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Estimated Time to Maximum Medical Improvement of Intra-articular Injections in the Treatment of Knee Osteoarthritis – A Systematic Review

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ABSTRACT

PUPROSE: The purpose of the current study is to perform a systematic review of the literature and evaluate maximum medical improvement and minimal clinically important difference (MCID) of different injectables in the treatment of symptomatic knee osteoarthritis.

METHODS: A systematic review was performed to evaluate maximum medical improvement and MCID in patients undergoing injections of different modalities for knee osteoarthritis. Demographic factors of the patients being reviewed were analyzed, with patient-reported outcomes as reported by VAS and WOMAC being used to evaluate the clinical trajectory of patients receiving intra-articular injections.

RESULTS: Overall, 79 (LOE I: 79) studies met inclusion criteria, with 8,761 patients. Corticosteroid (CS) injections, middle molecular weight hyaluronic acid (MMW-HA), and leukocyte-rich platelet rich plasma (LR-PRP) injections reached their maximum pain control at 4-6 weeks post injection, as measured by VAS. The lowest VAS scores were reached for low molecular weight hyaluronic acid (LMW-HA), high molecular weight hyaluronic acid (HMW-HA), and leukocyte-poor platelet rich plasma (LP-PRP) by 3 months post-injection. Similarly, the WOMAC scores were lowest at 4-6 weeks after CS and MMW-HA injections, and at 3 months following HMW-HA and LP-PRP injections. LP-PRP demonstrated the most prolonged pain relief relative to the other injection types, with the lowest VAS score of all groups measured at final follow-up. LP-PRP showed the lowest WOMAC scores at final follow-up, one year post-injection.

CONCLUSION: PRP injections provide continued pain relief at upto one-year post-injection. Corticosteroids and hyaluronic acid have good efficacy and are suitable for many patients but lack this longevity.

LEVEL OF EVIDENCE: I, A Systematic Review of Level I studies

INTRODUCTION

Osteoarthritis (OA) affects over 14 million people in the United States alone,[1] and imparts substantial morbidity including disability, reduction in quality of life, and financial burden.[2, 3] While OA can typically be slowed through a restoration of the equilibrium between load on the joint and joint strength through lifestyle modification, the inflammatory biochemical cascade ultimately contributes to the progression of disease with the potential subsequent need for arthroplasty. Despite this typically unavoidable clinical course, several conservative treatments exist in the form of intra-articular injections aimed at providing symptomatic relief and slowing the natural history of OA.

Of the various injectable therapies available, corticosteroids are the most widely used, with an estimated 38% of patients diagnosed with knee OA receiving at least one injection. More recently, other injection modalities such as hyaluronic acid (HA) and platelet rich plasma (PRP) have risen to prominence in the clinical setting as alternatives to corticosteroids.[4] Corticosteroids and PRP act upon the biochemical pathway to reduce inflammatory biomarkers that would otherwise continue to damage articular cartilage.[2, 5-7] Hyaluronic acid viscosupplementation has been shown to reduce intra-articular inflammation, improve the quality of endogenous HA production and may serve to protect articular cartilage.[8-12] Extensive research exists comparing these frequently used modalities, with each demonstrating favorable clinical outcomes. Despite an abundance of comparative studies present in the literature, data regarding the time course from initial injection to achievement of clinically important differences in OA related symptoms for each of these therapeutic modalities has yet to be amassed and systematically reviewed.

The purpose of the current study is to perform a systematic review of the literature and evaluate maximum medical improvement and minimal clinically important difference (MCID) of different injectables in the treatment of symptomatic knee osteoarthritis. We hypothesized that while all injectables achieve a clinically important difference, they will vary in terms of the time required and duration of effectiveness as determined by patient reported VAS and WOMAC scores.

METHODS

Study Selection

The literature search was performed by two independent reviewers (E.H. and D.M.), based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13] Search results were reviewed and any existing discrepancies were reconciled by a third author (K.C.). The title and abstract were reviewed for all search results and full-text review was performed for potentially eligible studies. Reference lists of the included studies as well as literature reviews found in the initial search were manually screened for any additional articles meeting the inclusion criteria that were missed in the initial screening.

Search Strategy

The following search terms were used in MEDLINE, EMBASE, and The Cochrane Library, databases in September 2020 as the search algorithm: [platelet rich plasma OR prp OR autologous conditioned plasma OR bone marrow aspirate OR corticosteroid OR acp OR hyaluronic acid OR ha OR mesenchymal stem cell OR msc OR ozone OR polydeoxyribonucleotide] AND [knee] and [osteoarthritis OR oa OR gonarthrosis OR cartilage]. No time limit was given to publication date.

Eligibility Criteria

Inclusion criteria were as follows: 1) prospective clinical studies comparing intra-articular injections in the knee, including i) randomized control trials, ii) prospective cohort studies, 2) published in a peer-reviewed journal, 3) included VAS and WOMAC outcome scores, 4) published in English, 5) full text of studies available. The exclusion criteria were the following: 1) case series, 2) review studies, 3) patient outcome scores not reported, 4) basic science studies, 5) abstract only.

Data Extraction/Analysis

Relevant information regarding study characteristics including the study design, population, outcome measures, type of injection, follow-up time points, level of evidence, and risk of bias (ROB) were collected by two blinded reviewers utilizing a predetermined data sheet. The risk of bias (ROB) and methodological quality of evidence (MQOE) was assessed according to the guidelines designed by the Cochrane Statistical Methods Group and Cochrane Methods Bias Group.[14]

Studies involving PRP were defined as leukocyte poor (LP-PRP) or leukocyte rich (LR-PRP) based on manufacturer's specifications as well as whether the leukocyte quantity fell above or below that of autologous blood. HA injections were categorized into one of the following: low molecular weight (LMW), middle molecular weight (MMW), or high molecular weight (HMW).

Analysis of patient-reported outcome measures utilized the means and standard deviations reported by studies at a given time-point. Clinical outcome scores of interest included the VAS and WOMAC. Both surveys are on 100-point scales, where better outcomes (lower pain, higher function) are indicated by lower scores. Clinical outcomes were compared by pooled averages in the following intervals: baseline to 4-6 weeks, 4-6 weeks to 3 months, 3 months to 6 months, 6 months to 1 year. Clinically significant improvements between time points were defined as an improvement in outcome scores which significantly exceeded the established MCID for the specific outcome measure ($P < .05$). MCID thresholds utilized for the VAS score and WOMAC scores were 10.37[15] and 10,[16] respectively. Maximal medical improvement was determined by identifying the latest period where the change in singular outcome score did not exceed the MCID.

Statistical Analysis

All statistical analysis was performed using SPSS version 25.0 (IBM Corporation, Armonk, NY). Heterogeneity was quantified using the I^2 statistic. A p-value of < 0.05 was considered to be statistically significant. The pooled mean scores for VAS and WOMAC were calculated using the number of patients followed up at each time point for each study. The distribution of these pooled statistics were reported using standard deviations. The independent or paired *t*-test for normally distributed variables, or the nonparametric Mann-Whitney U test or Wilcoxon signed-rank test was performed to compare continuous variables. For each outcome measure, a clinically significant difference was defined as a change in the mean outcome score exceeding the previously determined MCID ($p < .05$)

RESULTS

Literature Search

The initial literature search resulted in 5,942 total studies. Once duplicates were removed and articles were screened by title and abstract, 177 studies were included, and full texts were assessed for eligibility. Ultimately, 79 studies with 8,761 patients met inclusion and exclusion criteria. All included studies were randomized controlled clinical trials and qualified as level I evidence. ROB was evaluated for all included studies (27 low risk of bias, 40 medium risk of bias, 12 high risk of bias). The complete list of studies can be found in Appendix 1 and 2. The PRISMA flow chart is shown in Figure 1.

Study Characteristics/Patient Demographics

Of the 8,761 patients included, there were 3,119 (35.6%) males and 5,642 (64.4%) females, with a mean age of 61.1 ± 5.2 years. The mean follow-up time for patients was 7.3 ± 4.6 months. There was a difference in injection protocols which varied between the studies In addition to the pooled patient characteristics, the total number of patients receiving each injection type of interest is illustrated in Table 1.

Patient Reported Outcomes

i. VAS Pooled Means

When comparing pain scores among patients who received the same injection type at different follow-up points, the lowest relative pain scores were seen at 4-6 weeks after CS injection, MMW-HA, and LR-PRP injections. The lowest relative pain score within the LMW-HA group, HMW-HA group, and LP-PRP group were all 3 months post-injection. Of note, the lowest VAS score overall was reported in the cohort receiving LP-PRP 3-months post-injection. Pooled averages for the VAS scores at specific timepoints following each type of

injection are illustrated in Table 2. Boldened numbers indicate the time point for each respective injection type in which pain score was at its lowest.

ii. WOMAC Pooled Means

When comparing WOMAC scores among patients who received the same injection type at different follow-up points, the lowest scores (indicating best function) were seen at 4-6 weeks after CS injection, LMW-HA, and MMW-HA injections. The lowest relative WOMAC scores within the HMW-HA group and LP-PRP group were both 3 months post-injection. LR-PRP injection patients reported the best WOMAC scores after 1 year of follow-up relative to earlier time points. Of note, 1 year after LR-PRP injection demonstrated the lowest WOMAC score overall. Pooled averages for the WOMAC scores at specific timepoints following each type of injection, including normal saline, are illustrated in Table 3. Boldened numbers indicate the time point for each respective injection type in which WOMAC score was at its lowest.

iii. VAS Score MCID

Table 4 demonstrates the improvement (or deterioration) in pain scores over time for each injection type, including normal saline, using the difference between mean VAS scores in a given duration. Whether the change in mean VAS score was statistically significant is noted by the p-value. However, a statistically significant change does not equate to a clinically significant difference, as measured by minimal clinically important difference threshold (MCID). The maximum medical improvement (MMI), or the greatest improvement over a time span, is observed in all modalities in baseline to 4-6 weeks.

Figure 2 graphically details the progression of VAS over time. The lowest VAS pain scores are achieved by LP-PRP.

171 *iv. WOMAC Score MCID*

172 Table 5 demonstrates the improvement (or deterioration) in WOMAC scores over time
173 for each injection type using the difference between mean scores in a given duration. It is also
174 noted whether the difference is statistically significant as well as if it reaches minimal clinically
175 important difference (MCID). The MMI again is observed throughout the injectables in the
176 time from baseline to 4-6 weeks, except in the case of LR-PRP which sees the additional
177 clinically significant improvement in functionality in the period from 4-6 weeks to 3 months.
178 Figure 3 represents the WOMAC score progression over time. The lowest WOMAC scores
179 (indicating best outcome) are achieved by LR-PRP. Of note, LR-PRP is also the only
180 injection that after one year of follow-up continues to show improvement, unlike the other
181 injection types which have regressed, typically reaching an inflection point between 4-6
182 weeks and 3 months. The lowest WOMAC scores (indicating best outcome) are achieved by
183 LR-PRP.
184

DISCUSSION

The most important finding of this study was the direction and magnitude of change of patient-reported outcomes per injection modality. Both PRP modalities (LR-PRP and LP-PRP) demonstrated the most significant and prolonged improvement. LR-PRP had the greatest observed patient reported functional improvement of all injectables that persisted up to a year after injection. The three HA modalities were found to have varying results, with maximum improvement of each found to occur within 4-6 weeks of injection. While LMW-HA was shown to rival the PRP injectables in terms of improving patient-reported function, MMW-HA demonstrated some of the worst patient-reported outcomes observed. Finally, corticosteroids were shown to have maximum pain relief within 4-6 weeks of injection. WOMAC scores, mainly focusing on patient-reported knee function, demonstrated that corticosteroids provide improvement at the first point of follow-up (4-6 weeks) but progressively worsens thereafter, performing similarly to placebo.

Orthopaedic literature in recent years has evolved to focus on differences that result in clinically significantly improved outcomes.[17-20] Minimal clinically important difference (MCID) represents the lowest outcome difference that the patient perceives as clinically important.[20, 21] Maximum medical improvement (MMI), on the other hand, is defined as the time point where patient progress reaches a plateau, or the last time point in which patients experience improvement which reaches MCID.[21, 22] In the current study, PRP was the only observed injectable to continue improving through three months of follow-up, such that both cohorts of patients (those who received LR-PRP as well as those who received LP-PRP) reported clinically noticeable improvements in function between baseline to 1 month, as well as 1 month to 3 months. Patients also reported the best functional outcomes and lowest pain levels at final follow-up after PRP. While there may be a potential placebo effect when

receiving an intra-articular injection, it is important to note that at none of the time points in our study did the placebo cohort experience a clinically significant improvement in either the VAS or WOMAC scores. In contrast a prior meta-analysis by Gregori et al.[23] they found there was uncertainty around the estimates of effect size for change in pain for all comparisons with placebo. However, they recommended further larger studies were required and in the interim there has been another 32 studies published.

Previous studies have examined the timeline of patient improvement and decline after receiving intra-articular injections for knee OA. A randomized-controlled trial by de Menezes Freire et. al.[24] examined patient response to corticosteroids and PRP injections for OA of the knee, finding that both modalities demonstrate statistical improvement relative to baseline through six months post-injection. However, the corticosteroid group had regressed by six months, only maintaining an improvement of about 16 points on the WOMAC scale from baseline. In contrast, at six months follow-up, the PRP group had maintained an improvement from baseline of more than 41 points on the WOMAC scale. Similarly, another randomized-controlled trial by Huang et. al.[6] compared the efficacy of PRP, HA, and corticosteroids measured with VAS and WOMAC at the 3-, 6-, 9-, and 12-month timepoints. They again demonstrated only short-term benefits of corticosteroids along with the relative longevity of PRP effects. Improvement ceased around the 3-month mark for both the corticosteroid and HA groups. As they continued to decline, PRP scores were demonstrated to be statistically superior to corticosteroid and HA groups at 6, 9, and 12 months after treatment as reported by WOMAC. Furthermore, there have been several systematic reviews that have shown beneficial effects with PRP over HA.[4, 25, 26] Meheux et al.[25] found that PRP injection resulted in significant clinical improvements up to 12 months postinjection, and that clinical outcomes are significantly better after PRP versus HA at 3 to 12 months postinjection.

Corticosteroids act in a multi-faceted fashion; injected lidocaine provides short-term symptomatic relief, with subsequent activation of anti-inflammatory properties of the steroid activating subsequently.[27, 28] HA functions by restoring the elastic and viscous properties of the synovial fluid, and synthetic injectable HA also has the capacity to reduce inflammation and even improve the quality of endogenous HA.[10, 29, 30] The anti-inflammatory effects of HA are a result of both its' antioxidant properties and influence on a number of signalling pathways, particularly those of the immune system.[31, 32] Identifying the actions of HA is complex, however, as it demonstrates differential signalling depending upon its molecular weight. However, HMWHA has also demonstrated anti-inflammatory effects through upregulation of pro-resolution genes.[31] Finally, PRP's high therapeutic potential stems from the platelet's ability to deliver supraphysiologic amounts of growth factors to tissue with poor healing potential.[6, 33, 34] This composite of endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), as well as autologous chemokines and cytokines, results in potent anti-inflammatory and analgesic effects.

Limitations

This study is limited by its systematic review of the pre-existing literature, and thus subject to the potential the inherent biases in certain studies. The majority of the included studies demonstrated some potential risk of biases, with the most commonly being due to inappropriate blinding in 40% of studies. Additionally, it was unable to draw conclusions that differentiate the effectiveness of the injectables acting upon knee osteoarthritis of specified Kellgren-Lawrence grade or radiographic findings. However, baseline scores are provided in a way to balance this inherent limitation in the review of literature. The study does not

differentiate the specific steroid used in CS injections, however, since our study had such large numbers and the action of the commonly used steroids do not vary substantially, we do not feel it is necessary. This study did not evaluate stem cell injection therapy. Although this is an important injectable, there was insufficient data regarding the outcome scores at different time points in the available literature.[35] We therefore omitted it from analysis. However, we included it in the search terms in order to ensure that we did not miss a RCT comparing stem cells to one of the injections that was analyzed in our study.

Conclusion

PRP injections provide continued pain relief at upto one-year post-injection. Corticosteroids and hyaluronic acid have good efficacy and are suitable for many patients but lack this longevity.

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FIGURE LEGEND

Figure 1. PRISMA Figure

Figure 2. VAS Scores from baseline to 1 year post-injection. Of note, LP-PRP reaches the lowest VAS score overall at approximately 3 months post-injection. It also has the lowest VAS score at final follow-up of 1 year.

Figure 3. WOMAC scores from baseline to 1-year post-injection. While LP-PRP reaches the lowest WOMAC score overall at 3 months post-injection, LR-PRP provides the best outcome at final follow-up of 1 year.

TABLE LEGEND

Table 1. Pooled Characteristics and Patient Data

	n (%) or Mean ± SD
Total N	8,761
Mean Age, yrs	61.1 ± 5.2
Sex	
Male	3,119 (35.6%)
Female	5,642 (64.4%)
Mean Follow-Up, mos.	7.3 ± 4.6
Follow-Up Range, mos.	1 - 24
Injection Type, n (%)	
Placebo	2,134 (24.3%)
CS	927 (10.6%)
LMW	1,995 (22.8%)
MMW	546 (6.2%)
HMW	1,406 (16.0%)
PRP-LP	479 (5.5%)
PRP-LR	441 (5.0%)

CS, corticosteroid; LMW, low molecular weight (hyaluronic acid); MMW, middle molecular weight (hyaluronic acid); HMW, high molecular weight (hyaluronic acid); LP-PRP, leukocyte-poor platelet-rich plasma; LR-PRP, leukocyte-rich platelet-rich plasma

393

Table 2. Pooled Means and SDs for VAS

	Baseline	4-6 weeks	3 months	6 months	1 year
Saline	52.8 (12.7)	44.3 (12.8)	40.6 (14.0)	34.9 (11.8)	45.1 (8.9)
CS	61.5 (12.6)	**36.8 (12.4)**	56.5 (35.9)	43.7 (14.8)	49.8 (18.5)
LMW	56.8 (14.5)	33.5 (10.5)	**23.8 (3.7)**	31.4 (14.0)	45.7 (15.0)
MMW	63.7 (6.8)	**28.0 (2.1)**	46.1 (9.4)	31.6 (14.6)	N/A*
HMW	58.7 (11.8)	39.4 (9.0)	**35.3 (6.3)**	36.9 (9.1)	46.1 (6.9)
LP-PRP	62.5 (16.3)	30.3 (14.9)	**21.9 (10.4)**	31.2 (13.5)	30.2 (13.1)
LR-PRP	58.9 (13.5)	**31.4 (8.8)**	38.5 (12.9)	39.0 (7.5)	N/A*

394 CS, corticosteroid; LMW, low molecular weight (hyaluronic acid); MMW, middle molecular weight (hyaluronic
395 acid); HMW, high molecular weight (hyaluronic acid); LP-PRP, leukocyte-poor platelet-rich plasma; LR-PRP,
396 leukocyte-rich platelet-rich plasma
397 *sample size at these time points too low
398 Bold numbers indicate the time point in which pain scores were at their lowest for each injection type
399

400

Table 3. Pooled Means and SDs for WOMAC

	Baseline	4-6 weeks	3 months	6 months	1 year
Saline	48.9 (11.3)	39.9 (10.5)	35.5 (6.2)	39.1 (11.6)	44.7 (2.3)
CS	52.2 (9.7)	**35.2 (10.5)**	38.0 (9.9)	40.0 (8.5)	48.2 (10.8)
LMW	47.9 (10.5)	**29.1 (6.0)**	34.2 (9.1)	26.9 (6.9)	32.2 (7.8)
MMW	51.7 (11.8)	**28.3 (6.2)**	29.5 (4.4)	34.0 (6.7)	51.1 (21.0)
HMW	48.0 (14.1)	38.8 (9.2)	**29.7 (7.0)**	37.2 (8.2)	43.4 (13.7)
LP-PRP	50.5 (13.3)	32.7 (16.0)	**21.8 (7.8)**	30.7 (13.0)	36.2 (17.9)
LR-PRP	48.2 (19.2)	38.2 (11.6)	25.1 (12.2)	26.4 (14.2)	**21.1 (14.2)**

401 CS, corticosteroid; LMW, low molecular weight (hyaluronic acid); MMW, middle molecular weight (hyaluronic
402 acid); HMW, high molecular weight (hyaluronic acid); LP-PRP, leukocyte-poor platelet-rich plasma; LR-PRP,
403 leukocyte-rich platelet-rich plasma
404 *sample size at these time points too low
405

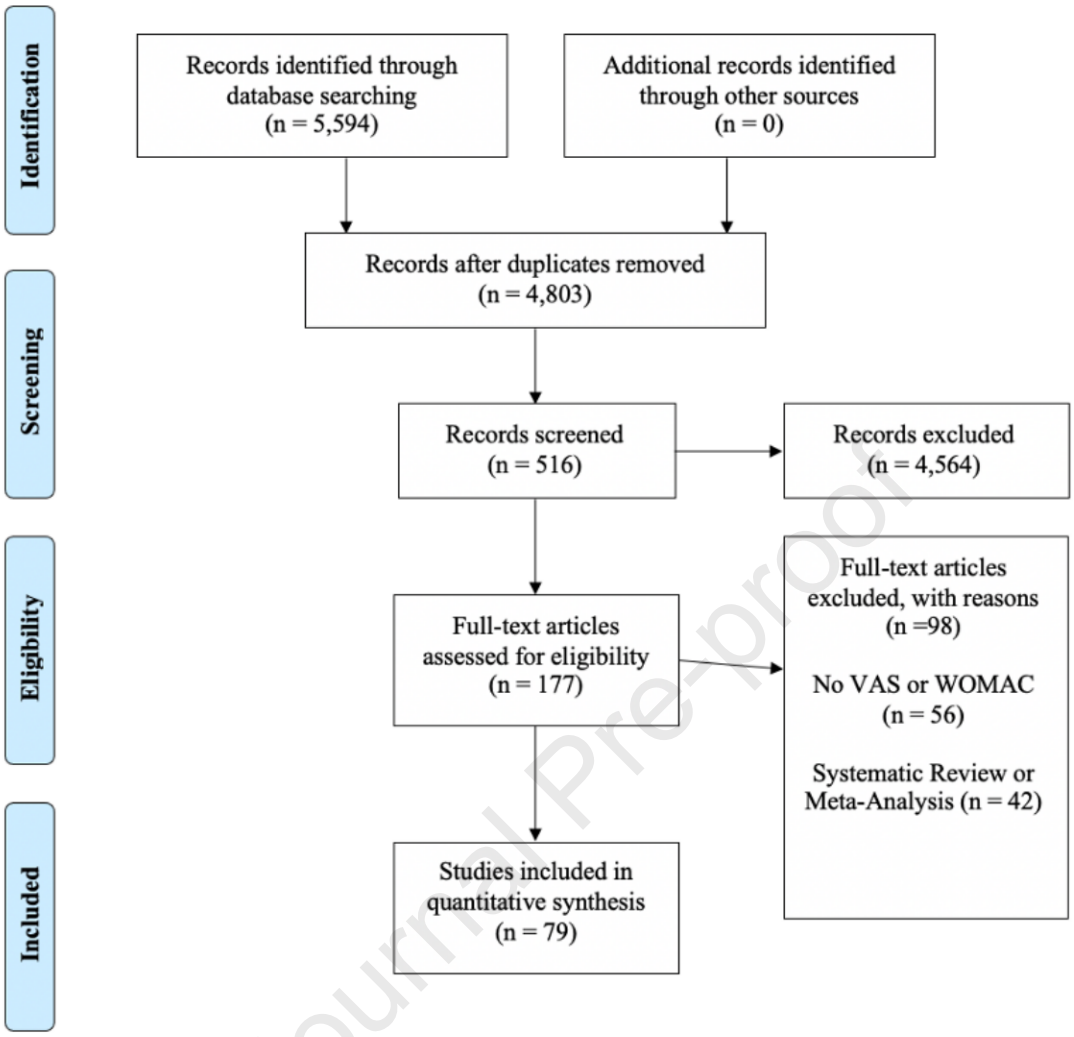
Table 4. Change in Patient Reported Outcomes Between Time Points
VAS

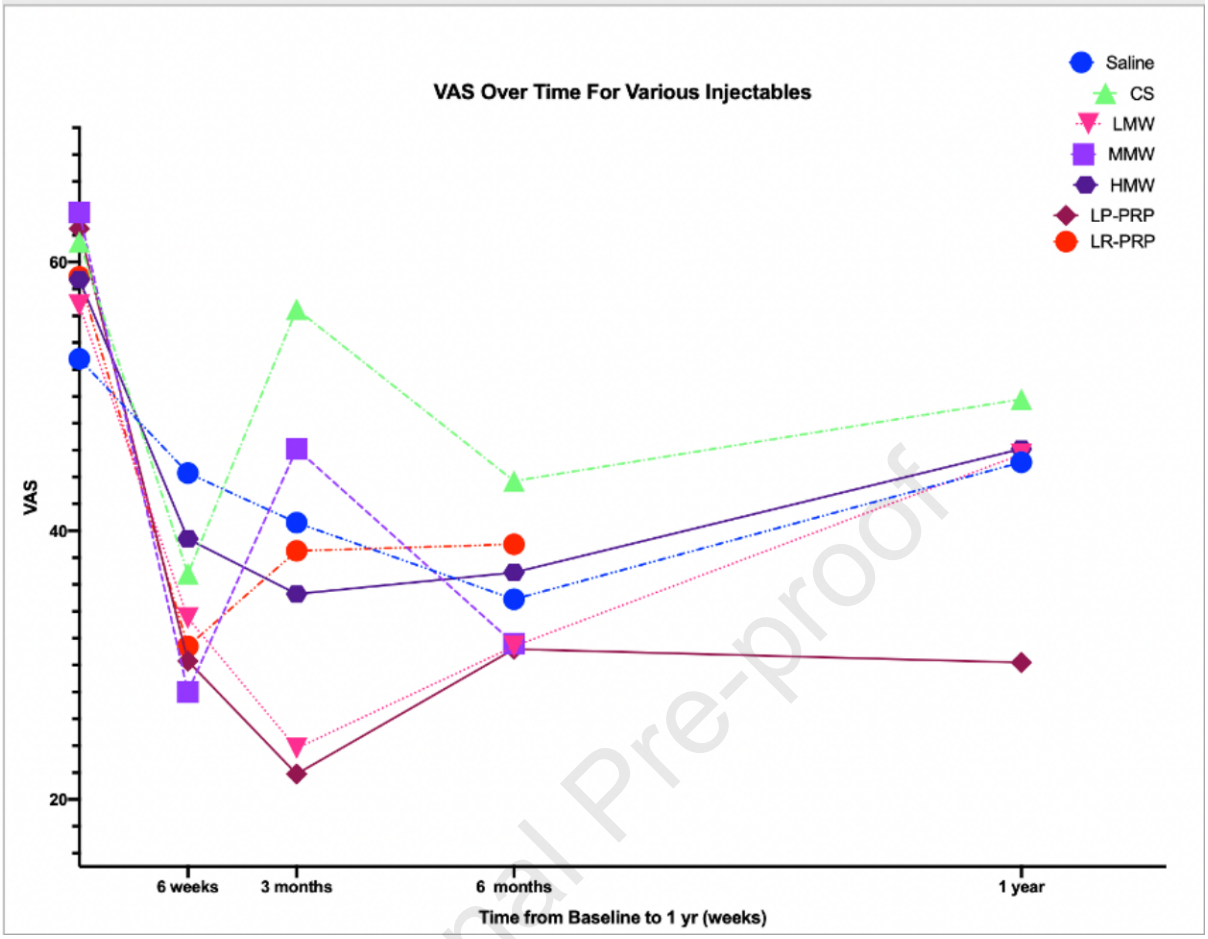
	Baseline to 4-6 weeks	4-6 weeks to 3 months	3 months to 6 months	6 months to 1 year
Saline				
Diff Means	8.5	3.7	5.7	-10.2
MCID?	No	No	No	No
p-value	< 0.0001	<0.0001	<0.0001	<0.0001
I^2	98%	85%	0%	0%
CS				
Diff Means	**22.9**	**-19.7**	**12.8**	-6.1
MCID?	**Yes**	**Yes**	**Yes**	No
p-value	< 0.0001	< 0.0001	<0.0001	0.0004
I^2	97%	91%	18%	0%
LMW				
Diff Means	**23.3**	9.7	-7.6	**-14.3**
MCID?	**Yes**	No	No	**Yes**
p-value	< 0.0001	< 0.0001	< 0.0001	< 0.0001
I^2	95%	36%	91%	0%
MMW				
Diff Means	**35.7**	**-18.1**	**14.5**	N/A*
MCID?	**Yes**	**Yes**	**Yes**	
p-value	< 0.0001	< 0.0001	0.0039	
I^2	95%	0%	93%	
HMW				
Diff Means	**19.3**	4.1	-1.6	-9.2
MCID?	**Yes**	No	No	No
p-value	< 0.0001	< 0.0001	0.0002	< 0.0001
I^2	96%	87%	45%	72%
LP-PRP				
Diff Means	**32.2**	8.4	-9.3	1
MCID?	**Yes**	No	No	No
p-value	< 0.0001	< 0.0001	< 0.0001	0.4862
I^2	99%	0%	83%	0%
LR-PRP				
Diff Means	**27.5**	-7.1	-0.5	NA*
MCID?	**Yes**	No	No	
p-value	<0.0001	<0.0001	0.6608	
I^2	83%	95%	81%	

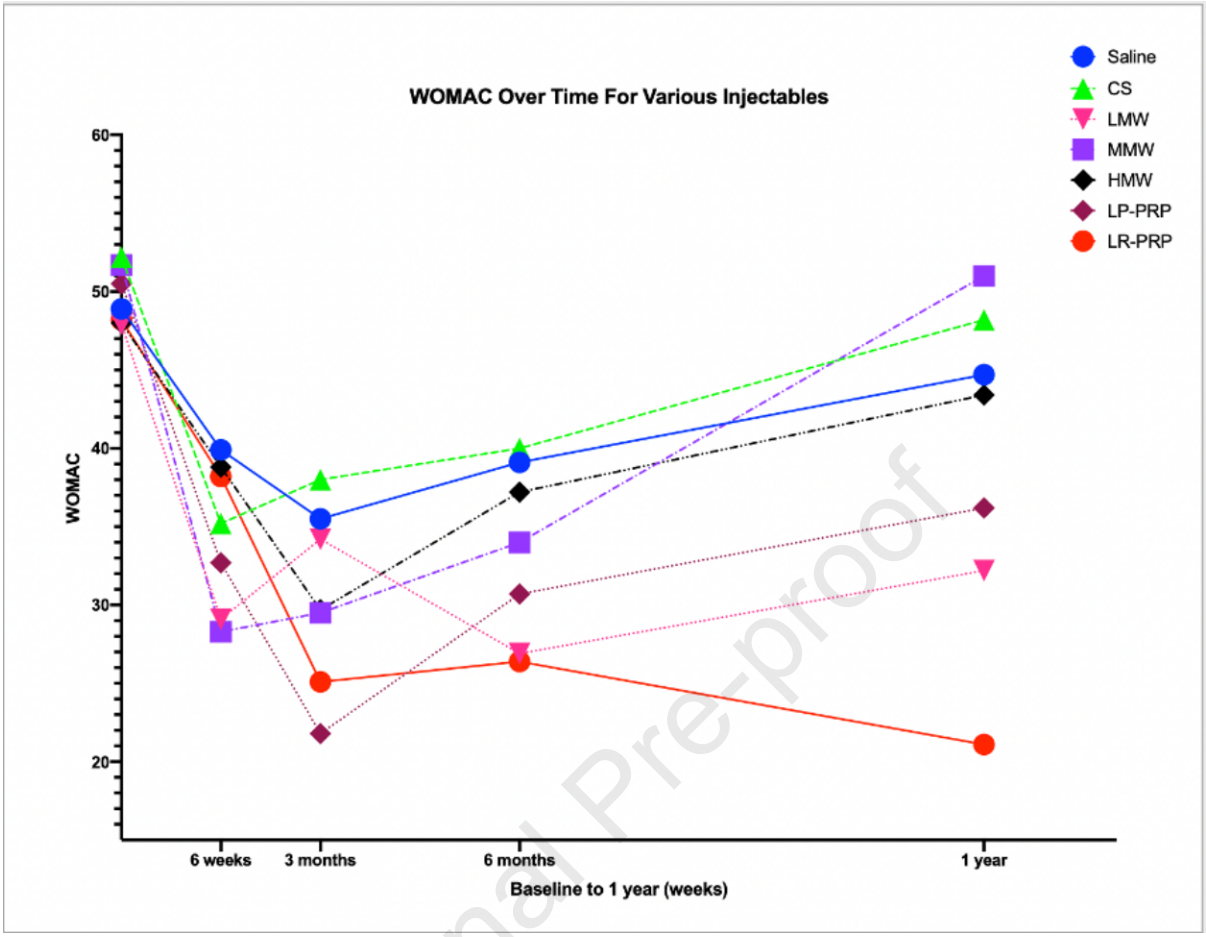
Table 5. Change in Patient Reported Outcomes Between Time Points WOMAC

	Baseline to 4-6 weeks	4-6 weeks to 3 months	3 months to 6 months	6 months to 1 year
Saline				
Diff Means	9	4.4	-3.6	-5.6
MCID?	No	No	No	No
p-value	**< 0.0001**	**<0.0001**	**<0.0001**	**0.0004**
I^2	86%	94%	92%	25%
CS				
Diff Means	**17**	-2.8	-2	-8.2
MCID?	**Yes**	No	No	No
p-value	**< 0.0001**	**0.0014**	**0.0027**	**< 0.0001**
I^2	75%	0%	89%	98%
LMW				
Diff Means	**18.8**	-5.1	7.3	-5.3
MCID?	**Yes**	No	No	No
p-value	**< 0.0001**	**< 0.0001**	**< 0.0001**	**< 0.0001**
I^2	0%	0%	69%	97%
MMW				
Diff Means	**23.4**	-1.2	-4.5	**-17.1**
MCID?	**Yes**	No	No	**Yes**
p-value	**< 0.0001**	0.169	**< 0.0001**	**< 0.0001**
I^2	90%	0%	29%	96%
HMW				
Diff Means	9.2	9.1	-7.5	-6.2
MCID?	No	No	No	No
p-value	**< 0.0001**	**< 0.0001**	**< 0.0001**	**< 0.0001**
I^2	94%	47%	0%	14%
LP-PRP				
Diff Means	**17.8**	**10.9**	-8.9	-5.5
MCID?	**Yes**	**Yes**	No	No
p-value	**< 0.0001**	**< 0.0001**	**< 0.0001**	**< 0.0001**
I^2	99%	78%	94%	0%
LR-PRP				
Diff Means	**10**	**13.1**	-1.3	5.3
MCID?	**Yes**	**Yes**	No	No
p-value	**< 0.0001**	**< 0.0001**	0.3069	**0.0002**
I^2	99%	94%	30%	5%

407







Study	LoE	Follow-Up (months)	Age (years)	Female (%)	Group 1 Treatment (N)	Group 2 Treatment (N)	Group 3 Treatment (N)
Ahmad et al. 2018	I	6	56.5	68.6	LR-PRP (45)	HMW (44)	
Altman et al. 1998	I	6	64	57	LMW (105)	Saline (115)	
Altman et al. 2004	I	6.5	63.1	54.9	LMW (172)	Saline (174)	
Altman et al. 2009	I	6.5	61.6	63.1	HMW (291)	Saline (295)	
Anz et al. 2020	I	12	54.1	41.7	BMAC (45)	LR-PRP (39)	
Arden et al. 2014	I	1.5	62.7	50.5	LMW (108)	Saline (110)	
Askari et al. 2016	I	3	57.8	85	CS (69)	LMW (71)	
Babaei-Ghazani et al. 2018	I	3	58	83.9	CS (31)	ozone (31)	
Bahrami et al. 2020	I	6	57.8	73.4	HMW (39)	LMW (40)	
Baltzer et al. 2009	I	6.5	56.9	55.1	ACS (134)	MMW (135)	Saline (107)
Bao et al. 2018	I	2	65.9	46.7	Saline (20)	BoNTA (20)	LMW (20)
Berenbaum et al. 2012	I	6.5	66.7	63	MMW (217)	LMW (209)	
Bisicchia et al. 2016	I	6.5	70.1	68.7	LMW (75)	CS (75)	
Buendía-López et al. 2018	I	6	56.4	52.3	LP-PRP (33)	HMW (32)	
Caborn et al. 2004	I	6.5	63.1	56.9	HMW (113)	CS (103)	
Chao et al. 2010	I	1	64.3	2.9	CS (33)	Saline (34)	
Cubukcu et al. 2005	I	2	53.9	60	HMW (30)	Saline (10)	
De campos et al. 2013	I	6	63	75.9	HMW (52)	HMW+CS (52)	
DeCaria et al. 2012	I	6	72.43	47	LMW (15)	Saline (15)	
Diracoglu et al. 2009	I	1	58.3	93.3	HMW (80)	Saline (40)	
Dougados et al. 1993	I	12	68	70.9	LMW (55)	Saline (55)	
Duymus et al. 2017	I	12	60	94.2	LP-PRP (33)	MMW (34)	ozone (35)
Elksnins et al. 2020	I	12	68.3	20	LP-PRP (19)	CS (17)	
Gaballa et al. 2019	I	3	55	76.7	LR-PRP (20)	Ozone (20)	Saline (20)
Garza et al. 2020	I	12	58.8	61.5	Saline (13)	SVF (13)	
Gigis et al. 2016	I	12	67.3	60	LMW (40)	HMW (40)	
Giombini et al. 2016	I	2	64.3	52.9	LMW (23)	ozone (23)	HA+ozone (24)
Henderson et al. 1994	I	1.25	66.5	77.8	LMW (35)	Saline (46)	
Hong et al. 2019	I	12	52	81.3	SVF (16)	HMW (16)	
Huang et al. 2011	I	6	65	76	LMW (100)	Saline (100)	

Huang et al. 2019	I	12	54.5	81.9	LMW (40)	CS (40)	LP-PRP (40)
Huskisson et al. 1999	I	6	65.3	67	LMW (39)	Saline (41)	
Jones et al. 1995	I	6	70.5	38	LMW (32)	CS (31)	
Joshi et al. 2017	I	6	66.8	72.3	LP-PRP (35)	CS (30)	
Jubb et al. 2003	I	12	64.8	67.8	LMW (137)	Saline (136)	
Kesiktas et al. 2021	I	3	55.8	81.6	HMW (18)	LR-PRP (18)	
Kuah et al. 2018	I	12	53.3	40	Saline (4)	MSC (16)	
Lamo-Espinosa et al. 2020	I	12	55.3	34	PRGF (26)	PRGF+MSC (24)	
Lana et al. 2016	I	12	61	84.7	HMW (36)	LR-PRP (36)	HMW + LR-PRP (33)
Lin et al. 2019	I	12	62	66.5	LP-PRP (31)	HMW (29)	Saline (27)
Lisi et al. 2018	I	12	55.3	38	LMW (28)	LR-PRP (30)	
Lopes et al. 2017	I	4	70.1	89.6	Saline (35)	ozone (61)	
Lu et al. 2019	I	12	57.3	88.5	MSC (26)	MMW (26)	
Lundsgaard et al. 2008	I	6	69.2	54.8	LMW (84)	Saline (84)	
Maia et al. 2019	I	6	57.1	70.5	CS (12)	HMW (16)	HMW+CS (16)
McAlindon et al. 2017	I	24	58.2	53.6	CS (70)	Saline (70)	
Mendes et al. 2019	I	3	64.2	91.4	BoNTA (35)	CS (35)	Saline (35)
Mochizuki et al. 2020	I	1.5	67	69.5	LMW (28)	MMW (31)	
Nishida et al. 2021	I	6	64.3	26.7	HMW (87)	saline (89)	
Park et al. 2021	I	6	61.5	78.2	HMW (55)	LR-PRP (55)	
Patel et al. 2013	I	6	52.8	70.7	LP-PRP (52)	Saline (23)	
Paterson et al. 2016	I	3	51.3	28.6	LR-PRP (11)	HMW (10)	
Petrella et al. 2002	I	1	65.5	39.6	LMW (28)	Saline (25)	
Petterson et al. 2019	I	6.5	59.1	58.2	HMW (162)	Saline (169)	
Pishgahi et al. 2020	I	12	59.41	53.3	saline (30)	LP-PRP (30)	ACS (32)
Puhl et al. 1993	I	2	61.43	63.59	LMW (95)	Saline (100)	
Raeissadat et al. 2015	I	12	59	82.7	LR-PRP (77)	LMW (62)	
Raeissadat et al. 2017	I	6	58.2	81.1	LMW (36)	LP-PRP (41)	
Raeissadat et al. 2018	I	6	59.7	76	ozone (67)	LMW (74)	
Raessadat et al. 2021	I	12	57.9	71.6	PRGF (60)	LMW (59)	

Ravaud et al. 1999	I	24	65	67.9	Saline (28)	CS (25)	
Sezgin et al. 2005	I	1	59.7	75.6	MMW (22)	Saline (19)	
Shimizu et al. 2010	I	6	75.6	75.7	LMW (26)	CS (25)	
Skwara et al. 2009	I	3	61.1	59.5	MMW (21)	CS (21)	
Skwara (2) et al. 2009	I	3	60.4	46	HMW (24)	CS (26)	
Smith et al. 2016	I	12	50.1	63.3	LP-PRP (15)	Saline (15)	
Spaková et al. 2012	I	6	53.1	47.5	LR-PRP (60)	MMW (60)	
Sun et al. 2017	I	6	59.5	51.3	LP-PRP (39)	LMW + LP-PRP (39)	
Sun et al. 2021	I	6	62.6	74	LMW (62)	HMW (59)	
Tammachote et al. 2016	I	6	61.8	78	HMW (50)	CS (49)	
Tasciotaoglu et al. 2003	I	6	58.8	100	HMW (30)	CS (30)	
Trueba et al. 2015	I	12	62.8	58	LMW (97)	CS (98)	
Uslu et al. 2018	I	6	61.6	92	CS (17)	LP-PRP (33)	
Vaquerizo et al. 2013	I	12	63.6	60.45	LP-PRP (48)	HMW (48)	
Vega et al. 2015	I	12	57	56.7	HMW (15)	MSC (15)	
Wu et al. 2018	I	6	63.25	75	LR-PRP (20)	Saline (20)	
Yaradilmis et al. 2020	I	12	60.7	86.7	HMW (30)	LP-PRP (30)	LR-PRP ()
Yavuz et al. 2012	I	3	60	63.3	Saline (30)	CS (90)	

LoE, Level of Evidence; CS, corticosteroid; LMW, low molecular weight (hyaluronic acid); MMW, middle molecular weight (hyaluronic acid); HMW, high molecular weight (hyaluronic acid); LP-PRP, leukocyte-poor platelet-rich plasma; LR-PRP, leukocyte-rich platelet-rich plasma; MSC, mesenchymal stem cells; ACS, autologous conditioned serum; BoNTA, botulinum toxin type A; PRGF, plasma rich in growth factor; SVF, stromal vascular fraction

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (selection bias)	Other sources of bias	Overall
Ahmad et al. 2018	Low	Low	Low	High	Low	Low	Low	Medium
Altman et al. 1998	Low	Low	High	Low	Low	Low	Low	Medium
Altman et al. 2004	Low	Low	Low	Low	Low	Low	Low	Low
Altman et al. 2009	Low	Low	Low	Low	Low	Low	Low	Low
Anz et al. 2020	Low	High	Low	High	Low	Low	Low	High
Arden et al. 2014	Low	Low	Low	Low	Low	Low	Low	Low
Askari et al. 2016	Low	Low	Low	High	Low	Low	Low	Medium
Babaei-Ghazani et al. 2018	Low	Low	Low	Low	Low	Low	Low	Low
Bahrami et al. 2020	Low	Low	Low	Low	Low	High	Low	Medium
Baltzer et al. 2009	Low	Low	Low	Low	Low	Low	Low	Medium
Bao et al. 2018	Low	Low	High	Low	Low	Low	Low	Medium
Berenbaum et al. 2012	Low	Low	Low	Low	Low	Low	Low	Low
Bisicchia et al. 2016	Low	Low	High	Low	Low	Low	Low	Medium
Buendía-López et al. 2018	Low	High	High	High	Low	Low	Low	High
Caborn et al. 2004	Low	Low	High	Low	kow	Low	Low	Medium
Chao et al. 2010	Low	Low	Low	Low	High	High	Low	Medium
Cubukcu et al. 2005	Low	High	High	Low	Low	Low	Low	High
De campos et al. 2013	High	Low	Low	Low	High	Low	Low	Medium
DeCaria et al. 2012	Low	Low	Low	Low	Low	Low	Low	Low
Diracoglu et al. 2009	Low	Low	High	Low	Low	Low	Low	Medium
Dougados et al. 1993	Low	Low	High	High	Low	Low	Low	High
Duymus et al. 2017	Low	Low	Low	High	Low	Low	Low	Medium
Elksnins et al. 2020	Low	Low	Low	High	Low	Low	Low	Medium
Gaballa et al. 2019	Low	Low	High	Low	Low	Low	Low	Medium
Garza et al. 2020	Low	High	Low	Low	Low	Low	Low	Medium
Gigis et al. 2016	Low	Low	Low	Low	Low	Low	Low	Low
Giombini et al. 2016	Low	Low	High	Low	Low	Low	Low	Medium
Henderson et al. 1994	Low	Low	High	High	Low	High	Low	High
Hong et al. 2019	Low	Low	Low	Low	Low	Low	Low	Low
Huang et al. 2011	Low	Low	Low	Low	Low	Low	Low	Low
Huang et al. 2019	Low	Low	High	High	Low	Low	Low	Medium

Huskisson et al. 1999	Low	Low	Low	Low	High	Low	Low	Medium
Jones et al. 1995	Low	Low	Low	Low	Low	Low	Low	Low
Joshi et al. 2017	Low	Low	Low	Low	Low	Low	Low	Low
Jubb et al. 2003	Low	Low	Low	Low	Low	Low	Low	Low
Kesiktas et al. 2021	Low	Low	Low	Low	Low	Low	Low	Low
Kuah et al. 2018	Low	Low	Low	Low	Low	Low	Low	Low
Lamo-Espinosa et al. 2020	Low	Low	Low	Low	High	Low	Low	Medium
Lana et al. 2016	Low	Low	Low	Low	Low	Low	Low	Low
Lin et al. 2019	Low	Low	Low	Low	Low	Low	Low	Medium
Lisi et al. 2018	High	Low	Low	Low	Low	Low	Low	Medium
Lopes et al. 2017	High	Low	Low	Low	Low	Low	Low	Medium
Lu et al. 2019	Low	Low	Low	Low	Low	Low	Low	Low
Lundsgaard et al. 2008	Low	Low	Low	Low	Low	High	Low	Medium
Maia et al. 2019	Low	Low	Low	Low	Low	Low	Low	Low
McAlindon et al. 2017	Low	Low	Low	Low	Low	Low	Low	Low
Mendes et al. 2019	Low	Low	Low	Low	Low	Low	Low	Low
Mochizuki et al. 2020	Low	Low	High	High	Low	Low	Low	High
Nishida et al. 2021	Low	Low	Low	Low	Low	Low	Low	Low
Park et al. 2021	Low	Low	Low	High	Low	Low	Low	Medium
Patel et al. 2013	Low	Low	Low	High	Low	Low	Low	Medium
Paterson et al. 2016	Low	Low	Low	Low	High	Low	Low	Medium
Petrella et al. 2002	Low	Low	Low	Low	Low	Low	Low	Low
Petterson et al. 2019	Low	Low	Low	Low	Low	Low	Low	Low
Pishgahi et al. 2020	Low	Low	High	Low	Low	Low	Low	Medium
Puhl et al. 1993	Low	Low	Low	Low	Low	Low	Low	Low
Raeissadat et al. 2015	Low	Low	High	High	High	High	Low	High
Raeissadat et al. 2017	Low	Low	High	Low	Low	Low	Low	Medium
Raeissadat et al. 2018	Low	Low	Low	Low	High	Low	Low	Low
Raessadat et al. 2021	Low	Low	High	High	Low	Low	Low	High
Ravaud et al. 1999	Low	Low	High	High	Low	Low	Low	High
Sezgin et al. 2005	Low	Low	High	Low	High	Low	Low	High
Shimizu et al. 2010	Low	Low	High	High	High	Low	Low	Medium
Skwara et al. 2009	Low	Low	Low	Low	High	Low	Low	Medium

Skwara (2) et al. 2009	Low	Low	Low	Low	Low	Low	Low	Medium
Smith et al. 2016	High	Low	Low	Low	High	High	Low	Medium
Spaková et al. 2012	Low	High	High	High	High	Low	Low	Medium
Sun et al. 2017	Low	Low	High	Low	Low	Low	Low	High
Sun et al. 2021	Low	Low	Low	Low	Low	Low	Low	Medium
Tammachote et al. 2016	Low	Low	Low	Low	Low	Low	Low	Medium
Tasciotaoglu et al. 2003	Low	Low	High	Low	Low	Low	Low	Medium
Trueba et al. 2015	Low	Low	Low	Low	Low	Low	Low	Low
Uslu et al. 2018	Low	Low	High	Low	High	Low	Low	Medium
Vaquerizo et al. 2013	Low	Low	Low	Low	Low	Low	Low	Low
Vega et al. 2015	Low	Low	High	High	Low	Low	Low	Medium
Wu et al. 2018	Low	Low	Low	Low	Low	Low	Low	Low
Yaradilmis et al. 2020	Low	Low	Low	Low	High	High	Low	Medium
Yavuz et al. 2012	Low	Low	Low	Low	High	High	Low	High