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REVIEW ARTICLE

Operative versus nonoperative treatment of proximal humeral fractures: a systematic review, meta-analysis, and comparison of observational studies and randomized controlled trials

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Background: There is no consensus on the choice of treatment for displaced proximal humeral fractures in older patients (aged > 65 years). The aims of this systematic review and meta-analysis were (1) to compare operative with nonoperative management of displaced proximal humeral fractures and (2) to compare effect estimates obtained from randomized controlled trials (RCTs) and observational studies.

Methods: The databases of MEDLINE, Embase, CENTRAL (Cochrane Central Register of Controlled Trials), and CINAHL (Cumulative Index to Nursing and Allied Health Literature) were searched on September 5, 2017, for studies comparing operative versus nonoperative treatment of proximal humeral fractures; both RCTs and observational studies were included. The criteria of the Methodological Index for Non-Randomized Studies, a validated instrument for methodologic quality assessment, were used to assess study quality. The primary outcome measure was physical function as measured by the absolute Constant-Murley score after operative or nonoperative treatment. Secondary outcome measures were major reinterventions, nonunion, and avascular necrosis.

No institutional review board approval was necessary for this study.

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Results: We included 22 studies, comprising 7 RCTs and 15 observational studies, resulting in 1743 patients in total: 910 treated operatively and 833 nonoperatively. The average age was 68.3 years, and 75% of patients were women. There was no difference in functional outcome between operative and nonoperative treatment, with a mean difference of -0.87 (95% confidence interval, -5.13 to 3.38; P = .69; $I^2 = 69\%$). Major reinterventions occurred more often in the operative group. Pooled effects of RCTs were similar to pooled effects of observational studies for all outcome measures.

Conclusions: We recommend nonoperative treatment for the average elderly patient (aged > 65 years) with a displaced proximal humeral fracture. Pooled effects of observational studies were similar to those of RCTs, and including observational studies led to more generalizable conclusions.

Level of evidence: Level III; Systematic Review

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Keywords: Proximal humeral fracture; operative treatment; nonoperative treatment; observational studies; randomized controlled trials; elderly; current evidence

The proximal humeral fracture is the third most common fracture seen in elderly persons, with an incidence of 82 per 100,000 person-years, with an annual increase in the rate by 13.7% over the past 33 years. The typical patient is a woman aged 65 years or older. Nearly 75% of patients are treated nonoperatively, and 1 of 5 will undergo surgery depending on fracture type and displacement.

Depending on related factors such as patient age, activity, and fracture pattern, operative treatment options include minimally invasive reduction and intramedullary fixation, open reduction and internal plate fixation, or arthroplasty of the glenohumeral joint. Nonoperative treatment usually starts with immobilization followed by passive and active rehabilitation.²² Despite the fact that the available literature is inconclusive regarding the superiority of either treatment option, it is common practice to attempt joint-saving operative procedures in younger patients.^{16,22} In addition, there is no consensus on whether surgery is beneficial for the older patient with a displaced proximal humeral fracture.

Increasing scientific evidence has demonstrated that metaanalyses of both high-quality observational studies and randomized controlled trials (RCTs) can be similar in value to meta-analyses of RCTs alone in the field of orthopedic trauma surgery. 1,2,19,41 Observational studies may give better insight into infrequent outcome measures, rare complications, and small effects of operative treatment while also increasing the generalizability of the results owing to an increase in patient numbers available for analysis or meta-analysis.

The aims of this systematic review and meta-analysis were (1) to compare operative versus nonoperative treatment of displaced proximal humeral fractures and (2) to compare effect estimates obtained from RCTs and observational studies. We hypothesized that (1) operative treatment of proximal humeral fractures does not improve functional outcomes as compared with nonoperative treatment and (2) including observational studies in this meta-analysis will lead to more robust conclusions without decreasing the quality of the results.

Methods

This systematic review and meta-analysis followed guidelines published by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and MOOSE (Meta-Analysis of Observational Studies in Epidemiology). ^{26,43} These checklists aim to improve the reporting of systematic reviews and meta-analyses for RCTs and observational studies, respectively.

Search strategy and eligibility criteria

Two reviewers (R.B.B. and Y.O.) independently searched the MEDLINE, Embase, CENTRAL (Cochrane Central Register of Controlled Trials), and CINAHL (Cumulative Index to Nursing and Allied Health Literature) databases on September 5, 2017, for studies comparing operative and nonoperative treatment of proximal humeral fractures. The search syntax is provided in Appendix S1. Both RCTs and observational studies were included. After screening of the titles and abstracts of identified records, studies were independently assessed based on full text. The eligibility criteria were proximal humeral fracture, operative versus nonoperative treatment, and reporting of functional outcomes, as well as complications. The exclusion criteria were language other than English, Dutch, or German; no availability of full text; inclusion of patients younger than 18 years; letters, meeting proceedings, and case reports; and external osteosynthesis as operative treatment. Disagreement over eligibility was resolved by discussion with a third reviewer (R.M.H.). The references of the included studies were screened for eligibility, and citation tracking was performed by using Web of Science to identify articles not found in the original search. Authors were approached via ResearchGate when no full-text version of the article was available.

Data extraction

Data extraction was done independently by 2 reviewers (R.B.B. and Y.O.) with a data extraction file. The following data were extracted: first author, journal, year of publication, study period, study design, country or countries in which the study was performed, fracture displacement, fracture classification system (Neer classification), follow-up, treatment groups, operative treatment, nonoperative treat-

ment, number of patients, loss to follow-up, implant removal, and outcome measures. Definitions of fracture characteristics, such as displacement, were applied according to the description in the original study. A major reintervention was defined as an additional, initially unplanned surgical procedure for implant failure, deep infection, symptomatic nonunion, subacromial impingement, or avascular necrosis. Planned implant removal was not considered a major reintervention. Fjalestad et al^{10,11} reported additional follow-up of previously published data that were merged with the original article for this meta-analysis.

Quality assessment

Two reviewers (R.B.B. and H.F.) independently assessed the methodologic quality of all included studies with the Methodological Index for Non-Randomized Studies (MINORS).³⁹ The MINORS is a validated instrument for methodologic quality assessment and clear reporting of observational studies of surgical interventions.³⁹ Other quality-assessment tools focus on a specific study design, while the MINORS is externally validated on RCTs by comparison with the CONSORT statement, making it a suitable instrument for meta-analyses of different study designs. The MINORS score ranges from 0-24; a higher score represents better methodologic quality. Further details on the MINORS criteria and scoring system are provided in Appendix S2. Disagreements were resolved by involving a third reviewer (R.M.H.).

Outcome measures

The primary outcome measure was physical function as measured by the absolute Constant-Murley score⁸ at least 1 year after initialization of either treatment. Normalized (sex- and age-adjusted) Constant-Murley scores were converted to absolute Constant-Murley scores using normal population–based values.⁷ Secondary outcome measures were major reinterventions, nonunion, and avascular necrosis. If available, other functional outcome measures, such as the American Shoulder and Elbow Surgeons shoulder score²⁷ or the Neer score,²⁸ were extracted as well.

Statistical analyses

Statistical analyses were performed using Review Manager (RevMan, version 5.3.5 [released in 2014]; Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). All continuous variables were converted to means and standard deviations when sufficient information was available using methods described in the *Cochrane Handbook for Systematic Reviews of Interventions*. ¹⁸

All analyses were performed stratified by study design (ie, RCTs and observational studies separately) as well as including both designs. Outcomes reported by 2 or more studies were pooled in a meta-analysis. Pooled effects of operative versus nonoperative treatment of dichotomous outcome measures were presented as risk ratios (RRs) with confidence intervals (CIs) using the Mantel-Haenszel method. Pooled effects of continuous outcome measures were presented as mean differences with CIs using the inverse-variance weighting method. Heterogeneity between studies was assessed by visual inspection of the forest plots and by estimating statistical measures for heterogeneity, that is, the I^2 statistic and the χ^2 test. The main quantitative assessment of heterogeneity was the I^2 statistic, for which

the following interpretation was used: 0%-40% might not be important, 30%-60% may represent moderate heterogeneity, 50%-90% may represent substantial heterogeneity, and 75%-100% may represent considerable heterogeneity. When heterogeneity was present, a random-effects model was used instead of a fixed-effects model. Inspection of a funnel plot of the primary outcome measure against its standard error was done to detect potential publication bias.

Sensitivity analyses

Several sensitivity analyses were performed for study quality, year of publication, osteosynthesis by (locking) plate fixation and arthroplasty, and Neer classification. For the analysis of study quality, only studies with an arbitrarily chosen MINORS score of 16 or higher were included, similar to previously published meta-analyses in orthopedic trauma surgery studying both study designs. 19,41 To assess the influence of the period in which the study was performed (and, consequently, development of different operative techniques), only studies published after 2005 were included in a separate analysis. Because the locking plate is the most commonly used type of osteosynthesis, another sensitivity analysis was conducted with studies in which at least 80% of patients were treated with a locking plate. Furthermore, a sensitivity analysis was performed for all studies in which arthroplasty was the operative intervention. Finally, to explore the impact of fracture type on the functional outcome, a sensitivity analysis was performed including only Neer 3- and 4-part fractures.

Different methods of meta-analysis may be differentially sensitive to studies with zero events in 1 or both study arms. Therefore, a sensitivity analysis regarding the choice of method of analysis was performed by means of the DerSimonian-Laird method with correction and the inverse variance with and without correction for zero-event data.⁵

Results

Figure 1 shows a flowchart of the literature search. In the end, 22 studies were included. 3.4.9-12.15,17,20.21,23,24.29-32,35,36,38,42,44,46.48 There were 7 RCTs and 15 observational studies, of which 9 were retrospective, 4 were prospective, and 2 were a combination of retrospective and prospective design.

Quality assessment

The MINORS score for all included studies ranged from 12 to 22, with a median of 17.5 (interquartile range [IQR], 14-21). The MINORS score ranged from 16 to 22, with a median of 21 (IQR, 21-22), for RCTs and from 12 to 21, with a median of 16 (IQR, 14-18), for observational studies. Study-specific MINORS scores are provided in Appendix S3. The MINORS criteria for unbiased assessment of study endpoints and prospective calculation of study size were rarely met.

Baseline characteristics of study participants

Details of the included studies and patients are provided in Table S1. The 22 studies provided 1743 patients for

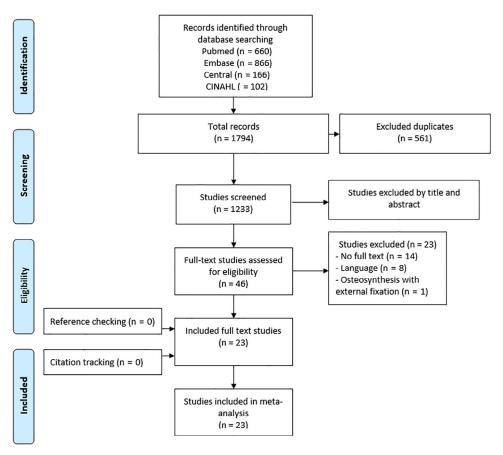


Figure 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram representing search and screen process of studies comparing surgical versus conservative treatment of proximal humeral fractures. *Central*, Cochrane Central Register of Controlled Trials; *CINAHL*, Cumulative Index to Nursing and Allied Health Literature.

meta-analysis: 910 treated operatively and 833 nonoperatively. The weighted average age was 68.3 years, and 75% of patients were women. Follow-up ranged from 12 to 86 months.

All studies but 1 included displaced proximal humeral fractures. The majority of the included studies excluded patients with pathologic fractures, patients with open fractures, fractures in skeletally immature patients, and patients with other injuries sustained on the affected side. Most studies (n = 18, 82%) used the Neer classification and included patients with Neer 2-, 3-, or 4-part proximal humeral fractures. In 7 studies, at least 80% of patients were treated with a locking plate. ^{10,11,15,17,30,32,35,38} In 4 studies, arthroplasty was investigated, with hemiarthroplasty in 3 and reverse shoulder arthroplasty in 1^{4,31,36,42}; 3 studies assessed proximal humeral nails ^{9,24,46}; and 8 studies used fixation by means of Kirschner wires, screws, a tension-band technique, or a combination of techniques.

Functional outcome

In 14 studies (64%, n = 817), the Constant-Murley score was reported after at least 1 year of follow-up

(Appendix S4). $^{3,4,10,11,15,17,21,23,24,30\cdot32,44,46}$ In patients with a proximal humeral fracture, the functional outcome as measured by the Constant-Murley score showed no difference in operative versus nonoperative treatment, with a mean difference of -0.87 (95% CI, -5.13 to 3.38; P = .69; $I^2 = 69\%$) (Fig. 2). Pooled effects of RCTs were similar to those of observational studies for all outcome measures (Fig. 1, Table I). Figure 3 shows a funnel plot of the mean difference and standard error of the included studies using the Constant-Murley score; no important asymmetry was observed.

For studies that did not use the Constant-Murley score, we performed additional analysis with the standardized mean difference of different functional outcome measures, which yielded the same result as the primary analysis (standardized mean difference, -0.06; 95% CI, -0.25 to 0.12; P=.52; $I^2=53\%$) (Appendix S5). In 7 studies (n = 327), functional outcomes of patients who underwent treatment of a Neer 3-or 4-part fracture were reported. 4.10,24,31,32,36,48 Of patients with Neer 4-part fractures, 43% were initially treated with arthroplasty (Table S1). A subgroup analysis of these studies showed no difference in the standardized mean difference of functional outcome measures between operative and nonoperative treatment, with a mean difference of 0.02 (95% CI, -0.20 to 0.24; P=.86; $I^2=0\%$) (Appendix S6).

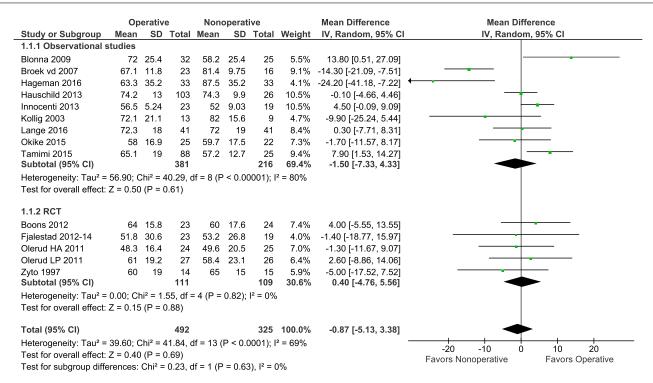


Figure 2 Functional outcome as measured with Constant-Murley score in systematic review of proximal humeral fractures comparing operative versus nonoperative treatment. *SD*, standard deviation; *IV*, inverse variance; *CI*, confidence interval; *RCT*, randomized controlled trial; *HA*, hemiarthroplasty; *LP*, locking plate.

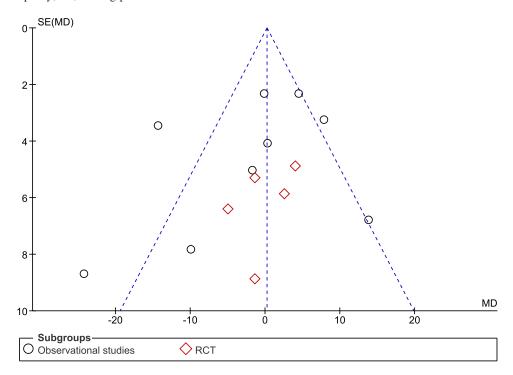


Figure 3 Funnel plot of studies included in meta-analysis reporting Constant-Murley scores after operative or nonoperative treatment of proximal humeral fractures. *SE*, standard error; *MD*, mean difference; *RCT*, randomized controlled trial.

Major reinterventions

A total of 15 studies (68%, n = 938) reported on major reinterventions (Appendix S4). ^{3,4,10,11,15,20,21,24,30-32,35,36,38,42,46} Two

studies had no major reinterventions in either treatment arm at follow-up. Major reinterventions occurred more often in the operative group than in the nonoperative group, with an RR of 2.72 (95% CI, 1.71-4.34; P < .0001; $I^2 = 0\%$)

Analysis description	Cons	Constant score		Majo	Major reintervention		Non	Nonunion		Ava	Avascular necrosis	
		MD (95% CI)	P value	_	n RR (95% CI)	P value		n RR (95% CI)	P value	_	P value n RR (95% CI)	P value
All studies	14	14 -0.87 (-5.13to 3.38) .69	69.	15	15 2.72 (1.71 to 4.34)	<.0001*	13	<.0001* 13 0.45 (0.23 to 0.89) .02*	.02*	13	13 1.24 (0.87 to 1.77) .24	.24
Subgroup analysis												
RCT	5	0.40 (-4.76to 5.56) .88	88.	9	1.45 (0.78 to 2.70)	.25	9	0.48 (0.19 to 1.20)	.12	9	0.88 (0.55 to 1.41)	.59
Observational studies	6	-1.50 (-7.33to 4.33)	.61	7	5.43 (2.51 to 11.74)	<.0001*	7	0.41 (0.15 to 1.16)	60.	7	1.93 (1.11 to 3.37)	*00.
Sensitivity analysis												
High-quality studies	11	0.55 (-2.93to 4.03)	.76	11	2.52 (1.55 to 4.11)	*2000.	11	0.44 (0.21 to 0.93)	*03*	10	1.14 (0.74 to 1.74)	.55
Studies after 2005	12	-0.14 (-4.65to 4.38)	.95	14	2.58 (1.59 to 4.20)	*1000.	12	0.41 (0.18 to 0.89)	*60.	10	1.10 (0.72 to 1.69)	.65
Locking plate	2	-0.15 (-0.43to 0.13)	.30	7	1.81 (1.04 to 3.16)	* 40.	9	0.37 (0.12 to 1.17)	60.	9	1.35 (0.86 to 2.11)	.19
Arthroplasty	2	1.50 (-5.24to 8.23)	99.	4	2.66 (0.72 to 9.77)	.14	m	0.52 (0.13 to 1.99)	.34	~	0.17 (0.02 to 1.37)	.10

Sensitivity analysis of locking plates includes studies comparing locking plates versus nonoperative treatment. Sensitivity analysis of arthroplasty includes studies comparing arthroplasty versus nonoperative mean difference; CI, confidence interval; RR, risk ratio; RCT, randomized controlled trial * Significant pooled effect (P < .05). treatment

(Appendix S7). Using different methods of incorporating studies in the meta-analysis with zero-event data in 1 or both arms yielded similar results (Appendix S8). Implant removal was reported in 10 studies (45%). The mean percentage of implant removal across studies was 21% (range, 0%-100%). When stratified by study design, observational studies showed a greater risk of major reinterventions in the operative treatment group compared with the nonoperative group (RR, 5.43; 95% CI, 2.51-11.74; P < .0001; $I^2 = 0\%$) (Table I). Five studies specified their reinterventions for nonoperatively treated patients: 4 patients received arthroplasty for displacement and malunion, 2 patients received open reduction and internal plate fixation for displacement, and 2 patients received acromioplasty for impingement complaints.

Nonunion

Of the studies, 13 (59%) reported on nonunion (Appendix S4). Operative treatment of proximal humeral fractures resulted in fewer nonunions than nonoperative treatment, with an RR of 0.45 (95% CI, 0.23-0.89; P = .02; $I^2 = 0\%$) (Appendix S9). When stratified by study design, both subgroups showed a similar, nonsignificant pooled effect (Table I).

Avascular necrosis

A total of 13 studies (59%) reported on avascular necrosis (Appendix S4). There was no difference in the rate of avascular necrosis between operative and nonoperative treatment of proximal humeral fractures, with an RR of 1.24 (95% CI, 0.87-1.77; P = .24; $I^2 = 24\%$) (Appendix S10). When stratified by study design, observational studies showed a higher risk of avascular necrosis for the operative group compared with the nonoperative group (RR, 1.93; 95% CI, 1.11-3.37; P = .02; $I^2 = 9\%$) (Table I).

Sensitivity analysis

Sensitivity analysis did not significantly alter the primary and secondary outcome measures (Table I).

Discussion

In this systematic review and meta-analysis of patients with displaced proximal humeral fractures, there was no difference in physical function as measured with the Constant-Murley score after operative or nonoperative treatment. Subgroup analysis for Neer 3- or 4-part fractures showed no differences in functional outcome. The results of the primary and secondary outcome measures from the pooled effects of RCTs and observational studies were similar. There was a higher risk of major reinterventions and a lower risk of non-union after operative treatment compared with nonoperative treatment. This is the largest meta-analysis in the current

literature owing to the inclusion of both RCTs and observational studies.

Compared with nonoperative treatment, there is no improvement in functional outcome after operative treatment of displaced proximal humeral fractures, which confirms findings of previous meta-analyses. 16,47 A recent systematic review of displaced proximal humeral fractures was based on only 7 RCTs with just over 500 patients. 16 With a total of 250 patients, the Proximal Fracture of the Humerus Evaluation by Randomization (PROFHER) trial represents the most substantial evidence currently available.³⁵ The patient demographic characteristics of the PROFHER trial are comparable with those of the included studies in our meta-analysis (Table S1). However, only 4.4% of patients in the PROFHER trial had a Neer 4-part fracture compared with 21% of patients in this meta-analysis. Therefore, compared with previous, smallermagnitude meta-analyses, this review contributes substantially to the current evidence and enables recommendations for a broader patient population. Furthermore, this is the first metaanalysis in which subgroup analysis of Neer 3- and 4-part fractures was possible, and the results showed no differences in operative versus nonoperative treatment.

This review showed similar pooled effects of observational studies and RCTs for the primary and secondary outcome measures. This finding is similar to previous meta-analyses in orthopedic trauma surgery including both study designs. ^{1,2,19,40,41} As such, this review speaks to the growing potential of observational studies in orthopedic trauma surgery and contributes to the expanding discussion about the value of different study designs. ¹³

In this review, the major reintervention rate included every additional surgical procedure except for implant removal because of patient preference, implant-related irritation, or a stiff shoulder. Therefore, the major reintervention rate in this review is a surrogate marker for severe complications (eg, implant failure, deep infection, nonunion, impingement, or avascular necrosis) after operative and nonoperative treatment of displaced proximal humeral fractures. This is the first review to show significantly more severe complications requiring surgical reintervention after operative treatment of displaced proximal humeral fractures. These procedures are in addition to second surgery for implant removal for a less serious indication in 21% of the patients.

Another new finding is the higher risk of nonunion for nonoperatively treated patients. RCTs and observational studies alone were not able to detect a significant difference in this outcome. This finding demonstrates the added value of increasing study power by including observational studies to detect rare outcomes. It is important to note that this difference is supported by the sensitivity analysis including only high-quality RCTs and observational studies (Table I).

This review found no difference in the rate of avascular necrosis between nonoperative and operative management. However, it should be noted that 3 of the 15 studies reporting on avascular necrosis had a follow-up period of 12 months while avascular necrosis can be detected at up to 2 years of

follow-up. For this outcome measure, the pooled effect of observational studies was significantly different than the pooled effect of RCTs. However, in the sensitivity analysis with high-quality studies, this contrasting result did not yield, and pooled effects of both study designs were again similar. This finding demonstrates the importance of evaluating the quality of the included studies (Table I). Therefore, including a study in a meta-analysis should be based on the quality of the study regardless of the study design. Generally, RCTs will be of higher quality and will thus be included for analysis; however, a high-quality observational study should be chosen over a low-quality RCT.

The results of this systematic review and meta-analysis should be interpreted in light of several limitations. First, the results of the meta-analysis may be influenced by missed studies in the database search or by publication bias. However, an extensive search was performed using multiple databases, and the citations and references of included studies were screened. Furthermore, a funnel plot of the primary outcome measure did not suggest possible bias due to selective publication. Second, the results of the observational studies were more heterogeneous than those of the RCTs in the metaanalysis of the Constant-Murley score. Still, it should be noted that, despite heterogeneity in the mean differences of the observational studies, the observed effects all were within a range of the Constant-Murley score that is clinically unimportant.⁴⁵ Third, in the analysis of functional outcome, we did not distinguish between 12 months and more than 12 months of follow-up because prior studies have shown that the greatest increase in functional outcome takes place in the first 6 months and no significant improvement is to be expected after 12 months. 9,10,31,32,35 This is further supported by an additional sensitivity analysis that showed no differences in functional outcome at 12 months and at 24 or more months. Fourth, the Neer classification for proximal humeral fractures is the most frequently used classification system in the literature even though it has been considered to have important limitations. However, no other system for evaluating these fractures is consistently more reliable than the Neer classification.⁶ Fifth, the majority of the included studies were European, and only 3 studies described patients from North America, let alone other continents. However, subgroup analyses revealed no differences for the primary and secondary outcome measures between these continents (data not shown). Finally, it should be noted that the majority of studies in this review excluded patients with pathologic fractures, patients with open fractures, fractures in skeletally immature patients, and patients with other sustained injuries to the affected arm. As a result, recommendations from this review are not applicable to these patients.

Although we acknowledge the vast number of existing systematic reviews on this topic, ^{14,16,34,47} we believe that the several unique qualities of this meta-analysis contribute to the existing knowledge. Strengths of this study include the consistent results of the different sensitivity analyses for time of publication, type of osteosynthesis, and arthroplasty. Furthermore,

by including observational studies in addition to the highly selective patient population of RCTs, the analyzed patients may be more representative of patients encountered in daily clinical practice and improve the generalizability of our results. We also demonstrated that the findings were consistent across study designs with respect to different outcome measures. Although no subgroup analysis of elderly patients (aged > 65 years) could be performed, the mean age of all patients in this review was 68 years, with a relatively small standard deviation for the majority of the included studies; therefore, we are confident that recommendations from this review apply to the average elderly patient. Finally, this is the largest metanalysis in the literature with the highest number of patients available for analysis of proximal humeral fractures.

Conclusions

We recommend nonoperative treatment for the average elderly patient (aged > 65 years) with a displaced proximal humeral fracture. Pooled effects of observational studies were similar to those of RCTs, and the inclusion of observational studies improved the generalizability of findings.

Disclaimer

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jse.2018.03.009.

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