Surgical treatment is not superior to nonoperative treatment for displaced proximal humerus fractures. A systematic review and meta-analysis.

Running Title: Meta-Analysis Proximal Humerus Fractures

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Conflict of Interest Statement:
The authors declare that they have no conflict of interest

Funding Sources:
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Abstract

Background:

The purpose of this study was to perform a systematic review and meta-analysis of both randomized controlled and observational studies comparing conservative to surgical treatment of displaced proximal humerus fractures.

Methods:

Systematic review of Medline, Embase, Scopus, and Google Scholar, including all level 1-3 studies from 2000 to 2022 comparing surgical treatment to conservative treatment. Clinical outcome scores, range of motion and complications were evaluated. Risk of bias was assessed using the Cochrane Collaboration's ROB2 tool and ROBINs-I tool. The GRADE system was used to assess the quality of the body of evidence, and heterogeneity was assessed using χ^2 and I^2 statistics.

Results:

Twenty-two studies were incorporated into the analysis. Ten studies had a high risk of bias, and all included studies were of low quality. The pooled estimates failed to identify differences for clinical outcomes (p=0.208), abduction (p=0.275), forward flexion (p=0.447), or external rotation (p=0.696). Complication rates between groups were significantly lower (p=0.00001) in the conservative group.

Conclusions:

This meta-analysis demonstrated that there were no statistically significant differences for either clinical outcomes or range of motion between surgically managed and conservatively treated displaced proximal humerus fractures. The overall complication rate was 3.3 times higher following surgical treatment. The validity of this result is compromised by the high risk of bias and very low level of certainty of the included studies, and the conclusion must therefore be interpreted with caution.

Keywords:

Proximal humerus fractures; surgical treatment; conservative treatment; displaced fractures; Neer proximal humerus; clinical outcomes.

Level of Evidence:

Systematic review and meta-analysis of level I-III studies

Introduction

Proximal humerus fractures are one of the most common fractures observed in the elderly population [11] and because of an increase in life expectancy the incidence of these fractures is expected to rise substantially. [13,45] The majority of proximal humerus fractures in elderly patients can be treated conservatively, and the functional and clinical outcomes are generally good. [29] Currently, the treatment of displaced fractures, however, remains controversial, and most often depends on the individual surgeons' choice and personal preference, rather than being based on strong evidence. [2]

The PROFHER trial has sparked further debate, concluding that patients with displaced proximal humerus do not exhibit any clinical benefit from surgical treatment two-years after injury. [43] The five-year results of the PROFHER trial subsequently confirmed the findings of the two-year outcomes; however, the trial lost 30% of patients to follow-up. [24] The PROFHER trial also included a cost-utility analysis, revealing that surgical treatment was associated with lower QALYs at two years. [10] Interestingly, the PROFHER trial had substantial impact, and responses from 265 surgeons indicated that approximately 50% changed practice based on the results. [30] The PROFHER trial was criticized because of the potential exclusion of eligible patients, the high rate of cross-over between treatment arms, the heterogeneity of the cohorts, and the low number of patients per surgeon. [20] An earlier Cochrane review concluded that there is moderate evidence in support of non-surgical treatment of displaced two-part fractures. [23] Conservative treatment for 3-part fractures achieved consolidation in 95% of patients, with satisfactory functional results. [47] In contrast, 4-part fractures resulted in inferior functional outcomes despite a high consolidation rate, and it has been suggested that nonoperative treatment should only be considered for patients with low functional expectations or significant comorbidities. [47] This agrees with a recent meta-analysis by Fu et al, that investigated overlapping meta-analyses and concluded that surgical treatment appears advantageous. [18] However, the findings of Fu et al are in contrast to earlier meta-analyses. [1,42] Beks et al included 23 studies and could not demonstrate any significant differences between surgical and conservative treatment, and recommended nonoperative treatment for patients over 65 years. [1] Rabi et al included six randomized studies, concluding that moderate quality evidence suggested no difference between surgical and non-surgical treatment for displaced fractures. [42] Given the ongoing controversies and conflicting opinions, the purpose of this study was therefore to perform an updated systematic review and meta-analysis of both randomized controlled and observational studies comparing surgical and non-surgical treatment for proximal humerus fractures.

Methods

The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines, [37] and the updated guidelines described in the Cochrane Handbook. [12]

Eligibility criteria

Studies that compared surgical to non-surgical treatment were included if they fulfilled the inclusion and exclusion criteria. Studies were included if they were of level 1-3 evidence and published between January 2000 and June 2022. The reason for the inclusion of level 3 studies was that they not only increase sample size, but they also increase the generalizability of the pooled results [1] without causing differences in the risk estimate of treatment effects of an intervention derived from meta-analysis of randomized controlled trials or observational studies. [5,21] Studies were also included if they compared various surgical interventions and incorporated a non-operative study arm. For analysis. each surgical intervention was individually compared to the non-surgical treatment group. Further inclusion criteria: minimum mean age of 50 years; minimum follow-up of 6 months; use of at least one validated functional outcome score (such as Constant, ASES, DASH, VAS, OSS, UCLA, or SANE); and preferably evaluation of range of motion and complications. Clinical case LOE IV studies, case series, abstracts, and conference proceeding were excluded. Although omission of "grey" data sources could potentially result in publication bias, it was considered unlikely that these studies would have fulfilled the eligibility criteria.

Literature search

A systematic review of the literature was performed to identify all publications in English and German, screening the databases Medline, Embase, Scopus, and Google Scholar. These databases were screened using the following terms and Boolean operators: "proximal humerus" AND/OR "fracture" AND/OR "Neer proximal humerus fracture" AND/OR "3-part"; AND/OR "4-part" AND/OR "2-part" AND/OR surgical treatment" AND/OR "operative treatment"; AND/OR "non-operative treatment"; AND/OR "non-surgical treatment"; AND/OR "conservative treatment". For the Medline search the following MeSH terms were used in addition to the above search strategy: "fracture, proximal humerus", "fractures, proximal humerus", "proximal humerus fracture", "humerus surgical neck fracture", "humeral surgical neck fracture", and "proximal humerus fractures". Two reviewers conducted independent title and abstract screening. Disagreements between reviewers were resolved by consensus, and if no consensus was reached they were carried forward to the full text review. All eligible articles were manually cross-referenced to ensure that other potential studies were identified.

Data extraction and quality assessment

An electronic data extraction form was used to obtain the following data from each article: level of evidence, country, age, gender, length of follow-up, sample size, clinical outcome scores, range of motion, and complications. Risk of bias was assessed using the Cochrane Collaboration's Risk of Bias Tool. [12] For LOE III studies the ROBINS-I tool was also used. The GRADE system was used by two reviewers to assess the quality of the body of evidence for each outcome measure. [12] The recommendations from the Cochrane Handbook were followed, and an initial level of certainty assigned. Studies were downgraded if there was a high risk of bias, inconsistency and imprecision of the results, and indirectness of evidence. Studies were upgraded if there were large treatment effects, a dose-response, or reasons to oppose plausible residual bias and confounding effects. Any disagreement between reviewers was resolved by consensus and/or by arbitration between the two senior authors.

Statistical analysis

Inter-observer differences for study eligibility and risk of bias were measured using Cohen's kappa coefficient. Heterogeneity of the data was assessed using χ^2 and I^2 statistics. Outcomes were pooled using a random effects model if the I^2 statistic was

>25%, and a fixed model was used if the statistic was <25%. Pooling of data for clinical outcomes, stability measures, and functional testing was only performed if a minimum of three studies were available. The prevalence of osteoarthritis between groups was pooled as a binary yes/no variable, and analyzed by calculating the odds ratios. If standard deviations were not reported the standard deviation was calculated using the following formula: SD = max-min/4. [12,26] All tests of significance were two-tailed, and an α of less than 0.05 was considered significant. Publication bias was assessed using funnel plots and Egger's test. Funnel and forest plots, and all statistical analyses, were performed using STATA SE (Version 13.0; StataCorp, College Station, Texas, USA) for Windows, and the comprehensive meta-analysis software package (CMA), version 3 (Biostat Inc, Englewood, NJ, USA).

Results

Study selection and characteristics

The initial literature search identified 3,725 studies for consideration. Of those, 2,488 studies were excluded for duplication, and the titles of the remaining 1,237 publications were checked for eligibility. Another 1,018 studies were excluded, and following abstract review of 219 studies, the full text manuscripts of 84 studies were examined. Twenty-two studies met all of the eligibility criteria and were included in the analysis (Figure 1). [3,4,6,15,16,19,22,25,27,31-33,35,39-41,43,44,46,48-50] Five studies were level I evidence [3,33,35,40,41] and two studies were level II evidence. [16,43] Fifteen studies were level III evidence. [4,6,15,19,22,25,27,31,32,39,44,46,48-50.] All 22 studies were published in English between 2003 and 2021 with a cumulative total of 1814 cases. A total of 817 cases were treated non-operatively and 997 cases underwent surgical treatment. Surgical treatment included reconstruction with locked plates, hemiarthroplasty, locked intramedullary nailing, and reverse total shoulder arthroplasty. The study characteristics are summarized in table 1. Overall agreement between the two reviewers for final eligibility was excellent (kappa value 0.92, 95% CI 0.89-0.95).

Figure 1: PRISMA Flow Diagram

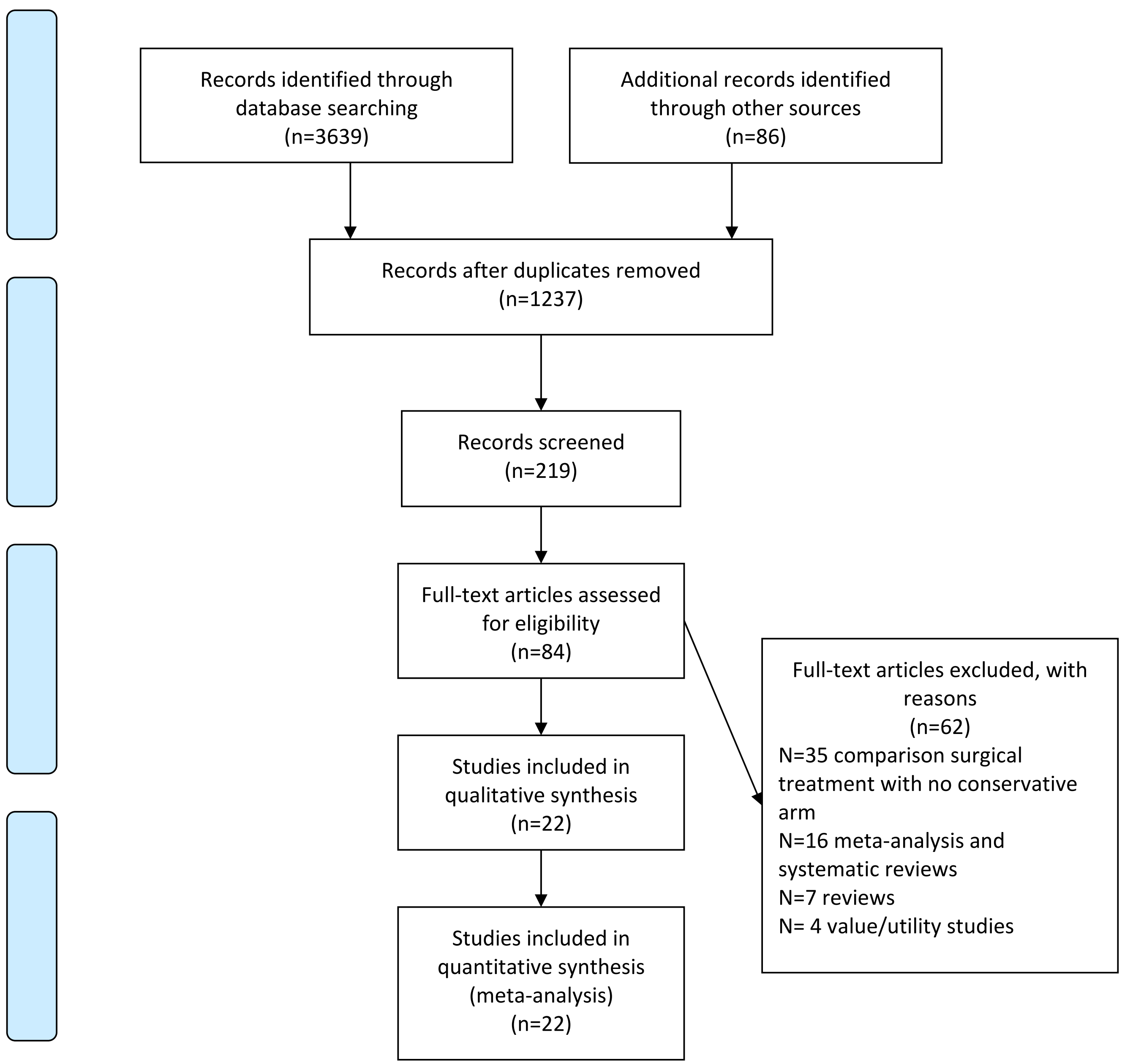

Table 1: Summary of all included studies

Authors	LOE	Country	Intervention	Patients (n) Surg -Cons	Age (years) Surg -Cons	Gender	Neer Surg -Cons	Follow-Up (months)	Outcome Surg - Cons
Kollig 2003	III	Germany	ORIF	13 9	52.5+14.7 52.7+11.5	M=9 F=13	3 part 6-1 4 part 7-8	52	Constant 72.1+21.1 – 82+15.6 HSS 64.7+20-73.6+17.6
Van den Broek 2007	III	Netherlands	Nail	23 16	64.6 (27-87) 69.4 (35-84)	M=6 F=18 M=2 F=14	4 part 24-16	15.8 (11-27) 68.8 (59-72.5)	VAS 3.9 (0-6) – 1.7 (0-5) Constant 67.1 (51-98) – 81.4 (71-100)
Olerud 2011	I	Sweden	Hemiarthroplasty	27 28	75.8 (58-90) 77.5 (60-92)	M=1 F=23 M=1 F=24	4 part: 24-25	24 24	Constant: 48.3+16.4 – 49.6+20.5 DASH: 30.2+18.3 – 36.9+21.3 VAS: 15-25 ROM Flexion 120-111 ROM Abduction: 114-106 Complications: 16% - 16%
Olerud 2011	I	Sweden	ORIF	30 29	72.9 (56-92) 74.9 (58-88)	M=6 F=24 M=5 F=24	3-part 30-29		Constant: 61.1+19.2 – 58.4+23.1 DASH: 26.4+25.2 – 35.0+26.8 VAS: 12.4+3.8 – 11.2+3.3 ROM Flexion 93-95 ROM Abduction: 86-87 Complications: 20% - 3.4%
Sanders 2011	III	Australia	ORIF	18 18	58+14 64+15	M=8 F=9 M=6 F=12	2 part: 3-3 3 part: 13-14 4 part: 2-1	37+12 42+26	EQ-5D VAS: 1.5 – 1.6 ASES: 71.6 – 82.5 Patient Satisfaction: 5.6 – 7.2 ROM Flexion: 131+37 – 157+28 ROM Extension: 43+11 – 40+16 ROM Ext. Rot.: 26+18 – 36+28 Complications: 56% - 11%
Boons 2012	I	Netherlands	Hemiarthroplasty	25 25	76.4+5.6 79.9+7.7	M=1 F=24 M=2 F=23	4 part: 25-25	12 12	VAS: 2.3 – 2.5 SST: 25 – 23 Constant 64+15.8 – 60+17.6 ROM Flexion: 98 (45-165) – 94 (45-165) ROM Ext. Rot. 17 (10-25) – 19 (15-25) Abduction: 77 (45-165) – 87 (30-130) Complications: 16% - 20%
Hausschild 2013	III	Germany	Plate, Nail	133 31	62.9+17.2 65.6+13.3	M=36 F=97 M=9 F=22		12	Constant 74.2+13 – 74.3+9.9 ROM Flexion: 166+17 – 113+32 ROM Abduction 132+38 – 131+35

									ROM Ext Rotation: 59+21 – 42+16 Complications: 47% - 10%
Innocenti 2013	III	Italy	Percut Wires	28 23	73.9+6 77.5+6.9	M=13 F=38		85 (48-108)	Constant: 80.7+5.2 – 76.4+9 VAS 3+2.1 – 3.1+1.7 ROM Flexion 151+25 – 123+23 Complications: none
Fjalestad 2014	II	Norway	ORIF	25 25	72.2 (60-86) 73.1 (60-88)	M=5 F=20 M=1 F=242	AO B2/C2 13/12 – 13/12	24	Constant: 75.1 (62-87) – 77.1 (68-85) ASES ADL: 14.8 (12-18) – 14.9 (13-18) Complications: 4% - 4% Nonunion 1 –1
Okike 2015	III	USA	ORIF	25 25	72.2 (60-88) 73.1 (60-88)	M=5 F=20 M=1 F=24	B2/C2 13/12 B2/C2 13/12	24	Constant: 88.2+8.8 – 82.2+9.1Tamimi Complications: 12% - 4%
Rangan 2015	II	UK	All	125 125	66.2+11.1 65.8+12	M=26 F=80 M=25 F=84		24	EQ-5D 0.43+0.35 – 0.35+0.36 OSS 40.1 (38.2-41.9) – 40.4 (38.6-42.1) SF 12 Phy: 45.7 (43.3-48.1) – 44.2 (41.9-46.5) SF 12 Ment: 49.3 (47-54.6) – 50.7 (48.4-53) Complications: 29% - 18%
Tamimi 2015	III	Canada	ORIF	44 25	65.3+15.2	M=15 F=29 M=6 F=19	2-4 part	25.9+15 28+8.5	Constant 62.9+16.8 – 57.2+2.7 DASH 38.4+19.2 – 38.4+19.2 Complications: 18% - 4%
Tamimi 2015	III	Canada	Nail	19 25	65.3+15.2	M=9 F=10 M=6 F=19	2-4 part	22.5+9.0 28+8.5	Constant 63.9+23.6 – 57.2+2.7 DASH 34.9+26.5– 38.4+19.2 Complications: 7% - 4%
Lange 2016	III	Germany	Nail	35 35	69.1 (37-88) 68.9 (42-93)	M=6 F=19 M=6 F=19	2-4 part	12	Constant 69-63 Complications: 37% - 0%
Ge 2017	III	China	ORIF	69 42	75.1+8.5 74.1+7.6	M=24 F=45 M=9 F=34	2 part: 38–23 3 part: 31-20	24	Constant 82.3+9.7 – 81.8+6.8 ASES 80.1+9.0 – 79.9+6.1 VAS: 0.81+0.6 – 0.95+0.51 ROM Flexion: 164+9 – 160+11.5 ROM Ext. Rot.: 48.3+6.9 – 42.6+6.9
Ge 2017	III	China	Nail	72 42	75.1+8.5 74.1+7.6	M=22 F=50 M=9 F=34	2 part: 38–23 3 part: 31-20	24	Constant 82.0+9.1 – 81.8+6.8 ASES 81.5+8.90 – 79.9+6.1 VAS: 0.83+0.7 – 0.95+0.51 ROM Flexion: 160.8+12.7 – 160+11.5 ROM External Rotation: 45.9+6.9 – 42.6+6.9
Hageman 2017	III	USA	K-wire, Plate, Nail	33 33	59.0+12.5 60.1+15.3	M=11F=22 M=9 F=24	2-part 19-12 3-part 11-16 4-part 3-5	36.1 68	DASH 19.0+7 – 8.3+5.2 Constant 67+10 -89+6.5 ROM Flexion: 120 (90-165) 170 (133-180) ROM Abduction 120 (90-165) – 160 (120-180) Complications: 15% - 6%

Roberson 2017	III	USA	Reverse Shoulder Arthroplasty	20 19	71 71	M=1 F=19 M=4 F=15	3+4 part	53 29	ASES 72 – 72 SANE 77-78 VAS 1.5-1.1 ROM Flexion: 119-120 ROM Ext. Rot.: 31-23 Complications: 15% - 0%
Brouwer 2019	III	Netherlands	Plate, Nail, hemi	33 33	72+4.8 72+5.9	M=6 F=26 M=5 F=54		58 (10-131)	EQ-5D 0.74+0.21 – 0.7+0.28 DASH 31+23.2-32.8+26.8 VAS 2.3+2.3 – 3+2.6 Complications: 28%-16%
Caliskan 2019	III	Turkey	ORIF	45 47	53.2 (26-78) 58.4 (25-89)	M=24 F=45 M=9 F=34	2 part: 11-12 3 part: 21-22 4 part: 13-13	25	ASES 93.2 – 82.3 VAS 1-2.3 ROM Flexion: 128-127 ROM Abduction: 100-110Roberson 2017
Launonen 2019	I	Finland	ORIF	33 39	72+7.4 73+7.7	M=2 F=31 M=5 F=34	2 part: 33-39	24	DASH 18.5+3.1 – 17.4+2.8 OSS 40.2+1.5-41.5+1.4 Constant 68+3.2-66+3.3 EQ-5D 0.89+0.02-0.87+0.02 VAS 9.9+2.7-11.5+3.3 Complications: 6% - 0%
Lopiz 2019	I	Spain	Reverse	29 30	82+3.4 85+4.8	M=4 F=25 M=4 F=26	3 part: 4–5 4 part: 25-25	14	Constant 81.2+12.1 – 79.6+12.4 DASH 20.7+13.9 – 28.8+19.6 VAS 0.9+0.9 – 1.6+2.2 EQ-5D 0.93+0.13 – 0.89+0.14 SF 12 Phys 37.1+6.3 SF 12 Mental 41.6+9.5 – 42.9+9.8 Complications: 6.9% - 0%
Spross 2019	III	Switzerland	Hemiarthroplasty	4 132	M= 58.4 F=69.1	M=58 F=134	2-4 part	12	Constant 44- 76 VAS 14.6-13.7 ROM Flexion 70-145 Complications 50% -2%
Spross 2019	III	Switzerland	ORIF	36 132	M= 58.4 F=69.1	M=58 F=134	2-4 part	12	Constant 63-76 VAS 12-13.7 ROM Flexion 122-145 Complications 44% - 2%
Spross 2019	III	Switzerland	Reverse	20 132	M= 58.4 F=69.1	M=58 F=134	2-4 part	12	Constant 69 – 76 VAS 13.3-13.7 ROM Flexion 134-145 Complications 0% -2%
Erpala 2021	III	Turkey	Hemiarthroplasty	15 14	68.5+11.3 77.1+6.5	M=5 F=10 M=3 F=11	3 part 10-12 4 part 5-2	42.3 (21-54) 33.1 (25-39)	DASH 23.3 (14.6-36.2) – 16.4 (12-37) Constant 49.7+11.8 – 69.9+19.2 ASES 54.9 (42-78) – 76.6 (45-88) ROM Flexion 61+23 – 100-31

									ROM Abduction 55+18-97+25 ROM External Rotation 30 (10-60) – 60 (30-67)
Erpala 2021	III	Turkey	ORIF	18 14	69.5+11.5 77.1+6.5	M=6 F=12 M=35 F=11	3 part 12-12 4 part 6-2	24.2 (20-38) 33.1 (25-39)	DASH 12.1 (5.2-24.2) – 16.4 (12-37) Constant 71.6+16.2 – 69.6+19.2 ASES 77.5 (51-97)- 76.6 (45-88) ROM Flexion 106+34-100+31 ROM Abduction 102+38 – 97+24 ROM External Rotation 52 (30-60)- 60 (30-60)

Table 2 Risk of Bias Cochrane Risk of Bias Assessment Tool Version 2

Authors	LOE	Bias from Randomization	Bias from Deviations from Intended Interventions	Bias due to Missing Outcome Data	Bias in Measurement of the Outcome	Bias in Selection of the Reported Results	Overall Risk of Bias
Olerud (Hemi) 2011	I	Some	Some	Low	Low	Low	Some
Olerud (Plate) 2011	I	Some	Low	Low	Low	Low	Some
Boons 2012	I	Low	Low	Low	Low	Low	Low
Launonen 2019	I	Some	Low	High	Low	Low	High
Lopiz 2019	I	Some	Low	Low	Low	Low	Some
Fjalestad 2014	II	High	Some	Some	Low	Low	High
Rangan 2015	II	Low	Some	Some	Low	Some	Some
Kollig 2003	III		Low	High	Low	Low	High
Van den Broek 2007	III		Low	High	Low	Low	High
Sanders 2011	III		Low	Low	Low	Low	Low
Hausschild 2013	III		Some	Some	Low	Low	Some
Innocenti 2013	III		Some	low	Low	Low	Some
Okike 2015	III		Some	High	Low	Low	High
Tamimi 2015	III		High	High	Low	Low	High
Lange 2016	III		Some	Some	Low	Some	Some
Ge 2017	III		High	Low	Low	Low	High
Hageman 2017	III		Low	Low	Low	Low	Low
Roberson 2017	III		Some	Some	Low	Low	Some
Brouwer 2019	III		Some	High	Low	Low	High
Caliskan 2019	III		Some	Low	Low	Low	Some
Spross 2019	III		Some	High	High	Low	High
Erpala 2021	III		Some	High	Low	Low	High

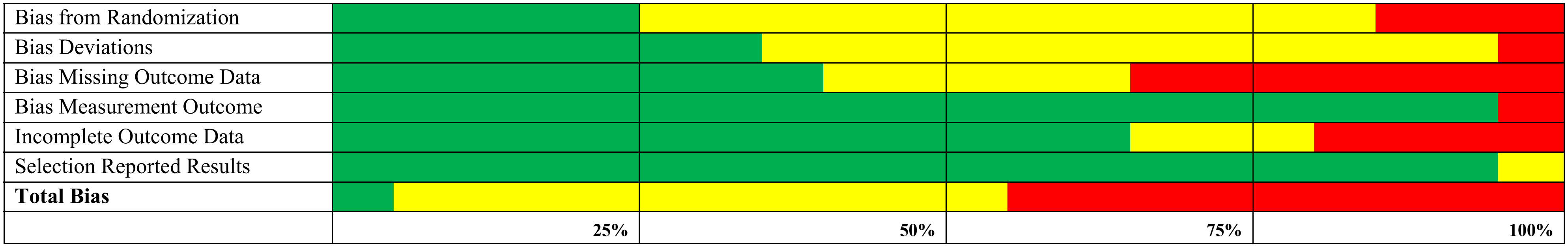
Bias from Randomization
Bias Deviations
Bias Missing Outcome Data
Bias Measurement Outcome
Incomplete Outcome Data
Selection Reported Results
Total Bias
25%
50%
75%
100%

Table 3 Risk of Bias ROBINS Cochrane Risk of Bias Assessment Tool Version 2

Authors	LOE	Bias due to Confounding	Bias in Selection of Participants	Bias in Classification of Interventions	Bias due to Deviations from Intended Interventions	Bias due to Missing Data	Bias in Measurement of Outcomes	Bias in Selection of the Reported Results	Overall Bias
Kollig 2003	III	Serious	Moderate	Moderate	Moderate	Critical	Low	Low	Critical
Van den Broek 2007	III	Low	Moderate	Low	Low	Critical	Low	Moderate	Critical
Sanders 2011	III	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Hausschild 2013	III	Moderate	Moderate	Moderate	Moderate	Moderate	Low	Moderate	Moderate
Innocenti 2013	III	Moderate	Moderate	Moderate	Moderate	Low	Low	Low	Moderate
Okike 2015	III	Moderate	Moderate	Moderate	Moderate	Critical	Low	Low	Critical
Tamimi 2015	III	Serious	Moderate	Serious	Critical	Serious	Low	Low	Critical
Lange 2016	III	Moderate	Moderate	Low	Moderate	Serious	Low	Moderate	Serious
Ge 2017	III	Serious	Moderate	Serious	Critical	Low	Low	Low	Critical
Hageman 2017	III	Low	Moderate	Low	Low	Low	Low	Low	Moderate
Roberson 2017	III	Moderate	Moderate	Serious	Lowe	Serious	Low	Low	Serious
Brouwer 2019	III	Serious	Moderate	Moderate	Serious	Critical	Low	Low	Critical
Caliskan 2019	III	Moderate	Moderate	Moderate	Moderate	Low	Low	Low	Moderate
Spross 2019	III	Serious	Serious	Moderate	Serious	Critical	Serious	Low	Critical
Erpala 2021	III	Critical	Moderate	Moderate	Moderate	Moderate	Low	Low	Critical

Risk of bias and quality assessment

The findings of the risk of bias assessment are summarized in tables 2 and 3.

Risk of bias Cochrane Assessment Tool Version 2

One of the LOE I study [33] was assessed as having a high risk of bias due to missing outcome data; three studies [35,40,41] had some risk of bias because of bias from randomization and only one study [3] had an overall low risk of bias. One LOE II study [16] had a high risk of bias because of bias from randomization and one study [43] had some bias. Eight of the fifteen level III studies [4,15,19,31,39,48,49,50] had a high risk of bias. Seven studies [4,15,31,39,48,49,50] had bias due to missing data and one study [19] deviated from the intended interventions. Four studies [25,27,32,44] had some bias mainly due to missing outcome data and bias deviations from the intended interventions. Two studies [22,46] were assessed as having an overall low risk of bias.

Risk of bias ROBINS-I Assessment Tool

For observational studies the ROBINS-I tool was also used to assess the risk of bias. Only five studies [6,22,25,27,46] had a moderate risk of bias. These studies [6,22,25,27,46] had bias due to confounding, bias in the selection of participants, [6,25,27,46] and bias due to deviations from the intended interventions. [6,25,27] Two studies [32,44] had a serious risk of bias due to missing data; for eight studies the main bias was attributed to missing data. [4,15,19,31,39,48-50]

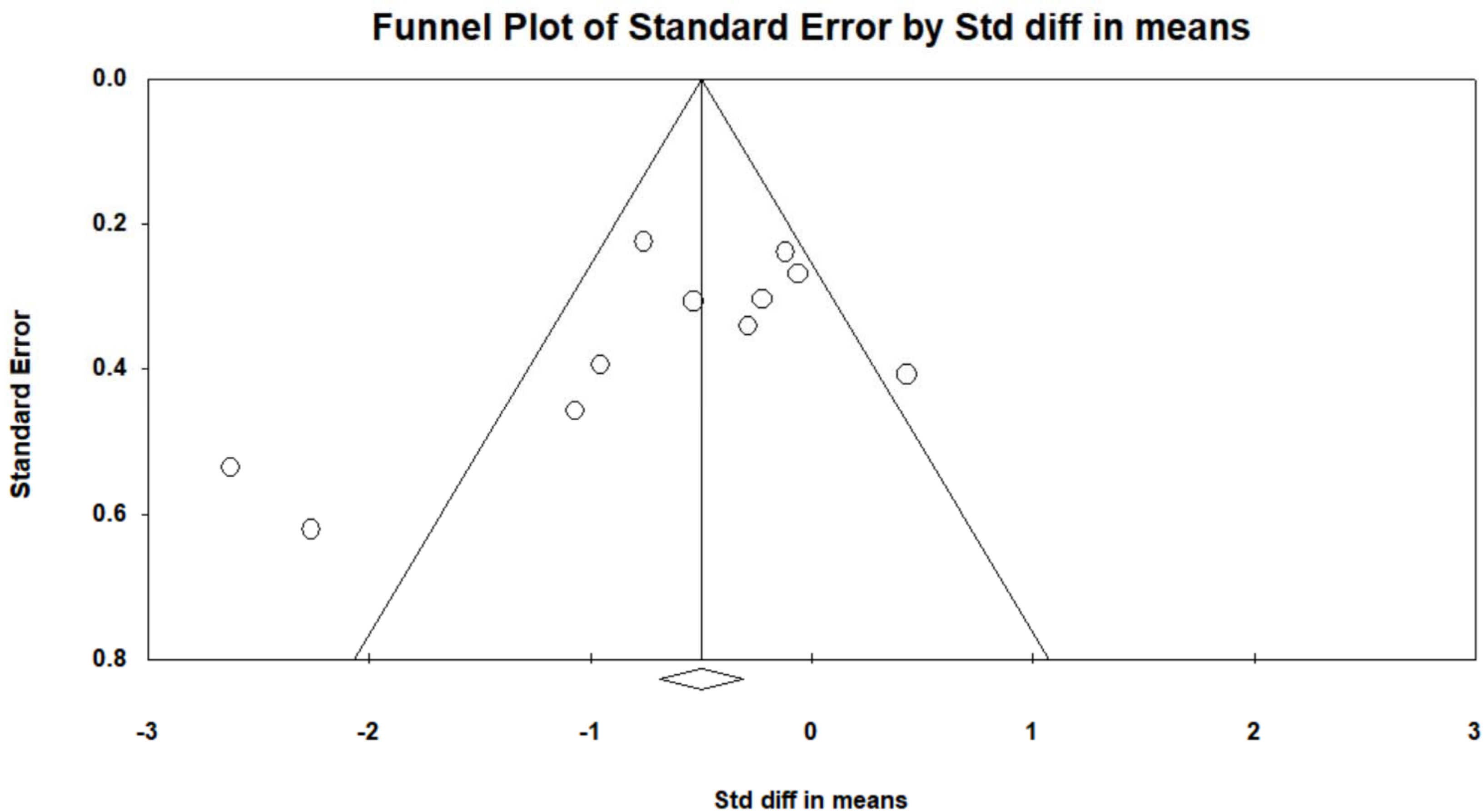

Figure 2. Publication bias: The funnel plot was symmetric but 3 studies were outside the triangle. Egger regression intercept (Intercept −3.803, t-value 2.109, p-level 0.06) was nearly significant.

Table 4: Quality Assessment using the Cochrane GRADE system

Authors	LOE	Initial Level of Certainty	**Final Level of Certainty**	Risk of Bias	Inconsistency of Results	Indirectness of evidence	Imprecision of Results	Large Effects (Upgrading)	Dose Response (Upgrading)	Opposing Plausible Residual Bias and Confounding (Upgrading)
Olerud (Hemi) 2011	I	High	**Very Low**	Some	Considerable I^2	N/A	95% CI missing	N/A	N/A	N/A
Olerud (Plate) 2011	I	High	**Very Low**	Some	Considerable I^2	N/A	95% CI missing	N/A	N/A	N/A
Boons 2012	I	High	**Very Low**	Low	Considerable I^2	N/A	95% CI missing	N/A	N/A	N/A
Launonen 2019	I	High	**Very Low**	High	Considerable I^2	N/A	95% CI missing	N/A	N/A	N/A
Lopiz 2019	I	High	**Very Low**	Some	Considerable I^2	N/A	95% CI missing	N/A	N/A	N/A
						N/A	95% CI missing	N/A	N/A	N/A
Fjalestad 2014	II	Low	**Very Low**	High	Considerable I^2	N/A	95% CI missing	N/A	N/A	N/A
Rangan 2015	II	Low	**Very Low**	Some	Considerable I^2	N/A	95% CI missing	N/A	N/A	N/A
Kollig 2003	III	Low	**Very Low**	High	Considerable I^2	N/A	95% CI missing	N/A	N/A	N/A
Van den Broek 2007	III	Low	**Very Low**	High	Considerable I^2	N/A	95% CI missing	N/A	N/A	N/A
Sanders 2011	III	Low	**Very Low**	Low	Considerable I^2	N/A	95% CI missing	N/A	N/A	N/A
Hausschild 2013	III	Low	**Very Low**	Some	Considerable I^2	N/A	95% CI missing	N/A	N/A	N/A
Innocenti 2013	III	Low	**Very Low**	Some	Considerable I^2	N/A	95% CI missing	N/A	N/A	N/A
Okike 2015	III	Low	**Very Low**	High	Considerable I^2	N/A	95% CI missing	N/A	N/A	N/A
Tamimi 2015	III	Low	**Very Low**	High	Considerable I^2	N/A	95% CI missing	N/A	N/A	N/A
Lange 2016	III	Low	**Very Low**	Some	Considerable I^2	N/A	95% CI missing	N/A	N/A	N/A
Ge 2017	III	Low	**Very Low**	High	Considerable I^2	N/A	95% CI missing	N/A	N/A	N/A
Hageman 2017	III	Low	**Very Low**	Low	Considerable I^2	N/A	95% CI missing	N/A	N/A	N/A
Roberson 2017	III	Low	**Very Low**	Some	Considerable I^2	N/A	95% CI missing	N/A	N/A	N/A
Brouwer 2019	III	Low	**Very Low**	High	Considerable I^2	N/A	95% CI missing	N/A	N/A	N/A
Caliskan 2019	III	Low	**Very Low**	Some	Considerable I^2	N/A	95% CI missing	N/A	N/A	N/A
Spross 2019	III	Low	**Very Low**	High	Considerable I^2	N/A	95% CI missing	N/A	N/A	N/A
Erpala 2021	III	Low	**Very Low**	High	Considerable I^2	N/A	95% CI missing	N/A	N/A	N/A

Grade Quality Assessment and Publication Bias

The Grade quality assessment is summarized in table 4. All included studies were downgraded to very low quality. Inconsistency of results due to a considerable I2, imprecision of results as none of the studies included the 95% confidence interval, and risk of bias assessment identified at least some bias in all 22 included studies. There is the potential for publication bias. Although the funnel plot was symmetric,three studies were outside the triangle. Egger regression intercept (Intercept -3.803, t-value 2.109, p-level 0.06) was nearly significant (Figure 2).

Clinical outcomes and between implant comparisons

The clinical outcomes for all studies are summarized in table 1. All studies with the exception of Rangan, et al. [43] either reported Constant or ASES scores, and were therefore included in the analysis. The pooled estimate for these studies did not demonstrate significant differences between surgical and conservative treatment (SMD -0.168, 95% CI: -1.259 to 0.208, p=0.208, I^2= 83%; Figure 3). According to Cohen the magnitude effect is small, suggesting that the differences between groups are negligible. [9]

Range of motion

Eleven studies evaluated range of motion of the shoulder. [3,6,15,22,25,27,40,41,46,48]

Abduction

Eight studies reported the range of motion for abduction. [3,6,15,22,25,40,41,48.] The pooled estimate did not demonstrate significant differences between surgical and conservative treatment (SMD -0.366, 95% CI: -1.022 to 0.275, p=0.275, I^2= 92%;

Surgical versus Conservative Treatment

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Kollig 2003	-0.519	0.441	0.194	-1.382	0.345	-1.177	0.239	3.22
Van den Broek 2007	-1.406	0.362	0.131	-2.117	-0.696	-3.881	0.000	3.63
Olerud 2011.1	-0.070	0.270	0.073	-0.599	0.459	-0.259	0.796	4.12
Olerud 2011.2	0.127	0.261	0.068	-0.384	0.638	0.488	0.625	4.17
Sanders 2011	-0.617	0.341	0.116	-1.285	0.052	-1.807	0.071	3.74
Boons 2012	0.239	0.284	0.081	-0.317	0.796	0.843	0.399	4.05
Hausschild 2013	-0.008	0.199	0.040	-0.399	0.383	-0.040	0.968	4.46
Innocenti 2013	0.601	0.288	0.083	0.037	1.164	2.088	0.037	4.03
Fjalestad 2014	-0.383	0.285	0.081	-0.943	0.176	-1.343	0.179	4.04
Okike 2014	0.670	0.291	0.084	0.101	1.240	2.306	0.021	4.01
Tamimi 2015.1	0.420	0.253	0.064	-0.075	0.916	1.662	0.097	4.21
Tamimi 2015.2	0.430	0.308	0.095	-0.173	1.033	1.397	0.162	3.92
Lange 2017	0.387	0.241	0.058	-0.086	0.860	1.604	0.109	4.27
Ge 2017.1	0.024	0.196	0.038	-0.360	0.408	0.123	0.902	4.48
Ge 2017.2	0.024	0.194	0.038	-0.357	0.405	0.124	0.902	4.49
Hageman 2017	-2.609	0.335	0.112	-3.265	-1.952	-7.789	0.000	3.78
Roberson 2017	0.000	0.320	0.103	-0.628	0.628	0.000	1.000	3.85
Caliskan 2019	0.453	0.211	0.045	0.039	0.867	2.146	0.032	4.41
Launonen 2019	0.615	0.242	0.059	0.140	1.089	2.539	0.011	4.26
Lopiz 2019	0.131	0.261	0.068	-0.380	0.642	0.501	0.616	4.17
Spross 2019.1	-1.697	0.518	0.268	-2.712	-0.682	-3.277	0.001	2.84
Spross 2019.2	-0.706	0.192	0.037	-1.082	-0.330	-3.679	0.000	4.50
Spross 2019.3	-0.373	0.241	0.058	-0.845	0.099	-1.549	0.121	4.27
Erpala 2021	-1.141	0.401	0.161	-1.926	-0.355	-2.847	0.004	3.42
Erpala 2021.2	0.114	0.357	0.127	-0.585	0.813	0.319	0.749	3.66
	-0.168	0.133	0.018	-0.429	0.093	-1.259	0.208	

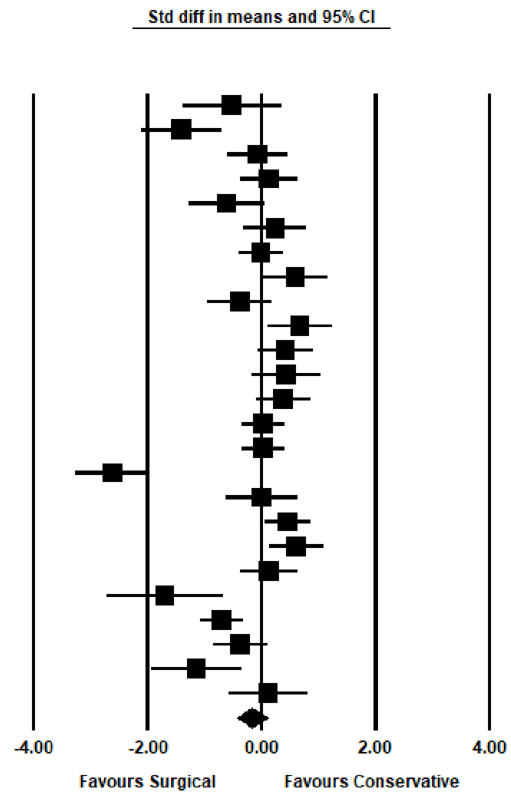

Figure 3. Forest plot comparing clinical outcomes between surgical and non-surgical treatment. The pooled estimate for all studies could not demonstrate significant differences (P = .208).

Surgical versus Conservative Treatment

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Olerud 2011.1	0.320	0.271	0.074	-0.212	0.852	1.179	0.238	11.28
Olerud 2011.2	0.706	0.297	0.088	0.124	1.289	2.376	0.017	11.12
Boons 2012	-0.362	0.285	0.081	-0.921	0.197	-1.270	0.204	11.20
Hausschild 2013	0.845	0.195	0.038	0.462	1.228	4.322	0.000	11.70
Hageman 2017	-2.495	0.328	0.108	-3.139	-1.852	-7.601	0.000	10.91
Caliskan 2019	-0.400	0.211	0.044	-0.813	0.013	-1.899	0.058	11.63
Spross 2019.3	-0.373	0.241	0.058	-0.845	0.099	-1.549	0.121	11.47
Erpala 2021	-1.940	0.451	0.203	-2.823	-1.057	-4.305	0.000	9.99
Erpala 2021.2	0.153	0.357	0.127	-0.546	0.852	0.429	0.668	10.71
	-0.366	0.335	0.112	-1.022	0.290	-1.093	0.275	

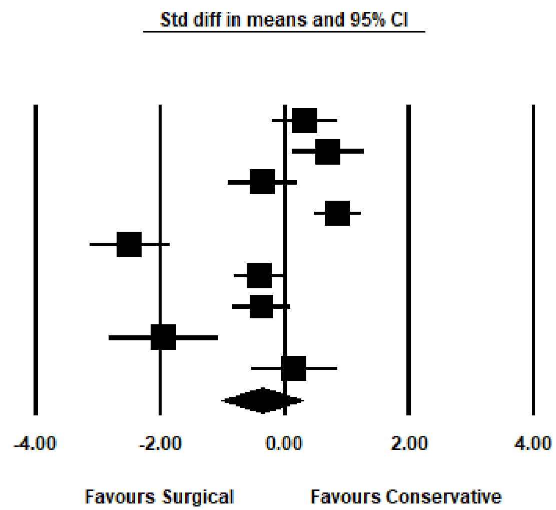

Figure 4. Forest plot comparing range of motion (abduction) between surgical and nonsurgical treatment. The pooled estimate for all studies could not demonstrate significant differences (P = .275).

Figure 4). Although the SMD favored surgical treatment the magnitude effect was small, strongly suggesting that the differences between groups were negligible. [9]

Forward Flexion

Eleven studies reported the range of motion for forward flexion. [3,6,15,22,25,27,40,41,46,48] The pooled estimate did not demonstrate significant differences between surgical and conservative treatment (SMD -0.206, 95% CI: -0.737 to 0.325, p=0.447, I^2= 94%; Figure 5). Although the SMD favored surgical treatment the magnitude effect was small, strongly suggesting that the differences between groups were negligible. [9]

External rotation

Five studies reported the range of motion for external rotation. [3,15,19,44,46] The pooled estimate did not demonstrate significant differences between surgical and conservative treatment (SMD 0.348, 95% CI: -0.819 to 0.547, p=0.696, I^2= 89%; Figure 6). Although the SMD favored surgical treatment the magnitude effect was small, strongly suggesting that the differences between groups were negligible.

Complications

A total of fifteen studies reported complications. [3,4,22,25,32,33,35,39,40,41,43,44,46,48,49]. The pooled estimates demonstrated significantly overall lower complication rates in the conservative (nonoperative) treatment group (Odds ratio 3.307, 95% confidence intervals 1.947-5.616, p=0.0001) (Figure 7). [7]

Surgical versus Conservative Treatment

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Olerud 2011.1	0.360	0.272	0.074	-0.173	0.893	1.324	0.185	6.69
Olerud 2011.2	-0.080	0.289	0.083	-0.646	0.486	-0.277	0.782	6.64
Sanders 2011	-0.792	0.346	0.120	-1.471	-0.114	-2.289	0.022	6.42
Boons 2012	0.160	0.283	0.080	-0.395	0.715	0.565	0.572	6.66
Hausschild 2013	2.528	0.235	0.055	2.068	2.988	10.769	0.000	6.81
Ge 2017	0.399	0.198	0.039	0.012	0.787	2.022	0.043	6.91
Ge 2017.2	0.065	0.194	0.038	-0.315	0.446	0.336	0.737	6.92
Hageman 2017	-2.828	0.348	0.121	-3.511	-2.146	-8.124	0.000	6.42
Roberson 2017	-0.040	0.295	0.087	-0.619	0.539	-0.136	0.892	6.61
Caliskan 2019	0.040	0.209	0.044	-0.369	0.449	0.192	0.848	6.88
Spross 2019.1	-0.793	0.193	0.037	-1.171	-0.414	-4.108	0.000	6.93
Spross 2019.2	-0.782	0.244	0.060	-1.260	-0.304	-3.203	0.001	6.78
Spross 2019.3	-0.374	0.241	0.058	-0.846	0.098	-1.552	0.121	6.79
Erpala 2021	-1.400	0.415	0.172	-2.212	-0.587	-3.376	0.001	6.14
Erpala 2021.2	0.183	0.357	0.128	-0.517	0.883	0.513	0.608	6.38
	-0.206	0.271	0.073	-0.737	0.325	-0.761	0.447	

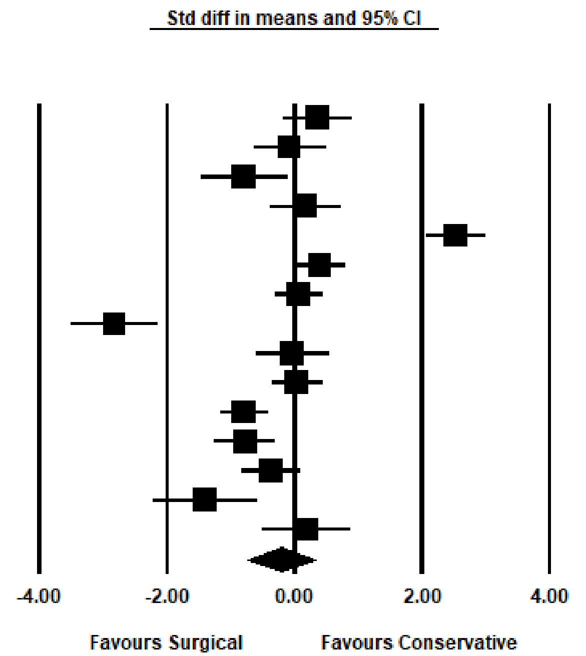

Figure 5. Forest plot comparing range of motion (forward flexion) between surgical and nonsurgical treatment. The pooled estimate for all studies could not demonstrate significant differences (P = .447) but favoured surgical treatment.

Surgical versus Conservative Treatment

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Sanders 2011	-0.425	0.337	0.114	-1.086	0.236	-1.260	0.208	14.12
Boons 2012	-0.600	0.289	0.084	-1.166	-0.033	-2.074	0.038	14.63
Ge 2017.1	0.826	0.203	0.041	0.427	1.225	4.061	0.000	15.42
Ge 2017.2	0.326	0.211	0.045	-0.089	0.740	1.540	0.124	15.35
Roberson 2017	1.285	0.352	0.124	0.596	1.975	3.653	0.000	13.96
Erpala 2021	-2.022	0.457	0.209	-2.917	-1.127	-4.427	0.000	12.72
Erpala 2021.2	-0.638	0.365	0.133	-1.354	0.077	-1.748	0.080	13.80
	-0.136	0.348	0.121	-0.819	0.547	-0.391	0.696	

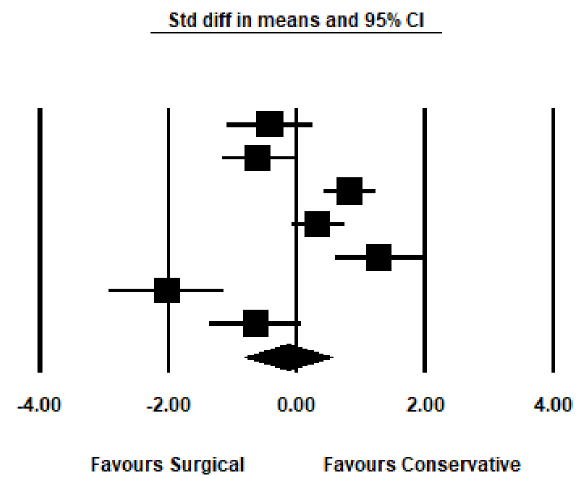

Figure 6. Forest plot comparing range of motion (external rotation) between surgical and nonsurgical treatment. The pooled estimate for all studies could not demonstrate significant differences (*P* = .696).

Surgical versus Conservative Treatment

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Olerud 2011.1	1.000	0.236	4.229	0.000	1.000	6.99
Olerud 2011.2	7.000	0.786	62.302	1.745	0.081	4.18
Sanders 2011	10.000	1.756	56.933	2.595	0.009	5.66
Boons 2012	0.762	0.179	3.249	-0.367	0.713	6.95
Hausschild 2013	8.150	2.362	28.120	3.320	0.001	8.09
Spross 2019	1.400	0.177	11.083	0.319	0.750	4.52
Okike 2015	3.273	0.317	33.837	0.995	0.320	3.80
Rangan 2015	1.894	1.038	3.456	2.081	0.037	12.23
Tamimi 2015.1	1.756	0.173	17.844	0.476	0.634	3.84
Tamimi 2015.2	1.806	0.126	25.979	0.435	0.664	3.10
Lange 2016	20.091	2.452	164.635	2.796	0.005	4.41
Hageman 2017	2.768	0.497	15.420	1.162	0.245	5.75
Roberson 2017	3.176	0.300	33.583	0.961	0.337	3.74
Brouwer 2019	2.100	0.619	7.125	1.190	0.234	8.19
Launonen 2019	2.452	0.212	28.321	0.718	0.473	3.54
Lopiz 2019	2.148	0.184	25.069	0.610	0.542	3.52
Spross 2019.1	34.400	9.189	128.775	5.253	0.000	7.63
Spross 2019.2	2.263	0.224	22.888	0.692	0.489	3.85
	3.307	1.947	5.616	4.425	0.000	

Odds ratio and 95% CI

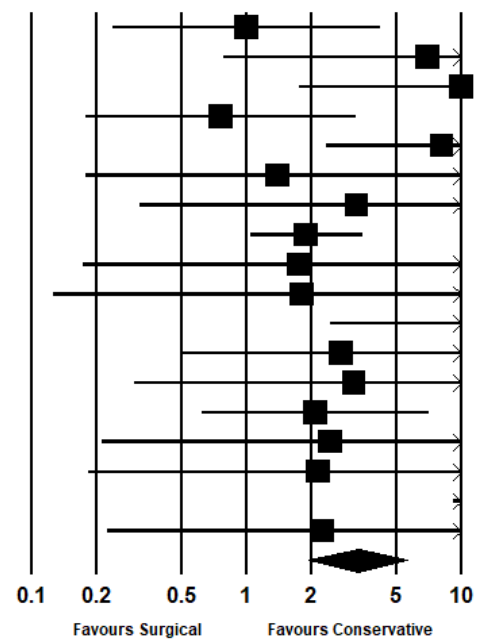

Figure 7. Forest plot comparing complication rates between surgical and nonsurgical treatment. The pooled estimate for all studies demonstrated significantly *Lower* complication rates for conservative treatment ($P = .0001$).

Discussion

The results of this meta-analysis demonstrated that there was no difference for either clinical outcomes or range of motion when comparing surgical and conservative treatment for proximal humerus fractures. However, complication rates were 3.3 times higher following surgical treatment.

Jadad et al. [28] rovided guidelines regarding how to interpret discordant systematic reviews based on identifying the sources and types of discordance, and recommended selecting the review with the highest evidence. Fu et al. [18] used this approach to perform a systematic review of overlapping meta-analyses, comparing surgical to non-surgical treatment for 3- and 4-part proximal humerus fractures. They applied the Jadad decision algorithm to select the most appropriate study from the ten included systematic reviews and meta-analyses, and concluded that the meta-analysis by Rabi et al. [42] was the most concordant study. Based on their analysis, Rabi et al supported surgical treatment for 3- and 4-part proximal humerus by demonstrating advantages compared to non-surgical treatment, but noted it is associated with a higher incidence of postoperative complications. Unfortunately, the Jadad algorithm was never validated and is not reproducible. [36] Lunny et al. therefore proposed that, in the absence of a validated algorithm, the most recent and comprehensive meta-analysis with the lowest risk of bias that most closely resembles the clinical question should be selected. [36] Currently, Rabi et al. [42] is the most recent publication and includes six studies; this was again generally supportive of operative treatment, and concluded that there was no significant difference in physical function, but significantly lower pain scores were reported in the surgical group.

An earlier meta-analysis by Fu et al. [17] included six studies and was also unable to demonstrate any significant clinical advantages of operative over conservative treatment for displaced proximal humerus fractures. Li et al. [34] compared internal fixation to nonoperative treatment for 3- and 4-part fractures, and their analysis also did not support operative treatment. The value of their meta-analysis was limited by the inclusion of only three studies and the omission of a risk of bias assessment, which severely limited internal validity. Du et al. [14] completed a network meta-analysis of randomized trials and established that reverse shoulder arthroplasty was associated with the best clinical outcomes and the lowest reoperation rates, followed by hemiarthroplasty, nonoperative treatment, and internal fixation. Their results were limited by low sample size, the inclusion of only seven studies, and a high risk of bias. [14] A previous network meta-analysis confirmed superiority of reverse shoulder arthroplasty for displaced humerus fractures, but considered internal fixation superior to nonoperative treatment, followed by hemiarthroplasty. [8] Beks et al included both observational and randomized controlled trials, and concluded that the pooled effects support nonoperative treatment for patients aged 65 years and older. [1] In addition, they demonstrated that there was no difference between the outcomes of observational or randomized controlled trials, increasing external validity. [1]

Compared to Rabi et al., [42] our meta-analysis has included sixteen newer studies, and this has increased the sample size by nearly 800%. Beks et al. [1] included studies until September 2017 with a total of 1743 patients, while our meta-analysis included a total of 1814 patients, increasing the total number by only 4 percent. Although nine more recent studies were added, this meta-analysis has not changed the conclusions that were drawn by Beks et al. Pooling studies that fulfilled the inclusion criteria, nonoperative treatment had similar clinical outcomes to surgical treatment.

The value and quality of the meta-analysis by Beks et al. [1] could be criticized for not strictly following the Cochrane guidelines. For example, risk of bias assessment was not performed and the study quality was assessed using the MINORS criteria rather than the prescribed assessment scores outlined in the Cochrane Handbook. However, they have instead performed a sensitivity analysis, substantially enhancing the validity of their conclusions.

The Cochrane Handbook stipulates that high risk of bias within and across trials will alter the results seriously, and is sufficient to affect the interpretation of results. [12] In this meta-analysis the across trial high risk of bias was 37%, and 50% had some bias. This is sufficient to therefore conclude that the results should be interpreted with caution. Similar, the quality assessment using the Cochrane GRADE system determined that the final level of certainty for all studies was very low, and the main variables that caused downgrading were the risk of bias assessment, the inconsistency of results, considerable heterogeneity, and imprecision of results. The Cochrane Handbook concludes that this reduces the confidence in the effect estimate and is sufficient to affect the interpretation of results, with the true effect potentially being different. The Grade Recommendations for clinicians are consequently considered to be very weak. [12] It is acknowledged that there are already a considerable number of existing systematic reviews on this topic. The current meta-analysis has added the latest publications and has not changed the overall direction of the previous recommendations. Nonetheless, this meta-analysis provides the most recent and comprehensive analysis, and as such supersedes previous publications. It has included the largest number of patients and greatest number of studies. However, the current evidence still appears to be unable to provide clear guidelines regarding how best to treat proximal humerus fractures. It likely will be necessary to isolate explicit fracture types, specific patient characteristics, and particular comorbidities to determine what type of patients with which fracture pattern would benefit from surgical intervention, or can instead be safely treated nonoperatively. Until then, it appears that factors such as age, comorbidities, patient expectations, previous function, life expectancy, dementia, and other variables should be considered when deciding on the preferred treatment option for an individual patient. [38]

Limitations

The results of this meta-analysis should be interpreted in light of the following limitations. The results may have been influenced by missed studies; although the search strategy was extensive and multiple databases were utilized, the search was limited to English and German publications only. It is possible that high quality evidence was published in other languages, and publication bias cannot entirely be excluded. However, the funnel plot and Eggers' intercept do not indicate publication bias was introduced. Both randomized controlled trials and comparative observational studies were included; it is possible that, unlike randomized trials, groups are unbalanced on confounding factors, introducing bias. The study did not specifically differentiate between 2-part, 3-part, or 4-part fractures, and sub-analysis was not performed. However, the majority of the included studies did not report results for specific fracture patterns making sub-analysis difficult. In addition, this study did not specifically control for either patient age or length of follow-up.

Conclusions

The results of this meta-analysis demonstrated that there were no statistically significant differences for both clinical outcomes and range of motion between surgical and conservative (nonoperative) treatment for displaced proximal humerus fracturs. However, the overall complication rates were 3.3 times higher with surgical treatment. The study validity is compromised by high risk of bias and very low level of certainty, and these results must, therefore, be viewed with caution.

Funding

No funding was received for this study

Declaration of Competing Interest

The authors declare no conflict of interest

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