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CHAPTER 4

Conservative versus operative treatment for humeral shaft fractures: a meta-analysis and systematic review of randomized clinical trials and observational studies

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Abstract

Background

This meta-analysis aimed to compare conservative vs. operative treatment for humeral shaft fractures in terms of the nonunion rate, reintervention rate, permanent radial nerve palsy rate, and functional outcomes. Secondarily, effect estimates from observational studies were compared with estimates of randomized clinical trials (RCTs).

Methods

The PubMed/Medline, Embase, CENTRAL (Cochrane Central Register of Controlled Trials), and CINAHL (Cumulative Index to Nursing and Allied Health Literature) databases were searched for both RCTs and observational studies comparing conservative with operative treatment for humeral shaft fractures.

Results

A total of 2 RCTs (150 patients) and 10 observational studies (1262 patients) were included. The pooled nonunion rate of all studies was higher in patients treated conservatively (15.3%) vs. operatively (6.4%) (risk difference, 8%; odds ratio [OR], 2.9; 95% confidence interval [CI], 1.8-4.5; I^2 = 0%). The reintervention rate was also higher for conservative treatment (14.3%) than for operative treatment (8.9%) (risk difference, 6%; OR, 1.9; 95% CI, 1.1-3.5; I^2 = 30%). The higher reintervention rate was predominantly attributable to the higher nonunion rate in patients treated conservatively. The permanent radial nerve palsy rate was equal in both groups (OR, 0.6; 95% CI, 0.2-1.9; I^2 = 18%). There appeared to be no difference in mean time to union and mean Disabilities of the Arm, Shoulder and Hand scores between the treatment groups. No difference was found between effect estimates form observational studies and RCTs.

Conclusion

This systematic review shows that satisfactory results can be achieved with both conservative and operative management; however, operative treatment reduces the risk of nonunion compared with conservative treatment, with comparable reintervention rates (for indications other than nonunion). Furthermore, operative treatment results in a similar permanent radial nerve palsy rate, despite its inherent additional surgery-related risks. No difference in mean time-to-union and short-term functional results was detected.

Introduction

Humeral shaft fractures represent 1%-3% of all fractures.[1] Traditionally, patients with humeral shaft fractures have been treated conservatively.[2] In the past few decades, however, operative treatment has become more popular, with more than half of patients undergoing either plate fixation or nailing.[3]

The optimal treatment of humeral shaft fractures remains a topic of debate. Two meta-analyses have previously been published.[4,5] Because of the lack of randomized clinical trials and the existence of only observational studies at the time, both concluded that the superiority of one treatment over the other could not be determined.

Meta-analyses of randomized clinical trials are considered the highest level of evidence for evaluation of treatment effects. Multiple studies have shown that the estimates of the effects of certain surgical treatments estimated from randomized clinical trials and observational studies tend to be similar.[6-8] The addition of observational studies to meta-analyses increases the sample size and could increase the power for detecting small differences in treatment effects. As randomized clinical trials usually include a highly selective study population, including observational studies in meta-analyses might improve the generalizability of results. Notably, randomized clinical trials and observational studies are increasingly being combined in orthopedic trauma meta-analyses for evaluation of treatment effects.[9-12]

The primary aim of this meta-analysis was to compare the nonunion rate, reintervention rate, permanent radial nerve palsy rate, and functional outcomes after conservative and operative treatment for humeral shaft fractures by considering evidence from randomized clinical trials as well as observational studies. The secondary aim was to determine whether there is a difference in effect estimates obtained from observational studies and from randomized clinical trials in this field of research.

Methods

This systematic review with meta-analysis was performed and reported according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines and Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist.[13,14] A published protocol for this review does not exist.

Search strategy and selection criteria

The PubMed/Medline, Embase, CENTRAL (Cochrane Central Register of Controlled Trials), and CINAHL (Cumulative Index to Nursing and Allied Health Literature) databases were searched on March 23, 2019, for studies comparing conservative with operative treatment for humeral shaft fractures. The search syntax is described in Supplementary Table S1. Duplicate articles were removed. Two reviewers (B.J.M.v.d.W. and Y.O.) independently screened titles and abstracts for eligibility. All published studies consisting of observational and randomized clinical trials and comparing conservative with operative treatment for humeral shaft fractures were included.

The same two reviewers independently performed the full-text screening. The inclusion criteria were humeral shaft fracture, conservative treatment (cast immobilization and/or functional bracing), operative treatment (minimally invasive or open plating, nail fixation, and external fixator), age 16 years or older, and reporting of outcomes of interest (nonunion, reintervention, time to union, radial nerve palsy, and functional outcomes). The exclusion criteria were pathologic fractures; treatment for delayed union or nonunion; studies with an average follow-up period of less than 6 months; languages other than English, French, German, or Dutch; no availability of full text; and letters, meeting proceedings, and case reports. Disagreements on the eligibility of full-text articles were resolved by consensus or by discussion with a third reviewer (M.R.H.). References of all included studies were screened to identify studies not found in the original literature search.

Data extraction

Two reviewers (B.J.M.v.d.W. and Y.O.) independently performed data extraction using a predefined data extraction sheet. The following baseline characteristics were extracted from the included studies: first author, year of publication, study period, country in which study was performed, study design, number of included patients, conservative method, operative method, sex, age, open or closed fracture, Arbeitsgemeinschaft für Osteosynthesefragen/Orthopaedic Trauma Association (AO/OTA) Fracture and Dislocation Classification, low- or high-energy trauma, and follow-up duration.[15,16]

Quality assessment

Two reviewers (B.J.M.v.d.W. and Y.O.) independently assessed the methodologic quality of included studies using the Methodological Index for Non-Randomized Studies (MINORS).[17] The MINORS is a validated instrument for assessing the methodologic quality of cohort studies, resulting in a score between 0 and 24. Randomized studies were appraised using the same tool to measure quality on the same scale as observational studies. Disagreements were resolved by consensus. Details on methodologic quality assessment are provided in Supplementary Table S2.

Primary and secondary outcomes

The primary outcome was the nonunion rate after conservative or operative treatment. Nonunion was defined as the absence of fracture consolidation 6 months after treatment with the absence of radiologic bridging callus at 3 of 4 cortices.[18,19] Secondary outcome measures included reintervention, radial nerve palsy, infection, and functional outcome scores. Functional outcome scores included the Disabilities of the Arm, Shoulder and Hand (DASH) score.[20] Measurements of the DASH score were subdivided according to follow-up, into short term (≤1 year) and long term (>1 year). Reintervention included all surgical procedures performed during follow-up. Radial nerve palsy was categorized into palsy at presentation (primary radial nerve palsy), palsy after surgery (secondary radial nerve palsy), or persistent radial nerve palsy at the end of the follow-up period (persistent radial nerve palsy). In other words, permanent radial nerve palsy encompassed all patients in whom nerve function was not restored following either primary or secondary nerve palsy. Infection was classified as either superficial or deep according the definition of the Centers for Disease Control and Prevention.

Statistical analysis

Data for continuous variables were presented as means with standard deviations (SDs) or ranges. The mean and SD were calculated for studies that presented descriptive statistics other than the mean, SD, or range using the methods described in the Cochrane Handbook for Systematic Reviews of Interventions.[21] Dichotomous variables were presented as counts and percentages. Effects of treatment options on binary outcomes were pooled using the (random-effects) Mantel-Haenszel method and presented as odds ratios (ORs) with 95% confidence intervals (CIs). In case of zero-cell counts in 1 of the 2 treatment groups, 0.5 was added to all cells of the contingency table of treatment and outcome of those studies in which this occurred. Effects of treatment options on continuous outcomes were pooled using the (random-effects) inversevariance weighting method and presented as mean differences with 95% CIs. None of the observational studies were corrected for confounding. Therefore, the estimated relations between treatment and outcome presented for these studies are unadjusted for possible confounding.

Heterogeneity between studies was assessed for all ORs by visual inspection of forest plots and by the I^2 statistic for heterogeneity. All analyses were stratified according to study design, that is, randomized clinical trials or observational studies. The difference in effect estimates between the 2 subgroups were assessed using the $\chi 2$ test as described in the Cochrane Handbook for Systematic Reviews of Interventions.[21] $P < 0.05$ was considered statistically significant. Publication bias was assessed by visual inspection of funnel plots.12 Review Manager (RevMan, version 5.3.5; The Cochrane Collaboration, London, UK) was used for all statistical analyses.

Sensitivity analyses

Sensitivity analysis for the primary outcome was performed on different types of operative fixation methods. The effect estimates of the primary meta-analysis were compared with the effect estimates of studies using only plate fixation as operative treatment. We performed additional sensitivity analyses using information from studies in which the mean age of included subjects was older than 50 years, as well as from high-quality studies. The cutoff point for age was based on the upper quartile of studies with the highest mean age of participants. High-quality studies were defined as those with a MINORS score (range, 0-24) of 16 or higher. Additional sensitivity analysis was performed on the secondary outcome of reintervention. The effect estimates of the primary meta-analysis on reintervention for all indications (including nonunion) were compared with the risk estimates of reintervention excluding nonunion.

Results

Search

Figure 1 presents the flowchart of the literature search and study selection. The full text could not be obtained for 1 observational study.[22] A total of 12 articles could be included for analyses in this study: 2 randomized clinical trials and 10 observational studies.[23-34]

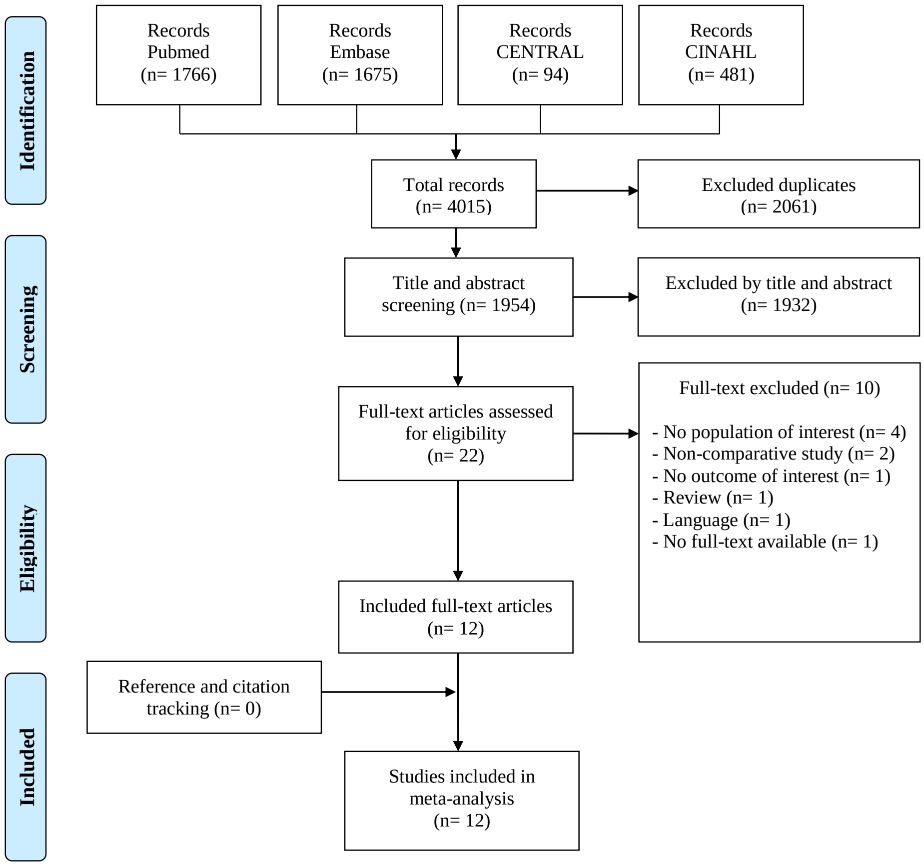

Figure 1. Flow diagram of search and selection of studies comparing operative vs. conservative treatment for humeral shaft fractures. CENTRAL, Cochrane Central Register of Controlled Trials; CINAHL, Cumulative Index to Nursing and Allied Health Literature.

Baseline study characteristics

The 12 studies included 1412 patients: 628 treated conservatively and 784 treated operatively. The overall weighted mean age was 42 years (range, 16-103 years), with 43 years in the conservative group and 42 years in the operative group. The studies included 380 female patients (26.9%). The overall mean follow-up period ranged from 6 to 72 months. Table 1 shows the baseline characteristics of all studies including AO/OTA Fracture and Dislocation Classification, fractures with a concomitant open wound (open fractures), energy of trauma, and treatment type.

The 2 randomized clinical trials included 150 patients, of whom 78 were treated operatively.[23,24] The weighted mean age, as well as age per treatment group, was 37 years (range, 18-83 years). The operative fixation method in both studies was plate fixation. As conservative management, bracing was used in one study and splinting in the other.

The 10 observational studies—1 prospective study and 9 retrospective studies—included 1262 patients, of whom 706 were treated operatively. [25-34] The weighted mean age was 44 years (range, 16-103 years), with 45 years in the conservative group and 43 years in the operative group. Conservative management consisted of bracing in 7 studies and a combination of bracing and splinting in 2, whereas 1 study did not further specify the type of conservative treatment. Operative treatment consisted of a combination of plating, nailing, and external fixation in 7 studies, of which 1 study also included intramedullary flexible nails. In the other 3 studies, either solely plating or nailing was used.

Quality assessment

The details and distribution of the MINORS scores are described in Supplementary Table S3. The overall mean MINORS score was 15.6 (SD, 2.6; range, 13-23), where the 2 randomized clinical trials had scores of 17 and 23.

Primary outcome measure

Nonunion rate

The nonunion rate was reported in 11 studies—2 randomized clinical trials and 9 observational studies.[23-33] The overall pooled effect showed that conservative treatment was associated with a higher nonunion rate compared with operative treatment (OR, 2.9; 95% CI, 1.8-4.5; I^2 = 0%) (Figure 2). The pooled effect for randomized clinical trials showed an OR of 5.7 (95% CI, 0.6-53.6; I^2 = 29%). The pooled effect estimate of observational studies demonstrated an OR of 2.8 (95% CI, 1.7-4.4; I^2 = 0%). Nonunion occurred in 15.3% of patients treated conservatively and 6.4% treated operatively (risk difference [RD], 8%; 95% CI, 4%-12%). No difference in pooled effect estimates was found between randomized clinical trials and observational studies (P = .43, test for subgroup difference; I^2 = 0%). The funnel plot is described in Supplementary Figure S1.

Secondary outcome measures

Intervention or reintervention rate

Reintervention was reported in 11 studies—2 randomized clinical trials and 9 observational studies.[23-33] The overall pooled effect showed that the reintervention rate was higher among patients treated conservatively than those treated operatively (OR, 1.9; 95% CI, 1.1-3.5; I^2 = 30%) (Figure 3). The pooled effect for randomized clinical trials was 2.7 (95% CI, 0-156.6; I^2 =

Table 1. Baseline characteristics of studies included in systematic review of conservative vs. operative treatment for humeral shaft fracture

Authors	Year	Design	Country	Study period	Total n:	Type of treatment	
					Cons/Op	Cons	Op
RCTs							
Kumar et al	2017	RCT	India	2012-2014	20/20	Splint	Plate
Matsunaga et al	2017	RCT	Brazil	2012-2015	52/58	Brace	Plate
Observational studies							
Harkin and Large et al	2017	RCS	Australia	2008-2015	96/30	Brace	Plate/nail
Westrick et al	2017	RCS	United States	2000-2012	69/227	Brace	Plate/nail/FX
Dielwart et al	2017	RCS	United States	2006-2011	31/40	Brace	Nail/ORIF
Mahabier et al	2013	RCS	The Netherlands	2002-2008	91/95	Brace	Nail/ORIF/FX
Broadbent et al	2010	PCS	United Kingdom	2006-2009	89/21	Brace/cast	Plate/nail/FX
Denard et al	2010	RCS	United States	2001-2006	63/150	Brace	Plate
Ekholm et al	2008	RCS	Sweden	1998-1999	20/7	NR	Plate/nail
Jawa et al	2006	RCS	United States	2000-2004	21/19	Brace	Plate
Osman et al	1998	RCS	France	1994-1997	32/72	Splint/brace	Plate/wires/nail
Wallny et al	1997	RCS	Germany	1990-1994	44/45	Brace	Nail

SD, standard deviation; Cons, conservative treatment; Op, operative treatment; NR, not reported; AO, arbeitsgemeinschaft osteosynthese; RCT, randomised clinical trial; PCS, prospective cohort study; RCS, retrospective cohort study; NA, not applicable; FX, fixator external; ORIF, open reduction internal fixation;

Table 1. Continued

Authors	Sex: female/male		Mean age (SD), yr		Open fracture		AO type: A/B/C		High-energy trauma		Mean follow-up, mo
	Cons	Op	Cons	Op	Cons	Op	Cons	Op	Cons	Op	
RCTs											
Kumar et al	16/6	5/15	33 (11)	38 (16)	0	0	20/0/0	20/0/0	NR	NR	6
Matsunaga et al	14/38	23/35	40 (17)	37 (15)	0	0	28/17/6	38/15/3	NR	NR	12
Observational studies											
Harkin and Large et al	64/33	21/9	NA	NA	0	4	49/14/17	16/8/3	NR	NR	>6
Westrick et al	35/34	75/152	41 (29)	37 (29)	7	92	140/112/40		46	180	>12
Dielwart et al	8/23	22/18	39 (18)	38 (18)	0	0	16/7/8	23/8/9	31	40	10
Mahabier et al	55/36	51/44	61 (24)	59 (26)	0	0	43/40/8	46/32/7	10	22	>6
Broadbent et al	68/42		59 (19)		0	3	52/46/12		NR	NR	12
Denard et al	29/34	68/82	36 (17)	35 (15)	NR	NR	NR	NR	NR	NR	7.9
Ekholm et al	15/5	3/4	53 (29)	48 (27)	0	0	NR	NR	8	2	72
Jawa et al	12/9	8/11	41 (17)	50 (19)	NR	NR	NR	NR	NR	NR	>6
Osman et al	44/60		48 (22)		0		60/38/6			39	18
Wallny et al	20/24	19/26	59 (20)	56 (17)	0	0	NR	NR	NR	NR	27

SD, standard deviation; Cons, conservative treatment; Op, operative treatment; NR, not reported; AO, arbeitsgemeinschaft osteosynthese; RCT, randomised clinical trial; PCS, prospective cohort study; RCS, retrospective cohort study; NA, not applicable; FX, fixator external; ORIF, open reduction internal fixation;

Study or Subgroup	conservative Events	conservative Total	Operative Events	Operative Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
1.1.1 Non-union observational studies							
Wallny	2	44	0	45	2.2%	5.35 [0.25, 114.74]	1997
Osman	2	32	3	72	6.1%	1.53 [0.24, 9.65]	1998
Jawa	0	21	0	19		Not estimable	2006
Ekholm	0	20	0	7		Not estimable	2008
Denard	13	63	13	150	29.7%	2.74 [1.19, 6.31]	2010
Broadbent	16	89	1	21	4.8%	4.38 [0.55, 35.09]	2010
Mahabier	0	0	0	0		Not estimable	2013
Harkin	22	96	1	30	4.9%	8.62 [1.11, 66.94]	2017
Westerick	16	69	23	227	41.4%	2.68 [1.32, 5.42]	2017
Dielwart	2	31	2	40	5.1%	1.31 [0.17, 9.86]	2017
Subtotal (95% CI)		**465**		**611**	**94.2%**	**2.77 [1.74, 4.43]**	
Total events	73		43				
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.59$, df = 6 (P = 0.86); $I^2 = 0\%$							
Test for overall effect: Z = 4.27 (P < 0.0001)							
1.1.2 Non-union randomised clinical trials							
Kumar	2	20	1	20	3.3%	2.11 [0.18, 25.35]	2017
Matsunaga	7	52	0	58	2.5%	19.29 [1.07, 346.60]	2017
Subtotal (95% CI)		**72**		**78**	**5.8%**	**5.67 [0.60, 53.62]**	
Total events	9		1				
Heterogeneity: $Tau^2 = 0.77$; $Chi^2 = 1.41$, df = 1 (P = 0.24); $I^2 = 29\%$							
Test for overall effect: Z = 1.51 (P = 0.13)							
Total (95% CI)		**537**		**689**	**100.0%**	**2.88 [1.83, 4.54]**	
Total events	82		44				
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.52$, df = 8 (P = 0.81); $I^2 = 0\%$							
Test for overall effect: Z = 4.57 (P < 0.00001)							
Test for subgroup differences: $Chi^2 = 0.37$, df = 1 (P = 0.54), $I^2 = 0\%$							

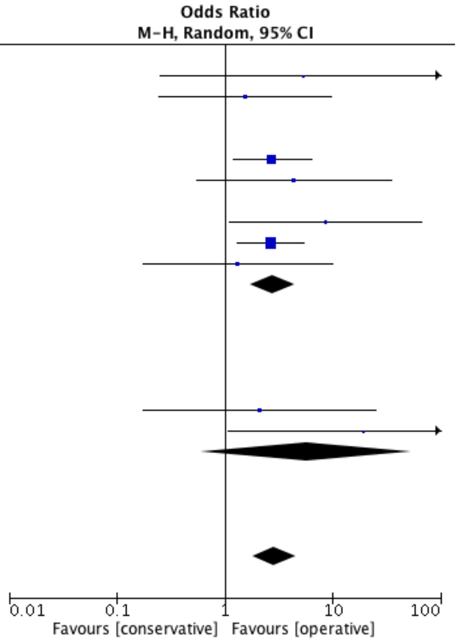

Figure 2. Forest plot of nonunion rate after conservative vs. operative treatment for humeral shaft fractures. CI, confidence interval; M-H, Mantel Haenszel.

Study or Subgroup	Conservative Events	Conservative Total	Operative Events	Operative Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
1.2.1 Re-intervention observational studies							
Wallny	2	44	4	45	9.3%	0.49 [0.08, 2.81]	1997
Osman	2	32	3	72	8.6%	1.53 [0.24, 9.65]	1998
Jawa	0	21	0	19		Not estimable	2006
Ekholm	0	20	1	7	3.1%	0.11 [0.00, 2.92]	2008
Broadbent	11	89	0	21	4.0%	6.30 [0.36, 111.25]	2010
Denard	15	63	24	150	25.5%	1.64 [0.79, 3.39]	2010
Mahabier	0	0	0	0		Not estimable	2013
Westerick	16	69	25	227	26.2%	2.44 [1.22, 4.90]	2017
Dielwart	6	31	3	40	11.9%	2.96 [0.68, 12.95]	2017
Harkin	18	96	0	30	4.1%	14.38 [0.84, 246.05]	2017
Subtotal (95% CI)		**465**		**611**	**92.8%**	**1.88 [1.07, 3.29]**	
Total events	70		60				
Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 9.00$, df = 7 (P = 0.25); $I^2 = 22\%$							
Test for overall effect: Z = 2.20 (P = 0.03)							
1.2.2 Re-intervention randomised clinical trials							
Matsunaga	7	52	0	58	4.0%	19.29 [1.07, 346.60]	2017
Kumar	0	20	1	20	3.2%	0.32 [0.01, 8.26]	2017
Subtotal (95% CI)		**72**		**78**	**7.2%**	**2.65 [0.04, 156.63]**	
Total events	7		1				
Heterogeneity: $Tau^2 = 6.20$; $Chi^2 = 3.51$, df = 1 (P = 0.06); $I^2 = 72\%$							
Test for overall effect: Z = 0.47 (P = 0.64)							
Total (95% CI)		**537**		**689**	**100.0%**	**1.93 [1.05, 3.54]**	
Total events	77		61				
Heterogeneity: $Tau^2 = 0.24$; $Chi^2 = 12.80$, df = 9 (P = 0.17); $I^2 = 30\%$							
Test for overall effect: Z = 2.11 (P = 0.03)							
Test for subgroup differences: $Chi^2 = 0.03$, df = 1 (P = 0.87), $I^2 = 0\%$							

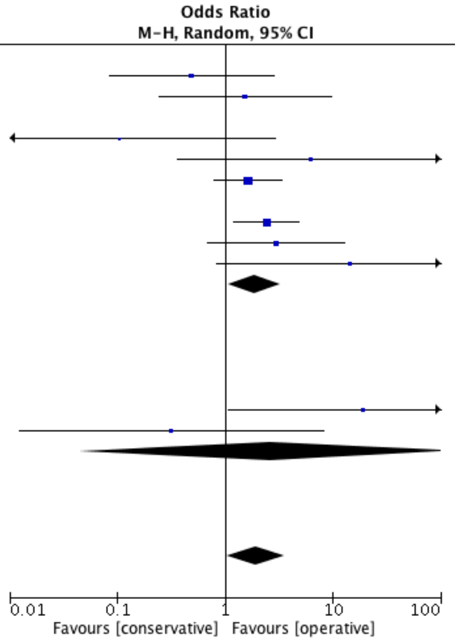

Figure 3. Forest plot of intervention (or reintervention) rate after conservative vs. operative treatment for humeral shaft fractures. CI, confidence interval; M-H, Mantel Haenszel.

72%). The pooled effect estimate of observational studies demonstrated an OR of 1.9 (95% CI, 1.1-3.3; I^2 = 22%). Reintervention occurred in 14.3% of patients treated conservatively and 8.9% treated operatively (absolute RD, 6%; 95% CI, 1%-12%). The most frequent indication for surgical intervention among patients treated conservatively was nonunion. Other indications included malalignment and intolerance of bracing (Supplementary Table S4). The most frequent indication for reintervention among patients treated surgically was nonunion as well. Other indications included infection, implant migration (only for nails), and implant irritation (Supplementary Table S5). No difference in pooled effect estimates was found between randomized clinical trials and observational studies (P = .83, test for subgroup difference; I^2 = 0%). The funnel plot is described in Supplementary Figure S2.

Mean time to union

Five studies reported on mean time to union—1 randomized clinical trial and 4 observational studies.[23,26,27,33,34] The overall pooled time to union did not differ between the treatment groups (mean difference, –1.2 weeks; 95% CI, –4.3 to 2.0 weeks; I^2 = 84%) (Figure 4). The weighted mean time to union was 16 weeks in the conservative group and 17 weeks in the operative group. Subgroup analysis was not possible as only 1 randomized clinical trial reported on time to union. The funnel plot is described in Supplementary Figure S3.

DASH score

Only the 2 randomized clinical trials reported on short-term DASH scores, both at 6 months.[23,24] The overall pooled DASH score did not differ between conservative and operative treatment (mean difference, 10.7; 95% CI, –0.7 to 22.2; I^2 = 68%) (Figure 5). The weighted mean DASH score was 27 among patients treated conservatively and 15 among those treated operatively. The funnel plot is described in Supplementary Figure S4. Long-term functional outcomes using the DASH score were not reported in the included studies.

Radial nerve palsy

Eleven studies reported on radial nerve palsy—2 randomized clinical trials and 9 observational studies.[23,24,26-34] Radial nerve palsy at presentation (primary radial nerve palsy) was found among 9.6% of patients treated conservatively (n = 52). Only 7 of these patients (1.5%) had permanent radial nerve palsy at the end of the study period. Among patients treated operatively, 16.1% (n = 123) had primary radial nerve palsy; of these, 19 (2.5%) had permanent palsy (Table 2). Radial

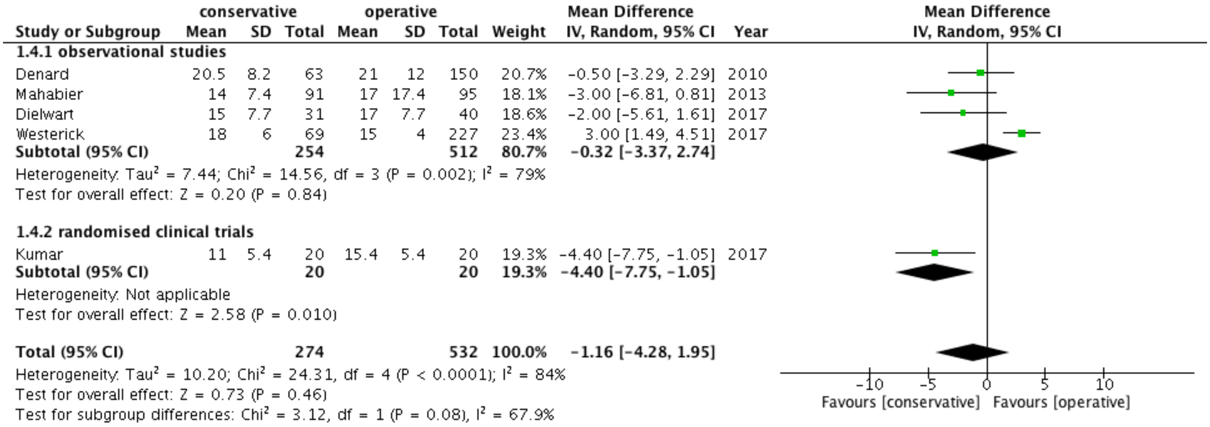

Figure 4. Forest plot of mean time to union after conservative vs. operative treatment for humeral shaft fractures. CI, confidence interval; IV, weighted mean difference

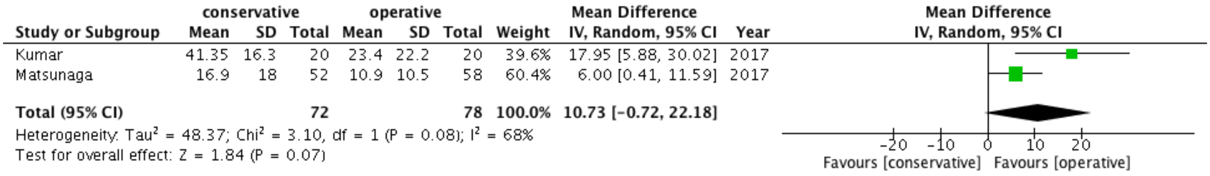

Figure 5. Forest plot of Disabilities of the Arm, Shoulder and Hand (DASH) score at 6 months after conservative vs. operative treatment for humeral shaft fractures. CI, confidence interval; IV, weighted mean difference.

nerve palsy due to the operation was found in 3.5% of patients in the operative group (n = 27). Only 1 patient had permanent damage. The other patients had full recovery of nerve function. The overall pooled permanent radial nerve palsy rate at the end of follow-up was equal in both groups (OR, 0.6; 95% CI, 0.2-1.9; I^2 = 18%) (Figure 6). Subgroup analysis could not be performed because of insufficient numbers of events between the randomized clinical trials. The funnel plot is described in Supplementary Figure S5.

Infection

Seven studies reported on postoperative infections in the operative group.[24,26,27,30-33] No distinction could be made between deep or superficial infection as none of the studies clearly defined infection or applied the definition of the Centers for Disease Control and Prevention. Infection was reported in 0.6% of patients treated conservatively (n = 2). In both, infection developed following a humeral shaft fracture caused by a gunshot injury. Symptoms resolved after antibiotic treatment in both patients. Infection occurred in 3.1% of patients treated operatively (n = 19). Twelve of these patients underwent subsequent wound débridement. The other 7 patients were treated conservatively with antibiotics.

Table 2. Primary, secondary, and persistent radial nerve palsy in studies of conservative vs. operative treatment for humeral shaft fractures

			Total n:	Primary radial nerve palsy at presentation, n				Secondary radial nerve palsy after surgery, n	
Authors	**Type**		**Cons/Op**	**Temporary**	**Persistent***	**Temporary**	**Persistent***	**Temporary**	**Persistent***
	Cons	**Op**		**Cons**		**Op**			
Randomized clinical trials									
Kumar et al	Splint	Plate	20/20	0	0	0	0	1	0
Matsunaga et al	Bracing	Plate	52/58	0	0	0	0	2	0
Observational studies									
Harkin and Large	Bracing	Plate/nail	96/30	7	1	5	2	4	0
Westrick et al	Bracing	Plate/nail/FX	69/227	14	1	82	14	2	0
Dielwart et al	Bracing	Nail/ORIF	31/40	5	1	10	1	2	0
Mahabier et al	Bracing	Nail/ORIF/FX	91/95	8	2	5	1	4	NR
Broadbent et al	Bracing/splint	Plate/nail/FX	89/21	NR	NR	NR	NR	NR	NR
Denard et al	Bracing	Plate	63/150	6	0	1	0	4	0
Ekholm et al	NR	Plate/nail	20/7	2	0	4	0	0	0
Jawa et al	Bracing	Plate	21/19	2	0	4	1	3	1
Osman et al	Splint/brace	Plate/wires/nail	32/72	2	0	6	0	4	0
Wallny et al	Bracing	Nail	44/45	6	0	6	0	1	0
Total				**52**	**7**	**123**	**19**	**27**	**1**

Cons, conservative treatment; Op, operative treatment; FX, fixator external; ORIF, open reduction internal fixation.* Persistent indicates the number of patients with primary or secondary radial nerve palsy in whom radial nerve palsy did not recover during follow-up.

Table 3. Sensitivity analysis on primary outcome (nonunion) after conservative vs. operative treatment for humeral shaft fractures

	n	**RD**	**OR (95% CI)**	**P value**	**I^2, %**
All studies	11	8%	2.9 (1.8-4.5)	<.001	0
Studies with plate fixation	4	8%	3.1 (1.4-6.6)	.004	0
Studies with age > 50 years	3	6%	4.7 (0.8-26.1)	.08	0
High-quality studies	5	8*	2.8 (1.4-5.6)	.005	0

RD, risk difference; OR, odds ratio; CI, confidence interval.

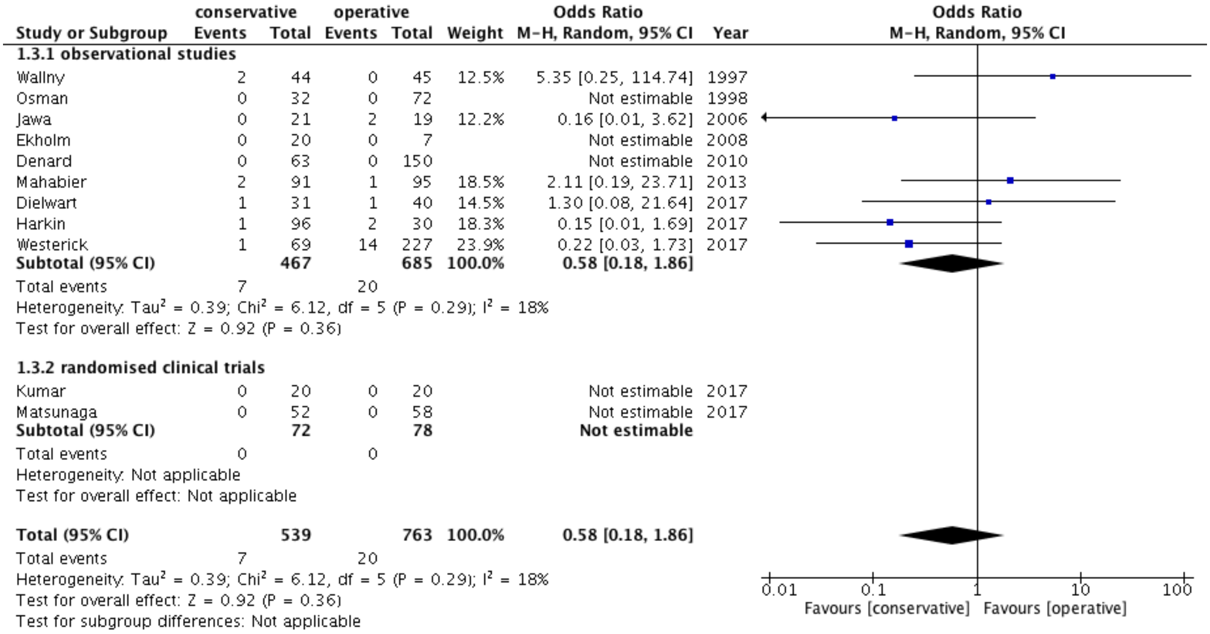

Figure 6. Forest plot of permanent radial nerve palsy rate after conservative vs. operative treatment for humeral shaft fractures. CI, confidence interval; M-H, Mantel Haenszel.

Other complications

All other reported complications are listed in Supplementary Table S6.

Sensitivity analysis

Table 3 shows the results of the sensitivity analysis on the primary outcome (nonunion). A total of 4 studies compared plate fixation with conservative treatment—2 randomized clinical trials and 2 observational studies.[23,24,26,30] The pooled estimate showed that the nonunion rate was higher among patients treated conservatively than among those treated by plate fixation (RD, 8%; OR, 3.1; 95% CI, 1.4-6.6; I^2 = 0%; Supplementary Figure S6). Only 3 studies—all observational studies—had a study population with a mean age older than 50 years.[28,32,34] The pooled analysis did not demonstrate a difference in nonunion rates between conservative and operative treatment (OR, 4.7; 95% CI, 0.8-26.1; I^2 = 0%; Supplementary Figure S7). There were 5 high-quality studies—2 randomized clinical trials and 3 observational studies.[23,24,26-28] The nonunion rate was higher among patients treated conservatively than those treated operatively (OR, 2.8; 95% CI, 1.4-5.6; I^2 = 0%) (Supplementary Figure S8). Reintervention for indications other than nonunion (Supplementary Tables S4 and S5) was reported in 11 studies—2 randomized clinical trials and 9 observational studies.[23,24,26-34] The pooled analysis showed no difference between groups (OR, 1.0; 95% CI, 0.4-2.8; I^2 = 53%) (Supplementary Figure S9).

Discussion

This systematic review and meta-analysis, including both randomized clinical trials and observational studies, compared conservative with operative treatment for humeral shaft fractures. The pooled effect estimates demonstrated that conservative treatment was associated with higher nonunion and reintervention rates compared with operative treatment. There appeared to be no difference in mean time to union and DASH scores. The pooled analysis also found no difference in the rate of persistent radial nerve palsy between the two treatment groups. Sensitivity analysis on the secondary outcome of reintervention showed that the higher reintervention rate in the conservative group was mainly caused by a high rate of intervention for nonunion. There appeared to be no difference in effect estimates from randomized clinical trials and observational studies for either the nonunion or reintervention rate.

To date, only 2 systematic reviews have been published comparing operative with conservative treatment for humeral shaft fractures.[4,5] Gosler et al.[4] performed a systematic review in 2012 but could not identify any randomized clinical trials. They therefore did not perform any formal analysis and concluded that there was insufficient evidence to support either of the 2 treatment modalities. Clement et al.[5] published a systematic review in 2015 and reached the same conclusion as Gosler et al. Clement, however, identified 1 ongoing randomized clinical trial, the results of which were unavailable at that time.[24] In contrast to the present meta-analysis, both previous meta-analyses did not include observational studies.

Our findings of a higher nonunion rate among patients treated conservatively compared with those treated operatively are in line with the general consensus in the literature. Nonunion rates among patients treated conservatively are usually found to be between 0% and 22.6% in noncomparative studies.[35] These rates range from 0% to 9% for operative management.[36] Given the large number of patients included in our meta-analysis, we were able to more reliably determine these incidences. We found an incidence of 15.3% in the conservative group vs. 6.4% in the operative group.

The reintervention rate appeared to be higher in patients treated conservatively. This was mainly caused by a higher reintervention rate for nonunion. The reintervention rate was equal for indications other than nonunion as described in the sensitivity analysis. It is interesting to note that operative treatment exposes patients to surgery-related complications that do not occur in patients treated conservatively (e.g. infections requiring débridement, implant removal, or migration). Despite the additional risk, the overall reintervention rate for indications other than nonunion was equal. This means that a great number of patients initially treated conservatively ultimately require surgery, with malalignment being the most frequent indication. In addition, it should be acknowledged that performing surgery in patients initially managed conservatively is generally less complex than that in patients initially treated operatively. In the conservative group, surgery is performed for treatment failure, and in the operative group, reintervention is performed for the treatment of complications. The lower complexity of performing reintervention in patients initially treated by conservative means might also explain the relatively high reintervention rate.

Surgical fixation of humeral shaft fractures carries a risk of 3.5% for radial nerve palsy following surgery, as found in our meta-analysis. Despite the added risk, the rate of persistent radial nerve palsy is equally rare in both patients treated conservatively and those treated operatively. Radial nerve palsy following surgery therefore appears to be a mostly temporary issue and rarely leads to permanent damage. In addition, this study emphasizes that the presence of radial nerve palsy in patients with humeral shaft fractures does not necessarily mandate exploration. As seen in our study and described in the literature, primary radial nerve palsy usually resolves spontaneously.[37,38]

Only the 2 randomized clinical trials reported on validated functional outcome scores (DASH score).[23,24] The other studies either did not report functional results or reported results of non-validated instruments. The pooled analysis showed a trend toward better functional results in patients treated operatively. This difference, however, did not reach statistical significance. As both randomized clinical trials found comparable results in favor of operative treatment, it is likely that the failure to detect a difference is mainly a result of underpowering rather than due to the fact that there is no actual difference.

The present meta-analysis found no difference in pooled effect estimates between randomized clinical trials and observational studies. Observational studies may provide valuable information about treatment effects.[39-41] Including this information in a meta-analysis increases the sample size and thus allows for evaluation of effects in subgroups of patients or effects on rare clinical endpoints. The benefit of including observational data has been previously demonstrated in meta-analyses on surgical interventions.[6,9,10,12,42] Similarly to our study, these meta-analyses found no difference in pooled treatment effects between observational studies and randomized clinical trials, although effect estimates of observational studies were more heterogeneous.

An important aspect in incorporating observational data in meta-analyses is that the chances of confounding should be deemed small. In this meta-analysis, the observed baseline patient characteristics were comparable between treatment groups, from which we inferred that this may also be the case for unobserved patient characteristics. On the basis of this observation, we consider the potential for confounding acceptably low to allow for the inclusion of observational data in the meta-analysis.

Several potential limitations in this review should be considered. First, the results might have been influenced by missing articles. There appeared to be some visual asymmetry in the funnel plot for the outcome of nonunion. This, however, might also have been caused by the relatively low number of studies. Second, a limited number of randomized clinical trials were available for comparison of risk estimates of observational studies and randomized clinical trials. Although less robust, our findings, suggesting comparable risk estimates between the 2 study designs, are in line with those of previous studies. Third, this meta-analysis investigated the difference between conservative and operative treatment, irrespective of type of operative management (nail, plate, minimally invasive techniques). Finally, to increase the power of the pooled analysis, we used a compound endpoint for reintervention. In other words, we did not take the severity of the indication or reintervention itself into account.

A trend is observed toward the increased use of operative fixation.[3] Possible reasons for this include a perceived quicker return to work, earlier initiation of shoulder and elbow rehabilitation, and avoidance of potential troublesome brace wear during the recovery period.[3] However, evidence supporting this is scarce. Investigating whether these patient-related outcomes truly exist would require prospective studies measuring these outcomes on a daily basis (e.g. patient diary) and not at a fixed point in time (e.g. during outpatient clinic visits), as frequently used in the studies in our meta-analysis. This would complement the already existing data indicating more favorable outcomes for surgical treatment.

The next step in determining optimal management for humeral shaft fractures would be to determine which type of surgical treatment is superior. Multiple meta-analyses have been performed comparing plate fixation with minimally invasive plating and nailing.[43-45] Although these meta-analyses found differences in procedure-related complications (e.g. shoulder complaints with nailing or radial nerve palsy with plate fixation), they failed to detect differences in other important outcomes including nonunion, infection, reintervention, and functional scores.

Conclusion

This systematic review shows that satisfactory results can be achieved with both conservative and operative management. However, operative treatment reduces the risk of nonunion compared with conservative treatment, with comparable reintervention rates (for indications other than nonunion). Intervention (or reintervention) is mostly performed because of treatment failure in the conservative group and for the treatment of complications in the operative group, which logically differ in complexity. Furthermore, operative treatment results in a similar permanent radial nerve palsy rate, despite its inherent additional surgery-related risks. There is also a trend toward better functional results for operative treatment.

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Supplementary materials to Chapter 4

Table S1. Search syntax performed last on March 23, 2019

Database	Syntax
PubMed/MEDLINE (n= 1766)	(((((("shaft"[Title/Abstract]) OR "Diaphysis"[Title/Abstract]) OR "diaphyseal"[Title/Abstract]) OR "mid shaft"[Title/Abstract])) AND (("fracture"[Title/Abstract]) OR "fractures"[Title/Abstract])) AND (("humeral"[Title/Abstract]) OR "humerus"[Title/Abstract]))
Embase (n= 1675)	(humeral:ti,ab OR humerus:ab,ti) AND (fracture:ti,ab OR fractures:ab,ti) AND (shaft:ti,ab OR diaphysis:ab,ti OR diaphyseal:ab,ti OR mid) AND shaft:ab,ti
CENTRAL (n= 94)	(AB (humerus OR humeral) AND AB (fracture or fractures) AND AB (shaft OR diaphysis OR diaphyseal OR mid shaft)) OR TI ((humerus OR humeral) AND (fracture or fractures) AND (shaft OR diaphysis OR diaphyseal OR mid shaft))
CINAHL (n= 481)	(AB (humerus OR humeral) AND AB (fracture or fractures) AND AB (shaft OR diaphysis OR diaphyseal OR mid shaft)) OR TI ((humerus OR humeral) AND (fracture or fractures) AND (shaft OR diaphysis OR diaphyseal OR mid shaft))

Table S4. Indications for (re)interventions other than non-union for patients treated conservatively

	Conservative (N)	
	Mal-alignment	Non-tolerance brace
Kumar et al		
Westerick et al		
Dielwart et al	4	
Osmann et al	8	
Jawa et al	2	
Denard et al		
Matsunaga et al	1	1
Wallny et al		
Ekholm et al		

Table S5. Indications for re-interventions other than non-union in patients treated operatively

	Implant irritation	Infection	Implant migration	Mal-reduction	Elbow stiffness**	Hematoma	Secondary dislocation
Kumar et al	1						
Westerick et al		2					
Dielwart et al		1					
Osmann et al			6*				
Jawa et al		1	1				
Denard et al		7		3	1		
Matsunaga et al							
Wallny et al		1				1	2*
Ekholm et al				1			

* intra-medullary nails, ** Elbow function impairment due to scar tissue. Under general anesthesia stretching scar tissue.

Table S2. Quality assessment according to the MINORS criteria

Criteria	Reported and adequate (2)	Reported but inadequate (1)	Not reported (0)
Clearly stated aim	Aim including outcomes reported	Aim reported without outcomes	Not reported
Inclusion consecutive patients	Inclusion/exclusion criteria reported	Unclear description inclusion/exclusion criteria	Not reported
Prospective collection data	Prospective	Not applicable	Not applicable
Appropriate endpoints	Appropriate endpoints to aim study	Endpoints not appropriate to aim study	Not reported
Unbiased assessment	Blinded evaluation of outcomes	Reason not blinding stated	Not reported
Appropriate follow-up	≥ 1 year	< 1 year	Not reported
Loss to follow-up < 5%	≤ 5%	> 5%	Not applicable
Prospective calculation study size	Prospective power-analysis performed	Prospective calculation without power-analysis	Not applicable
Adequate control group	Operative versus nonoperative treatment	Not applicable	Not applicable
Contemporary groups	Study/control group managed during same period	Study/control not managed during same period	Not reported
Baseline equivalence groups	Baseline characteristics described and comparable	Baseline characteristics not comparable	Not reported
Adequate statistical analyses	Statistical analysis described including type of analyses	Inadequate description statistical analysis	Not reported

Items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). The overall score ranging from 0 to 24 for comparative studies

Table S3. Quality assessment of included studies

MINORS criteria	RCTs	Kumar et al	Matsunaga et al	Observational studies	Harkin et al	Westerick et al	Dielwart et al	Mahabier et al	Broadbent et al	Denard et al	Ekholm et al	Jawa et al	Osman et al	Wallny et al
Clearly stated aim		2	2		2	2	2	2	2	2	2	2	2	2
Inclusion of consecutive patients		2	2		2	2	2	2	2	2	2	2	2	2
Prospective collection of data		2	2		0	0	0	0	2	0	0	0	0	0
Appropriate endpoints		2	2		2	2	2	1	2	2	2	2	1	1
Unbiased assessment endpoints		0	2		0	0	0	0	0	0	0	0	0	0
Appropriate follow-up		1	2		0	2	1	0	2	1	2	1	2	2
Loss to follow-up < 5%		0	1		1	0	1	0	0	1	1	1	1	0
Prospective calculation study size		0	2		0	0	0	0	0	0	0	0	0	0
Adequate control group		2	2		2	2	2	2	0	2	2	2	1	2
Contemporary groups		2	2		2	2	2	2	2	2	2	2	2	2
Baseline equivalence of groups		2	2		2	1	2	2	0	2	1	1	0	1
Adequate statistical analysis		2	2		2	2	2	2	2	2	2	2	2	2
Total MINORS score		**17**	**23**		**15**	**15**	**16**	**13**	**14**	**16**	**16**	**15**	**13**	**14**

Items are scored 0 (not reported/ not applicable), 1 (reported but inadequate) or 2 (reported and adequate). The overall score ranging from 0 to 24 for comparative studies

Table S6. Other complications reported in studies

Author	Year	Cons | Op (total)	Mal-alignment*		DVT		Contact dermatitis		Hypertrophic scare	
			Cons	Op	Cons	Op	Cons	Op	Cons	Op
Kumar et al	2017	20 | 20								
Harkin et al	2017	96 | 30								
Westerick et al	2017	69 | 227								
Matsunaga et al	2017	52 | 58	1				5			4
Dielwart et al	2017	31 | 40	4		1	1				
Mahabier et al	2013	91 | 95								
Broadbent et al	2010	89 | 21								
Denard et al	2010	63 | 150	8	12						
Ekholm et al	2008	20 | 7								
Jawa et al	2006	21 | 19	2							
Osman et al	1998	32 | 72								
Wallny et al	1997	44 | 45								

* Supplementary table 4 and 5 describe the number of patients with mal-alignment who were subsequently treated operatively. All other complications described in this table were treated conservatively. DVT Deep venous thrombosis

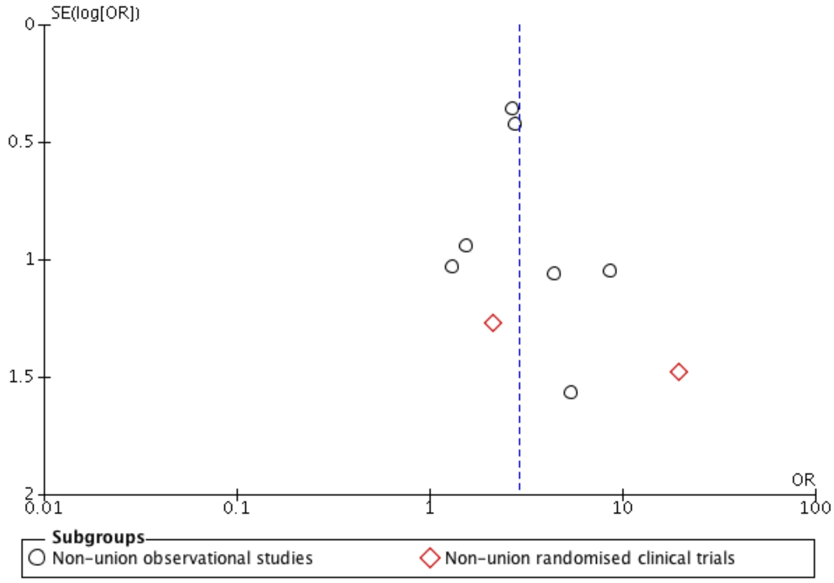


Figure S1. Funnel-plot of non-union rate (OR odds ratio; SE standard error).

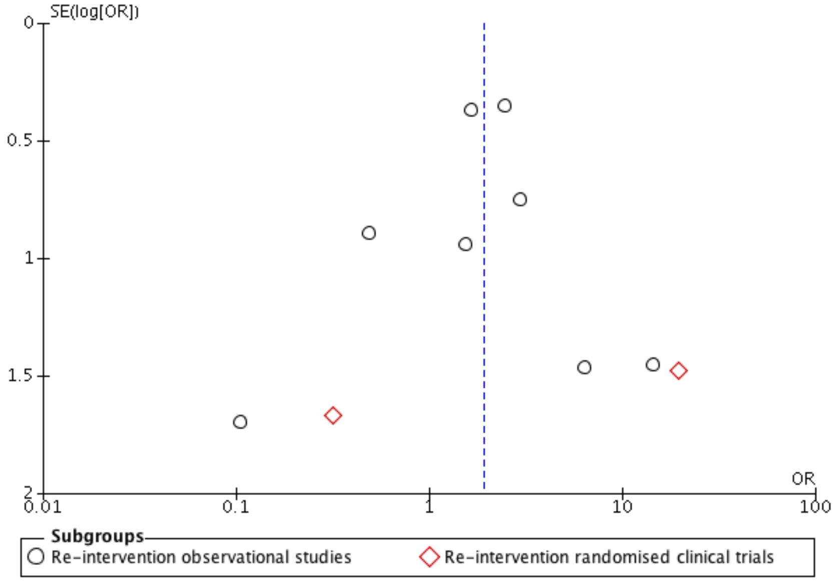


Figure S2. Funnel-plot of (re)intervention rate (OR odds ratio; SE standard error).

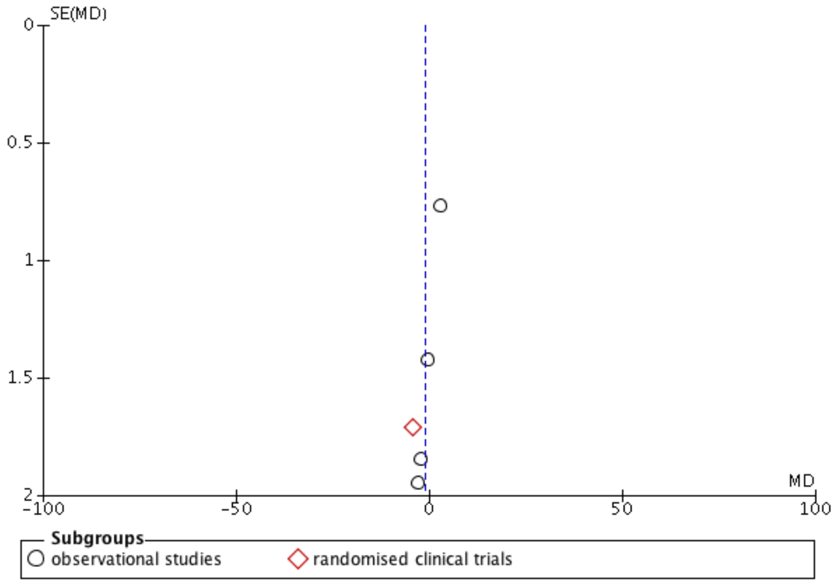


Figure S3. Funnel-plot mean time to union (MD mean difference; SE standard error).

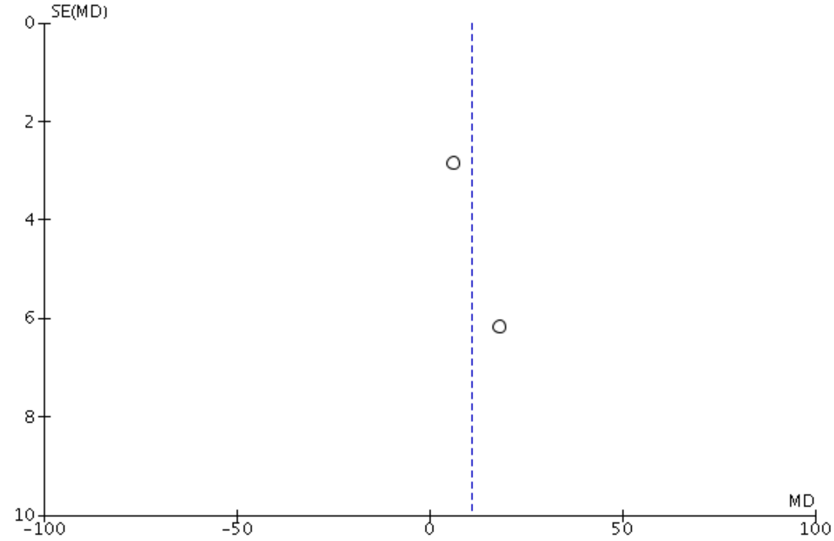


Figure S4. Funnel-plot DASH score at 6 months (MD mean difference; SE standard error).

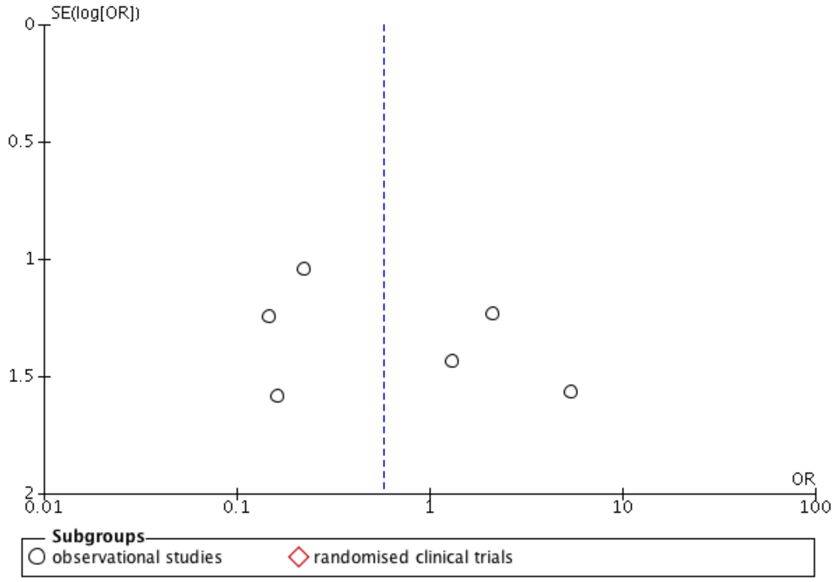


Figure S5. Funnel-plot permanent radial nerve palsy rate (OR odds ratio; SE standard error).

Study or Subgroup	conservative Events	conservative Total	Operative Events	Operative Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
1.1.1 Non-union observational studies							
Wallny	2	44	0	45	0.0%	5.35 [0.25, 114.74]	1997
Osman	2	32	3	72	0.0%	1.53 [0.24, 9.65]	1998
Jawa	0	21	0	19		Not estimable	2006
Ekholm	0	20	0	7		Not estimable	2008
Denard	13	63	13	150	83.6%	2.74 [1.19, 6.31]	2010
Broadbent	16	89	1	21	0.0%	4.38 [0.55, 35.09]	2010
Mahabier	0	0	0	0		Not estimable	2013
Harkin	22	96	1	30	0.0%	8.62 [1.11, 66.94]	2017
Westerick	16	69	23	227	0.0%	2.68 [1.32, 5.42]	2017
Dielwart	2	31	2	40	0.0%	1.31 [0.17, 9.86]	2017
Subtotal (95% CI)		**63**		**150**	**83.6%**	**2.74 [1.19, 6.31]**	
Total events	13		13				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.37 (P = 0.02)							
1.1.2 Non-union randomised clinical trials							
Kumar	2	20	1	20	9.4%	2.11 [0.18, 25.35]	2017
Matsunaga	7	52	0	58	7.0%	19.29 [1.07, 346.60]	2017
Subtotal (95% CI)		**72**		**78**	**16.4%**	**5.67 [0.60, 53.62]**	
Total events	9		1				
Heterogeneity: Tau² = 0.77; Chi² = 1.41, df = 1 (P = 0.24); I² = 29%							
Test for overall effect: Z = 1.51 (P = 0.13)							
Total (95% CI)		**135**		**228**	**100.0%**	**3.06 [1.43, 6.57]**	
Total events	22		14				
Heterogeneity: Tau² = 0.00; Chi² = 1.87, df = 2 (P = 0.39); I² = 0%							
Test for overall effect: Z = 2.88 (P = 0.004)							
Test for subgroup differences: Chi² = 0.35, df = 1 (P = 0.55), I² = 0%							

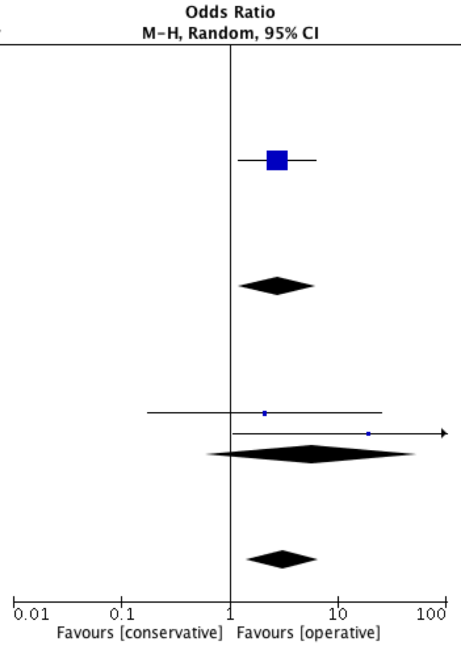


Figure S6. Forest-plot of non-union rate for studies comparing conservative treatment to plate fixation.

Study or Subgroup	conservative Events	conservative Total	Operative Events	Operative Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
1.1.1 Non-union observational studies							
Wallny	2	44	0	45	31.5%	5.35 [0.25, 114.74]	1997
Osman	2	32	3	72	0.0%	1.53 [0.24, 9.65]	1998
Jawa	0	21	0	19		Not estimable	2006
Ekholm	0	20	0	7		Not estimable	2008
Denard	13	63	13	150	0.0%	2.74 [1.19, 6.31]	2010
Broadbent	16	89	1	21	68.5%	4.38 [0.55, 35.09]	2010
Mahabier	0	0	0	0		Not estimable	2013
Harkin	22	96	1	30	0.0%	8.62 [1.11, 66.94]	2017
Westerick	16	69	23	227	0.0%	2.68 [1.32, 5.42]	2017
Dielwart	2	31	2	40	0.0%	1.31 [0.17, 9.86]	2017
Subtotal (95% CI)		**133**		**66**	**100.0%**	**4.67 [0.84, 26.10]**	
Total events	18		1				
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0%							
Test for overall effect: Z = 1.75 (P = 0.08)							
1.1.2 Non-union randomised clinical trials							
Kumar	2	20	1	20	0.0%	2.11 [0.18, 25.35]	2017
Matsunaga	7	52	0	58	0.0%	19.29 [1.07, 346.60]	2017
Subtotal (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total (95% CI)		**133**		**66**	**100.0%**	**4.67 [0.84, 26.10]**	
Total events	18		1				
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0%							
Test for overall effect: Z = 1.75 (P = 0.08)							
Test for subgroup differences: Not applicable							

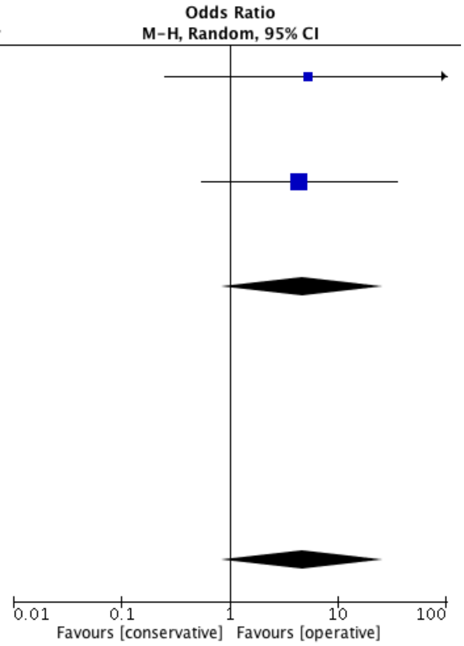
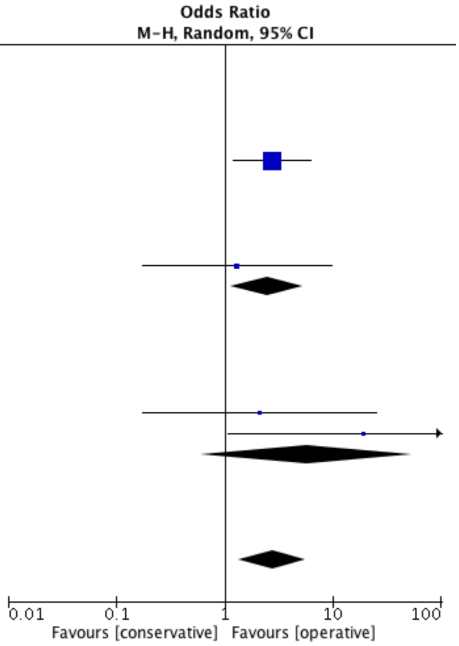
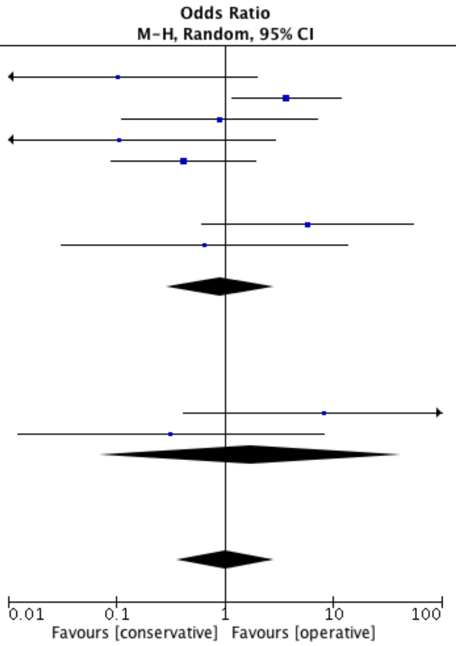


Figure S7. Forest-plot of non-union rate for studies comparing conservative treatment to plate fixation in patients older than 50 years.



Study or Subgroup	conservative Events	conservative Total	Operative Events	Operative Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
1.1.1 Non-union observational studies							
Wallny	2	44	0	45	0.0%	5.35 [0.25, 114.74]	1997
Osman	2	32	3	72	0.0%	1.53 [0.24, 9.65]	1998
Jawa	0	21	0	19		Not estimable	2006
Ekholm	0	20	0	7		Not estimable	2008
Denard	13	63	13	150	73.2%	2.74 [1.19, 6.31]	2010
Broadbent	16	89	1	21	0.0%	4.38 [0.55, 35.09]	2010
Mahabier	0	0	0	0		Not estimable	2013
Harkin	22	96	1	30	0.0%	8.62 [1.11, 66.94]	2017
Westerick	16	69	23	227	0.0%	2.68 [1.32, 5.42]	2017
Dielwart	2	31	2	40	12.5%	1.31 [0.17, 9.86]	2017
Subtotal (95% CI)		**94**		**190**	**85.7%**	**2.46 [1.14, 5.32]**	
Total events	15		15				
Heterogeneity: Tau² = 0.00; Chi² = 0.44, df = 1 (P = 0.51); I² = 0%							
Test for overall effect: Z = 2.29 (P = 0.02)							
1.1.2 Non-union randomised clinical trials							
Kumar	2	20	1	20	8.2%	2.11 [0.18, 25.35]	2017
Matsunaga	7	52	0	58	6.1%	19.29 [1.07, 346.60]	2017
Subtotal (95% CI)		**72**		**78**	**14.3%**	**5.67 [0.60, 53.62]**	
Total events	9		1				
Heterogeneity: Tau² = 0.77; Chi² = 1.41, df = 1 (P = 0.24); I² = 29%							
Test for overall effect: Z = 1.51 (P = 0.13)							
Total (95% CI)		**166**		**268**	**100.0%**	**2.75 [1.35, 5.62]**	
Total events	24		16				
Heterogeneity: Tau² = 0.00; Chi² = 2.45, df = 3 (P = 0.48); I² = 0%							
Test for overall effect: Z = 2.78 (P = 0.005)							
Test for subgroup differences: Chi² = 0.48, df = 1 (P = 0.49), I² = 0%							

Figure S8. Forest-plot of non-union rate for high quality studies.



Study or Subgroup	conservative Events	conservative Total	operative Events	operative Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
1.8.1 Observational studies							
Wallny	0	44	4	45	8.3%	0.10 [0.01, 1.98]	1997
Osman	8	32	6	72	20.1%	3.67 [1.15, 11.66]	1998
Jawa	2	21	2	19	12.8%	0.89 [0.11, 7.06]	2006
Ekholm	0	20	1	7	7.0%	0.11 [0.00, 2.92]	2008
Denard	2	63	11	150	16.8%	0.41 [0.09, 1.93]	2010
Broadbent	0	89	0	21		Not estimable	2010
Mahabier	0	0	0	0		Not estimable	2013
Dielwart	4	31	1	40	11.7%	5.78 [0.61, 54.58]	2017
Westerick	0	69	2	227	7.9%	0.65 [0.03, 13.68]	2017
Harkin	0	96	0	30		Not estimable	2017
Subtotal (95% CI)		**465**		**611**	**84.6%**	**0.90 [0.28, 2.83]**	
Total events	16		27				
Heterogeneity: Tau² = 1.14; Chi² = 12.44, df = 6 (P = 0.05); I² = 52%							
Test for overall effect: Z = 0.18 (P = 0.86)							
1.8.2 Randomised clinical trials							
Matsunaga	3	52	0	58	8.2%	8.27 [0.42, 164.06]	2017
Kumar	0	20	1	20	7.2%	0.32 [0.01, 8.26]	2017
Subtotal (95% CI)		**72**		**78**	**15.4%**	**1.73 [0.07, 42.78]**	
Total events	3		1				
Heterogeneity: Tau² = 2.82; Chi² = 2.11, df = 1 (P = 0.15); I² = 53%							
Test for overall effect: Z = 0.34 (P = 0.74)							
Total (95% CI)		**537**		**689**	**100.0%**	**1.01 [0.37, 2.81]**	
Total events	19		28				
Heterogeneity: Tau² = 1.00; Chi² = 14.55, df = 8 (P = 0.07); I² = 45%							
Test for overall effect: Z = 0.03 (P = 0.98)							
Test for subgroup differences: Chi² = 0.14, df = 1 (P = 0.71), I² = 0%							

Figure S9. Forest-plot of (re)intervention rate for indications other than non-union.