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- 1 **Title:** Proximal humeral fracture. A commentary on systematic reviews of surgical versus non-surgical
- 2 management in older adults.
- 3 Authors: Pauline May¹ (Senior Physiotherapist), Joanna Harrison² (Research Fellow), Charlotte Williams¹
- 4 (Advanced Clinical Practitioner), James Hill ² (Senior Research Fellow)
- ¹Integrated Musculoskeletal Pain and Rheumatology Service, East Lancashire Hospitals NHS Trust,
- 6 Burnley, UK.
- ²Synthesis, Economic Evaluation and Decision Science Group, University of Central Lancashire, Preston,
- 8 UK.
- 9 **Keywords:** Proximal Humeral Fracture, management, surgical, non-surgical, older adults
- 10 Abstract:
- 11 Background
- 12 Proximal humeral fractures (PHFs) are common fractures in older adults and their prevalence is on the
- rise. Recovery following this fracture can be complex and disabling. Treatment varies from non-surgical
- management such as immobilisation to surgical procedures, with choice dependent on type and severity
- of fracture and patient health.
- 16 Objective
- 17 Several systematic reviews have considered the evidence for non-surgical versus surgical management of
- 18 PHF in older adults. This commentary considers these findings for clinical practice and further research.
- 19 Methods

Three systematic reviews exploring non-surgical versus surgical management were selected based on the quality of their included evidence, and individually critically appraised. Findings from the reviews were reported for each outcome, and the implications considered for clinical practice and future research.

Results

Findings from the three reviews suggest that surgical management of PHF in older adults does not result in better functional outcomes or quality of life and non-surgical management should achieve acceptable upper limb function while decreasing the risks of surgery. More complex three-part fractures may also be managed non-surgically with fair to good functional results relative to fracture severity.

Conclusion

The findings align with current guidance to offer non-surgical management to uncomplicated cases of PHF in adults and older adults. More complex three-part PHFs may also be managed well non-surgically. There is however a lack of evidence and guidance on the specifics of rehabilitation for this type of management and further research is needed to evaluate the factors that contribute to the effectiveness of non-surgical interventions.

Introduction

Proximal humeral fractures (PHF, or shoulder fractures) are painful and debilitating injuries and account for approximately 6% of all adult fractures [1]. PHF symptoms include pain, swelling, and loss of movement [2], with functional capacity impaired for an average of two to three months [3]. Recovery from a shoulder fracture can be a long and often incomplete process that can be hindered by complications [4], including long-term consequences of mal union, non-union, avascular necrosis, and traumatic arthritis [5]. PHFs are also associated with a higher risk of hospitalisation or further fracture within the first year, and an increased utilisation of healthcare services and hospital costs [6,7].

The incidence of PHF varies with estimations ranging from 45.7 per 100,000 person years in Australia to 60.1 per 100,000 in Southern Europe and 74.2 per 100,000 in Northern Europe, during the period 2016-2018 [8-10]. The incidence of PHF is also increasing over time [9,10,11], with significant increases in females and older adults [8,9,11]. Shoulder fractures are most common in people over 65 who fall from a standing height, accounting for the third most common fracture in this population [12-15]. The escalating incidence of PHF in the older population is driven by an aging population, a suspected decline in the bone health of older adults and an increase in more severe falls [16,17]. The management of PHF varies from non-surgical management to surgical procedures, with choice of treatment depending on factors such as fracture type, severity and patient health status [18,19]. Nonsurgical management of PHF usually involves a period of immobilisation (typically of three-four weeks) providing support and pain relief, followed by physiotherapy to restore function and mobility [20]. Variation exists in the recommended period of immobilisation [21], however evidence suggests that early mobilisation (within one week) may have beneficial effects on function [22]. Current guidelines in England advise that surgical management should be considered for complex PHF in adults, whereas non-surgical management is recommended for uncomplicated injuries (National Institute for Health and Care Excellence [23]. The most common definition for PHF is the Neer classification system with fractures defined by the number of parts involved (one to four part) [24]. The increasing incidence of PHF, together with the uncertainty of treatment options, variations in practice and emerging research, all endorse the need for updated evidence. This commentary aims to critically appraise the methods used in three systematic reviews exploring surgical versus non-surgical management for PHF in older adults; Beks et al. 2018 [25], Handoll et al. 2022 [26], and non-surgical management in more complex three- and four-part fractures (Soler-Peiro et al. 2020) [27]. The findings are subsequently discussed in the context of clinical practice and further research.

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The selection of reviews for this commentary was based on surgical versus non-surgical management of PHF in older adults, where evidence from the included studies' outcomes of interest was deemed to be of moderate to good quality. The reviews that matched these criteria explored randomised controlled trials (RCTs) or quasi RCTs pertinent to the treatment and rehabilitation of PHF in adults [26] or focused on surgical versus non-surgical management through RCTs and observational studies [25]. One review also reported outcomes for comparisons such as early mobilization versus delayed [26]. As our focus was on the comparison of surgical versus non-surgical treatment, only the outcomes related to this comparison were reported here. Despite the inclusion of similar trials across the two systematic reviews, we incorporated the less recent review [25], as the authors argued that the addition of observational studies provided a broader study population. Furthermore, they included an analysis of function by Constant-Murley score which was reported in the more recent review [26], but with limited data. This commentary also reports on a review of non-surgical management for more complex fractures (three and four-part fractures) that explored RCTs and observational studies for three- or four-part PHFs [27]. Using the PICO (Population, Intervention, Control, Outcome) variables, methodological components of clinical evidence were compared for each review (Table 1). Inclusion criteria were not specific to older adults, however all three reviews subsequently included older populations (mostly over 60). Exclusion criteria from the studies within the reviews consisted of fracture dislocations, open fractures, multiple trauma, clear indication for surgery and comorbidities precluding surgery. Outcomes for the three reviews included upper-limb function, quality of life, additional surgery, and adverse events. In one review, secondary outcomes for constant score, pain and power were reported for a limited number of studies and downgraded to mostly low or very low certainty evidence [26], and are therefore not reported here. Two reviews reported outcome follow-up periods of at least one year [25, 27], and one review reported at six months, one and two years [26].

(Insert Table 1 here)

Using the Joanna Briggs Institute critical appraisal checklist for systematic reviews and research syntheses [28], all three systematic reviews were judged to be methodologically robust (Table 2) with some areas of concern. These were: 1) lack of publication bias assessment in [26, 27], explained as being due to an insufficient number of trials, and 2) an unclear description of the number of reviewers for critical appraisal [27]. The use of an arbitrary score for study quality [25] was also questioned due to the difficulties this poses for valuing the importance of individual items. However, the subsequent analysis included studies of all quality and good quality which allowed for comparison. Thus, despite some concerns, the three systematic reviews were overall deemed to provide an accurate and comprehensive summary of the evidence available.

(Insert Table 2 here)

Unions of effect

Effect sizes are reported as mean difference (MD), standardised mean difference (SMD) or Risk Ratio (RR). SMD effect sizes are interpreted as small (0.2), moderate (0.5) or large (0.80 with a significance level of p=0.05 [29]. Heterogeneity is reported using the I^2 statistic and interpreted as 0-40% (might not be important), 30-60% (may represent moderate), 50-90% (may represent substantial), 75-100% (may represent considerable) [30].

Results

Study characteristics (including reported primary outcome measures) are described for the three systematic reviews in Table 3.

(Insert Table 3 here)

Estimates of effectiveness from the meta-analyses reported in Beks et al. 2018 [25] and Handoll et al.

2022 [26] can be found in Table 4. These include the reported outcomes of function, quality of life,

mortality, major reinterventions, adverse events, and include as assessment of quality. The conservative treatment of more complex fractures including the review by Solar-Peiro 2020 [27] is reported as a narrative only.

(Insert Table 4 here)

Function

The most recent review [26] reported no important clinical difference in patient reported functional outcomes (physical function or shoulder and upper limb function) at six months, one- and two-years follow-up comparing surgical and non-surgical treatments of PHF, based on high certainty evidence [the authors have confidence that the true effect is similar to the estimated effect]. The earlier review [25] found similar findings in that there was no functional difference between the two groups at least one year post follow-up, based on mostly good quality evidence but with substantial heterogeneity. A sub-analysis of studies interpreted as good quality, showed no difference in surgical versus non-surgical treatment [25](MD=0.55, 95% CI: -2.93 to 4.03, p=0.76).

Quality of life

One review [26] reported no clinically important difference in quality of life (EQ-5D score >0.12) between surgical and non-surgical treatment at one and two years follow up, based on high-and moderate certainty evidence respectively.

Mortality

One review [26] reported no or little difference in mortality up to two years follow-up between surgical and non-surgical treatment, based on low certainty evidence [the true effect might be markedly different from the estimated effect] and no reported heterogeneity.

Major reinterventions

Major re-interventions (additional and unplanned surgery for implant removal) occurred statistically more often with surgical treatment compared to non-surgical based on mostly good quality evidence and no reported heterogeneity [25]. A sub-analysis of studies interpreted as good quality showed a similar result (RR=2.52, 95% CI: 1.55 to 4.11). One review [26] reported a statistically higher risk of additional or secondary surgery in the surgery treatment group at two-year follow-up based on low certainty evidence.

Adverse events

One review [26] reported a non-significant, higher risk of complications with surgery at two-year follow-up based on low certainty evidence (RR=1.46, 0.92 to 2.31, p=0.11). Looking at complications individually, one review [26] reported that nonunion and avascular necrosis were more common in the non-surgical group but stated that the clinical implications of these radiological findings were unclear as many cases were asymptomatic. One review [25] also reported that nonunion was statistically more common in the non-surgical group and there was no difference in the rate of avascular necrosis based on mostly good quality evidence and low reported heterogeneity. A sensitivity analysis of good quality studies maintained these findings.

Conservative treatment of more complex fractures

Treatment of three-part fractures with conservative management resulted in fair to good functional outcomes (mean constant score, 64.5) at a minimum of 12 month follow up, based on evidence considered by the study authors to be mostly good quality [27]. For four-part fractures, lower functional outcomes were achieved (mean constant score 54.9). There were some complications reported for three and four-part fractures treated conservatively (21% malunion, 9% avascular necrosis) with less avascular necrosis reported in three-part, compared to four-part fractures (7 and 10% respectively). Malunion however was higher in the three-part fractures (27%) compared to four-part fractures (17%). Consolidation was achieved in 96% of three-part fractures and 90% of four-part fractures.

A sub-group analysis in Beks et al. 2018 [25] reported that in studies where patients with a three- or four-part fracture underwent treatment, there was no difference in functional outcome between operative and non-operative treatment (SMD 0.02, 95% CI: -0.20 to 0.24, p=0.86).

Using the JBI checklist [28], the three reviews overall can be considered to provide an adequate

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Commentary

and comprehensive summary of evidence that address the question of interest. The findings suggest that for older adults, surgical management of PHF does not typically lead to better functional outcomes or quality of life compared to non-surgical approaches. Non-surgical management is likely to provide acceptable upper limb function while also reducing the risks associated with surgery. It is worth noting that in one review the functional outcome reported is based on studies of substantial heterogeneity [25]. However, the other review [26] reported high certainty GRADE evidence for functional outcomes. These results align with NICE recommendations to offer non-surgical management as a definitive treatment for uncomplicated PHF in adults [23], and the review findings show that this is also relevant for older adults. Based on the review of more complex fractures [27], most three-part PHFs can also be managed non-surgically with fair to good functional results (in accordance with the severity of the fracture), a high rate of consolidation and few complications. Four-part PHFs also achieved a high rate of consolidation from non-surgical management and few complications but with poorer functional results than three-part PHFs. It is worth noting that in Handoll et al. 2022 [26], 66% of the fractures in the study population were also three- or four-part fractures and in Beks et al. 2018 [25], a sub-group analysis of three- and four-part fractures showed no difference in functional outcome between surgical and non-surgical treatment. Current NICE guidance however recommends that surgical management is considered for those with complicated fractures such as fractural dislocation or a split of the humeral head [23].

Despite the data supporting the use of non-surgical management for PHF, there is a lack of current evidence and guidance on the specifics of rehabilitation for this type of management. The effectiveness of early versus delayed mobilisation after injury was explored, but the available data for this comparison were limited and uncertain [26]. Similarly, another systematic review found that early mobilisation may have a beneficial effect on function, but quality of evidence was low [31]. A more recent systematic review comparing early mobilisation (one week) to threeweek immobilisation suggested early mobilisation may be beneficial for improving function at 6 month follow-up with long-term results less certain [22]. Exercise programmes for PHF, supervised or non-supervised have not been shown to reduce impairment or improve activity [32]. The consequences of immobilising older people however, should be considered due to the potential impact of physical inactivity on both physical and mental health [33]. Where prescription of exercise is appropriate, evidence has suggested that starting exercise early combined with a shorter immobilisation period may be more effective than a longer immobilisation period [31,32,34]. When considering intensity of supervised exercise, one trial reported no advantages to a more intensive rehabilitation regime over a conventional programme [35]. Exercise programmes can also be managed at home [34] with high satisfaction levels reported by patients due to good functional outcome, the availability and ease of being at home and maintaining independence [36].

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Given the findings supporting a non-surgical approach to PHF management, it may be useful to provide further guidance on what this means to older patients, notably that non-surgical treatment should achieve acceptable upper limb function without the risks of surgery. Providing information to patients following a fracture is recommended within NICE guidelines [23] and should include expected outcomes of treatment, activities to work on independently, homecare options if needed and information on rehabilitation, mobilisation and weight bearing. For older patients, a booklet may be preferable to other formats [36]. In addition to information provision, positive relationships with healthcare professionals following PHF in the older population contributes to increased levels of patient trust, perceptions of recovery and improvement in emotional state [37]. Communication of treatment options and consideration of other risk factors for poor function could therefore be explored by healthcare professionals when treating patients post PHF. For example, social deprivation is associated with an increased incidence of adult fractures [38], and in those over 60, longer hospital stays, hospital readmission and higher mortality [39]. Another factor to consider for patients with PHF is psychological health and its impact on recovery. The reviews did not specifically address psychological outcomes for nonsurgical vs surgical treatment, yet in recovery from a fracture, high fear avoidance beliefs and levels of catastrophising have been shown to substantially increase the risk of future pain and less than full recovery of strength respectively [40]. Self-efficacy interventions such as goal focused rehabilitation may help to improve coping abilities, reduce anxiety and depression and improve quality of life in people with post-traumatic fractures [41]. At present, there is no clear guidance to provide direction for these psychological factors when considering PHF management and NICE guidelines would benefit from an update.

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Questions remain around the most effective rehabilitation protocol following non-surgical management of PHF. Further research is needed to evaluate the factors that contribute to the effectiveness of non-surgical interventions for PHF which may include sling use, exercise programmes, psychological support, and provision of patient information.

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- **Conflicts of interest:** The authors have no conflict of interest to report.

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Table 1: PICO variables for the three included systematic reviews

PICO Be	eks et al. (2018) [25]	Handoll et al. (2022) [26]	Solor Doiro of al (2020)
			Soler-Peiro et al. (2020)
			[27]
			[]
Population Ad	dults, proximal humeral	Adults, proximal humeral	Adults, three and four-part
fra	acture.	fracture.	proximal humeral fracture.
Intervention Su	urgical management.	Non-surgical and surgical	Conservative management.
Ex	cternal osteosynthesis as	management.	Surgical treatment was
an	n operative treatment was	Pharmacological, biological	excluded.
ex	ccluded.	and acupuncture trials were	
		excluded.	
Comparison No	on-surgical management.	Two or more treatments for	None.
		management of PHF (our	
		focus on surgical versus	
		non-surgical).	

Outcome	Functional outcomes and	For comparison of surgical	Functional outcomes,
	complications including	versus non-surgical:	complications and
	major reinterventions	functional outcomes, health	consolidation.
	(additional and unplanned	related quality of life,	
	surgery), and adverse	mortality, additional surgery	
	events.	and adverse events.	

Table 2: JBI critical appraisal checklist for systematic reviews [28]

Criteria	Beks et al. (2018) [25]	Handoll et al. (2022) [26]	Soler-Peiro et al. (2020)
			[27]
Is the review	Yes: 'To compare operative	Yes: 'To assess the effects	Yes: 'To assess criteria
question clearly	versus nonoperative	(benefits and harms) of	for indications,
and explicitly	treatment of displaced PHF'	treatment and	treatment protocols, and
stated?		rehabilitation interventions	outcomes obtained with
		for proximal humeral	conservative treatment
		fractures in adults'.	of threepart and four-
			part PHFs'.
Were the	Yes: PICO structure was	Yes: PICO structure was	Yes: PICO structure was
inclusion criteria	followed according to	followed according to	followed according to
appropriate for	question.	question.	question.

the review			
question?			
Was the search	Yes: A clear search strategy	Yes: A clear search strategy	Yes: A clear search
strategy	addressing each of the	addressing each of the	strategy addressing each
appropriate?	identifiable PICO	identifiable PICO	of the identifiable PICO
	components of the review	components of the review	components of the
	question was conducted up	question was conducted up	review question was
	to September 5 th , 2017.	to September 2020. No	conducted from 2000-
	Studies in a language other	language or publication	January 20 th , 2020.
	than English, Dutch or	restrictions.	Restricted to English
	German were excluded.		publications.
Were the	Yes: MEDLINE, Embase,	Yes: CENTRAL, MEDLINE,	Yes: PubMed and the
sources and	CENTRAL and CINAHL.	Embase, CINAHL, AMED and	Cochrane Library.
resources used	Reference and citation	PEDro. Trial databases,	
to search for	tracking was performed.	reference lists and	
studies		conference proceedings	
appropriate?		were also searched.	
Were the	Yes: Methodological quality	Yes: Risk of bias was	Yes: Risk of bias was
criteria for	was assessed using the	assessed using the	evaluated [33] and
appraising	Methodological Index for	Cochrane handbook, plus	considered to be low risk
studies	Non-Randomised Studies	four other aspects of trial	(good quality) when
appropriate?	(MINORS). Scores ranged	quality. The GRADE	6/12 criteria were met.
	from 0-24 with an author	approach was used to rate	
	interpreted score of 16+	the certainty of evidence:	
	representing good	very low, low, moderate or	
	methodological quality.	high.	
Was critical	Yes: Critical appraisal was	Yes: Critical appraisal was	Unclear: No indication as
appraisal	carried out by two	carried out by two	to how many reviewers
conducted by	reviewers independently	reviewers independently	evaluated risk of bias.
two or more	and disagreements resolved	and differences resolved	
	by a third reviewer.	through discussion.	

independently? Were there Yes: Data extraction was methods to completed independently independently completed a extraction form was data extraction? Were the Yes: Outcomes reported by methods used to two or more studies were combine studies present, a random-effects model was used. Was the Yes: Inspection of a funnel likelihood of plot of the primary undetected. Were Yes: Appropriate Yes: Appropriate recommendation sor for practice of the review. Were Yes: Appropriate Yes: Appropriate implications for practice supported by the reported by the reported by the review for new research were to address key treatment optimisation of non-surgical of PHFs, including present, and and methods used to two or more studies were pooled using both synthesis of outcomes was reported. Were Yes: Inspection of a funnel likelihood of plot of the primary insufficient number of trials to merit production of funnel plots. Were Yes: Appropriate Yes: Appropriate implications for practice were made based on the findings of the review. Were Yes: Appropriate Yes: Appropriate implications for practice were made based on the findings of the review. Were the N/A: no recommendations Yes: a need for similar trials Yes: Future research of conservative treatments directives for made uncertainties and optimisation of non-surgical of PHFs, including optimisation of non-surgical of PHFs, including	reviewers			
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	directives for	made	uncertainties and	conservative treatment
ammanuta ada a da	new research		optimisation of non-surgical	of PHFs, including
appropriate? treatments, plus decisions subgroups of fractures	appropriate?		treatments, plus decisions	subgroups of fractures

		on priority topics identified	and comparing diverse
		from the ongoing trial data.	treatment protocols
Total criteria	11/11	10/11	9/11

Table 3. Study characteristics of Beks et al. 2018 [25], Handoll et al. 2022 [26] and Soler-Peiro et al. 2020 [27]

Systematic	Number of	Participants	Primary outcome	Follow-up
Review	included studies			period
Beks et al.	22 studies (7 RCTs,	Total of 1743 patients	The primary outcome	Follow-up
(2018)	15 observational	of which the average	measure for function was	ranged
[25]	studies)	age was 68 years, and	the Constant-Murley	from 12 to
		75% were women.	Score.	86 months.
		Included patients with		Reported
		two-, three- or four		as at least
		part fractures (Neer		one year.
		classification).		
Handoll et	For the treatment	For the treatment	The primary outcome for	For the
al. (2022)	comparison of	comparison of surgical	function was measured	pooled
[26]	surgical versus	versus non-surgical,	using four different scores:	results, the
	non-surgical, there	there were 717	The American Shoulder	follow-up
	were 10 RCTs	participants of which	and Elbow Surgeons	period was
	included.	66% were three or	(ASES), the Disability of the	up to two
		four-part fractures	Arm, Shoulder, and Hand	years.
		(Neer classification).	questionnaire (DASH),	Reported
		Most participants were	Oxford Shoulder Score	as 6
		over 60 and over two-	(OSS) and Simple Shoulder	months, 1
		thirds were women.	Test (SST). Quality of life	and 2
			was evaluated using the	years.
			EQ-5D.	

Soler-	6 studies (3 RCTs,	133 patients, of which	The primary outcome for	Follow-up
Peiro et al.	3 observational)	the average age was function was the Constant-		was
(2020)		74, and 79% were	Murley Score.	between
[27]		women. Using the		12 to 68
		Neer classification,		months.
		there were 41% three-		Reported
		part fractures and 59%		as a
		four-part fractures.		minimum
				follow-up
				of one year

	Table 4. Estimates of effectiveness for surgical versus non-surgical treatment on outcomes of function,					
-	-			s et al. 2018 [25]; Handoll et a	1.2022[26])	
Systematic	Number and	Follow-up	Estimate of	Interpretation of effect and	Quality	
Review	type of trial	period	effect	heterogeneity	Assessment of	
			MD, SMD, RR		included studies	
			(95% CI), p		(summary)	
			value, I²			
Functional or	utcome					
Beks et al.	14 studies	At least 1	MD= -0.87 (-5.13	No difference in functional	Mostly good	
(2018) [25]	(5 RCTs, 9	year	to 3.38), p=0.69,	outcome between groups,	quality studies	
	observational)		$I^2=69\%$	substantial heterogeneity.	(11/14)	
Handoll et	3 RCTs	6 months	SMD = 0.17, (-	No clinically important	GRADE: Moderate	
al. (2022)			0.04 to 0.38)	difference in patient reported	Certainty	
[26]				functional scores between		
				groups, no reported		
				heterogeneity		

Handoll et	7 RCTs	1 year	SMD= 0.10 (-	No clinically important	GRADE:
al. (2022)			0.07 to 0.27), p	difference in patient	High certainty
[26]			=0.24, <i>I</i> ² =0%	reported functional scores	
				between groups, no	
				reported heterogeneity.	
Handoll et	5 RCTS	2 years	SMD= 0.06, (-	No clinically important	GRADE:
al. (2022)			0.13 to 0.25),	difference in patient	High certainty
[26]			ρ =0.54, I^2 =0%	reported functional scores	
				between groups, no	
				reported heterogeneity.	
Major Rein	tervention				
Beks et al.	15 studies	At least 1	RR= 2.72 (1.71	Major reinterventions	Mostly good
(2018) [25]	(6 RCTs, 9	year	to 4.34), <i>p</i> =	occurred more often in the	quality studies
	observational)		<.0001, <i>I</i> ² =0%	surgical treatment than in	(13/15)
				non-surgical, no	
				heterogeneity reported.	
Handoll et	9 RCTs	Up to 2	RR 2.06 (1.21 to	A higher risk of additional	GRADE: low
al. (2022)		years	3.51), <i>p</i> =0.007,	surgery in the surgery group,	certainty
[26]			<i>I</i> ² = 23%	low heterogeneity.	
Nonunion					
Beks et al.	13 studies	At least 1	RR =0.45 (0.23	Surgical treatment resulted in	Mostly good
(2018) [25]	(6 RCTs,	year	to 0.89), p=.02,	fewer nonunions than non-	(11/13)
	7 observational)		$I^2 = 0\%$	surgical treatment, no	
				heterogeneity reported.	
Handoll et	8 RCTs	Up to 2	RR =0.42 (0.19 to	Nonunion was more common	Unclear
al. (2022)		years	0.94), <i>p</i> =0.04,	in the non-surgical treatment	
[26]			<i>I</i> ² =0%	group, no heterogeneity	
				reported.	
Avascular N	Necrosis				

Beks et al.	13 studies	At least 1	RR 1.24 (0.87 to	No difference in the rate of	Mostly good
(2018) [25]	(6 RCTs, 7	year	1.77), <i>p</i> =0.24, <i>I</i> ²	avascular necrosis between	quality studies
	observational)		=24%	groups, low heterogeneity.	(10/13)
Handoll et	8 RCTs	Up to 2	RR 0.52 (0.33 to	Avascular Necrosis was more	Unclear
al. (2022)		years	0.81), <i>p</i> =0.004,	common in the non-surgical	
[26]			<i>I</i> ² =50%	treatment group, moderate	
				heterogeneity.	
Quality of L	ife				
Handoll et	6 RCTs	1 year	MD =0.01 (-	No clinically important	GRADE: high
al. (2022)			0.02 to 0.04),	difference in quality of life	certainty
[26]			p =0.51, I^2 =0%	between groups, no reported	evidence
				heterogeneity.	
Handoll et	5 RCTS	2 years	MD=0.01 (-0.02	No clinically important	GRADE:
al. (2022)			to 0.05),	difference in quality of life	moderate
[26]			<i>p</i> =0.42), <i>I</i> ² =56%	between groups, moderate	certainty
				heterogeneity.	evidence
Mortality					
Handoll et	8 RCTs	2 years	RR 1.35 (0.70 to	Little difference between	GRADE: low
al. (2022)			2.62), <i>p</i> =0.37,	groups, no reported	certainty
[26]			I ² =0%	heterogeneity.	evidence