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Factors explaining heterogeneity in studies comparing surgical and nonsurgical treatment of midshaft clavicle fractures: a meta-regression analysis of randomized controlled trials and high-quality observational studies

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Background: Previous meta-analyses comparing the surgical and nonsurgical treatment of midshaft clavicle fractures have demonstrated extensive heterogeneity, that is, treatment effect variation, in different pooled outcomes. We aimed to investigate the amount of heterogeneity seen in pooled treatment effects and to explore which moderator variables serve to explain this heterogeneity.
Methods: A follow-up literature search, based a previous study, was conducted. All randomized controlled trials and high-quality observational studies with suitable treatment cohorts were identified and included in this systematic review and meta-regression analysis. The proportions of male patients, patients with the dominant hand injured, and smokers, as well as fracture type and mean age, were included as covariates in meta-regression analyses investigating the effect on the pooled estimate of treatment effect heterogeneity. The pooled treatment effects assessed were nonunion rate, malunion rate, Disabilities of the Arm, Shoulder and Hand score, and Constant score at 1 year, as well as revision surgery rate.
Results: High heterogeneity was observed in 4 of 8 pooled treatment effects and moderate, in 2 of 8. An association between any of the covariates, including smoking, with the pooled treatment effect for the nonunion rate could not be established. Regarding malunion, the proportion of patients with the dominant hand injured showed linear dependency with the risk ratio. The proportion of male patients correlated with the pooled mean difference in both the Disabilities of the Arm, Shoulder and Hand score and Constant score. Mean age and fracture type correlated with the pooled mean difference in the Constant score.
Conclusion: On the basis of our results, several potential moderators influence the treatment effect when comparing surgical and nonsurgical treatment of midshaft clavicle fractures. These findings have implications for shared decision making and when making treatment recommendations.
Level of evidence: Level III; Meta-analysis

Keywords: Clavicle fracture; meta-regression; shared decision making; heterogeneity; treatment effect heterogeneity; meta-analysis

The incidence of clavicle fractures has almost doubled since the beginning of the century, being 59 per 100,000 person-years in 2012.[12] The rate of surgical treatment has, however, increased 7-fold during the same period. The

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greatest increase has been in the number of surgical treatments noted in the younger age groups.[12] Before the beginning of the century, only a fraction of clavicle fractures were treated operatively. However, the subsequent introduction of new, anatomic locking plates at the beginning of the 2000s has led to an increased operative rate for the most common upper-limb fractures, and the same trend seems to have been adopted in the treatment of clavicle fractures.[10,27]

For the treatment of patients with midshaft clavicle fractures (MCFs), there are a variety of possible measures to assess the overall outcome. These include the nonunion rate, malunion rate, secondary or revision surgery, complication rate, functional outcome using patient-reported outcome measures, return to work, return to sports, overall satisfaction, cosmesis, and overall cost. In addition to the numerous possible outcomes, there is usually some variability in baseline characteristics between studies. This includes factors such as the sex ratio, age, smoking, and fracture morphology. This variability may result in heterogeneity in the pooled estimate of the treatment effect, such as the nonunion rate or Disabilities of the Arm, Shoulder and Hand (DASH) score. Heterogeneity means that the estimate of the treatment effect varies between studies. Previous meta-analyses investigating MCFs have shown an extensive amount of heterogeneity for different pooled estimates of treatment effects. Thus, the decision to operate or to prefer nonsurgical treatment should potentially be a shared decision based on patient preferences and the best available evidence.

Meta-regression is a way to assess the effect of moderators on the pooled estimates of treatment effects and to provide more evidence for decision making between surgical and nonsurgical treatment regarding expected outcomes.[11] Hence, we sought to perform a follow-up study on a previous meta-analysis that included both randomized controlled trials (RCTs) and high-quality observational studies investigating the surgical and nonsurgical treatment of MCFs.[25] The aim of our study was to (1) investigate the amount of heterogeneity seen in pooled estimates of treatment effects and (2) explore which baseline covariates affect the treatment effect when comparing the surgical and nonsurgical treatment of MCFs.

Methods

Search and selection criteria

We performed a follow-up analysis based on the meta-analysis by Smeeing et al.[25] In their analysis, they systematically searched all RCTs and observational studies comparing the surgical and nonsurgical treatment of MCFs. They graded all studies according to the Methodological Index for Non-randomized Studies (MINORS) score to determine the quality of the studies.[24] For our study, we selected the same studies as Smeeing et al. In addition, we performed a follow-up literature search in the PubMed, CENTRAL (Cochrane Central Register of Controlled Trials), and CINAHL (Cumulative Index to Nursing and Allied Health Literature) databases using the exact same syntaxes described by Smeeing et al in Appendix 1 in their article. Embase was not searched because of the inability to access the database. The search period in the study by Smeeing et al ended on December 1, 2015; therefore, we searched for studies published between December 2, 2015, and December 31, 2018. The same inclusion and exclusion criteria were applied.[5] The search was conducted by 1 reviewer (A.R.). All records were screened by 2 reviewers (A.R. and J.P.). All potential studies were marked and the full texts reviewed. All RCTs and high-quality observational studies with suitable treatment cohorts were included. A flowchart of the literature search is presented in Figure 1. In total, 13 studies were included after full-text assessment.

Quality assessment and study inclusion

The methodologic quality was assessed as previously described.[5] Two reviewers (A.R. and A.L.) graded the selected studies according to the MINORS score.[24] The weighted Cohen κ for agreement was 0.71 (95% confidence interval [CI], 0.57-0.82). Disagreements were resolved by consensus. Details of the scoring are available in Supplementary Table S1. Of the 13 new studies identified in our follow-up search and included in the study, 8 had a MINORS score of 17 points or more, indicating inclusion in the final analysis. In the original study by Smeeing et al,[25] 12 of 20 studies had a MINORS score of 17 points or more; these studies were also included in our analysis. In total, 12 RCTs and 8 high-quality observational studies were included in the final analysis.

Data extraction

From the included studies, we extracted the first author, country, year of publication, study design, number of patients in both treatment arms, total number of male patients, total number of patients with the dominant hand injured, total number of patients who smoked, total number of patients with a comminuted fracture, fixation method used in the surgical group, and fracture classification. We did not differentiate between different surgical methods, but both plate fixation and intramedullary devices were included in surgical treatment. For fracture classification, we recorded whether the Robinson classification, the AO Foundation–Orthopaedic Trauma Association classification, or comminution in general was used. For the total number of male patients, patients with the dominant hand injured, patients with a comminuted fracture, and patients who smoked, we calculated the corresponding baseline proportions, which were then used as moderator variables. If fractures were classified according to the Robinson classification, we calculated the proportion of patients with grade

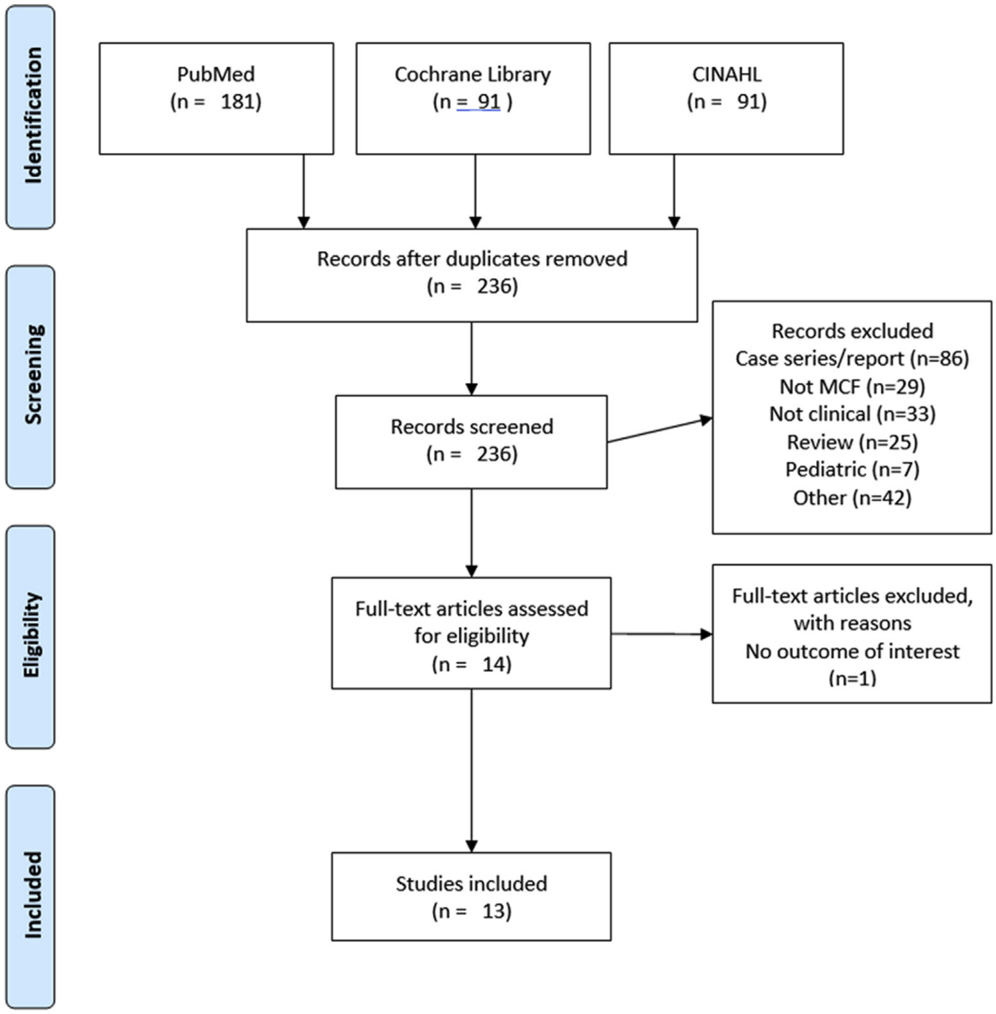

Figure 1 Flowchart of literature review. *CINAHL*, Cumulative Index to Nursing and Allied Health Literature; *MCF*, midshaft clavicle fracture.

2B2 fractures. For the AO Foundation–Orthopaedic Trauma Association classification, we calculated the proportion of class C fractures.

Outcome measures

The numbers of nonunions and malunions were extracted, as described in the original studies. DASH and Constant scores were extracted if reported in the studies. We only focused on functional outcome with a minimum of 1 year of follow-up. In 1 large RCT, functional outcome was only reported at the 9-month time point, and this trial was included.[1] Qvist et al[21] reported the point estimates for the DASH and Constant scores graphically, and they were contacted to provide the exact values. Means and standard deviations (SDs) were calculated from median values and interquartile ranges (IQRs). We defined revision surgery similarly to Smeeing et al[25]: Any secondary surgery in the surgical group and any delayed surgery in the nonsurgical group were considered revision surgery, and their number was extracted, as reported in the original studies. If the study had >2 arms, we selected only the nonsurgical arm and the one with a plate as the surgical treatment.

Statistical analysis

The data included in the study by Smeeing et al[25] were used. As previously mentioned, in one study the mean and SD for continuous outcomes were only reported graphically.[21] The authors of the study were therefore contacted and asked for point estimates. The data were reported as medians and IQRs and then transformed to means and SDs, as described by Wan et al.[32] For binary outcomes, the Mantel-Haenszel method was used to pool the results and construct 95% CIs. This was used for both fixed and random effect model. Continuity correction of 0.5 was used if needed. For the random-effects model, the DerSimonian-Laird estimator was used. For binary outcomes, we calculated both the risk ratio (RR) and the risk difference (RD) and investigated the effect of moderator variables with both outcome measures. Continuous outcomes were pooled using the inverse variance method, and the mean difference (MD) was used as a summary measure. Heterogeneity was assessed using the Cochran Q, and the χ^2 test was used to test the significance of heterogeneity. The amount of study heterogeneity in the pooled estimate of the treatment effect was calculated using the I^2 value. The amount of heterogeneity was classified as low (25%-50%), moderate (50%-75%), or high (>75%). Statistical analyses were done with R 3.5.4 (R foundation, Vienna, Austria) with meta package.

Table I Effect of moderator variables on treatment effect in meta-regression

Outcome	Effect size measure	Moderator	No. of studies in analysis	Moderator estimate (95% CI)	*P* value for moderator	Heterogeneity accounted for by moderator (pseudo R^2), %
Nonunion	RD	Smoking	9	−0.14 (−0.60 to 0.32)	.55	0
		Male	18	−0.088 (−0.28 to 0.11)	.38	0
		Mean age	19	−0.002 (−0.009 to 0.006)	.70	0
		Hand dominance	14	0.18 (−0.22 to 0.59)	.38	0
		Robinson grade 2B2	7	−0.10 (−0.39 to 0.19)	.48	0
		AO class C	6	−0.06 (−0.13 to 0.24)	.53	0
		Comminuted fracture	5	0.086 (−0.39 to 0.56)	.72	0
Malunion	RD	Smoking	5	−0.04 (−0.64 to 0.56)	.89	0
		Male	12	0.22 (−0.33 to 0.77)	.43	0
		Mean age	12	−0.002 (−0.018 to 0.014)	.83	0
		Hand dominance	10	0.88 (−0.26 to 2.0)	.13	0
		Robinson grade 2B2	3	−1.2 (−4.1 to 1.8)	.44	0
		AO class C	4	0.02 (−0.57 to 0.60)	.98	0
		Comminuted fracture	3	−2.4 (−4.2 to −0.65)	.0072	42
	RR	Smoking	5	6.3 (−0.33 to 13)	.062	100
		Male	12	0.98 (−7.7 to 9.7)	.82	0
		Mean age	12	−0.11 (−0.34 to 0.12)	.35	26
		Hand dominance	10	12 (6.0 to 18)	<.0001	95
		Robinson grade 2B2	3	−7.8 (−21.3 to 5.7)	.26	41
		AO class C	4	−1.0 (−6.1 to 4.0)	.69	0
		Comminuted fracture	3	−7.9 (−28 to 12)	.43	0
Constant score	MD	Smoking	6	8.6 (−14 to 31)	.44	42
		Male	9	−19 (−30 to −7.0)	.0017	66
		Mean age	10	−1.2 (−2.1 to −0.36)	.0056	50
		Hand dominance	7	24.7 (−14.4 to 63.7)	.21	36
		Robinson grade 2B2	3	−33 (−44 to −22)	<.0001	96
		AO class C	4	−2.3 (−11.4 to 6.8)	.62	0
		Comminuted fracture	3	61 (37 to 85)	<.0001	100
DASH score	MD	Smoking	8	−9.3 (−42 to 23)	.57	5
		Male	12	28 (8.7 to 47)	.0045	53
		Mean age	12	0.58 (−0.29 to 1.5)	.19	22
		Hand dominance	9	0.97 (−54 to 56)	.97	0
		Robinson grade 2B2	1	Not estimated		
		AO class C	5	3.1 (−7.2 to 13)	.56	0
		Comminuted fracture	3	−76 (−93 to −60)	<.0001	100
Revision surgery	RD	Smoking	7	−0.081 (−0.88 to 0.72)	.84	0
		Male	13	0.41 (−0.22 to 1.0)	.20	0
		Mean age	14	0.0049 (−0.013 to 0.023)	.60	0
		Hand dominance	10	0.32 (−1.1 to 1.7)	.65	0
		Robinson grade 2B2	4	−0.31 (−0.95 to 0.33)	.35	NA
		AO class C	5	0.34 (−0.02 to 0.70)	.06	39
		Comminuted fracture	5	0.31 (−0.46 to 1.1)	.43	0
	RR	Smoking	7	−2.3 (−13 to 8.4)	.67	0
		Male	12	3.4 (−3.7 to 10)	.35	1
		Mean age	13	0.038 (−0.15 to 0.23)	.70	8
		Hand dominance	10	0.96 (−11 to 13)	.88	0
		Robinson grade 2B2	4	−8.8 (−19 to 1.9)	.11	100
		AO class C	5	3.4 (1.2 to 5.6)	.022	100
		Comminuted fracture	5	5.4 (−2.6 to 13)	.18	13

CI, confidence interval; *RD*, risk difference; *RR*, risk ratio; *DASH*, Disabilities of the Arm, Shoulder and Hand; *MD*, mean difference.

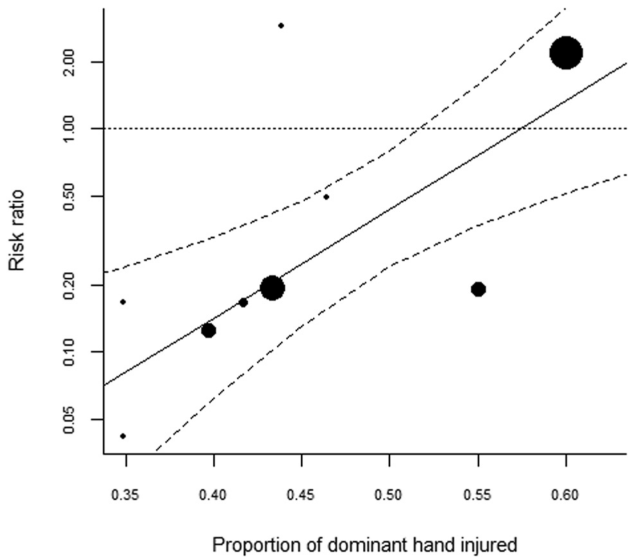

Figure 2 Effect of proportion of patients with dominant hand injury on risk ratio for malunion. *Dashed lines* depict the 95% confidence interval.

Results

Baseline characteristics

Twenty studies were included in the study analysis.[1-5,8,14,15,17-22,26,28-31,33] The characteristics of all the included studies are shown in Supplementary Table S2. The mean age of the patients varied from 26.5 to 40.6 years (median, 36.3 years; IQR, 32.5-38.0 years). The proportion of male patients was between 30.4% and 91.8% (median, 86.6%; IQR, 72.8%-87.8%). Variability was also seen in the proportion of patients who smoked and dominance of the injured hand.

Nonunion

The RD for nonunion was –10.1% (95% CI, –13.3% to –6.8%; $P < .0001$, $I^2 = 48\%$) in favor of surgical treatment (Supplementary Fig. S1). This corresponded to an RR of 0.14 (95% CI, 0.08-0.22; $P < .0001$, $I^2 = 0\%$) (Supplementary Fig. S2). For the RR, no study heterogeneity was observed ($I^2 = 0\%$, $P = .88$) and no meta-regression was performed. For the pooled RD, a small amount of heterogeneity was observed ($P = .012$). None of the moderator variables, however, showed clear linear dependency with the treatment effect (Table I).

Malunion

The RD for malunion was –9.8% (95% CI, –17.0% to –2.60%; $P = .011$, $I^2 = 88\%$) (Supplementary Fig. S3) in favor of surgical treatment. This corresponded to an RR of 0.31 (95% CI, 0.12-0.76; $P = .011$, $I^2 = 69\%$) (Supplementary Fig. S4). For the RD, high heterogeneity was observed ($P < .0001$), and for the RR, moderate heterogeneity ($P < .0001$). The proportion of patients with the dominant hand affected showed positive linear dependency with the RR (Table I). For the RR, a regression coefficient value of 12 indicates that for each 10% (0.1) increment in the proportion of patients with the dominant hand injured, the $\log_{10}$(RR) increases 1.2, indicating that the advantage of surgery is reduced with the increasing proportion of patients with the dominant hand affected (Fig. 2).

Constant score

The pooled MD for the Constant score in the long term was 4.51 (95% CI, 1.55-7.45; $P = .0028$, $I^2 = 93\%$) favoring surgical treatment (Supplementary Fig. S5). Again, high heterogeneity was observed ($P < .0001$). The proportion of male patients (Fig. 3, A), mean age (Fig. 3, B), and the proportion of patients with Robinson grade 2B2 fractures (Fig. 3, *C*) showed linear dependency with the MD of the Constant score. These moderators accounted for between 50% and 90% of the heterogeneity (Table I). All dependencies were negative, indicating that the higher the proportion of male patients or Robinson grade 2B2 fractures and the higher the mean age, the smaller the MD

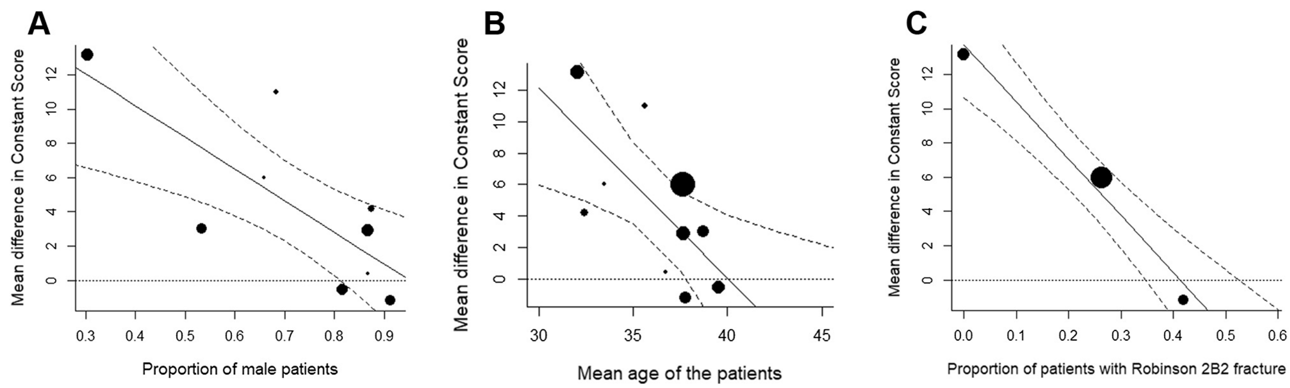

Figure 3 Effect of proportion of male patients **(A)**, mean age **(B)**, and patients with Robinson grade 2B2 fracture **(C)** on mean difference in Constant score. *Dashed lines* depict 95% confidence intervals.

favoring surgery. The proportion of comminution in fractures showed positive linear dependency with the treatment effect.

DASH score

The pooled MD for the DASH score in the long term was –2.62 (95% CI, –5.5 to 0.3; $P = .075$, $I^2 = 92\%$) favoring surgical treatment (Supplementary Fig. S6). The superiority of surgical treatment could not, however, be shown. High heterogeneity was observed ($P < .0001$). The proportion of male patients showed linear dependency with the MD of the DASH score accounting for 53% of the heterogeneity (Fig. 4). The proportion of comminution in fractures showed linear dependency with the treatment effect. However, the number of studies was only 3.

Revision surgery

The RD for revision surgery was –2.91% (95% CI, –9.2% to 3.4%) (Supplementary Fig. S7), corresponding to an RR of 0.67 (95% CI, 0.316-1.43) (Supplementary Fig. S8). On the basis of the CIs, the superiority of either treatment could not be established. High heterogeneity was seen in the RD estimate ($I^2 = 75.1\%$, $P < .001$) and moderate heterogeneity, in the RR estimate ($I^2 = 73.8\%$, $P < .001$). No strong moderator effects were seen (Table I).

Discussion

In this study, we updated the work by Smeeing et al[25] and made a further analysis by adding the most recent publications. Furthermore, we added the analysis of heterogeneity for a better understanding of the overall treatment effects and the interpretation of the studies included in the meta-analysis. Although the results regarding the superiority of either treatment option were similar to those of previous studies, we were able to establish several moderator variables that accounted for the high heterogeneity observed in the pooled estimates of treatment effects. Most important, we observed a clinically inconclusive difference between surgical and nonsurgical treatment regarding functional outcome, namely 4.5 points in the Constant score and 2.7 in the DASH score, both in favor of operative treatment. The heterogeneity in these estimates was explained by the proportion of male patients, mean age, and the proportion of patients with Robinson grade 2B2 fractures.

Surgery is associated with a lower risk of nonunion, a higher risk of complications, and better functional outcomes. However, the difference may not exceed the established minimal clinically important difference (MCID). Thus, it is fair to conclude that an objective superiority between surgical and nonsurgical treatment

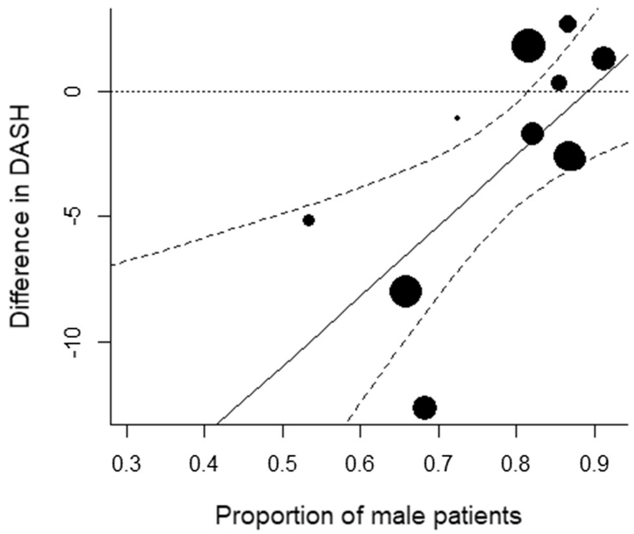

Figure 4 Effect of proportion of male patients on mean difference in Disabilities of the Arm, Shoulder and Hand *(DASH)* score. *Dashed lines* depict the 95% confidence interval.

cannot be clearly established. This approach is strongly supported when summing previous conflicting conclusions on this topic (Table II).

In addition to individual RCTs, several meta-analyses comparing surgical and nonsurgical treatment have been published. Regardless of minor fluctuations, the actual data in these studies are basically the same, but the studies lack inferential reproducibility, that is, even though the same data are used, the conclusions are different. Woltz et al[32] quite rightly stated that plate fixation reduces the risk of nonunion but found no advantage in functional outcome and concluded that routine plate fixation is not feasible. Woltz et al and Guerra et al[9] reported MDs in the DASH score of 4.3 and 4.4 points, respectively, in favor of surgery. Similar results were found by Woltz et al and Guerra et al for the CS, at 5.1 and 5.3 points, respectively, again in favor of surgery. In the study by Smeeing et al,[25] the MDs were lower but still favored surgery. Guerra et al, however, concluded that surgery leads to a better shoulder functional score. In their study, the 95% CI for the DASH score was 0.2-8.4 points, which means that their data were compatible with an improvement >0.2 or <8.4. MCIDs of 10-15 points in the DASH score and 10 points in the Constant score have been suggested.[6,16] As such, the MCID for the DASH score is excluded by this interval, meaning this group difference is not clinically significant. Clearly, the overall conclusion is based on how the possible advantage in functional outcome is valued by the investigators. From the aforementioned findings, we can conclude that superiority is objectively hard to set. Hence, shared decision making with the patient should be the dictating attribute in the process of decision making when an individual is given the choice between surgical and nonsurgical treatment. The previous

Table II Summary of findings in randomized controlled trials comparing nonsurgical and surgical treatment of midshaft clavicle fractures

Favoring nonsurgical treatment	Favoring surgery
"The results of the present study do not support routine primary open reduction and plate fixation for the treatment of displaced midshaft clavicular fractures."[22]	"ORIF [open reduction–internal fixation] is a safe and reliable intervention with superior early functional outcomes and should be considered for patients who sustain this common injury."[1]
"We therefore do not advocate routine operative treatment for displaced midshaft clavicular fractures."[32]	"This study supports primary plate fixation of completely displaced midshaft clavicular fractures in active adult patients."[3]
"In conclusion, this study did not demonstrate a difference in shoulder function between surgical and nonsurgical treatment of dislocated midshaft clavicle fractures."[28]	"Open reduction and internal fixation of comminuted fractures of the clavicle using a reconstruction plate is an effective treatment modality."[19]

activity of the patient, the beliefs of the patient, the level of knowledge delivered by the treating physician, and patient cooperation should all be taken into account during the process.

We postulate that the considerable heterogeneity between the studies in our review and those in other reviews, that is, the variability in the estimate of the treatment effect, is mainly because of the differing baseline characteristics of the research subjects. Moreover, because the interventions are similar and the outcomes measured have a high signal-to-noise ratio, the outcomes measured are accurate, are transferable, and have low levels of error sources. This finding further supports the conclusion that objective superiority does not exist between surgical and nonsurgical treatment. Therefore, the treatment decision should be made according to shared decision making. Moderators of heterogeneity can, however, be assessed using meta-regression, and these may be taken into account when making the final decision in the shared treatment process and when making informed decisions.

For many pooled outcomes, there were different moderators, which explained some of the heterogeneity. For malunion, the proportion of patients with the dominant side injured was a moderator for the pooled effect for malunion. However, malunion is not clearly defined in the literature and is most commonly defined by symptoms and radiologic findings. Assuming the association seen in our study is the true population value, we postulate that patients are more alert to symptoms in their nondominant hand whereas satisfaction is greater to the recovery of their dominant hand. This would mean that patients are more satisfied with less in their dominant side. The moderator effect of sex on functional outcome may be a result of female patients' higher demand for pain reduction and function. Preoperative expectations of and satisfaction with other surgical procedures have been shown to have noteworthy sex-based differences, namely female patients are more dissatisfied than male patients.[7,13,23] Hence, we assume that male patients are more satisfied with less compared with female patients, as observed in the functional outcome scores. We should also note the lack of capability of the moderator variables to explain the heterogeneity; this most clearly applied to smoking and the risk of nonunion. High heterogeneity was observed in the pooled RD for nonunion. The effect of smoking on the RD for nonunion could not be rejected, that is, the effect could not be shown in the meta-regression.

The moderators that explained the heterogeneity should not be taken as true population values but instead as preliminary findings that require validation in larger clinical cohorts. Moreover, it is paramount to understand that moderator variables, such as age or sex, suggested by a meta-regression analysis do not directly indicate that individual treatment effect heterogeneity is explained by these variables. Instead, these variables account for variability in the average treatment effect across different studies. When more studies are published, the point estimates reported in our studies should become more precise. The overall treatment effects seen in meta-analyses only highlight the population-level effects, which are prone to a lack of inferential reproducibility. Instead of another RCT investigating the difference between surgical and nonsurgical treatment, we advocate sufficiently large RCTs that focus on the potential effects of the moderator variables, such as the effect of sex on functional outcome, described in this study.

The main strength of our study is the number of studies included. Along with Achilles tendon rupture, clavicle fracture is probably the most common subject of RCTs in the field of orthopedics. Hence, there remain only a few topics for which meta-regression is feasible to assess the moderators of heterogeneity. The main methodologic weakness of our study lies in our research setting. In total, we had 5 hard outcomes and 7 moderator variables of interest, and we assessed the effect of each moderator on each outcome variable. Hence, we had 49 single meta-regression analyses. This raises the issue of multiplicity and increases the chance of a type I error. Therefore, our results should be interpreted with caution when CIs for coefficients are wide. Being the first in this particular field, our study was only exploratory in nature.

Conclusion

The literature on the treatment of MCFs is vast, and it is still increasing. Although the results of meta-analyses that have pooled the results of these studies are somewhat parallel, there is great variability in the inferences drawn from the results of the studies. As seen in our study, the heterogeneity of pooled estimates of treatment effects in the meta-analyses is high, and this indicates variability in the treatment effects. It is evident, therefore, that objective superiority between surgical and nonsurgical treatment relies on the values of both surgeons and patients. On the basis of our results, several potential moderators affect the treatment effect. This implies a possible treatment effect heterogeneity contradicting ''one-fits-all'' treatment decisions. Our study was only exploratory in nature; hence, further confirmatory studies are needed to verify our results and the validity of the guidance given on shared decision making between doctor and patient.

Disclaimer

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jse.2020.02.011.

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