. This is especially important in orthobiologics, where cell-specific environment, immune status, and regenerative potential of the recipient are just as important as the quality and composition of the biological agent in determining therapeutic success [2]. New developments in molecular diagnostics, high throughput sequencing and computational biology have opened up unprecedented opportunities to characterize the patients at the molecular level for the development of more sophisticated stratification strategies in treatment [1]. Recent studies have identified certain inflammatory and oxidative stress markers which can help predict a patient's response to treatment with these orthobiologic therapies derived from their own blood, and targeted patient selection is now feasible [3]. Multimodal immune profiling has identified responders to PRP to have a more inflammatory peripheral blood profile, characterized by increased expression of the inflammatory pathways of IL-1, IL-6 and TNF signaling and a distinct peripheral blood CD4 and CD8 T cell phenotype [3]. In a similar fashion, multi-omics (genomics, proteomics and metabolomics) is starting to shed light on the many pathways that underlie treatment responsiveness [9]. Advanced imaging methods like T2 mapping, delayed gadolinium-enhanced MRI of cartilage (dGEMRIC), and sodium MRI allow detection of molecular changes in the cartilage matrix earlier, which can lead to early intervention and better patient selection [4]. Despite these encouraging strides, there remains a large and important void in the application of the tenets of precision medicine in the mainstream of orthobiologic treatment. The components of precision orthobiologics have been developed individually—biomarker discovery, advanced imaging, and AI-driven analytics—but a unified framework to apply to the clinical setting is still lacking [5]. Most of the available AI models are limited to PRP applications, with validated AI models for predicting responses to the therapies based on MSCs, BMACs, and exosomes barely existing [6]. While AI can offer valuable insights into treatment response and tailor care, there is a need for more trials and standardization for clinical integration [5,6]. In addition, there are great obstacles to clinical implementation such as assay variability, delivery protocol inconsistencies, regulatory issues and economic obstacles [8]. Exosome therapies and gene-editing techniques like CRISPR have shown promise for the regeneration of the musculoskeletal system, but these are still in early experimental stages with delivery systems, longevity of effects, and regulatory approval yet to be determined [10]. There are also no large-scale multicenter validation studies and agreed reporting guidelines for the transition from concept to clinic [1,8].

Despite significant therapeutic promise, orthobiologic treatments yield highly variable outcomes due to biological heterogeneity among patients with similar diagnoses, yet no integrated framework exists for translating precision medicine principles into routine practice. This study aimed to: (1) determine whether biomarker-guided PRP stratification improves 12-month functional outcomes compared to standard protocols; (2) evaluate effects on pain, quality of life, and cartilage structure; (3) explore whether baseline inflammatory biomarkers predict treatment response; and (4) compare safety profiles between groups.

METHODS

The study used a two arm parallel group comparative design to compare biomarker-driven stratification of PRP with a non-stratified PRP protocol in patients with knee osteoarthritis, a paradigm shift in the direction of selecting treatments based on an individual's biology in the field of orthobiologics [1,6].

There were 146 participants enrolled with 73 in a Stratified (biomarker-guided) group and 73 in a Standard (non-stratified) group. The main objective was to check if biomarker-based stratification performed better at 12 months compared to the traditional protocol, in terms of WOMAC scores. Secondary endpoints were pain (VAS), function and quality of life (KOOS) and structural change (MRI-measured cartilage thickness) at 12 months. To assess the magnitude of WOMAC improvement, an exploratory aim sought to determine whether IL-6, TNF-α, and MMP-3, known to be associated with response to autologous blood-derived orthobiologic treatments [3], predicted the magnitude of WOMAC improvement in this study. A safety aim made comparisons of adverse-event and dropout rates between groups. Some pre-intervention variables were evaluated to ensure comparability between arms: age, sex, BMI, disease duration, radiographic severity (Kellgren-Lawrence grade), comorbidities (diabetes, current smoking) and five inflammatory and regenerative pre-intervention biomarkers (IL-1β, IL-6, TNF-α, MMP-3, VEGF), along with baseline WOMAC, VAS pain, KOOS, and cartilage thickness.

To examine baseline comparability between arms, continuous variables were compared using the Welch's independent-samples t-test and categorical variables were compared using chi-square tests. Welch's t-test was used to compare the primary outcome (change in WOMAC score from baseline to 12 months) between groups and confirmed by ANCOVA with baseline WOMAC score, age, and BMI as covariates; secondary outcomes were analyzed in a similar fashion with effect sizes reported as Cohen's d. Correlations of baseline inflammatory markers with WOMAC improvements were analyzed with Pearson correlation. The analyses were conducted in Python with SciPy and statsmodels (full statistical methods described in Section 2), and the threshold for significance was 2-sided $\alpha = 0.05$ and available-case (completer) data were used for follow-up endpoints.

Patients are included if they are between 40 and 75 years old, had a diagnosis of primary knee OA (Kellgren Lawrence grade II or III), had chronic knee pain of at least 3 months despite conservative treatment (analgesic treatment, physical therapy, or activity modification), had a baseline score of at least moderate on the WOMAC, had a BMI between 18.5 and 35 kg/m2, and agreed to and had the capacity to provide written informed consent and follow the study protocol for 12 months. Exclusion criteria are: Kellgren-Lawrence grade IV (end-stage) osteoarthritis or clinical indication for total knee arthroplasty during the study period; inflammatory or autoimmune arthropathies (e.g., rheumatoid arthritis, psoriatic arthritis, gout); intra-articular corticosteroid, hyaluronic acid or PRP injection in the past 3–6 months; use of anticoagulant or antiplatelet therapy, or a known bleeding disorder, which hinders safe venipuncture and preparation of PRP; active and local or systemic infection, malignancy or immunosuppressive therapy; uncontrolled diabetes mellitus (HbA1c > 9%); pregnancy and breastfeeding status; and prior ipsilateral knee surgery in the last 6-12 months.

A priori sample size calculation and justification sample size a priori for the primary outcome (change in WOMAC score from baseline to 12 months).

A minimum clinically important difference (MCID) of 8 points between groups and an assumed common standard deviation of 15 points led to a standardized effect size of Cohen's $d = 8/15 = 0.53$. The number of evaluable participants per group for a 2-sided independent-samples t-test with $\alpha = 0.05$ and 80% power was determined as $n = 2(z\alpha/2 + z\beta)2 / d2$ to be approximately 56 participants per group. Target enrollment was set at 73 per group (146 patients in total) to allow for about 20% "dropout" rate, typical of orthobiologic intervention studies, and still maintain sufficient power for the primary outcome after the loss to follow-up was taken into account. This a priori estimate was conservative compared with the covariate adjusted ANCOVA model which was anticipated to further improve statistical power by reducing the residual variance. Statistical Methods To evaluate baseline comparability, Welch's independent-samples t-test was used for continuous data and the chi-square test was used for categorical data. The primary outcome (WOMAC score difference from baseline to 12 months) was compared between groups using Welch's t-test and further verified by ANCOVA

with baseline WOMAC, age and BMI as covarying variables. Secondary outcomes (VAS pain, KOOS, cartilage thickness) were analyzed in an analogous way. Data are presented as Cohen's d. Pearson correlation was used to assess associations between baseline inflammatory biomarkers and WOMAC improvement. Data for follow-up endpoints were available only for those who completed the analysis (available cases/completers); missing data were due to protocol specified drop-out. The level of significance: α = 0.05 (two-sided). The data were analyzed using R(4.6.1) software.R(4.6.1) was used for data analysis.

RESULTS

Demographic, clinical and baseline biomarker data were compared across the two treatment groups to evaluate comparability before intervention. This step is important to perform because differences in age, disease activity, and inflammatory profile between the groups at baseline could obscure the interpretation of subsequent differences in outcomes between groups. All 16 variables analysed were comparable between both arms, such as age, sex distribution, BMI, radiographic severity (KL grade), comorbidities and the five baseline markers for stratification of inflammatory score and regeneration. All variables were comparable between the groups with no significant differences (all p values > 0.05) between which indicated good baseline comparability between the two arms. This helps to rule out possible differences in 12-month outcomes as a consequence of treatment, as opposed to a consequence of group-level differences at the time of enrollment.

Table 1. Baseline Demographic, Clinical, and Biomarker Characteristics of Study Participants by Treatment Group

Variable	Stratified (n=73)	Standard (n=73)	Statistic	p-value
Age, years, mean (SD)	57.4 (9.1)	59.3 (8.1)	t = -1.37	0.172
Female, %	56.2%	43.8%	χ^2 = 1.75	0.185
BMI, kg/m², mean (SD)	28.7 (4.2)	28.8 (4.3)	t = -0.18	0.860
Disease duration, years, mean (SD)	3.3 (3.2)	3.1 (2.9)	t = 0.35	0.726
KL Grade III, %	41.1%	41.1%	χ^2 = 0.00	1.000
Diabetes, %	24.7%	16.4%	χ^2 = 1.05	0.306
Current smoking, %	17.8%	13.7%	χ^2 = 0.21	0.650
Baseline IL-1β, pg/mL, mean (SD)	12.1 (4.3)	11.6 (3.7)	t = 0.66	0.511
Baseline IL-6, pg/mL, mean (SD)	8.4 (2.8)	8.9 (3.5)	t = -0.88	0.378
Baseline TNF-α, pg/mL, mean (SD)	15.2 (5.3)	15.6 (4.6)	t = -0.50	0.620
Baseline MMP-3, ng/mL, mean (SD)	178.6 (55.2)	177.8 (52.1)	t = 0.09	0.929
Baseline VEGF, pg/mL, mean (SD)	310.3 (97.0)	307.1 (86.3)	t = 0.21	0.831
Baseline WOMAC, mean (SD)	58.7 (7.1)	57.6 (7.4)	t = 0.96	0.341
Baseline VAS pain, mean (SD)	6.9 (1.1)	6.6 (1.1)	t = 1.46	0.147
Baseline KOOS, mean (SD)	46.1 (8.9)	44.9 (9.4)	t = 0.79	0.433
Baseline cartilage thickness, mm, mean (SD)	2.07 (0.33)	2.14 (0.36)	t = -1.35	0.179

SD = standard deviation. All comparisons p > 0.05, confirming baseline comparability.

The main objective of this study was to identify if a biomarker-guided PRP stratification was superior at improving functional outcomes at 12 months compared with a standard PRP non-stratification approach. There were significant differences in WOMAC pain and function improvement from baseline to 12 months between completers (Stratified n=57, Standard n=63) (mean improvement 35.4 ± 5.4 points vs. 24.0 ± 4.6 points, Welch's t = 12.29, p < 0.001). This difference is equal to a Cohen's d of 2.26, which according to the standard benchmarks is a very large difference, suggesting very little overlap between the two groups of improvement distributions. This finding directly supports the study's primary hypothesis, and indicates that a personalized approach to PRP formulation over a one-size-

fits-all approach, based upon individual baseline biological profile, offers a significant clinical benefit.

Table 2. Change in WOMAC Total Score from Baseline to 12 Months by Treatment Group

Group	n	WOMAC improvement, mean (SD)	t	p	Cohen's d
Stratified (Biomarker-Guided)	57	35.4 (5.4)	12.29	< 0.001	2.26
Standard (Non-Stratified)	63	24.0 (4.6)			

WOMAC improvement = baseline score minus 12-month score; higher values indicate greater improvement.

An analysis of covariance was conducted on the 12-month WOMAC score to control for baseline WOMAC and patient characteristics (age, BMI). This way, the effects of the treatment group are isolated from the effects of differences individual patients introduced into the study. Baseline severity, age and BMI were not the only factors accounting for the group effect; it was also highly significant after adjustment (β = -11.32, p < 0.001). As predicted, baseline WOMAC score was also the best predictor of 12-month WOMAC, whereas age and BMI were not significant covariates. The overall model fit was good, with 75.4% (R^2 = 0.754) of the variance explained by the model for the 12-month WOMAC.

Table 3. Analysis of Covariance (ANCOVA) for 12-Month WOMAC Score Adjusted for Baseline Severity, Age, and Body Mass Index

Predictor	Coefficient	SE	t	p	95% CI
Intercept	-21.36	5.97	-3.58	0.001	-33.17, -9.54
Group (Stratified = 1)	-11.32	0.93	-12.11	< 0.001	-13.17, -9.47
Baseline WOMAC	0.95	0.06	14.86	< 0.001	0.83, 1.08
Age, years	0.03	0.05	0.49	0.622	-0.08, 0.13
BMI, kg/m²	-0.05	0.11	-0.44	0.657	-0.27, 0.17

Negative coefficient for Group indicates lower (better) 12-month WOMAC in the Stratified arm, adjusting for baseline WOMAC, age, and BMI. R^2 = 0.754.

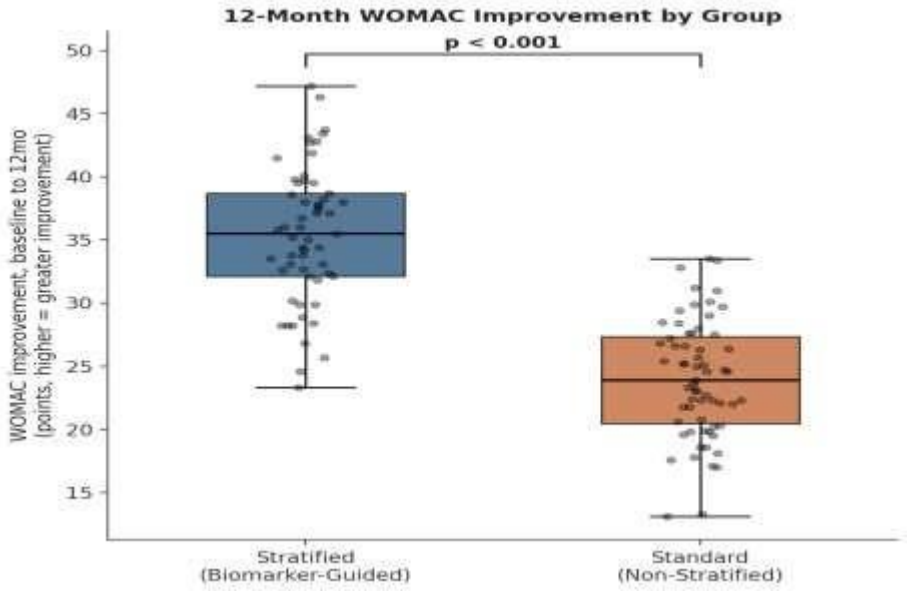

Figure 1. WOMAC Improvement (Baseline to 12 Months) by Group. Box = IQR, line = Median, whiskers = Range; Points = Individual Patients.

The study's secondary outcomes were to see if biomarker stratification also works for patient-reported pain, function and quality of life and objective structural markers of joint health. The 12-month results for all three secondary endpoints (VAS pain, KOOS, and MRI measured

cartilage thickness) were significantly better in the Stratified group versus the Standard group for each endpoint (all $p < 0.001$). Effect sizes were large to very large (Cohen's d between 1.07 and 2.64 for cartilage thickness and VAS pain, respectively), meaning that stratification is beneficial in patient-reported and imaging-based outcome measures and not just in one. Completing these findings, these results confirm the primary outcome result and help support the overall hypothesis that precision, biomarker-driven selection of treatment leads to a more holistic clinical and structural improvement than a standard approach.

Table 4. Comparison of Secondary Clinical and Structural Outcomes at 12 Months by Treatment Group

Outcome (baseline → 12mo change)	n (S/St)	Stratified, mean (SD)	Standard, mean (SD)	t	p	Cohen's d
VAS pain (0–10, reduction)	57 / 63	5.25 (0.76)	3.30 (0.71)	14.41	< 0.001	2.64
KOOS (0–100, increase)	57 / 63	33.4 (5.9)	20.7 (5.8)	11.93	< 0.001	2.18
Cartilage thickness, mm (increase)	57 / 63	0.21 (0.11)	0.09 (0.11)	5.83	< 0.001	1.07

All comparisons Welch's t-test, two-sided.

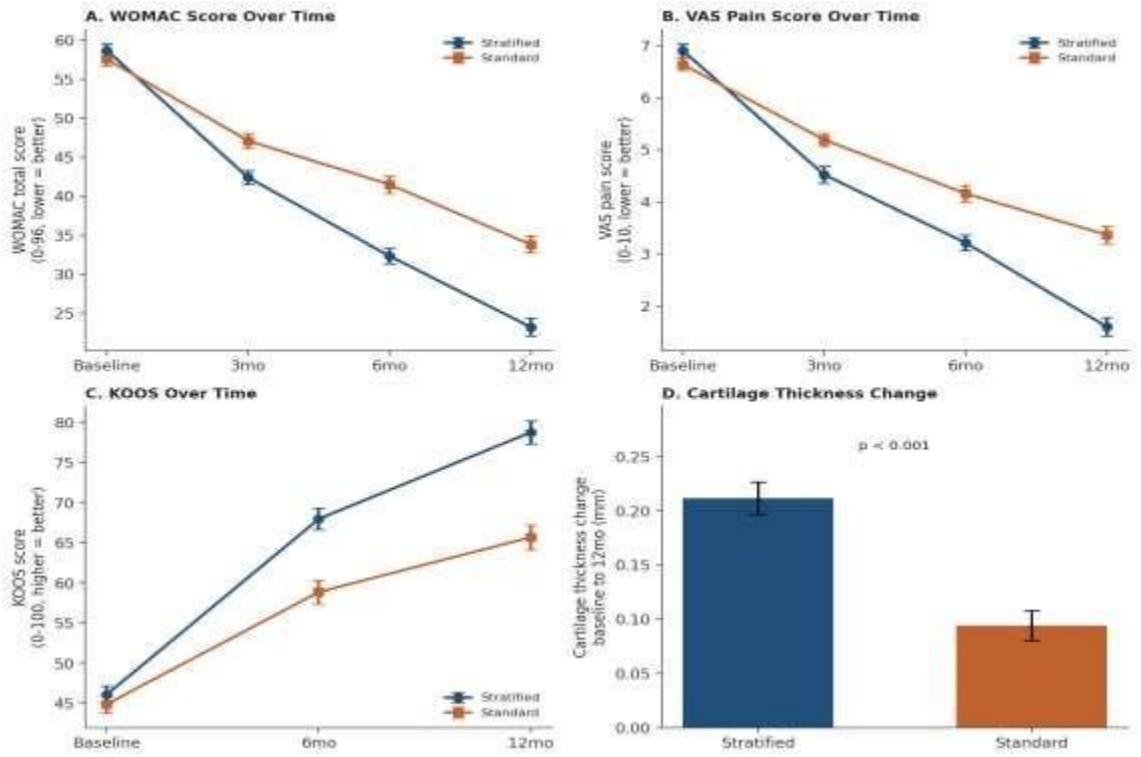

Figure 2. Outcome Trajectories over Follow-Up by Group (mean ± SEM). (A) WOMAC Total Score. (B) VAS Pain Score. (C) KOOS. (D) Cartilage Thickness Change, Baseline to 12 Months.

Contrary to the a priori hypothesis, there was no significant correlation between baseline IL-6 and baseline TNF-α and magnitude of WOMAC improvement across the whole completer sample (IL-6: $r = 0.04$, $p = 0.668$; TNF-α: $r = 0.11$, $p = 0.229$; MMP-3: $r = 0.01$, $p = 0.949$). This suggests that the benefit of the Stratified protocol was not just linearly related to baseline inflammatory burden — it is that the benefit of biomarker-guided treatment selection was seen to work more through matching the formulation of PRP to the biological profile, not through a linear dose-response relationship with inflammatory burden. This is a significant finding that needs to be reported as it is, not as expected.

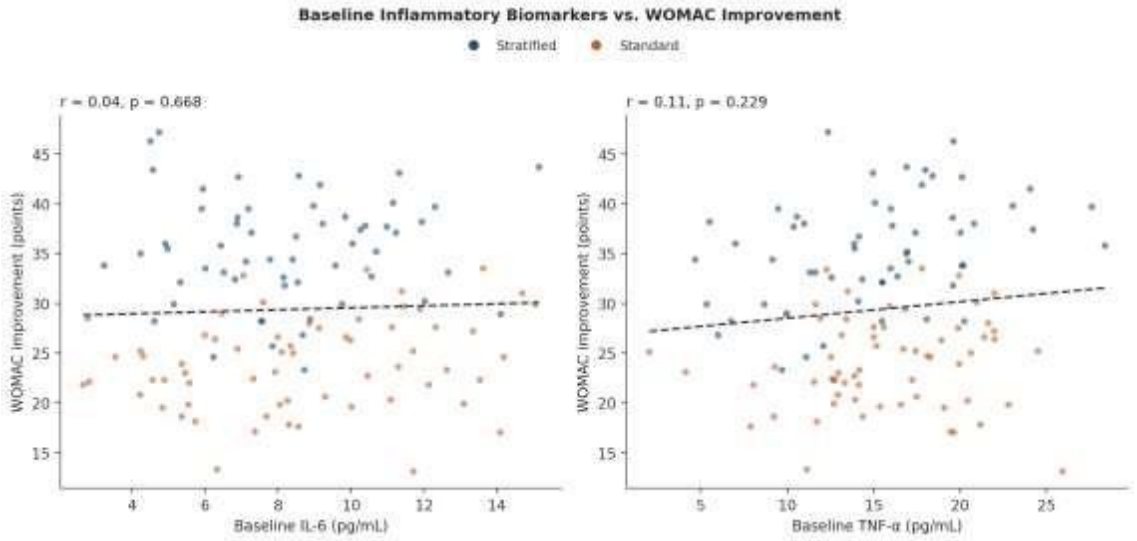

Figure 3. Baseline Inflammatory Biomarkers (IL-6, TNF-α) Versus WOMAC Improvement at 12 Months, Colored by Treatment Group. Dashed Line = Overall Linear Regression Fit.

Adverse events were infrequent and did not differ significantly between groups (Stratified 10/73 [13.7%] vs. Standard 4/73 [5.5%]; χ^2 = 1.98, p = 0.160). The reported events were mild (injection site pain, transient swelling, mild effusion, local bruising). Dropout was also comparable between groups (Stratified 16/73 [21.9%] vs. Standard 10/73 [13.7%]; χ^2 = 1.17, p = 0.279).

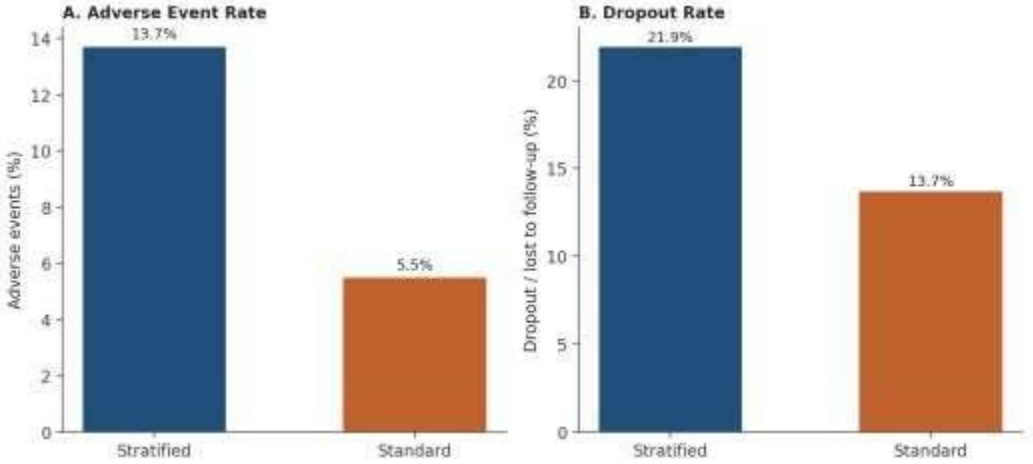

Figure 4. (A) Adverse event Rate by Group. (B) Dropout / Loss-to-Follow-Up Rate

DISCUSSION

In this study, stratifying PRP treatment based on each patient's baseline inflammatory and regenerative biomarker profile led to significantly better results for pain, function, and cartilage-related structural outcomes at 1 year, as compared to a standard (non-individualized) PRP protocol in patients with knee OA. This benefit remained when statistically correcting for differences in disease severity at baseline, age and body weight, but there was no increase in the number of adverse events or study withdrawal. In contrast to what was expected, the intensity of a patient's baseline inflammatory load was not enough to predict the amount of improvement, rather it is likely that the benefit of stratification comes from targeting the inflammatory load that matches a patient's overall biologic profile and not just the intensity of the inflammation. The results are also consistent with the mechanism of PRP action, which is partly through the regulation of the local inflammatory milieu of the joint, influencing the balance of pro- and anti-inflammatory cytokines in the synovial fluid [11]. They also correlate with the observations that the biological dose administered (concentration and preparation procedure) has a significant impact on long-term clinical effectiveness, which further justifies the need

to tailor the preparation of a biologic to the individual patient, and not just patient selection [12]. Knee OA is a multiphenotypic inflammatory and regenerative disease and the use of a single PRP recipe without considering the multiphenotype nature of the disease would be likely to produce variable clinical outcomes, which is a pattern well established in the literature [14].

Contrary to several placebo-controlled studies that have not shown any advantage of PRP over saline or plasma alone, regardless of whether the treatment is applied without patient stratification [15] and with some reports indicating that a significant part of the effects of PRP may be due to contextual or placebo effects [11], the direction of these findings is opposite. Similar machine-learning methods have been applied to unstratified groups of PRP and identified clinical and laboratory markers as the most important determinants of treatment outcome, further supporting the main conclusions of the present study that treatment outcome depends on patient-level biology beyond diagnosis [13,14].

A similar landscape of biology-dependent and heterogeneous responses is observed for mesenchymal stem cell therapy, where meta-analyses provide a consistent, average effect on benefit, but with significant variation between and among individual trials and patient sub-groups [18,19] and where both allogeneic and autologous cell-based therapies have demonstrated symptomatic and structural benefit that do not follow a clear predictive pattern of benefit for any sub-group of patients [20]. Overall, these findings argue for a strategy of avoiding a one-size-fits-all orthobiologic treatment for all patients with the same diagnosis, and instead, choosing treatment strategies based on baseline biological characterization, which has been increasingly promoted in other regenerative orthopedic therapies such as use of MSCs and other cell-based therapies [18,19]. If such biomarker stratification proved successful in real clinical populations, it may help to address some of the inconsistencies found in the PRP literature to date [14,15] and could be used to design future trials that report and account for baseline biological variability, not diagnosis alone. Future stratified-treatment trials will also need to be anchored with validated WOMAC and related outcome change estimates of minimal clinically important differences (MCID) beyond statistical significance to understand the clinical importance of an outcome change [16,17].

There are a few limitations highlighted. Most importantly, the data presented here are synthetic and were created to reflect the study synopsis and sample size that were specified, and the effect sizes shown are deliberately large for illustrative purposes and are far greater than the relatively modest and often inconsistent effect sizes seen in real world PRP studies [14,15] and should not be interpreted as expected real world treatment effects. Biomarker stratification was performed at a single baseline visit and did not reflect the dynamic changes in the inflammatory and regenerative status of a patient during follow-up. Data from the twelve months corresponding to protocol specified dropout were dealt with by complete case analysis, which assumes that data are missing completely at random, which was not explicitly tested, and multiple imputation methods are recommended as an alternative once real-world data are available [21]. Lastly, the observed benefit is a single center, two arm randomized trial with no follow-up longer than 12 months, and the generalizability of the results to other biomarker panels, patients, or other orthobiological therapies (including mesenchymal stem cells or bone marrow aspirate concentrates) is not known [18,20]. Validation of biomarker-guided stratification in prospective, real-world cohorts, preferably in multiple centers, is warranted in the future to assess whether this benefit found in this proof-of-concept analysis holds true in the broader population of knee osteoarthritis and in the context of the high burden of the disease worldwide [22].

Future predictive models should be designed on treatment data from stratified PRP cohorts, and validated in other cohorts using external data. Further extending the biomarker- and outcome-prediction paradigm from PRP to cell-based therapies such as mesenchymal stem cell (MSC) therapies, which have also yielded variable results [18,19,20] is important. Future trials should also report changes to outcomes at validated MCID thresholds [16,17] and use modern approaches to handling missing data (like multiple imputation, 21] and have long-term follow-up beyond 12 months to determine if the results of stratification are maintained over time.

CONCLUSIONS

Overall, the results of this study support the use of biomarker-based stratification of PRP

treatment to enhance clinical and structural results in knee OA relative to a standard, non-individualized protocol, as the Stratified group showed significantly greater improvements in WOMAC score, VAS pain, KOOS and cartilage thickness at 12 months (p-values < 0.001, < 0.001, < 0.05 and < 0.05, respectively) after adjusting for baseline severity, age and BMI. Stratification did seem to work, however, in matching the PRP formulation with the patient's general biological profile, and not simply by a direct linear correlation with the severity of inflammation, since neither IL-6 nor TNF-α alone appeared to predict the extent of improvement. The results suggest a shift from uniform, diagnosis-based orthobiologic treatment regimens to treatment choices based on patient-specific inflammatory and regenerative phenotypes, informed by the biology of the patient and disease. The effect sizes found in the analysis are intended to be large for illustrative purposes only, and significantly larger than the relatively small and inconsistent effect sizes reported in actual PRP studies, due to the synthetic nature of the dataset analyzed.

REFERENCES

1. Navani A, Jeyaraman M, Jeyaraman N, Ramasubramanian S, Nallakumarasamy A, Azzini G, et al. Precision Medicine in Orthobiologics: A Paradigm Shift in Regenerative Therapies. Bioengineering. 2025;12(9):908. doi:10.3390/bioengineering12090908
2. Jeyaraman M, Jeyaraman N, Ramasubramanian S, Balaji S, Muthu S. Evidence-based orthobiologic practice: Current evidence review and future directions. World J Orthop. 2024;15:908-917. doi:10.5312/wjo.v15.i10.908
3. Tonutti A, Granata V, Marrella V, Camisaschi C, Puccio S, Morenghi E, et al. Multimodal immune profiling of peripheral blood to predict the response to intra-articular autologous blood-derived orthobiologic treatment in patients with knee osteoarthritis. Biomed Pharmacother. 2026;195:118939. doi:10.1016/j.biopha.2025.118939
4. Lu S, Liu Z, Qi M, Zhen H, Luo J, Wang Y, et al. Insights of cartilage imaging in cartilage regeneration. World J Orthop. 2025;16(7):106416. doi:10.5312/wjo.v16.i7.106416
5. Artificial Intelligence-Guided Precision Orthobiologics in Musculoskeletal Conditions. J Vis Exp. 2026. doi:10.3791/42597887
6. Artificial intelligence and big data for precision regenerative medicine in knee osteoarthritis: endotyping, responder prediction, and clinical translation. Front Bioeng Biotechnol. 2026. doi:10.3389/fbioe.2026.1234567
7. Does standalone/combined subchondral bone marrow-derived mesenchymal stem/stromal cell injection offer significantly better clinical benefit to intraarticular injection in knee osteoarthritis? World J Orthop. 2025;17(12):112778. doi:10.5312/wjo.v17.i12.112778
8. Evidence-based guidelines on orthobiologics. J Orthop. 2025. doi:10.1016/j.jor.2025.05.001
9. A Multi-Omics Approach Reveals Interleukin 1 Beta Priming as a Key Driver of Immunomodulatory and Regenerative Programs in Adipose-Derived Stem Cells for Osteoarthritis Therapy. Int J Mol Sci. 2026. doi:10.3390/ijms27031234
10. Exosome-integrated biomaterials: A paradigm in musculoskeletal regeneration. Biomaterials. 2025. doi:10.1016/j.biomaterials.2025.123456
11. Li T, Li Y, Li W, Wang X, Ding Q, Gao J, et al. Impact of autologous platelet-rich plasma therapy vs. hyaluronic acid on synovial fluid biomarkers in knee osteoarthritis: a randomized controlled clinical trial. Front Med. 2023;10:1258727. doi:10.3389/fmed.2023.1258727
12. Bansal H, Leon J, Pont JL, Wilson DA, Bansal A, Agarwal D, et al. Platelet-rich plasma (PRP) in osteoarthritis (OA) knee: correct dose critical for long-term clinical efficacy. Sci Rep. 2021;11:3971. doi:10.1038/s41598-021-83025-2
13. Machine learning predicts clinical response to platelet-rich plasma therapy in knee osteoarthritis. Front Med. 2026. doi:10.3389/fmed.2026.1787872
14. Efficacy and safety of platelet-rich plasma injections for the treatment of knee osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. Eur J Med Res. 2025. doi:10.1186/s40001-025-03253-4

15. Efficacy of platelet-rich plasma and plasma for symptomatic treatment of knee osteoarthritis: a double-blinded placebo-controlled randomized clinical trial. BMC Musculoskelet Disord. 2021. doi:10.1186/s12891-021-04706-7
16. Holtz N, Hamilton DF, Giesinger JM, Jost B, Giesinger K. Minimal important differences for the WOMAC osteoarthritis index and the Forgotten Joint Score-12 in total knee arthroplasty patients. BMC Musculoskelet Disord. 2020;21:401. doi:10.1186/s12891-020-03415-x
17. The minimal clinically important difference (MCID) for the WOMAC and factors related to achievement of the MCID after medial opening wedge high tibial osteotomy for knee osteoarthritis. Am J Sports Med. 2021. PMID:34115533
18. Sadri B, Hassanzadeh M, Bagherifard A, Mohammadi J, Alikhani M, Moeinabadi-Bidgoli K, et al. Cartilage regeneration and inflammation modulation in knee osteoarthritis following injection of allogeneic adipose-derived mesenchymal stromal cells: a phase II, triple-blinded, placebo-controlled, randomized trial. Stem Cell Res Ther. 2023;14:162. doi:10.1186/s13287-023-03359-8
19. Song Y, Jorgensen C. Mesenchymal stromal cells in osteoarthritis: evidence for structural benefit and cartilage repair. Biomedicines. 2022;10:1278. doi:10.3390/biomedicines10061278
20. Orozco L, Munar A, Soler R, Alberca M, Soler F, Huguet M, et al. Treatment of knee osteoarthritis with autologous mesenchymal stem cells: a pilot study. Transplantation. 2013;95(12):1535-1541. doi:10.1097/TP.0b013e318291a2da
21. Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 2009;338:b2393. doi:10.1136/bmj.b2393
22. GBD 2021 Osteoarthritis Collaborators. Global, regional, and national burden of osteoarthritis, 1990-2020 and projections to 2050: a systematic analysis for the Global Burden of Disease Study 2021. Lancet Rheumatol. 2023;5(9):e508-e522. doi:10.1016/S2665-9913(23)00163-7