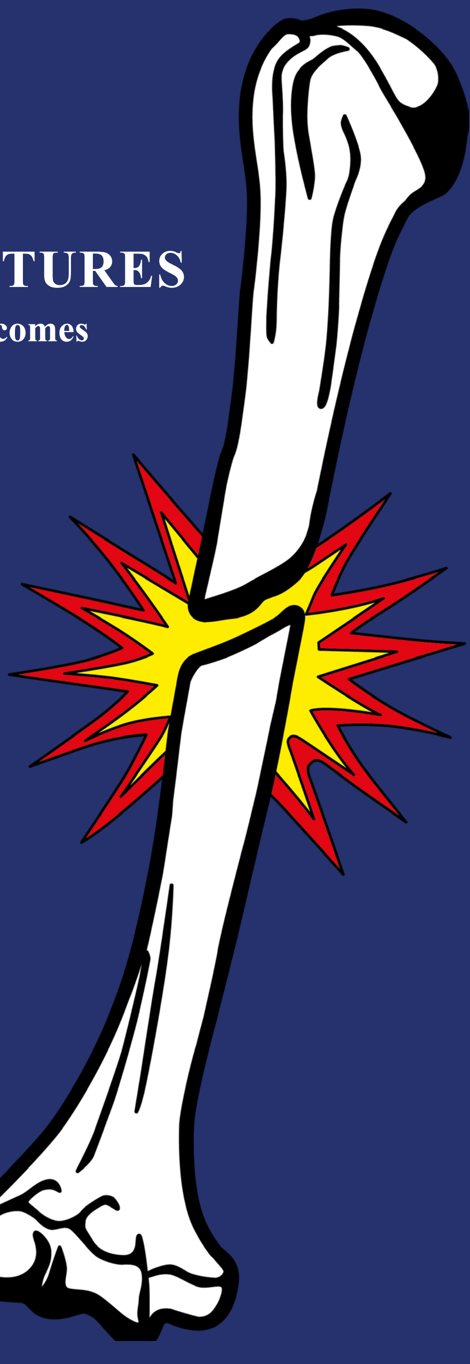
HUMERAL SHAFT FRACTURES

Epidemiology, Management, And Outcomes



Saskia H. Van Bergen

STELLINGEN

Behorende bij het proefschrift

HUMERAL SHAFT FRACTURES

EPIDEMIOLOGY, MANAGEMENT, AND OUTCOMES

1. Operative treatment, and specifically plate osteosynthesis, should be considered the preferred treatment for humeral shaft fractures. (this thesis)
2. Plate osteosynthesis of a humeral shaft fracture results in fewer complications than intramedullary nailing. (this thesis)
3. Patients should be informed that radial nerve palsy is rare and most often transient. (this thesis)
4. Cost-effectiveness analyses of the treatment of a humeral shaft fracture performed with disease-specific measures are more useful than those performed with generic measures. (this thesis)
5. The methodological and statistical approaches of the HUMMER study allowed for as valid answers on the treatment of a humeral shaft fracture as a similar randomized controlled trial would have generated. (this thesis)
6. There is no correlation between the number of research publications and dexterity. (Maan, Br J Surg 2012)
7. Consensus on treatment and expected outcomes of proximal humeral fractures is lacking even beyond the human species. (Razaeian, BMJ 2020)
8. Een posterpresentatie is de klimaatimpact van een intercontinentale vlucht niet waard. (Cohen, NTvG 2023)
9. Het delen van wetenschap met een breed publiek is onderdeel van de valorisatie opdracht van academici. (Harbers, NTvG 2022)
10. No intervention is too ineffective for an excuse. (Hartley, BMJ 2018)
11. Discomfort is a wise teacher. (Marcus Aurelius)

S.H. Van Bergen

HUMERAL SHAFT FRACTURES

EPIDEMIOLOGY, MANAGEMENT, AND OUTCOMES

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HUMERAL SHAFT FRACTURES
EPIDEMIOLOGY, MANAGEMENT, AND OUTCOMES

Humerusschachtfracturen
Epidemiologie, behandeling en uitkomsten

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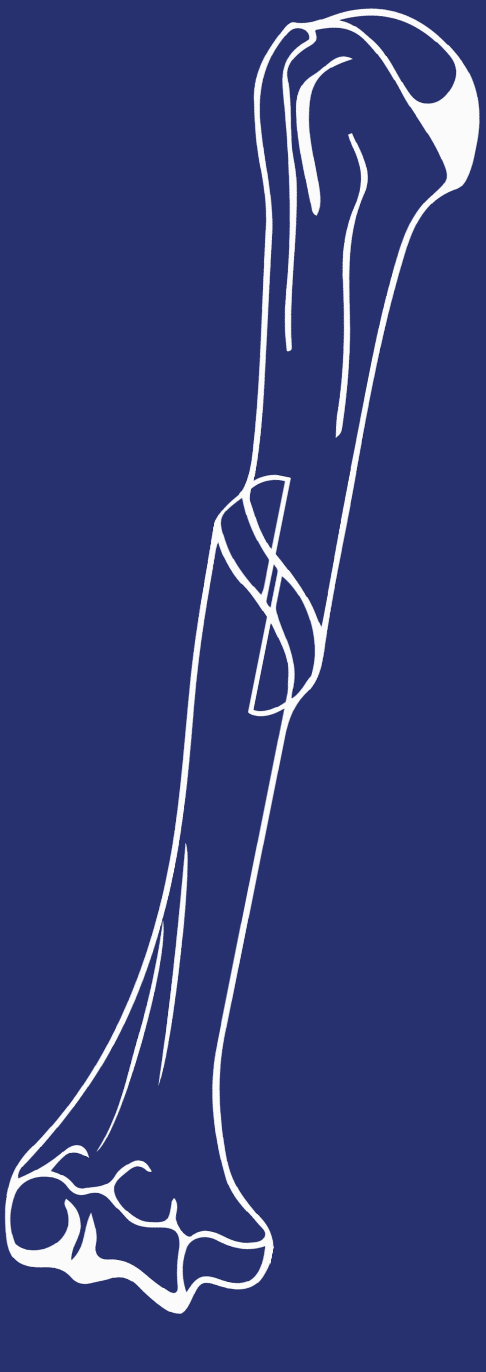
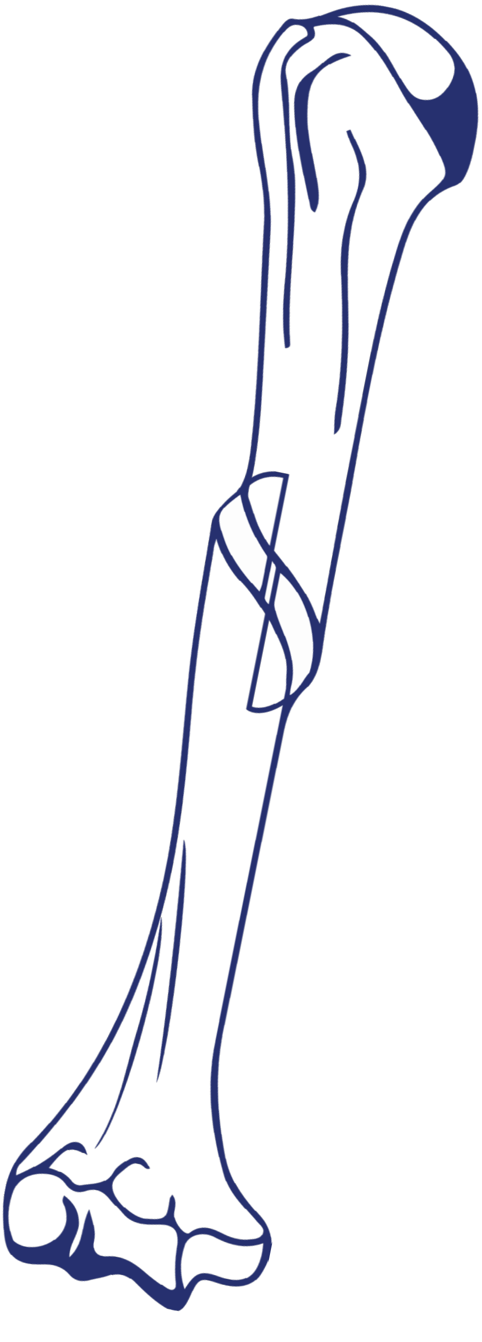


PART 1

General Introduction

Chapter 1
General introduction, aim, and outline of the thesis



CHAPTER 1

General introduction, aim, and outline of the thesis

GENERAL INTRODUCTION

Epidemiology

Humeral shaft fractures account for 1-3% of all adult fractures and approximately 20% of fractures of the humerus.[1,2] In the Netherlands, the overall incidence rate of patients admitted for a humeral shaft fracture has risen by 132% to 7.2 per 100,000 person years from 1986 to 2012, partly attributable to an aging population.[3] The incidence rate is characterized by a bimodal age distribution, with a peak in the working and elderly population.[1]

Basic anatomy

The humerus is a long bone of the upper limb, which provides strength and resistance to both torsional and bending forces. Proximally, the humeral head and its surrounding structures of the shoulder joint, mainly the rotator cuff, allow for relative stability and high mobility in terms of range of motion (ROM). Distally, the capitellum and trochlea of the distal humerus form the elbow joint with the ulna and radius, stabilized by the collateral ligaments. The humeral shaft extends from the surgical neck proximally to the supracondylar ridge distally. Multiple osseous landmarks of the humeral shaft are the insertion and origin sites of muscles. On the anterolateral aspect, muscles inserting include the pectoralis major, deltoid, coracobrachialis, brachialis, and brachioradialis. Posteriorly the medial and lateral head of the triceps are attached. Regarding important neurological structures, the radial nerve runs in a circuitous course around the humeral shaft, from posterolateral proximal to anterior distally, tightly bound in the radial groove (Fig. 1).[4] The radial nerve innervates the extensors of the wrist and provides sensory function to the dorsal surface of the hand.

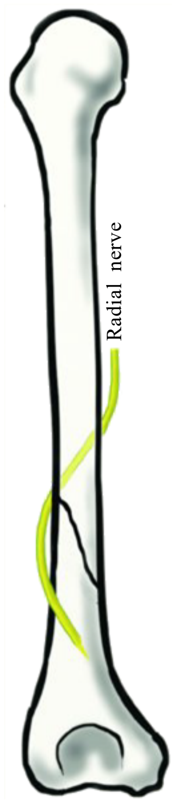


Figure 1. Humeral bone with the course of the radial nerve
From Tornetta & Ricci, 2019. Reprinted with permission from Christos Garnavos.[4]

Etiology and clinical presentation

A humeral shaft fracture can be caused by transmitted rotational or axial loading forces or direct trauma to the arm. Depending on the location of the fracture, the aforementioned muscles, most notably the pectoralis major and deltoid, can cause dislocation in the direction of the muscle contraction. In elderly (female) patients, a humeral shaft fracture is mainly caused by a simple fall.[5] In younger patients, the mechanism of injury is predominated by sports and traffic accidents. More complex fractures usually occur due to high-energy trauma, often resulting in more associated injuries to the surrounding tissues, *i.e.*, neurological, vascular, or soft tissue damage.[1]

Patients with a humeral shaft fracture present with pain and restricted use of the shoulder and arm.[5] Physical examination may show swelling, hematomata, varus deformity, shortening of the arm, and motion and crepitus on manipulation. Accompanying injury to vascular structures and the median and ulnar nerve is relatively uncommon, whereas radial nerve injury is rather typical. Therefore, meticulous documentation of the neurovascular status, in particular the radial nerve function, is warranted after a patient has sustained a humeral shaft fracture. Furthermore, accurate documentation of the type of fracture is indicated. Correct classification (1) allows for reliable and reproducible communication between professionals, (2) ideally guides selecting the optimal treatment, (3) predicts prognosis, and (4) facilitates research.[6]

Long bone fractures, such as a humeral shaft fracture, are most often classified using the OTA classification system, based on the original AO classification developed by Müller *et al.* (Fig. 2).[7] Humeral shaft fractures are coded in three lettered categories: type A (simple fractures), B (wedge fractures), and C (complex fractures). Further subdivision in groups is based on the specific fracture pattern (12-A1/2/3, 12-B1/2/3, 12-C1/2/3). The AO/OTA classification for humeral shaft fractures has a moderate inter-observer and substantial intra-observer agreement for fracture types and groups.[6] This enables a reliable means of communication but warrants specific attention to discriminating between certain fracture patterns.

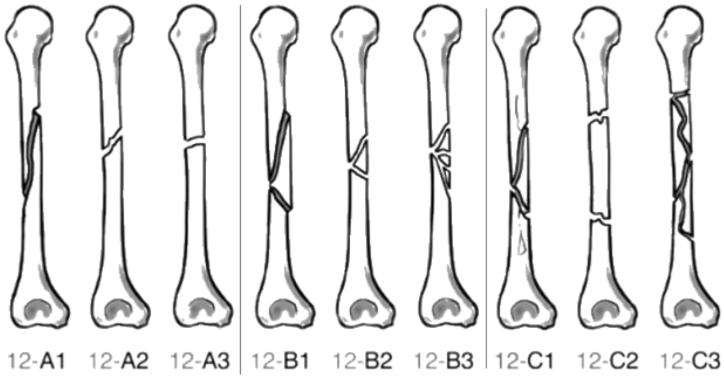


Figure 2. AO/OTA classification for humeral shaft fractures
From Tornetta & Ricci, 2019. Reprinted with permission from Christos Garnavos.[4]

Treatment of a humeral shaft fracture

Treatment of a closed humeral shaft fracture has changed over time. Before the 21th century, nonoperative treatment was considered the gold standard. It was regarded safe and satisfactory, as good functional recovery was achieved without surgical restoration of anatomy.[5] Nonoperative treatment starts with immobilization in a sling between wrist and neck. Due to gravity the humerus regains length. In former days the unstable upper arm was splinted with a 'hanging cast' consisting of plaster of paris. This practice has been replaced in the last 20 years by immobilization with a synthetic brace which compresses the surrounding soft tissue.[8] Mostly after 1-3 weeks the pain subsides and the sling can be taken off. The brace is prolonged as a so called 'functional brace'. As the adjacent joints of the shoulder and elbow are not rigidly immobilized, controlled motion is possible if the soft tissues are not too thick and provided the brace fits well. This relative immobilization creates a desirable stimulus for secondary fracture healing.[8] Furthermore, operative risks such as iatrogenic radial nerve palsy, postoperative infections, and implant failure can be avoided.

However, the very good results of this nonoperative technique as published in the landmark paper by Sarmiento *et al.*, a retrospective study of nearly 1,000 patients treated with functional bracing, could not be reproduced by others.[9] In the short term, the absence of fracture stability of the fracture may be associated with more pain and discomfort.[9,10] In the long term, nonoperative treatment may be associated with nonunion and malunion, if gravity fails to facilitate re-alignment of the fracture or deforming muscle contraction results in dislocation, shortening, and angulation. Both complications result in a delay in functional recovery and could result in impaired ROM of especially the shoulder joint.[9, 10] The flaws of nonoperative treatment of a humeral shaft fracture led to the need for development of appropriate operative treatment.

Operative treatment for a closed humeral shaft fracture mostly starts with fracture reduction (closed or open) and is followed by stabilization with an intramedullary nail (IMN) or plate osteosynthesis. An IMN, can be placed antegrade or retrograde. In antegrade nailing the implant is placed through the rotator cuff and humeral head into the intramedullary canal of the humerus and locked in both sides of the fracture with screws. This approach ensures the implant is in line with its mechanical axis and, assuming closed reduction can be achieved, fracture biology and periosteal blood supply can be preserved. Compared with open reduction and plate osteosynthesis, less soft tissue stripping is required.[11] In general, fracture healing rates and functional outcomes are good as the immediately achieved relative stability allows for early recovery. However, complications, such as pain and restriction of shoulder movement, due to damage to the rotator cuff, implant failure, impingement or malrotation, are not uncommon.[12-15]

Open reduction and plate osteosynthesis requires extensive soft tissue exposure, but therefore offers the possibility of anatomic reduction, compression of fracture fragments, and exploration of the radial nerve with full visibility.[16] The more recently introduced technique of minimally invasive plate osteosynthesis (MIPO) entails limited soft tissue dissection but does not allow for exploration of the radial nerve.[17] The immediately achieved stability of plate osteosynthesis might enable patients to regain daily activities faster at an early stage. However, complications such as (temporary) postoperative radial nerve palsy, hardware failure, or infection may occur.[17]

The continuing development of a variety of internal fixation techniques has led to an increase in surgical management in the last two decades.[18-21] Regardless of advances in surgical care, operative treatment comes with the risk of surgical and implant-related complications, lest not forget the risk of nonunion. Therefore, some still advocate nonsurgical management of a humeral shaft fracture. Due to lack of reliable scientific research, the optimal management strategy of a humeral shaft fracture remains subject to debate.

Outcomes

One of the primary goals of treatment of a humeral shaft fracture is fracture healing. This is defined clinically as the absence of pain, tenderness or movement at the fracture site or radiologically as cortical bridging of at least three or four cortices on radiological imaging. However, assessment of union is often difficult and reported in a highly variable manner. Same holds for nonunion (failure to heal at twenty-six weeks post fracture with no progress towards healing) or malunion (fracture healing in abnormal position).[22]

Besides fracture healing and prevention of complications, treatment aims to achieve full functional recovery of the upper extremity. Functional recovery can be defined in terms of subjective measures of pain and regaining the ability to perform activities of daily living, as well as objective measures of strength and ROM of the shoulder and elbow joints. In order to evaluate functional recovery and clinical outcomes from the patient's perspective, patient-reported outcome measures (PROMs) are used.[23] The Disabilities of the Arm, Shoulder and Hand (DASH) and Constant-Murley score are proven to be reliable and valid for evaluating outcome in patients with a humeral shaft fracture.[24]

Radial nerve palsy

Peripheral nerve injuries may accompany a humeral shaft fracture. Most frequently, the radial nerve is affected, whether primary due to the initial trauma or secondary as a consequence of treatment.[25-32] The radial nerve is vulnerable due to its circuitous course, winding around the humeral shaft, and its close relationship to the bone with limited mobility.[25-27, 31, 32] A lesion can result in a dropping hand with inability to extend and stabilize the wrist, which causes difficulties in daily life as it severely compromises function and hand use and dysesthesia on the dorsal side of the forearm and hand.[25, 33]

Radial nerve palsy at presentation can result from trauma, due to stretching of the nerve by displacement of soft tissues, contusion of the nerve due to entrapment between mobile fracture ends, or complete laceration of the nerve over the sharp edges of the fractured bone.[25, 26, 29, 31-35] Radial nerve palsy can also be a consequence of treatment, either due to fracture reduction for the purpose of nonoperative treatment or due to manipulation or iatrogenic damage during surgical procedures. With IMN, postoperative radial nerve palsy may be a result of manipulation of the fracture, reaming and passing of the nail, or distal locking of the nail with screws.[36-40] Even though plate osteosynthesis with open reduction allows for exploration and visualization of the radial nerve, it is still vulnerable during manipulation and fracture reduction and at risk for laceration or compression by the fixation hardware.[25]

The course of recovery is unpredictable and the identification of those less likely to recover is not straightforward, leading to a debate on the optimal treatment of radial nerve palsy and its influence on the choice of treatment of a humeral shaft fracture. Therefore, the consequences of a radial nerve palsy for patients with a closed humeral shaft fracture, in terms of recovery and functional outcome, should be examined.

Societal burden

Humeral shaft fractures pose a burden on society as they are costly in terms of direct and indirect medical costs.[41] Direct costs can be attributed to the costs of surgery, possible reinterventions, and the physical rehabilitation of patients.[42] Indirect costs are caused by work absence and lost productivity in young employed patients and prolonged informal care in the elderly population. In total, the cumulative medical costs in the Netherlands of patients admitted due to a humeral shaft fracture only, added up to 10.6 million euro in 2012.[3] However, there is a paucity of evidence in the area of cost-utility and cost-effectiveness of the treatment of a humeral shaft fracture.[43] It is unknown, whether the benefits of either operative or nonoperative treatment, can outweigh their respective costs of surgical care and hospital admission versus prolonged work absence and rehabilitation costs. Therefore, the cost-effectiveness of the possible treatments of a humeral shaft fracture should be examined.

Polytraumatized patients

Even though nearly 50% of patients with a humeral shaft fracture has an Injury Severity Score ≥17, most studies' stringent inclusion criteria exclude polytraumatized patients.[44-47] This results in a knowledge gap of the epidemiology of humeral shaft fractures in this patient group. It is possible that the fracture location and pattern, presence of associated and other more life-threatening injuries, influence the clinical management. Delay in diagnosis and treatment of the humeral shaft fracture in the initial phase may interfere with the recovery of the humeral shaft fracture.[48] This is of importance, as the recovery of arm function is crucial for rehabilitation, *e.g.*, the use of crutches, personal hygiene, and independent living.[49] Patient-reported outcomes are therefore essential for evaluating the long-term consequences in terms of disability and health-related quality of life in polytraumatized patients with a humeral shaft fracture. However, whether additional injuries and postponing treatment has an effect on fracture healing, complications, and (long-term) functional outcome is hardly described. Therefore, a need for a comprehensive overview of this diverse population, a determination of the AO/OTA classification, treatment, and functional recovery of a humeral shaft fracture in polytraumatized patients exists.

AIM AND OUTLINE OF THIS THESIS

The aim of this thesis was to examine the optimal treatment of a humeral shaft fracture in order to improve outcome for these patients and facilitate informed shared-decision making. Primarily, an overview of what is known about the treatment of a humeral shaft fracture is given. Secondly, fracture healing, complications, and functional outcomes of the different treatment options are studied. In addition the cost-effectiveness of both operative and nonoperative treatment is calculated. Lastly, the classification, treatment, and functional outcomes of a humeral shaft fracture in polytraumatized patients are determined.

What is already known?

In **Chapter 2**, the results of 173 recent comparative and non-comparative cohort studies are assessed with a systematic literature review and pooled analysis. This chapter provides an overview of fracture healing, complications, and functional outcomes after nonoperative and operative treatment of a humeral shaft fracture.

Functional and clinical outcome

Furthermore, this thesis presents a part of the results of the HUMMER study, which is a multicenter prospective cohort study designed to examine the effect of nonoperative versus operative treatment of a closed humeral shaft fracture, AO/OTA type 12A and B. Between 2012 and 2018, 390 patients were included, of whom 145 were treated nonoperatively and 245 were treated operatively, and followed for one year.

In **Chapter 3**, the primary outcome of the HUMMER study, *i.e.,* functional outcome and pain of the upper extremity reflected by the Disabilities of the Arm, Shoulder, and Hand (DASH) score, after operative versus nonoperative treatment of a humeral shaft fracture is examined. Furthermore, secondary outcomes such as the effect of treatment on the number of complications, health-related quality of life, range of motion of the shoulder and elbow joint, and time to resumption of work and activities were evaluated. In **Chapter 4**, the functional and clinical outcomes of operatively treated HUMMER patients, either with plate osteosynthesis or intramedullary nailing, are described. This study focuses, besides functional outcomes, on complications of treatment and range of motion. **Chapter 5** describes the rate and recovery of radial nerve palsy, at presentation or postoperatively, associated with a humeral shaft fracture.

Societal burden

In **Chapter 6**, an economic evaluation is performed alongside the HUMMER study, calculating the cost-effectiveness of operative versus nonoperative treatment of a humeral shaft fracture.

Polytrauma

Chapter 7 describes the fracture type, treatment, and functional outcomes of a humeral shaft fracture in adult polytraumatized patients.

General discussion and future perspectives

Chapter 8 presents a general discussion and future perspectives on the research in the field of humeral shaft fracture management. **Chapter 9** summarizes the findings of this thesis in English and **Chapter 10** in Dutch.

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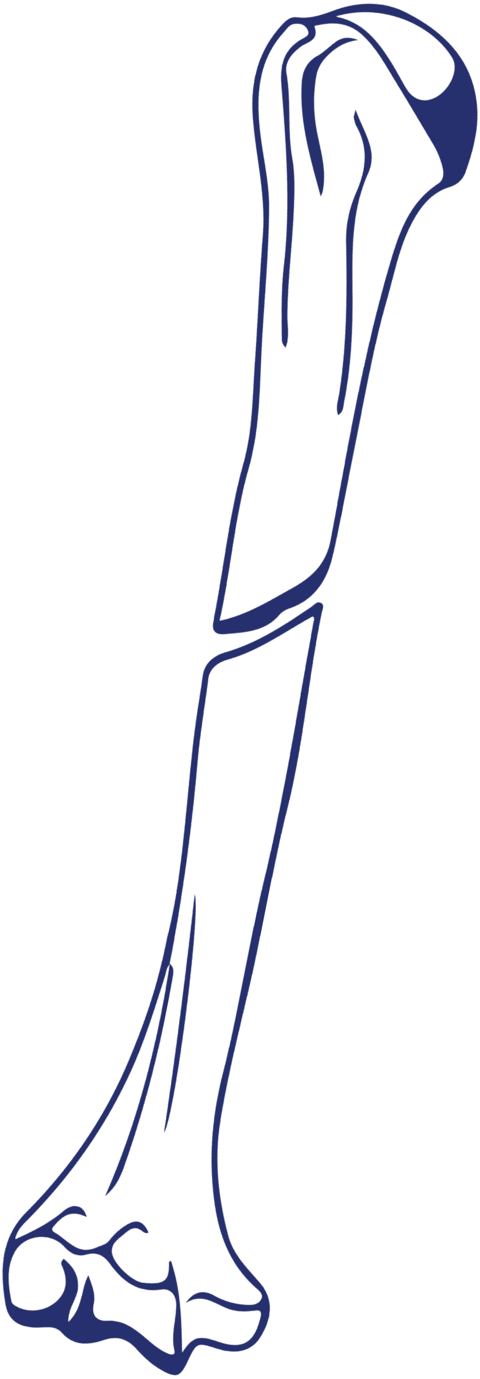
PART 2

What is already known?

Chapter 2
Humeral shaft fracture:
systematic review of non-operative and operative treatment
Archives of Orthopaedic and Trauma Surgery



CHAPTER 2

Humeral shaft fracture: systematic review of non-operative and operative treatment

Archives of Orthopaedic and Trauma Surgery 2023

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ABSTRACT

Introduction: Humeral shaft fractures can be treated non-operatively or operatively. The optimal management is subject to debate. The aim was to compare non-operative and operative treatment of a humeral shaft fracture in terms of fracture healing, complications, and functional outcome.

Methods: Databases of Embase, Medline ALL, Web-of-Science Core Collection, and the Cochrane Central Register of Controlled Trials (CENTRAL) were systematically searched for publications reporting clinical and functional outcomes of humeral shaft fractures after non-operative treatment with a functional brace or operative treatment by intramedullary nailing (IMN; antegrade or retrograde) or plate osteosynthesis (open plating or minimally invasive). A pooled analysis of the results was performed using MedCalc.

Results: A total of 173 studies, describing 11,868 patients, were included. The fracture healing rate for the non-operative group was 89% (95% confidence interval (CI) 84–92%), 94% (95% CI 92–95%) for the IMN group and 96% (95% CI 95–97%) for the plating group. The rate of secondary radial nerve palsies was 1% in patients treated non-operatively, 3% in the IMN, and 6% in the plating group. Intraoperative complications and implant failures occurred more frequently in the IMN group than in the plating group. The DASH score was the lowest (7/100; 95% CI 1–13) in the minimally invasive plate osteosynthesis group. The Constant–Murley and UCLA shoulder score were the highest [93/100 (95% CI 92–95) and 33/35 (95% CI 32–33), respectively] in the plating group.

Conclusion: This study suggests that even though all treatment modalities result in satisfactory outcomes, operative treatment is associated with the most favorable results. Disregarding secondary radial nerve palsy, specifically plate osteosynthesis seems to result in the highest fracture healing rates, least complications, and best functional outcomes compared with the other treatment modalities.

INTRODUCTION

Treatment modalities for humeral shaft fractures have evolved over time. Non-operative treatment has been the preferred method for decades since the healing potential of the humerus was considered very good in terms of speed and fracture healing rates, restoration of anatomy is not a prerequisite for good functional outcome, and patients are not exposed to operative risks such as iatrogenic radial nerve palsy, postoperative infections, and implant failure. However, the very good results from functional bracing as published in landmark papers in the 70's and 80's by, e.g., Sarmiento, could not be reproduced by others.[1] Despite the possibility of early mobilization of the shoulder and elbow joints, impairment of range of motion (ROM) of especially the shoulder joint was often reported.[2,3] The persisting clinical need led to the development of new and improved implants for surgical treatment.

Operative treatment for humeral shaft fractures is mostly performed using intramedullary nailing (IMN) or plate osteosynthesis. An IMN is placed in the medullary cavity of the humerus and is, thus, in line with its mechanical axis. If closed reduction can be achieved, periosteal blood supply and fracture biology can be preserved. Incisions are small and require less soft tissue stripping than open reduction and plate osteosynthesis.[4] However, shoulder-related complaints, such as pain and restriction of shoulder movement due to malrotation and impingement of the proximal nail tip or locking head screw, are frequently reported.[5-8] Open reduction and plate osteosynthesis (ORPO) offers the possibility of anatomic reduction and, depending on the fracture configuration, compression of fragments, as it requires extensive soft tissue exposure.[9] A potential disadvantage is a possible higher rate of (temporary) secondary radial nerve palsy.[10] Minimally invasive plate osteosynthesis (MIPO) has the advantage of limited soft tissue dissection and avoids the need to expose the radial nerve.[10]

The development of anatomical and angular locked plate systems since approximately 2002 has led to a variety of reliable surgical techniques and a shift from non-operative management toward osteosynthesis, even when no absolute indication for surgery is present.[11-15] Some authors recommend to use IMN, whereas recently MIPO has been proposed as the preferred treatment.[6, 8, 16-22] The debate on the most optimal treatment strategy of humeral shaft fractures remained inconclusive after previous reviews, which only included 6–17 published randomized controlled trials and comparative prospective cohort studies in total.[8, 16-26]

The primary aim of the current systematic review and pooled analysis was to compare fracture healing between non-operative and operative treatment of a humeral shaft fracture. The secondary aims were to compare complications and functional outcome.

MATERIALS AND METHODS

This systematic literature review and pooled analysis was conducted and reported according to the standards set out in Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[27] Methods used for the analysis, search strategy, and inclusion criteria were specified in advance.

Search strategy

Databases of Embase, Medline ALL, Web-of-Science Core Collection, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched. Search strings were made by an experienced librarian and are shown in Table 1. The final search was done on July 30, 2021.

Eligibility criteria

Studies were included if they reported primary treatment of a humeral shaft fracture in patients aged 16 years or older with functional bracing, intramedullary nailing, or plate osteosynthesis. All study designs, except case reports, meta-analyses, and reviews, were included. Studies were excluded if they met one or more of the following exclusion criteria: (1) recurrent, pathological, or periprosthetic fractures, (2) proximal or distal metaphyseal fracture extension, (3) grade III Gustilo Anderson open fractures, (4) treatment with external fixator, (5) experimental treatment, (6) outcome of less than five patients reported, (7) less than 6 months follow-up, (8) published before the year 2000 or (9) alternative operative methods for humeral shaft fractures (e.g., Ender nails, Marchetti nails, Rushs nails, Hackethal nailing, K wires, expandable, and flexible or elastic nails). Studies that reported on patients with concomitant injuries, such as vascular injury, compartment syndrome, or ipsilateral forearm fractures, were not excluded.

Table 1. Search Strategy

Database searched	**Via**	**Query**	**Records**	**Records after duplicates removed**
Embase	Embase.com	((('humerus fracture'/de OR 'humerus shaft fracture'/de OR 'forearm fracture'/de) NOT (proximal OR distal):ab,ti,kw) OR (((humeral-shaft* OR humerus-shaft* OR forearm-shaft* OR arm-shaft*) NEAR/3 (fracture*))):ab,ti,kw) AND (surgery/exp OR surgery:lnk OR 'orthopedic fixation device'/exp OR 'bone plate'/de OR 'conservative treatment'/exp OR brace/de OR 'plaster cast'/de OR splinting/de OR immobilization/exp OR (surg* OR operat* OR nailing OR nails OR pins OR plate* OR plating OR (extern* NEAR/3 fix*) OR screw* OR conservative* OR brace* OR bracing OR sling* OR plaster* OR cast OR casting OR nonoperat* OR nonsurg* OR Sarmiento OR splint* OR traction OR immobili*):ab,ti,kw) NOT ((animal/exp OR animal*:de OR nonhuman/de) NOT ('human'/exp)) NOT ([Conference Abstract]/lim) NOT ('child'/exp NOT ('adult'/exp OR 'adolescent'/de))	5809	5769
Medline ALL	Ovid	((("Humeral Fractures"/) NOT (proximal OR distal).ab,ti,kf.) OR (((humer* OR forearm OR arm) ADJ3 shaft* ADJ3 fracture*)).ab,ti,kf.) AND (surgery.xs. OR exp "Orthopedic Fixation Devices"/ OR braces/ OR immobilization/ OR (surg* OR operat* OR nailing OR nails OR pins OR plate* OR plating OR (extern* ADJ3 fix*) OR screw* OR conservative* OR brace* OR bracing OR sling* OR plaster* OR cast OR casting OR nonoperat* OR nonsurg* OR Sarmiento OR splint* OR traction OR immobili*).ab,ti,kf.) NOT (exp Animals/ NOT Humans/) NOT (news OR congres* OR abstract* OR book* OR chapter* OR dissertation abstract*).pt. NOT ((exp Child/ OR exp Infant/) NOT (exp Adult/ OR exp Adolescent/))	2975	861

Database searched	Via	Query	Records	Records after duplicates removed
Web of Science Core Collection	Web of Knowledge	TS=((((humer* OR forearm OR arm) NEAR/3 shaft* NEAR/3 fracture*)) AND ((surg* OR operat* OR nailing OR nails OR pins OR plate* OR plating OR (extern* NEAR/3 fix*) OR screw* OR conservative* OR brace* OR bracing OR sling* OR plaster* OR cast OR casting OR nonoperat* OR nonsurg* OR Sarmiento OR splint* OR traction OR immobili*)) NOT ((child* OR infan* OR pediatric*) NOT (adult* OR elderly* OR geriatric*)) NOT ((animal* OR rat OR rats OR mouse OR mice OR murine OR dog OR dogs OR canine OR cat OR cats OR feline OR rabbit OR cow OR cows OR bovine OR rodent* OR sheep OR ovine OR pig OR swine OR porcine OR veterinar* OR chick* OR zebrafish* OR baboon* OR nonhuman* OR primate* OR cattle* OR goose OR geese OR duck OR macaque* OR avian* OR bird* OR fish*) NOT (human* OR patient* OR women OR woman OR men OR man))) AND DT=(Article OR Review OR Letter OR Early Access)	749	91
Cochrane Central Register of Controlled Trials	Wiley	(((humer* OR forearm OR arm) NEAR/3 shaft* NEAR/3 fracture*)):ab,ti,kw AND ((surg* OR operat* OR nailing OR nails OR pins OR plate* OR plating OR (extern* NEAR/3 fix*) OR screw* OR conservative* OR brace* OR bracing OR sling* OR plaster* OR cast OR casting OR nonoperat* OR nonsurg* OR Sarmiento OR splint* OR traction OR immobili*):ab,ti,kw) NOT ((child* OR infan* OR pediatric*) NOT (adult* OR elderly* OR geriatric*)):ab,ti,kw	92	33
Total			**9625**	**6754**

Search performed July 30, 2021.

Study selection

First, four reviewers (KCM, SHVB, TVDT, and CAWN) independently screened the titles and abstracts of the studies to identify eligible studies. Inconsistencies were resolved by consensus. Second, the full-text articles of the remaining eligible publications were retrieved. The corresponding authors of studies with no available full-text version were contacted once by email. Third, the full-text articles were independently reviewed by the aforementioned reviewers. Any disagreement was resolved through consensus. Furthermore, the references of the included studies were reviewed for additional studies that may have been missed.

Data collection and data items

Data were extracted from the reports independently by three reviewers (KCM, SHVB, and PAJ) using a predefined data sheet. From each study, information was extracted on: study design, publication characteristics, demographics, treatment characteristics (including type of treatment, antegrade or retrograde IMN, ORPO, or MIPO), fracture classification according to the AO/OTA classification, complications, range of motion, and functional outcome scores, including patients-reported outcome measures (PROMs).

Fracture healing (time) was defined as (time to) radiologic or clinical fracture healing. Nonunion was defined as failure to heal at 6 months post-fracture with no progress toward healing seen on the most recent radiographs. Malunion was defined as fracture healing in an abnormal position. Primary radial nerve palsy was defined as radial nerve palsy as a result of initial trauma. Secondary radial nerve palsy was defined as radial nerve palsy as a result of reposition, during non-operative treatment or surgery. Implant failure was defined as the failure of the medical implant. Intraoperative complications included any deviation from the ideal intraoperative course occurring between skin incision and skin closure. Infection was defined as clinically diagnosed infection of (surgical) wounds as a consequence (of the treatment) of the humeral shaft fracture. Shoulder dysfunction was defined as experiencing pain or limited range of motion of the shoulder. Nail protrusion was defined as migration and subsequent protrusion of the intramedullary nail. Subacromial impingement was defined as irritation of the rotator cuff muscles in the subacromial space. (Sub)cutaneous problems included bursitis, cellulitis, granuloma's, hypertrophic scarring of the wound, and skin irritation, macerations, or abrasions due to prolonged contact with the brace.

When measurements were done at different time points, the outcomes at the 12 months follow-up were used for calculation. The extracted data were compared, and disagreements were resolved by discussion between the three reviewers. Consensus was reached by discussion.

Risk of bias assessment

The Methodological Index for Non-Randomized Studies (MINORS) instrument was used to assess methodological quality of the included publications.[28] The MINORS scale yields a maximum score of 24 for comparative cohort studies and a maximum of 16 for non-comparative cohort studies, with a higher score indicating better quality. Studies were scored for the various items by three authors (KCM, SHVB, and PAJ) independently. Any disagreement was resolved by consensus. Funnel plots, for each outcome and per treatment type separately, were used to determine the risk of publication bias.

Statistical analysis

Data were analyzed using MedCalc Statistical Software (Version 18.2.1; MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018). Binary outcomes were transformed using a double arcsine transformation to ensure normal distribution.[29] The transformed rates and 95% confidence intervals were transformed back to prevalence estimates. Forest plots were constructed with 95% confidence intervals. Heterogeneity was quantified with Cochran's Q test and I^2 statistic. For the Cochran's Q test, a p value <0.10 was considered statistically significant. A random effects model was used if the I^2 statistic >40%. Otherwise, a fixed-effect model was used. Pooled percentages and means were calculated for binary and continuous variables, respectively, and are reported with their 95% confidence intervals (CI). Results are reported per treatment modality or per subgroup if differences between subgroups were deemed relevant.

RESULTS

Study selection

The search strings identified 9625 publications (Fig. 1). Duplicates were removed, resulting in 6754 unique publications. Two additional records were identified through other sources (citation searching). The remaining 6756 publications were reviewed for inclusion and exclusion criteria. A total of 192 eligible publications were identified. For 39 studies the full-text manuscripts were not available online. Of these, 13 publications had no contact details available. The remaining corresponding authors were contacted. This revealed seven full-text publications. After full-text assessment, 173 publications were included in this review and meta-analysis (Supplemental Table S1).

Study characteristics

Supplemental Table S1 shows the study characteristics of all included studies.

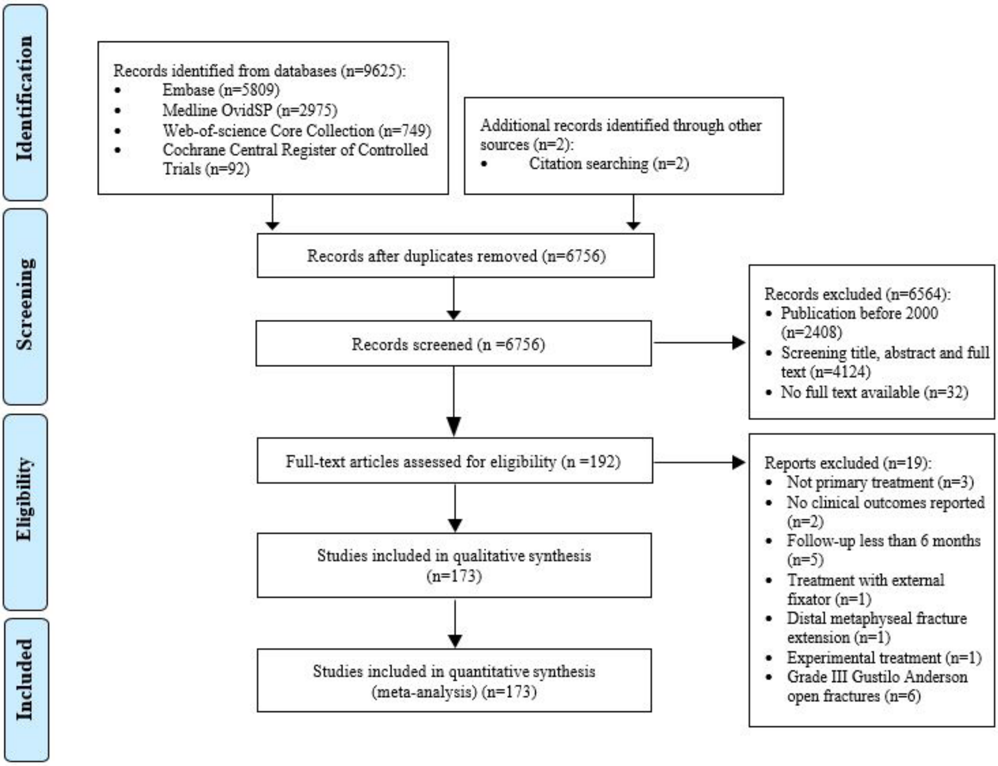


Fig. 1 Flow diagram of study selection

Of the 173 included studies, 23 were randomized controlled trials, 55 were prospective cohort studies, and 95 were retrospective cohort studies. A total of 79 studies were comparative studies and 94 studies were non-comparative. The included studies report on a total of 11,868 patients. Of these, 2204 were treated non-operatively with a functional brace, 3545 were treated with intramedullary nailing, and 6119 by plate osteosynthesis. The pooled mean age of the patients was 44 years in the non-operative group, 45 in the IMN group, and 41 in the plating group. The pooled mean percentage of males was 57% in the nonoperative group, 62% in the IMN group, and 64% in the plate group. The pooled percentage of patients with AO type A fractures was 67% in the non-operative group, 53% in the IMN group, and 46% in the plating group. The pooled percentage of patients with AO type B fractures was 23% in the non-operative group, 34% in the IMN group, and 36% in the plating group. The pooled percentage of patients with AO type C fractures was 9% in the non-operative group, 12% in the IMN group, and 15% in the plating group.

Risk of bias assessment

The outcome of the methodological quality assessment, according to the MINORS score, is shown in Supplemental Table S2. The average score of the quality assessment for comparative studies was 20/24 (range 11–23) and 12/16 points (range 9–15) for non-comparative studies.

Fracture healing - time to union

Time to fracture healing (radiologic or clinical) was reported in 37 studies (Table 2). The pooled estimate time to fracture healing was 16 weeks (95% CI 14–18 weeks) for the non-operative group, 14 weeks (95% CI 13–15 weeks) for the IMN group, and 15 weeks (95% CI 14–16 weeks) for the plate group. An antegrade IMN approach resulted in a pooled estimate time to fracture healing of 14 weeks (95% CI 12–15 weeks) versus 12 weeks (95% CI 9–16 weeks) after a retrograde approach. Furthermore, considering plate osteosynthesis, ORPO resulted in a pooled estimate time to fracture healing of 16 weeks (95% CI 15–17 weeks) versus 14 weeks (95% CI

12–16 weeks) after MIPO. Much heterogeneity of effects was seen across studies in all treatment groups, varying from 91% in the MIPO group to 98% in the (antegrade) IMN group.

Fracture healing rate

In 160/173 (92%) studies consisting of 10,206 patients the fracture healing rate was reported (Table 2). The pooled fracture healing rate for the non-operative group was 89% (95% CI 84–92%), 94% (95% CI 92–95%) for the IMN group, and 96% (95% CI 95–97%) for the plating group. The pooled fracture healing rate was the highest in the MIPO group (98%; 95% CI 97–98%). In the non-operative group, high heterogeneity across studies was found (I^2=87%) and seen in the funnel plot (Supplemental Fig. S1). In the IMN and plate group, the funnel plots showed comparable asymmetry and the heterogeneity was moderate (I^2=54% and I^2=41%, respectively; Supplemental Fig. S1).

Fracture healing - nonunion

The pooled nonunion rate showed variation between the treatment groups (Table 2). In the non-operative group, 182 nonunions were reported in 1959 patients, resulting in a pooled estimate of 11% (95% CI 7–15%). In the IMN group, 156 nonunions were reported in 2787 patients, resulting in a pooled estimate of 6% (95% CI 5–7%) and in the plating group, 163 nonunions were reported in 5098 patients, resulting in a pooled estimate of 3% (95% CI 3–4%). In the plating group, an open approach resulted in more nonunions than a minimally invasive approach [4% (95% CI 3–5%) and 2% (95% CI 2–3%), respectively].

Fracture healing - malunion

Pooled malunion rates were 6% (95% CI 2–12%) in the nonoperatively treated group, 3% (95% CI 1–5%) in the IMN group, and 1% (95% CI 1–2%) in the plating group (Table 2). However, malunion was often poorly defined and is expected to be reported differently across studies.

Table 2. Fracture healing of a humeral shaft fracture per treatment group

	Treatment		Study arms *N*	Population *N*	Cases *N*	Heterogeneity: Cochran's Q (p-value)	Heterogeneity: I^2 (%) (95% CI)	Pooled value (95% CI)
Fracture healing time[a] (weeks) 7, 10, 13, 57, 58, 60, 66, 70, 96, 106, 107, 112, 118, 119, 121, 126, 129, 131, 132, 134, 135, 144, 150, 151, 160, 162, 163, 166, 171, 176, 177, 181-184, 186, 192	**Nonoperative**		5	286	N.A.	60 (<0.001)	93 (87-97)	16.4 (14.4-18.4)
	IMN		21	819	N.A.	977 (<0.001)	98 (98-98)	13.8 (12.5-15.1)
		Antegrade	17	654	N.A.	777 (<0.001)	98 (97-98)	13.8 (12.4-15.2)
		Retrograde	3	87	N.A.	56 (<0.001)	96 (92-98)	12.4 (9.1-15.8)
	Plate		41	1392	N.A.	1555 (<0.001)	97 (97-98)	15.4 (14.4-16.4)
		ORPO	31	1194	N.A.	1416 (<0.001)	98 (98-98)	15.8 (14.7-17.0)
		MIPO	10	198	N.A.	101 (<0.001)	91 (86-94)	14.1 (12.2-15.9)
Fracture healing[b] (%) 1, 3, 5, 7, 10, 11, 13, 22, 30-76, 79-85, 87-97, 99, 100, 102-107, 110-120, 122-139, 141-150, 152-186, 188-194	**Nonoperative**		26	1979	1770	193 (<0.001)	87 (82-91)	89 (84-92)
	IMN		73	2990	2811	156 (<0.001)	54 (40-65)	94 (92-95)
		Antegrade	55	2195	2060	88 (<0.001)	39 (15-56)	94 (92-95)
		Retrograde	8	265	255	9 (0.221)	26 (0-67)	94 (91-97)
	Plate		136	5226	5030	227 (<0.001)	41 (27-52)	96 (95-97)
		ORPO	91	3896	3728	171 (<0.001)	47 (33-59)	96 (95-96)
		MIPO	45	1330	1302	46 (0.394)	4 (0-31)	98 (97-98)
Nonunion[c] (%) 1, 5, 7, 10, 22, 30-33, 35-39, 41-50, 53-60, 62-76, 79-90, 92-95, 97, 99, 100, 102-106, 110-114, 116-120, 122-139, 141-150, 152-194	**Nonoperative**		24	1959	182	175 (<0.001)	87 (82-91)	11 (7-15)
	IMN		70	2787	156	106 (<0.001)	35 (12-51)	6 (5-7)
		Antegrade	55	2181	127	80 (0.013)	32 (5-51)	6 (5-8)
		Retrograde	7	238	10	7 (0.278)	20 (0-64)	5 (2-8)
	Plate		129	5098	163	205 (<0.001)	37 (22-50)	3 (3-4)
		ORPO	88	3865	139	167 (<0.001)	48 (33-60)	4 (3-5)
		MIPO	41	1233	24	33 (0.764)	0 (0-23)	2 (2-3)
Malunion[d] (%) 5, 30, 31, 33, 43, 49, 50, 53, 57, 64, 69-71, 76, 79-81, 85-87, 91, 92, 94, 97, 99, 103-107, 110, 114, 115, 132, 138, 143, 144, 146, 148-151, 157, 160, 161, 163, 166, 168, 171, 176, 178, 180, 182, 183, 185, 188, 191-194	**Nonoperative**		11	486	34	48 (<0.001)	79 (63-88)	6 (2-12)
	IMN		22	798	23	53 (<0.001)	61 (37-75)	3 (1-5)
		Antegrade	17	555	20	50 (<0.001)	68 (47-81)	3 (1-6)
		Retrograde	1	N.A.	N.A.	N.A.	N.A.	0 (0-4)
	Plate		59	1939	15	29 (1.000)	0 (0-0)	1 (1-2)
		ORPO	37	1293	6	11 (1.000)	0 (0-0)	1 (1-2)
		MIPO	22	646	9	15 (0.805)	0 (0-26)	2 (1-3)

95% CI 95% Confidence interval, IMN Intramedullary nailing, MIPO Minimally invasive plate osteosynthesis, N.A. not applicable, ORPO Open reduction plate osteosynthesis

[a] Fracture healing time was defined as time to radiologic or clinical fracture healing

[b] Fracture healing was defined as radiologic or clinical fracture healing

[c] Nonunion was defined as failure to heal at six months post fracture with no progress towards healing seen on the most recent radiographs

[d] Malunion was defined as fracture healing in an abnormal position

Complications - radial nerve palsy

The pooled primary radial nerve palsy rate showed no variation between the treatment groups (Table 3). Secondary radial palsy was reported in 146 studies (Table 3). The pooled secondary radial nerve palsy rate was 1% (95% CI 0–2%, 18 studies, *N*=1377, 10 patients) in the nonoperatively treated group, 3% (95% CI 2–3%, 58 studies, *N*=2576, 66 patients) in the IMN group, 4% (95% CI 3–5%, 42 studies, *N*=1292, 43 patients) in the MIPO group, and 7% (95% CI 6–9%, 82 studies, *N*=4232, 275 patients) in the ORPO group.

Complications - intraoperative complications

The pooled rate of intraoperative complications was 5% (95% CI 3–8%) in patients treated with an IMN and 1% (95% CI 0–1%) in patients treated with plate osteosynthesis (Table 3). Heterogeneity across studies was especially low in the plate group (I^2=0%).

Complications - implant-related complications

Implant failures were reported more frequently in the IMN group (51/1034, pooled estimate of 4%; 95% CI 3–6%) than in patients in the plate group [pooled estimate of 2% (95% CI 1–2%), 40/2839 patients; Table 3]. An antegrade IMN approach resulted in less implant failures than a retrograde approach [4% (95% CI 3–6%) and 7% (95% CI 3–12%), respectively]. Implant failure did not differ between the surgical approaches in the plating group [ORPO 2% (95% CI 1–3%) and MIPO 2% (95% CI 1–4%)].

Complications - infection

The infection rate was reported in 124 studies consisting of 7986 patients, and was low in all treatment groups, especially in the non-operative [1% (95% CI 0–2%), 3/462 patients] and MIPO group [1% (95% CI 1–2%), 8/1126 patients; Table 3]. The infection rate in the IMN and ORPO group was 2% (95% CI 1–2%) and 3% (95% CI 3–4%), respectively.

Table 3. Complication rates of (treatment of) a ahumeral shaft fracture per treatment group

Complication	Treatment		Study arms *N*	Population *N*	Cases *N*	Heterogeneity: Cochran's *Q* (*p*-value)	Heterogeneity: I^2 (%) (95% CI)	Pooled value (%) (95% CI)
Primary radial nerve palsy[a] 1, 5, 7, 13, 22, 30, 33-36, 38-42, 44-49, 53-58, 60, 63, 65, 67, 69, 71, 73-75, 77, 80, 81, 83-85, 88, 89, 92-95, 98, 102-104, 106, 110, 112, 115, 116, 118, 119, 126, 131-136, 139-142, 145, 148, 149, 156, 157, 159, 160, 162, 166-170, 172-174, 176, 178-188, 190-194	**Nonoperative**		23	1739	142	24 (0.364)	7 (0-40)	8 (7-10)
	IMN		44	1933	116	172 (<0.001)	75 (67-81)	6 (4-8)
		Antegrade	31	1255	74	148 (<0.001)	80 (72-85)	5 (3-8)
		Retrograde	6	213	11	8 (0.166)	36 (0-75)	5 (3-9)
	Plate		85	3371	291	494 (<0.001)	83 (79-86)	6 (4-8)
		ORPO	62	2603	29	398 (<0.001)	85 (81-88)	7 (4-9)
		MIPO	23	768	262	65 (<0.001)	66 (48-78)	4 (2-7)
Secondary radial nerve palsy[b] 1, 5, 7, 10, 11, 13, 22, 30-43, 46-51, 53-56, 58-61, 63-71, 73, 75, 76, 78-85, 87-100, 102-108, 110-115, 117-123, 125-136, 139, 142-145, 147-152, 155-158, 160-162, 165-176, 178-188, 190-194	**Nonoperative**		19	1377	10	36 (0.001)	50 (15-71)	1 (0-2)
	IMN		62	2576	66	81 (0.044)	25 (0-45)	3 (2-3)
		Antegrade	47	1872	39	57 (0.121)	20 (0-45)	2 (2-3)
		Retrograde	7	224	8	3 (0.751)	0 (0-50)	4 (2-8)
	Plate		136	5524	318	348 (<0.001)	61 (53-68)	6 (5-7)
		ORPO	92	4232	275	287 (<0.001)	68 (61-74)	7 (6-9)
		MIPO	44	1292	43	49 (0.250)	12 (0-40)	4 (3-5)
Intraoperative complications[c] 7, 22, 30, 31, 38, 39, 43, 58-60, 62, 63, 66, 67, 71, 73, 78, 80, 83-85, 90, 94, 97, 99, 104, 108, 112, 113, 119, 131, 135, 136, 139, 149, 150, 158, 162, 165, 167, 174, 176, 178-186, 188, 193, 194	**Nonoperative**		N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
	IMN		40	1489	59	180 (<0.001)	78 (71-84)	5 (3-8)
		Antegrade	27	872	33	62 (<0.001)	58 (35-73)	4 (2-6)
		Retrograde	6	202	10	13 (<0.001)	63 (9-85)	5 (1-11)
	Plate		43	1868	6	25 (0.980)	0 (0-0)	1 (0-1)
		ORPO	29	1409	4	18 (0.933)	0 (0-7)	1 (0-1)
		MIPO	14	459	2	7 (0.897)	0 (0-18)	1 (0-2)
Implant failure[d] 5, 7, 10, 11, 31-33, 41, 42, 46, 48, 49, 54-56, 58-60, 62-64, 67, 68, 71, 73, 75, 76, 78, 83, 84, 86, 88, 90-92, 96, 97, 104, 105, 109, 113, 118, 119, 121, 122, 125, 132, 134, 135, 150, 152, 161, 162, 167-169, 176, 178-180, 182-186, 188, 193, 194	**Nonoperative**		N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
	IMN		28	1034	51	48 (<0.001)	44 (12-64)	4 (3-6)
		Antegrade	20	668	31	41 (<0.001)	54 (23-72)	4 (2-6)
		Retrograde	3	128	8	3 (0.232)	32 (0-98)	7 (3-12)
	Plate		71	2839	40	88 (0.076)	20 (0-41)	2 (1-2)
		ORPO	50	2300	31	67 (0.043)	27 (0-49)	2 (1-3)
		MIPO	21	539	9	19 (0.515)	0 (0-45)	2 (1-4)
Infection[e] 5, 7, 10, 22, 30-32, 37-39, 41, 43, 46, 48-50, 52, 54-56, 58, 60, 64, 67-73, 76-88, 90-93, 96, 97, 99, 100, 102-106, 108, 110-119, 121-123, 125-127, 129, 131, 133-135, 137, 139, 142-150, 152, 153, 155, 156, 158, 160-162, 165-176, 178-188, 190-194	**Nonoperative**		9	462	3	6 (0.685)	0 (0-51)	1 (0-2)
	IMN		60	2416	34	71 (0.143)	16 (0-40)	2 (1-2)
		Antegrade	48	1863	28	63 (0.059)	25 (0-48)	2 (1-2)
		Retrograde	6	235	2	5 (0.431)	0 (0-75)	1 (0-3)
	Plate		117	5108	124	193 (<0.001)	40 (25-52)	3 (2-3)
		ORPO	83	3982	116	158 (<0.001)	48 (33-60)	3 (3-4)
		MIPO	34	1126	8	22 (0.934)	0 (0-7)	1 (1-2)

95% CI 95% Confidence interval, IMN Intramedullary nailing, MIPO Minimally invasive plate osteosynthesis, N.A. not applicable, ORPO Open reduction plate osteosynthesis

[a] Primary radial nerve palsy was defined as radial nerve palsy as a result of initial trauma

[b] Secondary radial nerve palsy was defined as radial nerve palsy as a result of reposition, during nonoperative treatment or surgery

[c] Intraoperative complications were defined as any deviation from the ideal intraoperative course occurring between skin incision and skin closure

[d] Implant failure was defined as the failure of the medical implant

[e] Infection was defined as clinically diagnosed infection of (surgical) wounds as a consequence (of the treatment) of the humeral shaft fracture

Table 4. Range of motion after treatment of a humeral shaft fracture per treatment group

	Treatment		Study arms N	Population N	Heterogeneity Cochran's Q (p-value)	Heterogeneity I^2 (%) (95% CI)	Pooled value (degrees) (95% CI)
Shoulder abduction 76, 79, 115, 125, 153	**Nonoperative**		0	N.A.	N.A.	N.A.	N.A.
	IMN		2	34	309 (<0.001)	100 (99-100)	132 (76-189)
		Antegrade	2	34	309 (<0.001)	100 (99-100)	132 (76-189)
		Retrograde	0	N.A.	N.A.	N.A.	N.A.
	Plate		9	194	25,064 (<0.001)	100 (100-100)	151 (116-186)
		ORPO	8	146	19,692 (<0.001)	100 (100-100)	148 (111-186)
		MIPO	1	N.A.	N.A.	N.A.	N.A.
Shoulder anteflexion 10, 76, 79, 96, 107, 115, 153	**Nonoperative**		0	N.A.	N.A.	N.A.	N.A.
	IMN		2	34	181 (<0.001)	100 (99-100)	120 (33-207)
		Antegrade	2	34	181 (<0.001)	100 (99-100)	120 (33-207)
		Retrograde	0	N.A.	N.A.	N.A.	N.A.
	Plate		14	289	5444 (<0.001)	100 (100-100)	148 (137-160)
		ORPO	10	181	5202 (<0.001)	100 (100-100)	141 (124-158)
		MIPO	4	108	24 (<0.001)	87 (70-95)	167 (164-171)

95% CI 95% Confidence interval, IMN Intramedullary nailing, MIPO Minimally invasive plate osteosynthesis, N.A. not applicable, ORPO Open reduction plate osteosynthesis

Complications - shoulder dysfunction

The pooled rate of shoulder dysfunction was the highest in patients treated with an IMN (11%; 95% CI 8–15%) and the lowest in patients treated with plate osteosynthesis (6% (95% CI 4–8%); Supplemental Table S3). An antegrade IMN resulted in more shoulder dysfunction than a retrograde IMN [13% (95% CI 10–16%) and 5% (95% CI 1–15%), respectively].

Complications - nail protrusion

The pooled rate of nail protrusion was 10% (95% CI 6–14%) in patients treated with an IMN (17 studies, 61/666 patients; Supplemental Table S3).

Complications - subacromial impingement

Subacromial impingement was seen more in the antegrade IMN group than in the plate osteosynthesis group [pooled rate of 13% (95% CI 9–18%) and 2% (95% CI 1–3%), respectively; Supplemental Table S3].

Complications - (sub)cutaneous problems

The pooled rate of (sub)cutaneous problems in patients treated non-operatively was 6% (95% CI 4–9%, nine studies, 20/347 patients; Supplemental Table S3).

Range of motion

In the plating group, the pooled estimates of shoulder abduction and anteflexion were 151° (95% CI 116–186°) and 148° (95% CI 137–160°), respectively (Table 4). Anteflexion was better after MIPO than after ORPO [167° (95% CI 164–171°) and 141° (95% CI 124–158°), respectively]. In the IMN group, consisting of only two studies with a total of 34 patients, the pooled estimates of shoulder abduction and antefexion were 132° (95% CI 76–189°) and 120° (95% CI 33–207°), respectively. All treatment groups showed high heterogeneity across studies, varying from 87% in the MIPO group to 100% in all other operative treatment groups.

Table 5. Functional outcome scores after treatment of a humeral shaft fracture per treatment group

Instrument	Treatment		Study arms *N*	Population *N*	Heterogeneity Cochran's Q (p-value)	Heterogeneity I^2 (%) (95% CI)	Pooled value (points) (95% CI)
DASH score[a] 88, 115, 125, 134, 153, 161, 166, 168, 171, 173, 176, 182, 186, 188, 191	**Nonoperative**		3	114	141 (<0.001)	99 (98-99)	17 (3-31)
	IMN		5	192	181 (<0.001)	98 (97-99)	23 (17-29)
		Antegrade	5	192	181 (<0.001)	98 (97-99)	23 (17-29)
		Retrograde	0	N.A.	N.A.	N.A.	N.A.
	Plate		13	378	1292 (<0.001)	99 (99-99)	13 (8-19)
		ORPO	9	280	936 (<0.001)	99 (99-99)	17 (9-24)
		MIPO	4	98	97 (<0.001)	97 (94-98)	7 (1-13)
Constant-Murley score[b] 7, 11, 62, 66, 79, 110, 125, 128, 143, 153, 158, 161, 172, 176	**Non-operative**		1	N.A.	N.A.	N.A.	N.A.
	IMN		9	499	2071 (<0.001)	100 (100-100)	90 (85-95)
		Antegrade	7	440	375 (<0.001)	98 (98-99)	89 (85-93)
		Retrograde	2	23	N.A.	N.A.	N.A.
	Plate		13	569	199 (<0.001)	94 (91-96)	93 (92-95)
		Open	10	295	147 (<0.001)	94 (91-96)	93 (91-95)
		MIPO	3	274	48 (<0.001)	96 (91-98)	93 (89-97)
UCLA shoulder score[c] 10, 107, 114, 115, 118, 127, 131, 160, 173	**Non-operative**		0	N.A.	N.A.	N.A.	N.A.
	IMN		2	49	17 (<0.001)	94 (81-98)	28 (22-34)
		Antegrade	2	49	17 (<0.001)	94 (81-98)	28 (22-34)
		Retrograde	0	N.A.	N.A.	N.A.	N.A.
	Plate		15	501	385 (<0.001)	96 (95-97)	33 (32-33)
		Open	8	346	311 (<0.001)	98 (97-98)	32 (32-33)
		MIPO	7	155	69 (<0.001)	91 (85-95)	33 (32-34)

95% CI 95% Confidence interval, DASH Disabilities of the Arm, Shoulder and Hand, IMN Intramedullary nailing, MIPO Minimally invasive plate osteosynthesis, N.A. not applicable, ORPO Open reduction plate osteosynthesis, UCLA University of California at Los Angeles

[a] The DASH (Disabilities of the Arm, Shoulder, and Hand) score ranges from 0 to100 points, with a lower score representing less disability[196, 197]

[b] The Constant-Murley score ranges from 0 to 100 points, with a higher score representing better outcome[198]

[c] The University of California at Los Angeles (UCLA) shoulder score ranges from 0 to 35 points, with a higher score representing better outcome[199]

Functional outcome - DASH

The DASH score after on average 1 year (ranging from 6 to 24 months) showed variation in mean scores between the treatment groups (Table 5). For the non-operative group, the pooled estimate score was 17/100 (95% CI 3–31); for the IMN group, it was 23/100 (95% CI 17–29); and for the plating group, it was 13/100 (95% CI 8–19; Table 4). The DASH score was the highest in the antegrade IMN group (23/100; 95% CI 17–29) and the lowest in the MIPO group (7/100; 95% CI 1–13).

Functional outcome - Constant–Murley

The pooled estimate of the Constant–Murley score was 90/100 (95% CI 85–95) in the IMN group and 93/100 (95% CI 92–95) in the plating group (Table 5). The Constant–Murley score did not differ between the surgical approaches in the treatment groups.

Functional outcome - UCLA

The pooled estimate of the UCLA shoulder score in the IMN group was 28/35 (95% CI 22–34) and 33/35 (95% CI 32–33) in the plating group (Table 5). The UCLA shoulder score did not differ between the surgical techniques in the treatment groups.

Functional outcome - other

Little to no differences were observed in the other functional outcome scores after IMN or plating osteosynthesis (Supplemental Table S4). Heterogeneity was high (I^2>70%) in all subgroups for all functional outcomes, most likely due to the low number of studies with available data. For the nonoperatively treated patients, little to no data of functional outcome scores were available for analyses.

The Broberg–Morrey, Gill, Hospital for Special Surgery, l'Insalata, Neer Shoulder, Oxford Shoulder Score, *Quick*DASH, Rommens, Simple Shoulder Test, Short

Musculoskeletal Functional Assessment, and Short Form-36, as well as the Hunter criteria did not have enough data reported for analyses. The nowadays seldom used Rodriguez–Merchan criteria were analyzed but not reported.

DISCUSSION

This systematic review compared fracture healing, complications, and functional outcome of non-operative and operative treatment for humeral shaft fractures and results suggest that although all treatment modalities result in satisfactory outcomes, operative treatment, and specifically plate osteosynthesis, should be considered the preferred treatment as it results in the most favorable fracture healing rates, least complications, and best functional outcomes.

The current systematic review reveals that the risk to develop a nonunion after non-operative treatment is much higher (11%) than after any kind of surgical stabilization (6% and 3% in the IMN and plating group, respectively). This is in line with previous systematic reviews reporting higher absolute risks of nonunion after non-operative treatment (15% and 18%) and a risk ratio of 0.49 for nonunion in the operative group compared with in the non-operative group.[8, 24, 25] A first requirement for good functional recovery is fracture stability since it relieves pain in the upper limb. Stability can be achieved by fracture union, but also by relative or absolute surgical stabilization of a fresh fracture with IMN and plate osteosynthesis, respectively. A nonunion after non-operative treatment implicates that the patient has experienced pain and loss of function for months, whereas a patient who has been operated upon immediately after his injury has been able to recover functionally despite the development of the nonunion. In the balance of shared decision-making, such numbers call for a surgical and not a non-operative treatment.

The final goal of any type of treatment should be a good functional outcome. Overall, all treatment modalities result in satisfactory functional outcomes after 1 year, indicating that a good functional outcome can be achieved irrespective of treatment. However, a slight advantage of functional recovery can be found after operative treatment with plate osteosynthesis considering the Constant–Murley, DASH, and UCLA shoulder score. This is in line with a meta-analysis of RCTs describing better functional outcomes in patients treated with plate osteosynthesis than in patients treated with IMN.[26] Less complications and rotator cuff problems might enable these patients treated with plate osteosynthesis to regain function faster. These favorable results of functional recovery may tip the scale of the scientific debate toward plate osteosynthesis as the preferred treatment.

However, speed of functional recovery and a lower risk of nonunion after a humeral shaft fracture comes at a price. Both non-operative and operative treatment generate complications. The major complication is considered a radial nerve palsy. Primary nerve palsies are caused by the trauma itself, not by the therapy given to treat the injury. Secondary radial nerve palsy occurs from fracture reduction during non-operative treatment or manipulation during surgery. Not surprisingly, the rate of radial nerve palsy after non-operative treatment is much lower—albeit not absent—than after surgery in which the nerve is exposed. Within the operative group, the current systematic review showed a higher rate of secondary radial nerve palsy in the patients treated with (open) plating. However, the rate of persistent radial nerve palsy could not be defined due to the heterogeneity in reporting, and therefore questions about permanent disability after radial nerve palsy cannot be addressed. A meta-analysis of RCTs and observational studies, comparing non-operative and operative treatment, reported no difference in permanent (primary or secondary) radial nerve palsy rate between both groups suggesting that the risk of persistent radial nerve palsy should no longer be a deterrent for operative treatment.[8] Other complications inherent to operative treatment were more frequently reported in the IMN group than in the plating group. Results of other reviews are comparable, describing lower number of complications in the plating group than in the IMN group, suggesting plating is superior to IMN.[18, 21, 26]

All previous meta-analyses only included randomized control trials and comparative prospective cohort studies of 6–17 published studies in total.[8, 16-26] A strength of the current study is that by including many study designs, it included all relevant recent comparative and non-comparative studies, resulting in 173 included studies reporting the results of 11,868 patients. In this way, this systematic review provides information on results of all relevant aspects of each treatment option, and therefore empowers both the patient and the doctor in their respective roles in the desired shared decision-making process.

However, some limitations of this study are the low methodological quality of the included studies as reflected by the MINORS scores. The studies meeting the inclusion criteria often had small sample sizes and lacked an adequate power calculation. Unfortunately, due to the lack of homogeneous reporting of, e.g., patient characteristics and treatment regimens of functional bracing, risk factor and subgroup analyses could not be performed. Furthermore, different outcome parameters and methods of reporting the results were used. Results were frequently reported without a standard deviation and thus could not be included in the pooled analysis. Therefore, the results of this study should be interpreted with care given the large statistical and clinical heterogeneity.

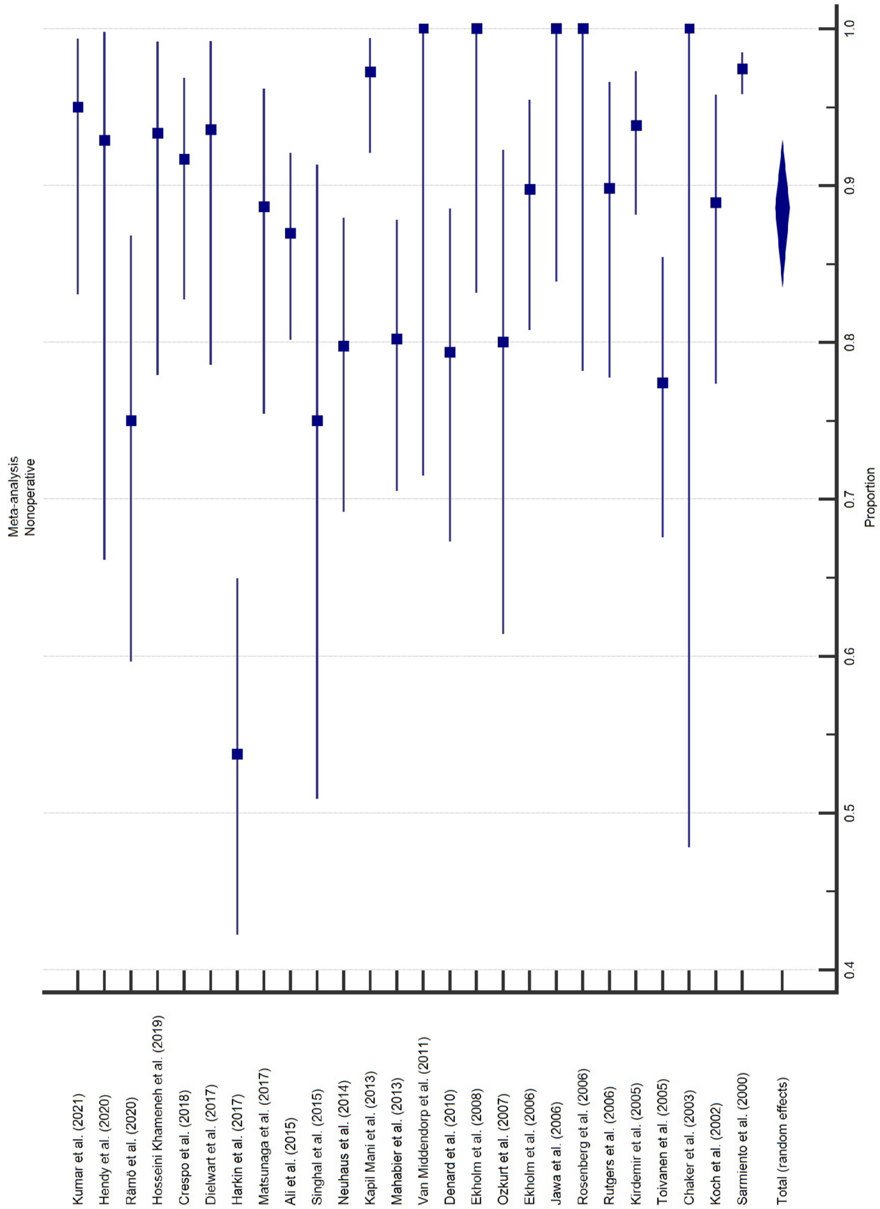
In the literature, a definitive answer on the optimal treatment strategy remains as high-quality data are lacking. This causes practice variation. Furthermore, uniform reporting of outcome of treatment is needed to compare the results of different studies. For instance, in the included studies, 18 different functional outcome scores were reported. The use of different instruments makes it hard to compare results. The DASH and Constant–Murley score have been validated and are recommended as preferred instruments for future studies.[195]

CONCLUSION

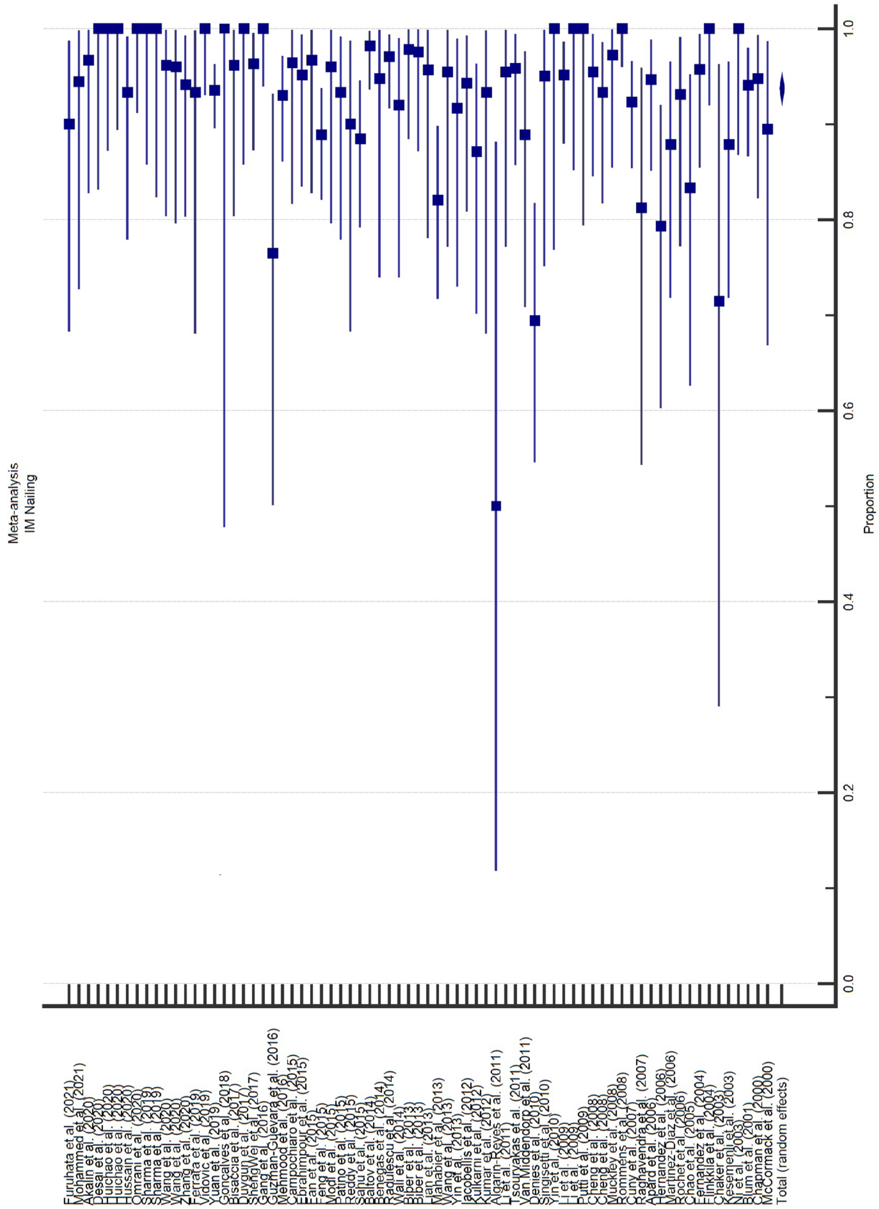
This study suggests that even though all treatment modalities result in satisfactory outcomes, operative treatment is associated with the most favorable results. Disregarding secondary radial nerve palsy, specifically plate osteosynthesis seems to result in the highest fracture healing rates, least complications, and best functional outcomes compared with the other treatment modalities.

Supplemental Figure S1. Fracture healing rate per treatment: non-operative (A), IMN (B), and plate osteosynthesis (C)

(A)

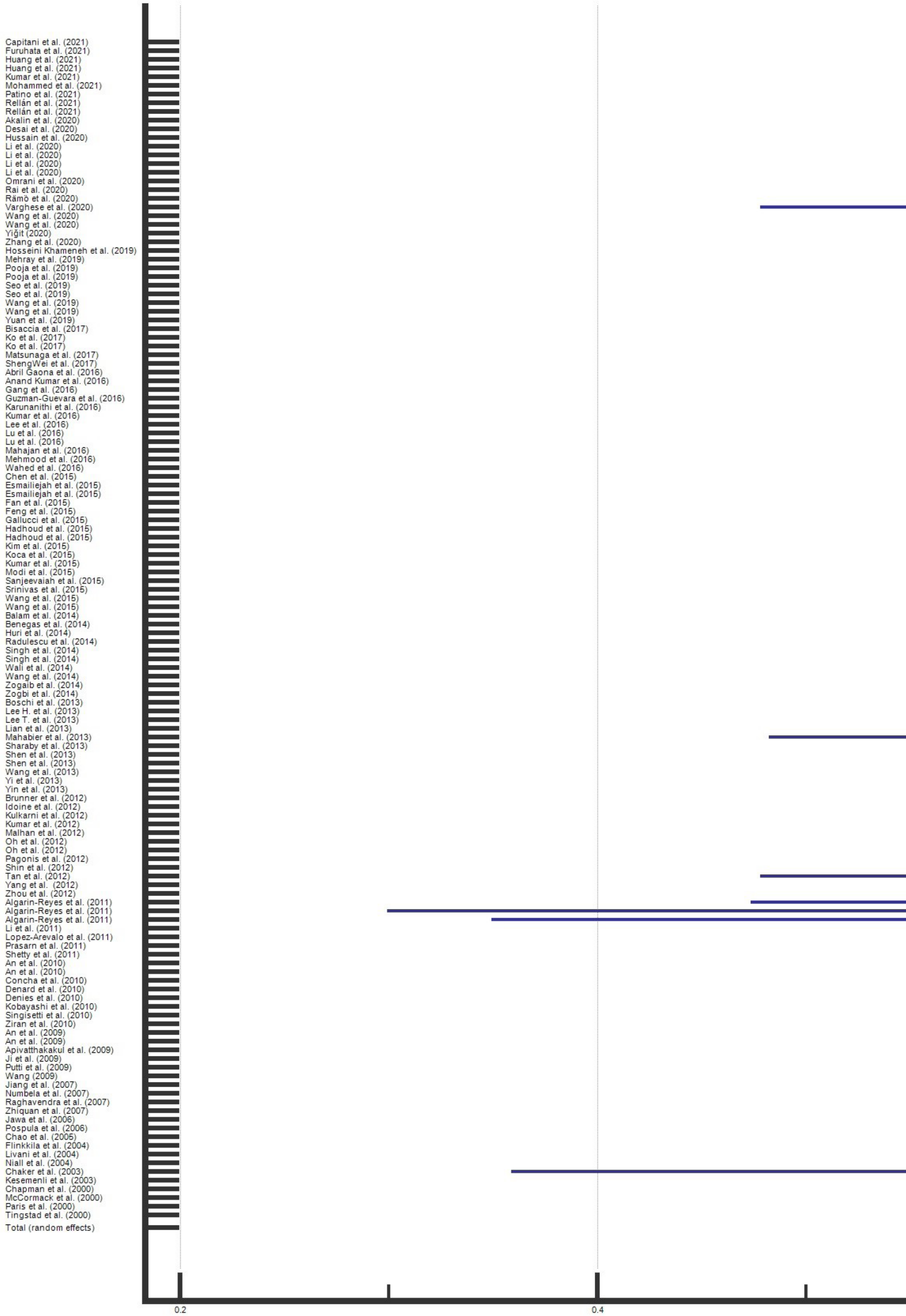


(B)



IM Nailing, Intramedullary nailing

(C)



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Chaker et al. (2003)
Kesemenli et al. (2003)
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Paris et al. (2000)
Tingstad et al. (2000)
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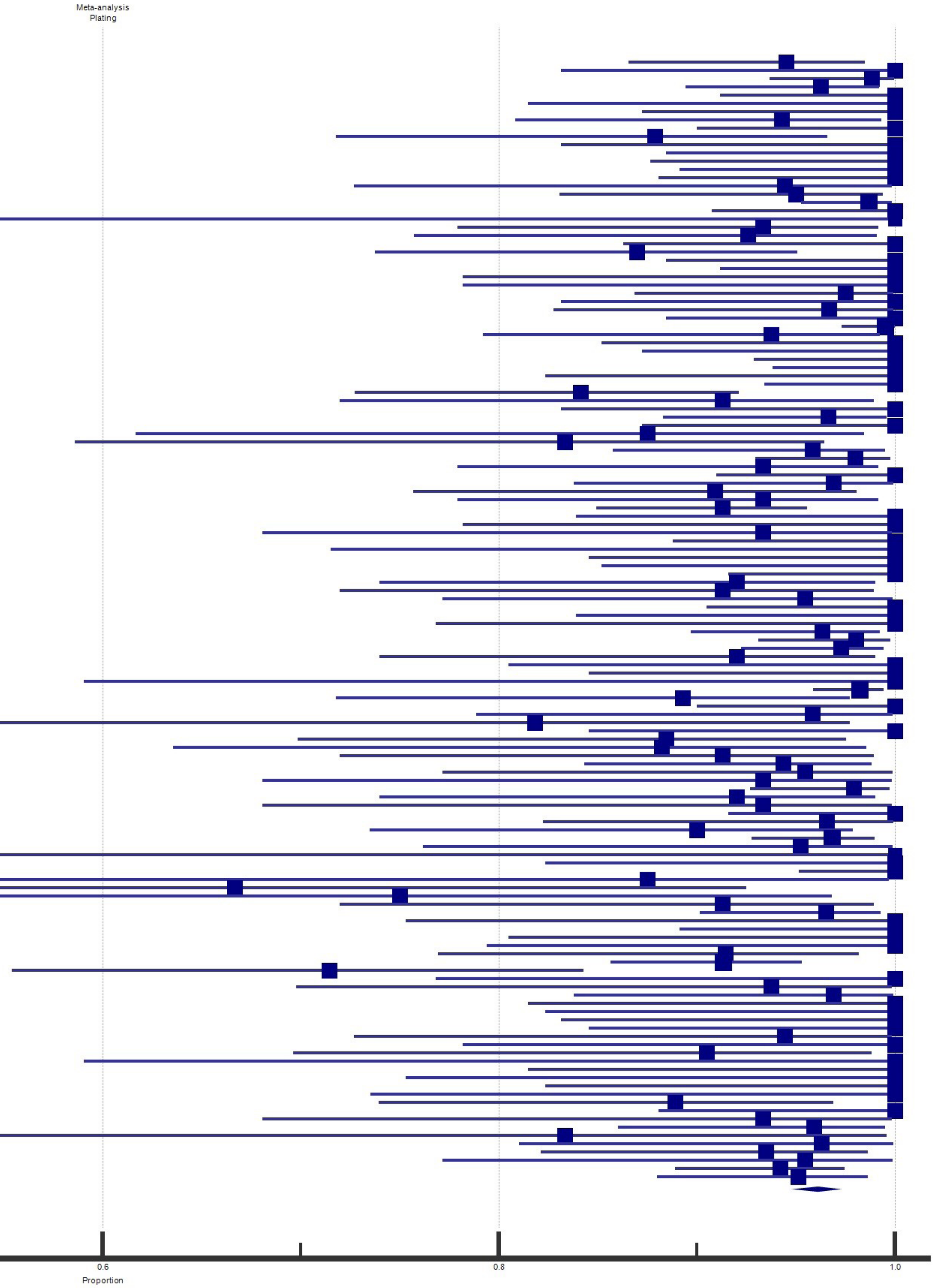
0.4


Meta-analysis
Plating
0.6
0.8
1.0
Proportion

Supplemental Table S1. Study characteristics

	Study design	Single or multicenter	Treatment per group	*N*	Age (mean (range)) (years)	Males *N* (%)	Follow-up per group (mean) (range)) (months)	OTA/AO class *N* (%) A	B	C
Sarmiento *et al.* 2000 [1]	Prospective	Single center	Nonoperative	620	36 (16-83)	391 (63%)	N.R.	N.R.	N.R.	N.R.
Chapman *et al.* 2000 [30]	RCT	Single center	Antegrade IMN	38	33 (18-70)	26 (68%)	15 (4-48)	N.R.	N.R.	N.R.
			ORPO	46	34 (18-83)	25 (54%)	12 (4-48)	N.R.	N.R.	N.R.
McCormack *et al.* 2000 [31]	RCT	Multicenter	Antegrade and retrograde IMN	21	40 (19-82)	13 (62%)	14 (6-33)	3 (48%)	11 (38%)	5 (14%)
			ORPO	23	49 (20-81)	15 (65%)	14 (6-33)	8 (35%)	10 (48%)	4 (17%)
Paris *et al.* 2000 [32]	Retrospective	Single center	ORPO	156	45 (16-96)	95 (61%)	N.R.	N.R.	N.R.	N.R.
Tingstad *et al.* 2000 [33]	Retrospective	Single center	ORPO	82	33 (13-79)	44 (54%)	N.R.	N.R.	N.R.	N.R.
Blum *et al.* 2001 [34]	Prospective	Multicenter	Antegrade and retrograde IMN	84	56 (17-91)	46 (55%)	12 (6-23)	45 (53%)	30 (36%)	9 (11%)
Koch *et al.* 2002 [35]	Retrospective	Single center	Nonoperative (monotrauma)	54	39 (N.R.)	35 (65%)	N.R.	32 (59%)	14 (26%)	8 (15%)
			Nonoperative (polytrauma)	13	23 (N.R.)	N.R.	N.R.	9 (67%)	3 (25%)	1 (8%)
Chaker *et al.* 2003 [36]	Retrospective	Single center	Nonoperative	5	31 (16-59)	5 (28%)	38 (18-72)	N.R.	N.R.	N.R.
			Retrograde IMN	7	31 (16-59)	7 (39%)	38 (18-72)	N.R.	N.R.	N.R.
			ORPO	6	31 (16-59)	6 (33%)	38 (18-72)	N.R.	N.R.	N.R.
Kesemenli *et al.* 2003 [37]	Prospective	Single center	Antegrade IMN	33	42 (21-61)	24 (73%)	42 (28-72)	N.R.	N.R.	N.R.
			ORPO	27	33 (19-47)	19 (70%)	42 (28-72)	N.R.	N.R.	N.R.
Ni *et al.* 2003 [38]	Retrospective	Single center	Antegrade and retrograde IMN	26	N.R. (18-55)	19 (73%)	16 (6-24)	22 (85%)	3 (12%)	1 (4%)
Fernandez *et al.* 2004 [39]	Prospective	Single center	Retrograde IMN	51	48 (17-89)	31 (61%)	15 (6-44)	35 (69%)	15 (29%)	1 (2%)
Flinkkila *et al.* 2004 [40]	Retrospective	Single center	Antegrade IMN	44	51 (16-75)	24 (55%)	66 (24-240)	30 (68%)	12 (27%)	2 (5%)
			ORPO	29	41 (17-69)	18 (62%)	74 (12-180)	19 (66%)	10 (34%)	N.R.
Livani *et al.* 2004 [41]	Prospective	Single center	MIPO	15	36 (14-66)	11 (73%)	24 (21-28)	5 (33%)	7 (47%)	3 (20%)
Niall *et al.* 2004 [42]	Retrospective	Single center	ORPO	49	33 (17-72)	30 (61%)	N.R.	30 (61%)	18 (37%)	1 (2%)
Chao *et al.* 2005 [43]	Retrospective	Single center	Antegrade IMN	24	47 (20-72)	15 (63%)	20 (12-44)	N.R.	N.R.	N.R.
			ORPO	36	53 (19-85)	20 (56%)	92 (12-130)	N.R.	N.R.	N.R.
Kirdemir *et al.* 2005 [44]	Retrospective	Single center	Nonoperative	129	26 (18-58)	85 (66%)	13 (3-24)	N.R.	N.R.	N.R.
Toivanen *et al.* 2005 [45]	Retrospective	Single center	Nonoperative	93	53 (16-90)	38 (41%)	N.R.	83 (89%)	10 (11%)	N.R.
Rosenberg *et al.* 2006 [3]	Prospective	Single center	Nonoperative	15	42 (25-71)	10 (67%)	30 (12-57)	9 (60%)	4 (27%)	2 (13%)
Apard *et al.* 2006 [46]	Prospective	Single center	Retrograde IMN	58	55 (16-95)	30 (52%)	10 (N.R.)	32 (57%)	13 (24%)	11 (19%)
Ekholm *et al.* 2006 [47]	Retrospective	Multicenter	Nonoperative	78	53 (N.R.)	33 (42%)	N.R.	N.R.	N.R.	N.R.
Hernandez *et al.* 2006 [48]	Retrospective	Single center	Antegrade IMN	35	51 (19-84)	21 (60%)	5 (3-6)	19 (63%)	10 (37%)	N.R.
Jawa *et al.* 2006 [49]	Retrospective	Single center	Nonoperative	21	41 (24-92)	9 (43%)	21 (2-45)	N.R.	N.R.	N.R.
Martinez-Diaz *et al.* 2006 [50]	Retrospective	Single center	Antegrade IMN	33	73 (60-89)	7 (21%)	15 (2-48)	26 (79%)	5 (15%)	2 (6%)
Pospula *et al.* 2006 [51]	Retrospective	Single center	MIPO	12	30 (17-46)	11 (92%)	N.R.	N.R.	N.R.	N.R.
Rochet *et al.* 2006 [52]	Retrospective	Single center	Antegrade IMN	29	42 (17-81)	18 (62%)	36 (9-84)	N.R.	N.R.	N.R.
Rutgers *et al.* 2006 [53]	Retrospective	Single center	Nonoperative	49	42 (19-86)	25 (51%)	14 (2-50)	N.R.	N.R.	N.R.
Cuny *et al.* 2007 [54]	Retrospective	Single center	Antegrade IMN	104	53 (N.R.)	62 (42%)	32 (6-72)	65 (55%)	34 (30%)	5 (15%)
Jiang *et al.* 2007 [55]	Prospective	Single center	MIPO	21	43 (18-75)	14 (67%)	29 (19-37)	N.R.	N.R.	21 (100%)
Numbela *et al.* 2007 [56]	Prospective	Single center	MIPO	7	N.R.	N.R.	12 (N.R.)	N.R.	5 (72%)	2 (28%)
Ozkurt *et al.* 2007 [57]	Prospective	Single center	Nonoperative	30	34 (18-64)	19 (63%)	20 (10-58)	N.R.	N.R.	N.R.
Raghavendra *et al.* 2007 [58]	Prospective	Single center	Antegrade IMN	18	40 (18-70)	15 (83%)	N.R.	11 (61%)	7 (39%)	N.R.
			ORPO	18	41 (22-70)	17 (94%)	N.R.	16 (89%)	2 (11%)	N.R.

Zhiquan *et al.* 2007 [59]	Prospective	Single center	MIPO	13	38 (25-60)	9 (69%)	13 (7-19)	10 (8%)	1 (77%)	2 (15%)
Rommens *et al.* 2008 [22]	Retrospective	Single center	Antegrade and retrograde IMN	99	63 (N.R.)	36 (36%)	28 (N.R.)	43 (43%)	40 (40%)	16 (16%)
Cheng *et al.* 2008 [60]	RCT	Single center	Antegrade IMN	44	43 (N.R.)	26 (59%)	19 (14-26)	28 (64%)	13 (30%)	3 (7%)
			Retrograde IMN	45	48 (N.R.)	28 (62%)	20 (14-27)	36 (80%)	7 (16%)	2 (5%)
Ekholm *et al.* 2008 [61]	Retrospective	Single center	Nonoperative	20	58 (16-91)	5 (25%)	26 (N.R.)	39 (50%)	26 (33%)	13 (17%)
Muckley *et al.* 2008 [62]	Prospective	Single center	Antegrade and retrograde IMN	36	48 (19-83)	21 (58%)	22 (6-34)	13 (36%)	21 (58%)	2 (6%)
An *et al.* 2009 [63]	Retrospective	Single center	ORPO	21	39 (24-62)	13 (62%)	32 (13-48)	14 (67%)	7 (33%)	N.R.
			MIPO	19	39 (19-60)	14 (74%)	25 (14-44)	3 (16%)	13 (68%)	3 (16%)
Apivatthakakul *et al.* 2009 [64]	Retrospective	Single center	MIPO	20	46 (20-72)	16 (70%)	14 (N.R.)	4 (20%)	5 (25%)	11 (55%)
Ji *et al.* 2009 [65]	Retrospective	Single center	MIPO	22	N.R. (24-62)	N.R.	17 (11-14)	N.R.	N.R.	N.R.
Li *et al.* 2009 [66]	Retrospective	Single center	Antegrade IMN	82	38 (N.R.)	59 (72%)	N.R.	49 (60%)	8 (10%)	25 (31%)
			Retrograde IMN	23	34 (N.R.)	19 (83%)	N.R.	15 (65%)	N.R.	8 (35%)
Putti *et al.* 2009 [67]	RCT	Single center	Antegrade IMN	16	36 (23-84)	N.R.	24 (N.R.)	N.R.	N.R.	N.R.
			ORPO	18	39 (22-65)	N.R.	24 (N.R.)	N.R.	N.R.	N.R.
Wang *et al.* 2009 [68]	Retrospective	Single center	MIPO	15	35 (16-59)	11 (73%)	10 (5-18)	6 (40%)	8 (53%)	1 (7%)
An *et al.* 2010 [10]	Retrospective	Single center	ORPO	16	37 (24-62)	9 (56%)	33 (13-48)	N.R.	N.R.	N.R.
			MIPO	17	38 (19-60)	12 (71%)	26 (14-44)	N.R.	N.R.	N.R.
Concha *et al.* 2010 [69]	Prospective	Single center	MIPO	35	33 (19-54)	26 (74%)	12 (6-24)	7 (20%)	1 (29%)	18 (51%)
Denard *et al.* 2010 [70]	Retrospective	Multicenter	Nonoperative	63	36 (N.R.)	34 (54%)	7 (N.R.)	N.R.	N.R.	N.R.
			ORPO	150	35 (N.R.)	82 (55%)	8 (N.R.)	N.R.	N.R.	N.R.
Denies *et al.* 2010 [71]	Retrospective	Single center	Antegrade and retrograde IMN	49	52 (N.R.)	21 (43%)	N.R.	32 (65%)	14 (29%)	3 (6%)
			ORPO	42	48 (N.R.)	25 (60%)	N.R.	23 (55%)	15 (36%)	4 (10%)
Kobayashi *et al.* 2010 [72]	Prospective	Single center	MIPO	14	37 (19-75)	11 (79%)	14 (12-21)	5 (36%)	9 (64%)	N.R.
Singisetti *et al.* 2010 [73]	Prospective	Single center	Antegrade IMN	20	N.R.	N.R.	12 (10-24)	N.R.	N.R.	N.R.
			ORPO	16	N.R.	N.R.	12 (10-24)	N.R.	N.R.	N.R.
Yin *et al.* 2010 [74]	Retrospective	Single center	Antegrade and retrograde IMN	18	36 (20-56)	14 (78%)	11 (8-15)	N.R.	N.R.	N.R.
Ziran *et al.* 2010 [75]	Retrospective	Multicenter	MIPO	32	N.R.	N.R.	16 (3-38)	N.R.	N.R.	N.R.
Algarin-Reyes *et al.* 2011 [76]	Retrospective	Single center	Antegrade IMN	6	31 (18-50)	2 (33%)	3 (N.R.)	4 (67%)	2 (33%)	N.R.
			ORPO (anterior approach)	8	31 (8-64)	4 (50%)	3 (N.R.)	2 (25%)	3 (38%)	3 (38%)
			ORPO (posterior approach)	9	29 (19-46)	6 (67%)	3 (N.R.)	4 (44%)	3 (33%)	2 (22%)
			ORPO (multiple plates)	8	31 (18-52)	7 (88%)	3 (N.R.)	2 (25%)	6 (75%)	N.R.
Grass *et al.* 2011 [77]	Retrospective	Single center	Antegrade IMN	38	53 (16-92)	18 (47%)	25 (N.R.)	N.R.	N.R.	N.R.
Kirin *et al.* 2011 [78]	Retrospective	Single center	ORPO	420	38 (N.R.)	340 (81%)	N.R.	N.R.	N.R.	N.R.
Li *et al.* 2011 [79]	RCT	Single center	Antegrade IMN	22	40 (N.R.)	16 (73%)	12 (N.R.)	10 (45%)	9 (41%)	3 (14%)
			ORPO	23	36 (N.R.)	16 (70%)	12 (N.R.)	5 (22%)	12 (52%)	6 (26%)
Lopez-Arevalo *et al.* 2011 [80]	Retrospective	Single center	MIPO	86	44 (14-78)	60 (70%)	N.R.	44 (51%)	34 (40%)	8 (9%)
Prasarn *et al.* 2011 [81]	Retrospective	Single center	ORPO	15	50 (21-86)	7 (47%)	30 (13-37)	5 (40%)	4 (33%)	4 (27%)
Shetty *et al.* 2011 [82]	Prospective	Single center	MIPO	32	39 (22-70)	19 (59%)	31 (24-40)	9 (28%)	10 (31%)	13 (41%)
Tsourvakas *et al.* 2011 [83]	Prospective	Single center	Antegrade IMN	52	52 (18-72)	36 (69%)	18 (12-24)	20 (42%)	15 (31%)	13 (27%)
Van Middendorp *et al.* 2011 [84]	Prospective	Multicenter	Nonoperative	14	51 (17-84)	5 (36%)	12 (N.R.)	9 (79%)	2 (21%)	N.R.
			Retrograde IMN	33	53 (17-86)	19 (58%)	12 (N.R.)	25 (70%)	2 (30%)	N.R.
Brunner *et al.* 2012 [85]	Retrospective	Single center	MIPO	15	62 (40-96)	7 (47%)	27 (12-38)	5 (33%)	7 (47%)	3 (20%)
Firat *et al.* 2012 [86]	Retrospective	Single center	Nonoperative	62	39 (18-69	38 (61%)	74 (20-132)	53 (85%)	7 (11%)	2 (3%)
			Antegrade IMN	30	39 (18-69	23 (77%)	74 (20-132)	26 (87%)	4 (13%)	N.R.
			ORPO	36	39 (18-69)	20 (56%)	74 (20-132)	28 (78%)	7 (19%)	1 (3%)

CHAPTER 2

Supplemental Table S1. Study characteristics

	Study design	Single or multicenter	Treatment per group	*N*	Age (mean (range)) (years)	Males *N* (%)	Follow-up per group (mean) (range)) (months)	OTA/AO class *N* (%)		
								A	B	C
Iacobellis *et al.* 2012 [87]	Prospective	Single center	Antegrade IMN	35	65 (25-92)	14 (40%)	24 (12-38)	14 (40%)	11 (31%)	10 (29%)
Idoine *et al.* 2012 [88]	Retrospective	Single center	ORPO	96	35 (16-80)	55 (57%)	58 (12-120)	N.R.	N.R.	N.R.
Kulkarni *et al.* 2012 [89]	Retrospective	Single center	Antegrade IMN	31	39 (20-60)	25 (81%)	10 (N.R.)	16 (52%)	14 (45%)	1 (3%)
			ORPO	25	39 (22-77)	19 (76%)	12 (N.R.)	17 (60%)	7 (28%)	N.R.
Kumar *et al.* 2012 [90]	Prospective	Single center	Antegrade IMN	15	46 (17-69)	8 (53%)	N.R. (16-19)	10 (67%)	5 (33%)	N.R.
			ORPO	15	45 (17-69)	10 (67%)	N.R. (16-19)	14 (93%)	1 (7%)	N.R.
Malhan *et al.* 2012 [91]	Prospective	Single center	MIPO	42	34 (18-68)	28 (67%)	25 (14-35)	26 (62%)	16 (38%)	N.R.
Oh *et al.* 2012 [92]	Retrospective	Single center	ORPO	30	42 (17-82)	16 (53%)	22 (N.R.)	15 (50%)	8 (27%)	7 (23%)
			MIPO	29	40 (16-83)	16 (55%)	18 (N.R.)	11 (38%)	11 (38%)	7 (24%)
Pagonis *et al.* 2012 [93]	Retrospective	Single center	ORPO	158	67 (57-87)	40 (22%)	163 (84-288)	107 (62%)	15 (14%)	36 (25%)
Shin *et al.* 2012 [94]	Prospective	Single center	MIPO	21	43 (19-75)	13 (62%)	17 (13-25)	11 (52%)	9 (43%)	1 (5%)
Tan *et al.* 2012 [95]	Retrospective	Single center	MIPO	5	35 (20-96)	5 (100%)	6 (N.R.)	3 (60%)	2 (40%)	N.R.
Yang *et al.* 2012 [96]	Prospective	Single center	ORPO	19	37 (20-75)	15 (79%)	17 (12-20)	9 (47%)	8 (42%)	2 (11%)
Zhou *et al.* 2012 [97]	Retrospective	Single center	MIPO	74	57 (34-86)	26 (35%)	17 (12-24)	9 (12%)	45 (61%)	20 (27%)
Mahabier *et al.* 2013 [13]	Retrospective	Multicenter	Nonoperative	91	49 (N.R.)	36 (40%)	N.R.	6 (N.R.)	4 (N.R.)	1 (N.R.)
			Antegrade and retrograde IMN	78	60 (N.R.)	32 (41%)	N.R.	44 (N.R.)	28 (N.R.)	6 (N.R.)
			ORPO	11	60 (N.R.)	6 (55%)	N.R.	43 (N.R.)	41 (N.R.)	7 (N.R.)
Aydin *et al.* 2013 [98]	Retrospective	Single center	Nonoperative	5	20 (19-22)	5 (100%)	N.R.	N.R.	N.R.	N.R.
Biber *et al.* 2013 [99]	Retrospective	Single center	Antegrade IMN	46	57 (N.R.)	22 (48%)	N.R.	N.R.	N.R.	N.R.
			Retrograde IMN	41	41 (N.R.)	34 (83%)	N.R.	N.R.	N.R.	N.R.
Boschi *et al.* 2013 [100]	Retrospective	Single center	ORPO	280	34 (30-36)	280 (100%)	101 (N.R.)	210 (75%)	70 (25%)	N.R.
Chen *et al.* 2013 [101]	Retrospective	Single center	Antegrade and retrograde IMN	310	75 (N.R.)	77 (25%)	12 (N.R.)	N.R.	N.R.	N.R.
			ORPO	201	73 (N.R.)	42 (21%)	12 (N.R.)	N.R.	N.R.	N.R.
Kapil Mani *et al.* 2013 [102]	Prospective	Single center	Nonoperative	108	39 (17-77)	63 (58%)	N.R.	N.R.	N.R.	N.R.
Lee *et al.* 2013 [103]	Prospective	Single center	ORPO	35	38 (14-70)	26 (74%)	28 (24-50)	N.R.	N.R.	N.R.
Lee *et al.* 2013 [104]	Retrospective	Single center	MIPO	28	37 (18-77)	19 (68%)	21 (14-31)	7 (24%)	16 (59%)	5 (17%)
Lian *et al.* 2013 [105]	RCT	Single center	Antegrade and retrograde IMN	23	38 (17-77)	16 (70%)	15 (10-16)	8 (35%)	12 (52%)	3 (13%)
			MIPO	24	39 (17-76)	15 (63%)	14 (7-20)	9 (38%)	9 (38%)	6 (25%)
Sharaby *et al.* 2013 [106]	Prospective	Single center	ORPO	22	44 (25-67)	15 (68%)	25 (17-36)	12 (55%)	8 (36%)	2 (9%)
Shen *et al.* 2013 [107]	Retrospective	Single center	MIPO (DCP)	26	37 (20-60)	18 (69%)	32 (13-62)	5 (19%)	15 (58%)	6 (23%)
			MIPO (LCP)	17	43 (18-78)	10 (59%)	17 (12-18)	6 (35%)	5 (30%)	6 (35%)
Tyllianakis *et al.* 2013 [108]	Retrospective	Single center	Antegrade IMN	64	42 (17-76)	33 (52%)	78 (24-120)	36 (56%)	22 (34%)	6 (9%)
Verdano *et al.* 2013 [109]	Retrospective	Single center	Antegrade IMN	48	51 (16-75)	26 (54%)	33 (12-61)	N.R.	N.R.	N.R.
Wang *et al.* 2013 [110]	RCT	Single center	Antegrade IMN	22	40 (N.R.)	16 (73%)	18 (N.R.)	10 (45%)	9 (41%)	3 (14%)
			ORPO	23	36 (N.R.)	16 (70%)	18 (N.R.)	5 (22%)	12 (52%)	6 (26%)
Yi *et al.* 2013 [111]	Prospective	Single center	ORPO	53	39 (16-82)	34 (64%)	17 (8-45)	39 (74%)	14 (26%)	N.R.
Yin *et al.* 2013 [112]	Retrospective	Single center	Antegrade IMN	24	38 (21-70)	14 (58%)	17 (12-24)	N.R.	19 (79%)	5 (21%)
			ORPO	22	40 (25-74)	12 (55%)	17 (12-24)	N.R.	18 (82%)	4 (18%)
Balam *et al.* 2014 [113]	Prospective	Single center	MIPO	37	28 (19-43)	33 (89%)	18 (12-24)	N.R.	N.R.	N.R.
Baltov *et al.* 2014 [5]	Retrospective	Single center	Antegrade and retrograde IMN	111	49 (17-83)	71 (64%)	42 (12-72)	38 (34%)	46 (41%)	27 (24%)
Benegas *et al.* 2014 [114]	RCT	Single center	Antegrade IMN	19	38 (N.R.)	14 (74%)	12 (N.R.)	9 (47%)	4 (21%)	6 (32%)

			MIPO	21	45 (N.R.)	12 (57%)	12 (N.R.)	12 (57%)	7 (33%)	2 (10%)
Huri *et al.* 2014 [115]	Retrospective	Single center	ORPO	14	42 (19-66)	8 (62%)	18 (13-30)	7 (50%)	5 (36%)	2 (14%)
Neuhaus *et al.* 2014 [116]	Retrospective	Multicenter	Nonoperative	79	48 (18-91)	46 (58%)	9 (2-52)	79 (100%)	N.R.	N.R.
Radulescu *et al.* 2014 [117]	Prospective	Single center	Antegrade IMN	102	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.
			ORPO	82	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.
Singh *et al.* 2014 [118]	Retrospective	Single center	ORPO (DCP)	102	37 (18-65)	73 (72%)	12 (N.R.)	51 (51%)	40 (39%)	11 (10%)
			ORPO (LCP)	110	38 (22-64)	75 (68%)	12 (N.R.)	55 (50%)	43 (39%)	12 (11%)
Wali *et al.* 2014 [119]	RCT	Single center	Antegrade IMN	25	37 (N.R.)	21 (84%)	N.R.	16 (64%)	6 (24%)	3 (12%)
			ORPO	25	38 (N.R.)	20 (80%)	N.R.	17 (68%)	6 (24%)	2 (8%)
Wang *et al.* 2014 [120]	Retrospective	Single center	MIPO	17	36 (19-51)	11 (65%)	17 (13-31)	1 (6%)	15 (88%)	1 (6%)
Yin *et al.* 2014 [121]	Retrospective	Single center	ORPO (lateral approach)	30	38 (22-71)	16 (53%)	16 (12-22)	5 (17%)	16 (53%)	9 (30%)
			ORPO (posterior approach)	26	38 (20-73)	14 (54%)	16 (12-22)	6 (23%)	12 (46%)	8 (31%)
Zogaib *et al.* 2014 [122]	Retrospective	Single center	MIPO	22	34 (18-66)	15 (56%)	52 (6-126)	N.R.	N.R.	N.R.
Zogbi *et al.* 2014 [123]	Retrospective	Single center	MIPO	7	30 (N.R.)	5 (71%)	30 (N.R.)	N.R.	N.R.	N.R.
Chen *et al.* 2015 [11]	Retrospective	Single center	ORPO	43	72 (52-88)	15 (35%)	37 (18-48)	5 (14%)	11 (28%)	23 (58%)
Ali *et al.* 2015 [124]	Retrospective	Single center	Nonoperative	156	54 (18-92)	71 (46%)	N.R.	N.R.	N.R.	N.R.
Campochiaro *et al.* 2015 [125]	Retrospective	Single center	Antegrade IMN	28	68 (20-97)	9 (32%)	19 (6-32)	N.R.	25 (89%)	3 (11%)
Ebrahimpour *et al.* 2015 [126]	Prospective	Single center	Antegrade IMN	41	39 (21-59)	34 (83%)	12 (10-24)	N.R.	N.R.	N.R.
Esmailiejah *et al.* 2015 [127]	Prospective	Single center	ORPO	33	35 (16-56)	8 (25%)	N.R.	12 (36%)	10 (30%)	11 (33%)
			MIPO	32	33 (16-53)	24 (75%)	N.R.	10 (31%)	9 (28%)	13 (41%)
Fan *et al.* 2015 [128]	RCT	Single center	Antegrade IMN	30	39 (N.R.)	18 (60%)	N.R.	11 (37%)	14 (47%)	5 (17%)
			ORPO	30	39 (N.R.)	19 (63%)	N.R.	12 (40%)	15 (50%)	3 (10%)
Feng *et al.* 2015 [129]	RCT	Single center	Antegrade IMN	126	37 (25-68)	78 (62%)	N.R.	59 (47%)	18 (14%)	49 (39%)
			ORPO	126	38 (24-67)	69 (55%)	N.R.	61 (48%)	23 (18%)	42 (33%)
Gallucci *et al.* 2015 [130]	Retrospective	Single center	MIPO	21	37 (23-73)	13 (62%)	22 (12-50)	N.R.	20 (95%)	1 (5%)
Hadhoud *et al.* 2015 [131]	RCT	Single center	ORPO	15	36 (20-65)	11 (73%)	N.R. (6-10)	10 (67%)	4 (27%)	1 (7%)
			MIPO	15	40 (22-67)	9 (60%)	N.R. (6-10)	9 (60%)	3 (20%)	3 (20%)
Kim *et al.* 2015 [132]	Retrospective	Single center	ORPO	31	26 (18-34)	31 (100%)	16 (12-23)	23 (74%)	6 (19%)	2 (7%)
Koca *et al.* 2015 [133]	Retrospective	Single center	ORPO	11	36 (28-50)	7 (64%)	14 (6-24)	N.R.	11 (100%)	N.R.
Kumar *et al.* 2015 [134]	Prospective	Single center	ORPO	22	33 (21-58)	N.R.	15 (14-17)	7 (32%)	13 (59%)	2 (9%)
Modi *et al.* 2015 [135]	RCT	Single center	Antegrade IMN	30	36 (N.R.)	20 (80%)	10 (6-14)	N.R.	N.R.	N.R.
			ORPO	30	36 (N.R.)	17 (74%)	10 (6-14)	N.R.	N.R.	N.R.
Patino *et al.* 2015 [136]	Retrospective	Single center	Antegrade IMN	30	42 (19-77)	20 (67%)	36 (24-60)	22 (73%)	7 (23%)	1 (3%)
Reddy *et al.* 2015 [137]	Prospective	Single center	Antegrade IMN	20	N.R. (20-60)	14 (70%)	N.R.	10 (50%)	8 (40%)	2 (10%)
Sahu *et al.* 2015 [138]	Prospective	Single center	Antegrade IMN	78	N.R.	65 (83%)	N.R.	N.R.	N.R.	N.R.
Sanjeevaiah *et al.* 2015 [139]	Prospective	Single center	MIPO	42	34 (18-68)	28 (67%)	25 (14-35)	26 (62%)	16 (38%)	N.R.
Shields *et al.* 2015 [140]	Retrospective	Single center	Nonoperative	32	45 (18-84)	N.R.	47 (12-104)	20 (63%)	11 (34%)	1 (3%)
Singhal *et al.* 2015 [141]	Retrospective	Single center	Nonoperative	20	N.R. (16-89)	10 (50%)	3 (1-14)	14 (70%)	3 (15%)	3 (15%)
Srinivas *et al.* 2015 [142]	Prospective	Single center	ORPO	25	39 (21-58)	21 (84%)	N.R.	N.R.	N.R.	N.R.
Wang *et al.* 2015 [143]	Prospective	Single center	ORPO	23	36 (N.R.)	16 (70%)	N.R.	5 (22%)	12 (52%)	6 (26%)
			MIPO	22	39 (N.R.)	14 (64%)	N.R.	5 (23%)	8 (36%)	9 (41%)
Abril Gaona *et al.* 2016 [144]	Prospective	Single center	ORPO	19	38 (17-78)	12 (63%)	N.R.	6 (32%)	8 (42%)	5 (26%)
Anand Kumar *et al.* 2016 [145]	Prospective	Single center	ORPO	54	N.R. (21-65)	41 (76%)	9 (N.R.)	45 (83%)	9 (17%)	N.R.
Gang *et al.* 2016 [146]	Retrospective	Single center	Antegrade IMN	59	48 (N.R.)	31 (53%)	10 (N.R.)	22 (37%)	27 (46%)	10 (17%)
			ORPO	63	51 (N.R.)	36 (57%)	10 (N.R.)	25 (40%)	32 (51%)	6 (10%)

Supplemental Table S1. Study characteristics

	Study design	Single or multicenter	Treatment per group	*N*	Age (mean (range)) (years)	Males *N* (%)	Follow-up per group (mean) (range)) (months)	OTA/AO class *N* (%) A	B	C
Guzmán-Guevara *et al.* 2016 [147]	Prospective	Single center	Antegrade IMN	17	44 (19-81)	N.R.	N.R.	N.R.	N.R.	N.R.
			ORPO	23	41 (16-79)	N.R.	N.R.	N.R.	N.R.	N.R.
Karunanithi *et al.* 2016 [148]	Prospective	Single center	MIPO	20	41 (21-65)	N.R.	8 (6-17)	N.R.	N.R.	N.R.
Kumar *et al.* 2016 [149]	Prospective	Single center	ORPO	59	N.R.	41 (69%)	N.R.	N.R.	N.R.	N.R.
Lee *et al.* 2016 [150]	Retrospective	Single center	ORPO	31	41 (23-75)	11 (41%)	40 (26-60)	15 (48%)	12 (41%)	4 (11%)
Lee *et al.* 2016 [151]	Retrospective	Single center	ORPO	28	48 (27-82)	18 (64%)	26 (12-40)	N.R.	N.R.	N.R.
			MIPO	24	51 (16-89)	15 (63%)	25 (6-36)	N.R.	N.R.	N.R.
Lu *et al.* 2016 [152]	Retrospective	Single center	ORPO (medial approach)	16	34 (18-56)	10 (67%)	12 (N.R.)	8 (50%)	5 (31%)	3 (19%)
			ORPO (anterolateral approach)	18	35 (23-59)	12 (63%)	12 (N.R.)	10 (56%)	4 (22%)	4 (22%)
Mahajan *et al.* 2016 [153]	Prospective	Single center	MIPO	57	N.R.	36 (75%)	N.R.	32 (60%)	15 (25%)	10 (15%)
Mehmood *et al.* 2016 [154]	RCT	Single center	Antegrade IMN	100	39 (20-59)	82 (82%)	N.R.	N.R.	N.R.	N.R.
			ORPO	100	39 (20-59)	81 (81%)	N.R.	N.R.	N.R.	N.R.
Wahed *et al.* 2016 [155]	Prospective	Single center	ORPO	30	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.
Bisaccia *et al.* 2017 [156]	Prospective	N.R.	Antegrade IMN	32	53 (N.R.)	15 (47%)	12 (9-16)	22 (69%)	5 (16%)	5 (16%)
			ORPO	26	59 (N.R.)	11 (42%)	12 (9-16)	17 (65%)	6 (23%)	3 (12%)
Dielwart *et al.* 2017 [157]	Retrospective	Single center	Nonoperative Brace	31	39 (18-93)	23 (74%)	10 (2-34)	16 (52%)	7 (23%)	8 (26%)
Duygun *et al.* 2017 [158]	Prospective	Single center	Antegrade IMN	24	42 (23-55)	12 (50%)	24 (12-72)	21 (88%)	N.R.	3 (13%)
Harkin *et al.* 2017 [159]	Retrospective	Single center	Nonoperative Brace	96	N.R.	32 (33%)	N.R.	N.R.	N.R.	N.R.
Ko *et al.* 2017 [160]	Retrospective	Single center	ORPO	23	56 (35-67)	16 (70%)	19 (N.R.)	N.R.	N.R.	N.R.
			MIPO	27	56 (37-70)	18 (67%)	19 (N.R.)	N.R.	N.R.	N.R.
Matsunaga *et al.* 2017 [161]	RCT	Single center	Nonoperative Brace	52	40 (N.R.)	38 (73%)	12 (N.R.)	29 (55%)	17 (33%)	6 (12%)
			ORPO	58	37 (N.R.)	35 (60%)	12 (N.R.)	39 (68%)	16 (27%)	3 (5%)
ShengWei *et al.* 2017 [162]	Retrospective	Single center	Antegrade IMN	54	31 (20-41)	40 (74%)	15 (6-24)	28 (52%)	18 (33%)	8 (15%)
			ORPO	58	31 (18-44)	38 (67%)	15 (6-24)	30 (52%)	20 (34%)	8 (14%)
Crespo *et al.* 2018 [163]	Retrospective	Multicenter	Nonoperative Brace	72	N.R.	N.R.	9 (3-13)	N.R.	N.R.	N.R.
Goncalves *et al.* 2018 [164]	Retrospective	Single center	Antegrade IMN	5	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.
Ferrara *et al.* 2019 [165]	Retrospective	Single center	Antegrade IMN	22	76 (65-88)	5 (23%)	N.R.	8 (36%)	12 (55%)	2 (9%)
Hosseini Khameneh *et al.* 2019 [166]	RCT	Single center	Nonoperative Brace	30	49 (19-77)	26 (87%)	12 (N.R.)	21 (70%)	5 (17%)	4 (13%)
			ORPO	30	38 (18-71)	23 (77%)	12 (N.R.)	18 (60%)	4 (13%)	8 (27%)
Mehraj *et al.* 2019 [167]	Prospective	Single center	MIPO	40	34 (20-53)	26 (65%)	22 (18-28)	N.R.	N.R.	N.R.
Pooja *et al.* 2019 [168]	RCT	Single center	ORPO	15	37 (21-56)	10 (67%)	26 (24-31)	9 (60%)	4 (27%)	2 (13%)
			MIPO	15	38 (20-56)	9 (60%)	27 (25-30)	10 (67%)	3 (20%)	2 (13%)
Seo *et al.* 2019 [169]	Prospective	Single center	ORPO (single plating)	40	44 (N.R.)	29 (73%)	14 (N.R.)	18 (45%)	16 (40%)	6 (15%)
			ORPO (dual plating)	20	45 (N.R.)	11 (55%)	9 (N.R.)	10 (50%)	6 (30%)	4 (20%)
Vidovic *et al.* 2019 [170]	Retrospective	Single center	IMN	51	61 (N.R.)	20 (39%)	N.R.	28 (55%)	14 (27%)	9 (18%)
Wang *et al.* 2019 [171]	Retrospective	Single center	ORPO	30	43 (19-71)	17 (57%)	N.R. (6-24)	8 (27%)	13 (43%)	9 (30%)
			MIPO	30	38 (21-66)	12 (40%)	N.R. (6-24)	7 (23%)	12 (40%)	11 (37%)
Yuan *et al.* 2019 [172]	Retrospective	Single center	Antegrade IMN	204	42 (N.R.)	119 (58%)	26 (N.R.)	115 (56%)	64 (31%)	25 (12%)
			MIPO	232	41 (N.R.)	128 (55%)	26 (N.R.)	127 (55%)	79 (34%)	26 (11%)

Li *et al.* 2020 [7]	Retrospective	Single center	ORPO (posterior approach) (A)	28	39 (N.R.)	22 (79%)	4 (N.R.)	28 (100%)	N.R.	N.R.
			ORPO (anterolateral approach) (A)	32	38 (N.R.)	19 (59%)	4 (N.R.)	32 (100%)	N.R.	N.R.
			ORPO (posterior approach) (B/C)	29	39 (N.R.)	16 (55%)	4 (N.R.)	N.R.	19 (66%)	10 (35%)
			ORPO (anterolateral approach) (B/C)	18	38 (N.R.)	12 (67%)	4 (N.R.)	N.R.	13 (72%)	5 (28%)
Akalin *et al.* 2020 [173]	RCT	Single center	Antegrade IMN	33	42 (22-88)	17 (57%)	24 (N.R.)	18 (55%)	9 (27%)	6 (18%)
			ORPO	33	45 (18-88)	24 (73%)	24 (N.R.)	17 (52%)	11 (33%)	5 (15%)
Desai *et al.* 2020 [174]	RCT	Single center	Antegrade IMN	20	34 (N.R.)	N.R.	N.R.	N.R.	N.R.	N.R.
			ORPO	20	38 (N.R.)	N.R.	N.R.	N.R.	N.R.	N.R.
Hendy *et al.* 2020 [175]	Retrospective	Single center	Nonoperative Brace	14	51 (N.R.)	7 (50%)	5 (3-9)	8 (57%)	2 (14%)	4 (29%)
Huichao *et al.* 2020 [176]	Retrospective	Single center	Antegrade IMN	27	48 (N.R.)	19 (70%)	14 (N.R.)	9 (33%)	14 (52%)	4 (15%)
			Antegrade IMN	33	49 (N.R.)	22 (67%)	15 (N.R.)	12 (36%)	18 (55%)	3 (9%)
Hussain *et al.* 2020 [177]	RCT	Single center	Antegrade IMN	30	34 (N.R.)	24 (80%)	N.R.	N.R.	N.R.	N.R.
			ORPO	30	34 (N.R.)	23 (77%)	N.R.	N.R.	N.R.	N.R.
Omrani *et al.* 2020 [178]	RCT	Single center	Antegrade IMN	40	31 (N.R.)	25 (63%)	N.R.	N.R.	N.R.	N.R.
			ORPO	40	30 (N.R.)	22 (55%)	N.R.	N.R.	N.R.	N.R.
Rai *et al.* 2020 [179]	Prospective	Single center	ORPO	150	N.R. (19-65)	130 (87%)	N.R. (6-24)	101 (67%)	21 (14%)	28 (19%)
Rämö *et al.* 2020 [180]	RCT	Multicenter	Nonoperative	44	48 (19-80)	24 (55%)	12 (N.R.)	36 (82%)	7 (16%)	1 (2%)
			ORPO	38	50 (19-81)	20 (53%)	12 (N.R.)	34 (90%)	4 (11%)	N.R.
Sharma *et al.* 2020 [181]	RCT	Single center	Antegrade IMN	24	42 (N.R.)	N.R.	N.R.	12 (50%)	4 (17%)	8 (33%)
			Retrograde IMN	19	44 (N.R.)	N.R.	N.R.	9 (47%)	6 (32%)	4 (21%)
Varghese *et al.* 2020 [182]	Prospective	Single center	MIPO	5	43 (33-55)	3 (60%)	8 (3-12)	1 (20%)	4 (80%)	N.R.
Wang *et al.* 2020 [183]	Retrospective	Single center	Antegrade IMN	25	39 (18-56)	16 (64%)	N.R.	6 (24%)	15 (60%)	4 (16%)
			MIPO	30	37 (18-56)	17 (57%)	N.R.	10 (33%)	14 (47%)	6 (20%)
Wang *et al.* 2020 [184]	Prospective	Single center	Antegrade IMN	26	46 (20-79)	16 (62%)	12 (N.R.)	15 (58%)	11 (42%)	N.R.
			ORPO	30	45 (18-88)	17 (57%)	12 (N.R.)	18 (60%)	10 (33%)	2 (7%)
Yiğit *et al.* 2020 [185]	Retrospective	Single center	ORPO	25	40 (20-65)	16 (64%)	46 (12-84)	15 (60%)	8 (32%)	2 (8%)
Zhang *et al.* 2020 [186]	Retrospective	Single center	Antegrade IMN	34	43 (18-65)	19 (56%)	25 (N.R.)	24 (71%)	10 (29%)	N.R.
			ORPO	46	41 (18-65)	31 (67%)	23 (N.R.)	30 (65%)	16 (35%)	N.R.
Cannada *et al.* 2021 [187]	Prospective	Multicenter	Nonoperative Brace	57	42 (N.R.)	32 (56%)	6 (N.R.)	30 (53%)	20 (35%)	7 (12%)
			ORPO	45	41 (N.R.)	31 (69%)	6 (N.R.)	26 (57%)	17 (38%)	2 (5%)
Capitani *et al.* 2021 [188]	Prospective	Single center	ORPO	73	55 (N.R.)	32 (44%)	48 (N.R.)	26 (36%)	34 (47%)	13 (18%)
Furuhata *et al.* 2021 [189]	Retrospective	Single center	Antegrade IMN	20	45 (15-89)	N.R.	N.R.	N.R.	N.R.	N.R.
			ORPO	20	45 (15-89)	N.R.	N.R.	N.R.	N.R.	N.R.
Huang *et al.* 2021 [190]	Retrospective	Single center	ORPO (anterolateral approach)	86	45 (N.R.)	44 (51%)	N.R.	40 (47%)	29 (34%)	17 (20%)
			ORPO (posterior median approach)	80	47 (N.R.)	37 (46%)	N.R.	33 (41%)	32 (40%)	15 (18%)
Kumar *et al.* 2021 [191]	Retrospective	Single center	Nonoperative Brace	40	36 (18-50)	32 (80%)	10 (N.R.)	22 (55%)	13 (33%)	5 (13%)
			ORPO	40	36 (18-50)	30 (75%)	11 (N.R.)	20 (50%)	14 (35%)	6 (15%)
Mohammed *et al.* 2021 [192]	Prospective	Multicenter	Antegrade IMN	18	36 (21-54)	7 (38%)	5 (3-10)	9 (50%)	8 (44%)	1 (6%)
			ORPO	18	38 (21-54)	12 (66%)	5 (4-8)	8 (44%)	6 (33%)	4 (22%)
Patino *et al.* 2021 [193]	Retrospective	Single center	ORPO	27	37 (N.R.)	17 (63%)	28 (N.R.)	16 (59%)	7 (26%)	4 (15%)
Rellán *et al.* 2021 [194]	Retrospective	Single center	MIPO	35	N.R. (47-75)	10 (29%)	8 (6-12)	35 (100%)	N.R.	N.R.
			ORPO	35	N.R. (55-80)	8 (23%)	9 (6-18)	35 (100%)	N.R.	N.R.

DCP Dynamic Compression plate, IMN Intramedullary nailing, LCP Locking compression plate, MIPO Minimally invasive plate Osteosynthesis, N.R. not reported, ORPO Open reduction plate osteosynthesis, RCT Randomized controlled trial

Supplemental Table S2. MINORS score per study

Study	Study design	Comparative or noncomparative	A clearly stated aim	Inclusion of consecutive patients	Prospective collection of data	Endpoint appropriate to the aim of the study	Unbiased assessment of the study endpoint	Follow-up period appropriate to the aim of the study	Loss of follow up less than 5%	Prospective calculation of the study size	Additional criteria for comparative studies: An adequate control group	Contemporary group	Baseline equivalent of groups	Adequate statistical analysis	Total score	out of
Sarmiento *et al*. 2000 [1]	Prospective	Noncomparative	2	2	2	2	1	0	1	1	N.A.	N.A.	N.A.	N.A.	11	16
Chapman *et al*. 2000 [30]	RCT	Comparative	2	2	2	2	1	2	0	1	2	2	2	1	19	24
McCormack *et al*. 2000 [31]	RCT	Comparative	2	2	2	2	1	2	2	1	2	2	2	1	21	24
Paris *et al*. 2000 [32]	Retrospective	Noncomparative	2	2	1	2	1	0	1	1	N.A.	N.A.	N.A.	N.A.	10	16
Tingstad *et al*. 2000 [33]	Retrospective	Noncomparative	2	2	1	2	1	0	0	1	N.A.	N.A.	N.A.	N.A.	9	16
Blum *et al*. 2001 [34]	Prospective	Noncomparative	2	2	2	2	1	2	0	1	N.A.	N.A.	N.A.	N.A.	12	16
Koch *et al*. 2002 [35]	Retrospective	Comparative	2	2	1	2	1	0	0	1	1	2	1	1	14	24
Chaker *et al*. 2003 [36]	Retrospective	Comparative	2	2	1	2	1	2	0	1	2	2	2	1	18	24
Kesemenli *et al*. 2003 [37]	Prospective	Comparative	2	2	2	2	1	2	0	1	1	2	2	1	18	24
Ni *et al*. 2003 [38]	Retrospective	Noncomparative	2	2	1	2	1	2	2	1	N.A.	N.A.	N.A.	N.A.	13	16
Fernandez *et al*. 2004 [39]	Prospective	Noncomparative	2	2	2	1	1	2	1	1	N.A.	N.A.	N.A.	N.A.	12	16
Flinkkila *et al*. 2004 [40]	Retrospective	Comparative	2	2	1	2	1	2	0	1	2	2	2	1	18	24
Livani *et al*. 2004 [41]	Prospective	Noncomparative	2	2	2	1	1	2	2	1	N.A.	N.A.	N.A.	N.A.	13	16
Niall *et al*. 2004 [42]	Retrospective	Noncomparative	2	2	1	2	1	0	1	1	N.A.	N.A.	N.A.	N.A.	10	16
Chao *et al*. 2005 [43]	Retrospective	Comparative	2	2	1	2	1	2	0	1	2	2	2	1	18	24
Kirdemir *et al*. 2005 [44]	Retrospective	Noncomparative	2	2	1	2	1	2	2	1	N.A.	N.A.	N.A.	N.A.	13	16
Toivanen *et al*. 2005 [45]	Retrospective	Noncomparative	2	2	1	2	1	0	2	1	N.A.	N.A.	N.A.	N.A.	11	16
Rosenberg *et al*. 2006 [3]	Prospective	Noncomparative	2	2	2	2	1	2	0	1	N.A.	N.A.	N.A.	N.A.	12	16
Apard *et al*. 2006 [46]	Prospective	Noncomparative	2	1	2	2	1	2	2	1	N.A.	N.A.	N.A.	N.A.	13	16
Ekholm *et al*. 2006 [47]	Retrospective	Comparative	2	2	1	2	1	0	0	1	2	2	2	2	17	24
Hernandez *et al*. 2006 [48]	Retrospective	Noncomparative	2	2	1	2	1	1	1	1	N.A.	N.A.	N.A.	N.A.	11	16
Jawa *et al*. 2006 [49]	Retrospective	Comparative	2	2	1	2	1	2	0	1	2	2	2	2	19	24
Martinez-Diaz *et al*. 2006 [50]	Retrospective	Noncomparative	2	2	1	2	1	2	0	1	N.A.	N.A.	N.A.	N.A.	11	16
Pospula *et al*. 2006 [51]	Retrospective	Noncomparative	2	2	1	1	1	0	2	1	N.A.	N.A.	N.A.	N.A.	10	16

Rochet *et al*. 2006 [52]	Retrospective	Noncomparative	2	2	1	2	1	2	1	1	N.A.	N.A.	N.A.	N.A.	12	16
Rutgers *et al*. 2006 [53]	Retrospective	Noncomparative	2	2	1	2	1	2	1	1	N.A.	N.A.	N.A.	N.A.	12	16
Cuny *et al*. 2007 [54]	Retrospective	Noncomparative	2	2	1	2	1	2	1	1	N.A.	N.A.	N.A.	N.A.	12	16
Jiang *et al*. 2007 [55]	Prospective	Noncomparative	2	2	2	2	1	2	1	1	N.A.	N.A.	N.A.	N.A.	13	16
Numbela *et al*. 2007 [56]	Prospective	Noncomparative	2	1	2	2	1	2	0	1	N.A.	N.A.	N.A.	N.A.	11	16
Ozkurt *et al*. 2007 [57]	Prospective	Noncomparative	2	1	2	2	1	2	0	1	N.A.	N.A.	N.A.	N.A.	11	16
Raghavendra *et al*. 2007 [58]	Prospective	Comparative	2	2	2	2	1	0	2	1	2	2	2	2	20	24
Zhiquan *et al*. 2007 [59]	Prospective	Noncomparative	2	1	2	2	1	2	2	1	N.A.	N.A.	N.A.	N.A.	13	16
Rommens *et al*. 2008 [22]	Retrospective	Noncomparative	2	2	1	2	1	2	1	1	N.A.	N.A.	N.A.	N.A.	12	16
Cheng *et al*. 2008 [60]	RCT	Comparative	2	2	2	2	1	2	2	2	2	2	2	2	23	24
Ekholm *et al*. 2008 [61]	Retrospective	Noncomparative	2	2	1	2	1	2	1	1	N.A.	N.A.	N.A.	N.A.	12	16
Muckley *et al*. 2008 [62]	Prospective	Noncomparative	2	2	2	2	1	2	2	1	N.A.	N.A.	N.A.	N.A.	14	16
An *et al*. 2009 [63]	Retrospective	Comparative	2	2	1	2	1	2	1	1	2	2	2	2	20	24
Apivatthakakul *et al*. 2009 [64]	Retrospective	Noncomparative	2	1	1	2	1	2	1	1	N.A.	N.A.	N.A.	N.A.	11	16
Ji *et al*. 2009 [65]	Retrospective	Noncomparative	2	1	1	2	1	2	2	1	N.A.	N.A.	N.A.	N.A.	12	16
Li *et al*. 2009 [66]	RCT	Comparative	2	2	2	2	2	2	2	1	2	2	2	2	23	24
Putti *et al*. 2009 [67]	RCT	Comparative	2	2	2	2	1	2	0	1	2	2	2	2	20	24
Wang *et al*. 2009 [68]	Retrospective	Comparative	2	2	1	2	1	2	0	1	2	2	2	2	19	24
An *et al*. 2010 [10]	Retrospective	Comparative	2	2	1	2	1	2	2	1	2	2	2	2	21	24
Concha *et al*. 2010 [69]	Prospective	Noncomparative	2	1	2	1	1	2	2	1	N.A.	N.A.	N.A.	N.A.	12	16
Denard *et al*. 2010 [70]	Retrospective	Comparative	2	2	1	2	1	2	0	1	2	2	2	2	19	24
Denies *et al*. 2010 [71]	Retrospective	Comparative	2	2	1	1	1	0	2	1	2	2	2	2	18	24
Kobayashi *et al*. 2010 [72]	Prospective	Noncomparative	2	2	2	2	1	2	2	1	N.A.	N.A.	N.A.	N.A.	14	16
Singisetti *et al*. 2010 [73]	Prospective	Comparative	2	2	2	2	1	2	1	1	2	2	2	0	19	24
Yin *et al*. 2010 [74]	Retrospective	Comparative	2	2	1	2	1	2	2	1	2	2	2	2	21	24
Ziran *et al*. 2010 [75]	Retrospective	Noncomparative	2	2	1	2	1	2	1	1	N.A.	N.A.	N.A.	N.A.	12	16
Algarin-Reyes *et al*. 2011 [76]	Retrospective	Comparative	2	2	1	2	1	1	2	1	2	2	2	2	20	24
Grass *et al*. 2011 [77]	Retrospective	Noncomparative	2	2	1	2	1	2	1	1	N.A.	N.A.	N.A.	N.A.	12	16
Kirin *et al*. 2011 [78]	Retrospective	Noncomparative	2	2	1	2	1	0	0	1	N.A.	N.A.	N.A.	N.A.	9	16
Li *et al*. 2011 [79]	Retrospective	Comparative	2	2	1	2	1	2	2	1	2	2	2	2	21	24
Lopez-Arevalo *et al*. 2011 [80]	Retrospective	Noncomparative	2	2	1	2	1	0	2	1	N.A.	N.A.	N.A.	N.A.	11	16
Prasarn *et al*. 2011 [81]	Retrospective	Noncomparative	2	1	1	2	1	2	1	1	N.A.	N.A.	N.A.	N.A.	11	16
Shetty *et al*. 2011 [82]	Prospective	Noncomparative	2	2	2	2	2	2	2	1	N.A.	N.A.	N.A.	N.A.	15	16
Tsourvakas *et al*. 2011 [83]	Prospective	Noncomparative	2	2	2	2	1	2	1	1	N.A.	N.A.	N.A.	N.A.	13	16
Van Middendorp *et al*. 2011 [84]	Prospective	Comparative	2	1	2	2	1	2	2	2	2	2	2	2	22	24
Brunner *et al*. 2012 [85]	Retrospective	Noncomparative	2	2	1	2	1	2	0	1	N.A.	N.A.	N.A.	N.A.	11	16
Firat *et al*. 2012 [86]	Retrospective	Comparative	2	2	1	2	1	2	1	1	2	2	2	2	20	24
Iacobellis *et al*. 2012 [87]	Prospective	Noncomparative	2	2	2	2	1	2	2	1	N.A.	N.A.	N.A.	N.A.	14	16
Idoine *et al*. 2012 [88]	Retrospective	Noncomparative	2	2	1	2	1	2	1	1	N.A.	N.A.	N.A.	N.A.	12	16
Kulkarni *et al*. 2012 [89]	Retrospective	Comparative	2	1	1	2	1	2	2	1	2	2	1	2	19	24
Kumar *et al*. 2012 [90]	Prospective	Comparative	2	2	2	2	1	2	2	1	2	2	2	0	20	24
Malhan *et al*. 2012 [91]	Prospective	Noncomparative	2	2	2	2	1	2	0	1	N.A.	N.A.	N.A.	N.A.	12	16
Oh *et al*. 2012 [92]	Retrospective	Comparative	2	2	1	2	1	2	1	1	2	1	2	2	19	24
Pagonis *et al*. 2012 [93]	Retrospective	Noncomparative	2	2	1	2	1	2	1	1	N.A.	N.A.	N.A.	N.A.	12	16
Shin *et al*. 2012 [94]	Prospective	Noncomparative	2	1	2	2	1	2	2	1	N.A.	N.A.	N.A.	N.A.	13	16

Supplemental Table S2. MINORS score per study

Study	Study design	Comparative or noncomparative	A clearly stated aim	Inclusion of consecutive patients	Prospective collection of data	Endpoint appropriate to the aim of the study	Unbiased assessment of the study endpoint	Follow-up period appropriate to the aim of the study	Loss of follow up less than 5%	Prospective calculation of the study size	Additional criteria for comparative studies: An adequate control group	Contemporary group	Baseline equivalent of groups	Adequate statistical analysis	Total score	out of
Tan *et al*. 2012 [95]	Retrospective	Noncomparative	2	1	1	2	1	2	0	1	N.A.	N.A.	N.A.	N.A.	10	16
Yang *et al*. 2012 [96]	Prospective	Noncomparative	2	2	2	2	1	2	0	1	N.A.	N.A.	N.A.	N.A.	12	16
Zhou *et al*. 2012 [97]	Retrospective	Noncomparative	2	1	1	2	1	2	1	1	N.A.	N.A.	N.A.	N.A.	11	16
Mahabier *et al*. 2013 [13]	Retrospective	Comparative	2	2	1	2	1	0	0	1	2	2	2	2	17	24
Aydin *et al*. 2013 [98]	Retrospective	Noncomparative	2	2	1	2	1	0	2	1	N.A.	N.A.	N.A.	N.A.	11	16
Biber *et al*. 2013 [99]	Retrospective	Comparative	2	2	1	2	1	0	2	1	2	2	2	2	19	24
Boschi *et al*. 2013 [100]	Retrospective	Noncomparative	2	2	1	2	1	2	2	1	N.A.	N.A.	N.A.	N.A.	13	16
Chen *et al*. 2013 [101]	Retrospective	Noncomparative	2	2	1	2	1	2	1	1	N.A.	N.A.	N.A.	N.A.	12	16
Kapil Mani *et al*. 2013 [102]	Prospective	Noncomparative	2	2	2	2	1	0	1	1	N.A.	N.A.	N.A.	N.A.	11	16
Lee *et al*. 2013 [103]	Prospective	Noncomparative	2	2	2	2	1	2	0	1	N.A.	N.A.	N.A.	N.A.	12	16
Lee *et al*. 2013 [104]	Retrospective	Noncomparative	2	2	1	2	1	2	1	1	N.A.	N.A.	N.A.	N.A.	12	16
Lian *et al*. 2013 [105]	RCT	Comparative	2	2	2	2	1	2	1	1	2	2	2	2	21	24
Sharaby *et al*. 2013 [106]	Prospective	Noncomparative	2	2	2	2	1	2	2	1	N.A.	N.A.	N.A.	N.A.	14	16
Shen *et al*. 2013 [107]	Retrospective	Comparative	2	2	1	2	1	2	1	1	2	2	2	2	20	24
Tyllianakis *et al*. 2013 [108]	Retrospective	Noncomparative	2	2	1	2	1	2	1	1	N.A.	N.A.	N.A.	N.A.	12	16
Verdano *et al*. 2013 [109]	Retrospective	Noncomparative	2	2	1	2	1	2	1	1	N.A.	N.A.	N.A.	N.A.	12	16
Wang *et al*. 2013 [110]	RCT	Comparative	2	2	2	2	1	2	1	1	1	2	2	2	20	24
Yi *et al*. 2013 [111]	Prospective	Noncomparative	2	2	2	2	1	2	1	1	N.A.	N.A.	N.A.	N.A.	13	16
Yin *et al*. 2013 [112]	Retrospective	Noncomparative	2	2	1	2	1	2	1	1	N.A.	N.A.	N.A.	N.A.	12	16
Baltov *et al*. 2014 [5]	Retrospective	Noncomparative	2	2	1	2	1	2	2	1	N.A.	N.A.	N.A.	N.A.	13	16
Balam *et al*. 2014 [113]	Prospective	Noncomparative	2	2	2	2	1	2	2	1	N.A.	N.A.	N.A.	N.A.	14	16
Benegas *et al*. 2014 [114]	RCT	Comparative	2	2	2	2	1	2	2	2	2	2	2	2	23	24
Huri *et al*. 2014 [115]	Retrospective	Noncomparative	2	2	1	2	1	2	0	1	N.A.	N.A.	N.A.	N.A.	11	16
Neuhaus *et al*. 2014 [116]	Retrospective	Noncomparative	2	2	1	2	1	2	2	1	N.A.	N.A.	N.A.	N.A.	13	16
Radulescu *et al*. 2014 [117]	Prospective	Comparative	2	2	2	2	1	0	0	1	2	2	2	1	17	24

Singh *et al*. 2014 [118]	Retrospective	Comparative	2	2	1	2	1	2	2	1	2	2	2	2	21	24
Wali *et al*. 2014 [119]	RCT	Comparative	2	2	2	2	1	0	0	1	2	2	2	1	17	24
Wang *et al*. 2014 [120]	Prospective	Comparative	2	2	2	2	1	2	1	1	2	2	2	2	21	24
Yin *et al*. 2014 [121]	Retrospective	Comparative	2	2	1	2	1	2	2	1	2	2	2	2	21	24
Zogaib *et al*. 2014 [122]	Retrospective	Noncomparative	2	2	1	2	1	2	2	1	N.A.	N.A.	N.A.	N.A.	13	16
Zogbi *et al*. 2014 [123]	Retrospective	Noncomparative	2	2	1	2	1	2	1	1	N.A.	N.A.	N.A.	N.A.	12	16
Chen *et al*. 2015 [11]	Retrospective	Comparative	2	2	1	2	1	2	1	2	2	2	2	2	21	24
Ali *et al*. 2015 [124]	Retrospective	Noncomparative	2	2	1	2	1	0	1	1	N.A.	N.A.	N.A.	N.A.	10	16
Campochiaro *et al*. 2015 [125]	Retrospective	Noncomparative	2	2	1	2	1	2	1	1	N.A.	N.A.	N.A.	N.A.	12	16
Ebrahimpour *et al*. 2015 [126]	Prospective	Noncomparative	2	2	2	2	1	2	2	1	N.A.	N.A.	N.A.	N.A.	14	16
Esmailiejah *et al*. 2015 [127]	Prospective	Comparative	2	2	2	2	1	0	2	1	2	2	2	2	20	24
Fan *et al*. 2015 [128]	RCT	Comparative	2	2	2	2	1	0	0	2	2	2	2	2	19	24
Feng *et al*. 2015 [129]	RCT	Comparative	2	2	2	2	1	2	1	1	2	2	2	2	21	24
Gallucci *et al*. 2015 [130]	Retrospective	Noncomparative	2	2	1	2	1	2	2	1	N.A.	N.A.	N.A.	N.A.	13	16
Hadhoud *et al*. 2015 [131]	RCT	Comparative	2	2	2	2	1	2	0	1	2	2	2	2	20	24
Kim *et al*. 2015 [132]	Retrospective	Noncomparative	2	2	1	2	1	2	1	1	N.A.	N.A.	N.A.	N.A.	12	16
Koca *et al*. 2015 [133]	Retrospective	Noncomparative	2	2	1	2	1	2	0	1	N.A.	N.A.	N.A.	N.A.	11	16
Kumar *et al*. 2015 [134]	Prospective	Noncomparative	2	2	2	2	1	2	0	1	N.A.	N.A.	N.A.	N.A.	12	16
Modi *et al*. 2015 [135]	RCT	Comparative	2	2	2	2	1	2	1	1	2	2	2	0	19	24
Patino *et al*. 2015 [136]	Retrospective	Noncomparative	2	2	1	2	1	2	1	1	N.A.	N.A.	N.A.	N.A.	12	16
Reddy *et al*. 2015 [137]	Prospective	Noncomparative	2	2	2	2	1	1	0	1	N.A.	N.A.	N.A.	N.A.	11	16
Sahu *et al*. 2015 [138]	Prospective	Noncomparative	2	2	2	2	1	0	2	1	N.A.	N.A.	N.A.	N.A.	12	16
Sanjeevaiah *et al*. 2015 [139]	Prospective	Noncomparative	2	2	2	2	1	2	2	1	N.A.	N.A.	N.A.	N.A.	14	16
Shields *et al*. 2015 [140]	Retrospective	Noncomparative	2	2	1	2	1	2	1	1	N.A.	N.A.	N.A.	N.A.	12	16
Singhal *et al*. 2015 [141]	Retrospective	Noncomparative	2	2	1	2	1	1	2	1	N.A.	N.A.	N.A.	N.A.	12	16
Srinivas *et al*. 2015 [142]	Prospective	Noncomparative	2	2	2	2	1	1	0	1	N.A.	N.A.	N.A.	N.A.	11	16
Wang *et al*. 2015 [143]	Prospective	Comparative	2	2	2	2	1	2	1	2	2	2	2	2	22	24
Abril Goano *et al*. 2016 [144]	Prospective	Noncomparative	2	2	2	2	1	1	0	1	N.A.	N.A.	N.A.	N.A.	11	16
Anand Kumar *et al*. 2016 [145]	Prospective	Noncomparative	2	2	2	2	1	2	2	1	N.A.	N.A.	N.A.	N.A.	14	16
Gang *et al*. 2016 [146]	Retrospective	Comparative	2	2	1	2	1	2	0	1	2	2	1	0	16	24
Guzmán-Guevara *et al*. 2016 [147]	Prospective	Comparative	2	2	2	2	1	2	2	1	2	2	2	1	21	24
Karunanithi *et al*. 2016 [148]	Prospective	Noncomparative	2	2	2	2	1	2	0	1	N.A.	N.A.	N.A.	N.A.	12	16
Kumar *et al*. 2016 [149]	Prospective	Comparative	2	2	2	2	1	0	0	1	2	2	2	2	18	24
Lee *et al*. 2016 [150]	Retrospective	Noncomparative	2	2	1	2	1	2	1	1	N.A.	N.A.	N.A.	N.A.	12	16
Lee *et al*. 2016 [151]	Retrospective	Comparative	2	2	1	2	1	2	2	1	2	2	2	2	21	24
Lu *et al*. 2016 [152]	Retrospective	Comparative	2	2	1	2	1	2	0	1	2	2	2	1	18	24
Mahajan *et al*. 2016 [153]	Prospective	Noncomparative	2	2	2	2	1	2	1	1	N.A.	N.A.	N.A.	N.A.	13	16
Mehmood *et al*. 2016 [154]	RCT	Comparative	2	2	2	2	1	1	0	1	2	2	2	2	19	24
Wahed *et al*. 2016 [155]	Prospective	Noncomparative	2	2	2	2	1	2	0	1	N.A.	N.A.	N.A.	N.A.	12	16
Bisaccia *et al*. 2017 [156]	Retrospective	Comparative	2	2	1	2	1	2	0	1	2	2	2	2	19	24
Dielwart *et al*. 2017 [157]	Retrospective	Comparative	2	2	1	2	1	2	1	1	2	2	2	2	20	24
Duygun *et al*. 2017 [158]	Prospective	Noncomparative	2	2	2	2	1	2	2	1	N.A.	N.A.	N.A.	N.A.	14	16
Harkin *et al*. 2017 [159]	Retrospective	Comparative	2	2	1	2	1	1	1	1	2	2	2	2	19	24
Ko *et al*. 2017 [160]	Retrospective	Comparative	2	1	1	2	1	2	0	1	2	2	2	2	18	24
Matsunaga *et al*. 2017 [161]	RCT	Comparative	2	2	2	2	2	2	1	2	2	2	2	2	23	24

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Supplemental Table S2. MINORS score per study

Study	Study design	Comparative or noncomparative	A clearly stated aim	Inclusion of consecutive patients	Prospective collection of data	Endpoint appropriate to the aim of the study	Unbiased assessment of the study endpoint	Follow-up period appropriate to the aim of the study	Loss of follow up less than 5%	Prospective calculation of the study size	Additional criteria for comparative studies: An adequate control group	Contemporary group	Baseline equivalent of groups	Adequate statistical analysis	Total score	out of
ShengWei *et al*. 2017 [162]	Retrospective	Comparative	2	2	1	2	1	2	0	1	2	2	2	2	19	24
Crespo *et al*. 2018 [163]	Retrospective	Noncomparative	2	2	1	2	1	2	2	1	N.A.	N.A.	N.A.	N.A.	13	16
Goncalves *et al*. 2018 [164]	Retrospective	Comparative	2	2	1	2	1	2	1	1	2	2	1	2	19	24
Ferrara *et al*. 2019 [165]	Retrospective	Noncomparative	2	2	1	2	1	2	1	1	N.A.	N.A.	N.A.	N.A.	12	16
Hosseini Khameneh *et al*. 2019 [166]	RCT	Comparative	2	2	2	2	1	2	0	1	2	2	2	2	20	24
Mehraj *et al*. 2019 [167]	Prospective	Noncomparative	2	2	2	2	1	2	0	1	N.A.	N.A.	N.A.	N.A.	12	16
Pooja *et al*. 2019 [168]	RCT	Comparative	2	2	2	2	2	2	2	1	2	2	2	2	23	24
Seo *et al*. 2019 [169]	Prospective	Comparative	2	2	2	2	1	2	2	1	2	2	2	2	22	24
Vidovic *et al*. 2019 [170]	Retrospective	Noncomparative	2	2	1	2	1	1	0	1	N.A.	N.A.	N.A.	N.A.	10	16
Wang *et al*. 2019 [171]	Retrospective	Comparative	2	2	1	2	2	2	0	1	2	2	2	2	20	24
Yuan *et al*. 2019 [172]	Retrospective	Comparative	2	2	1	2	1	2	0	1	2	2	2	2	19	24
Li *et al*. 2020 [7]	Retrospective	Comparative	2	2	1	2	1	0	0	1	2	2	2	2	17	24
Akalin *et al*. 2020 [173]	RCT	Comparative	2	2	2	2	1	2	2	1	2	2	2	2	22	24
Desai *et al*. 2020 [174]	RCT	Comparative	2	2	2	2	1	1	0	1	2	2	2	2	19	24
Hendy *et al*. 2020 [175]	Retrospective	Comparative	2	2	1	2	1	2	1	1	2	2	2	2	20	24
Huichao *et al*. 2020 [176]	Retrospective	Comparative	2	2	1	2	1	2	0	1	2	2	2	1	18	24
Hussain *et al*. 2020 [177]	RCT	Comparative	2	2	2	2	1	1	0	1	2	2	2	1	18	24
Omrani *et al*. 2020 [178]	RCT	Comparative	2	2	2	2	1	2	0	1	2	2	2	2	20	24
Rai *et al*. 2020 [179]	Prospective	Noncomparative	2	2	2	2	1	2	0	1	N.A.	N.A.	N.A.	N.A.	12	16
Rämö *et al*. 2020 [180]	RCT	Comparative	2	2	2	2	1	2	1	2	2	2	2	2	22	24
Sharma *et al*. 2020 [181]	RCT	Comparative	2	2	2	2	1	2	2	1	2	2	2	2	22	24
Varghese *et al*. 2020 [182]	Prospective	Noncomparative	2	2	2	2	1	2	2	1	N.A.	N.A.	N.A.	N.A.	14	16

Wang *et al*. 2020 [183]	Retrospective	Comparative	2	2	1	2	1	2	0	1	2	2	2	2	19	24
Wang *et al*. 2020 [184]	Prospective	Comparative	2	2	2	2	1	2	1	1	2	2	2	2	21	24
Yiğit *et al*. 2020 [185]	Retrospective	Noncomparative	2	2	1	2	1	2	0	1	N.A.	N.A.	N.A.	N.A.	11	16
Zhang *et al*. 2020 [186]	Retrospective	Comparative	2	2	1	2	1	2	0	1	2	2	2	2	19	24
Cannada *et al*. 2021 [187]	Prospective	Comparative	2	2	2	2	1	2	1	2	2	2	2	2	22	24
Capitani *et al*. 2021 [188]	Prospective	Noncomparative	2	2	2	2	1	2	2	1	N.A.	N.A.	N.A.	N.A.	14	16
Furuhata *et al*. 2021 [189]	Retrospective	Comparative	2	2	1	2	1	1	0	1	2	2	2	2	18	24
Huang *et al*. 2021 [190]	Retrospective	Comparative	2	2	1	2	1	2	0	1	2	2	2	2	19	24
Kumar *et al*. 2021 [191]	Prospective	Noncomparative	2	2	2	2	1	1	0	1	N.A.	N.A.	N.A.	N.A.	11	16
Mohammed *et al*. 2021 [192]	Prospective	Comparative	2	2	2	2	1	1	0	1	2	2	2	1	18	24
Patino *et al*. 2021 [193]	Retrospective	Comparative	2	2	1	2	1	2	0	1	2	2	2	2	19	24
Rellán *et al*. 2021 [194]	Retrospective	Comparative	2	2	1	2	1	2	0	1	2	2	2	2	19	24

N.A. not applicable, RCT Randomized controlled trial

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Supplemental Table S3. Complication rates of (treatment of) a humeral shaft fracture per treatment group

	Treatment		Study arms *N*	Population *N*	Cases *N*	Heterogeneity Cochran's Q (p-value)	Heterogeneity I^2 (%) (95% CI)	Pooled value (%) (95% CI)
Shoulder dysfunction[a] 30, 32, 34, 50, 66, 67, 73, 75, 84, 86, 90, 114, 119, 136-138, 141, 147, 149, 165, 174, 177, 181, 183, 184, 191	**Nonoperative**		3	122	9	17 (<0.001)	88 (67-96)	9 (0-29)
	IMN		22	693	74	43 (<0.001)	52 (21-70)	11 (8-15)
		Antegrade	19	563	70	28 (0.061)	37 (0-64)	13 (10-16)
		Retrograde	2	46	2	2 (0.196)	40 (0-0)	5 (1-15)
	Plate		15	560	34	24 (0.048)	41 (0-68)	5 (3-8)
		ORPO	12	477	30	20 (0.048)	44 (0-72)	5 (3-9)
		MIPO	3	83	4	4 (0.148)	48 (0-85)	5 (1-12)
Nail protrusion[b] 5, 31, 38, 43, 46, 48, 50, 52, 54, 58, 67, 84, 86, 87, 105, 108, 158	**Nonoperative**		N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
	IMN		17	666	61	40 (<0.001)	60 (32-77)	10 (6-14)
		Antegrade	11	404	31	27 (0.002)	63 (30-81)	9 (5-14)
		Retrograde	2	83	4	0 (0.866)	0 (0-0)	6 (2-13)
	Plate		N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
		ORPO	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
		MIPO	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
Subacromial impingement[c] 37, 50, 58, 60, 86, 90, 97, 112, 119, 135-137, 158, 162, 183, 186	**Nonoperative**		N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
	IMN		17	500	67	33 (0.007)	52 (16-72)	14 (10-19)
		Antegrade	15	432	55	29 (0.012)	51 (11-73)	13 (9-18)
		Retrograde	0	N.A.	N.A.	N.A.	N.A.	N.A.
	Plate		10	368	5	8 (0.507)	0 (0-59)	2 (1-3)
		ORPO	8	264	1	3 (0.903)	0 (0-20)	1 (0-3)
		MIPO	2	104	4	2 (0.142)	54 (0-89)	4 (1-10)
(Sub)cutaneous[d] 35, 49, 53, 57, 84, 86, 140, 161, 180	**Nonoperative**		9	347	20	14 (0.087)	42 (0-73)	6 (4-9)
	IMN		1	N.A.	N.A.	N.A.	N.A.	N.A.
		Antegrade	1	N.A.	N.A.	N.A.	N.A.	N.A.
		Retrograde	0	N.A.	N.A.	N.A.	N.A.	N.A.
	Plate		10	387	8	11 (0.310)	14 (0-56)	2 (1-4)
		ORPO	7	255	3	6 (0.374)	7 (0-73)	1 (0-4)
		MIPO	3	132	5	1 (0.743)	0 (0-89)	5 (2-10)

95% CI 95% Confidence interval, IMN Intramedullary nailing, MIPO Minimally invasive plate osteosynthesis, N.A. not applicable, ORPO Open reduction plate osteosynthesis

[a] Shoulder dysfunction was defined as experiencing pain or limited range of motion of the shoulder

[b] Nail protrusion was defined as migration and subsequent protrusion of the intramedullary nail

[c] Subacromial impingement was defined as irritation of the rotator cuff muscles in the subacromial space

[d] (Sub)cutaneous problems included but were not limited to bursitis, cellulitis, granuloma's, hypertrophic scarring of the wound, and skin irritation, macerations, or abrasions due to prolonged contact with the brace

Supplemental Table S4. Functional outcome scores after treatment of a humeral shaft fracture per treatment group

Instrument	Treatment		Study arms *N*	Population *N*	Heterogeneity Cochran's Q (p-value)	Heterogeneity I^2 (%) (95% CI)	Pooled value (points) (95% CI)
ASES score[a] 7, 110, 115, 128, 143, 160, 183, 184	**Nonoperative**		0	N.A.	N.A.	N.A.	N.A.
	IMN		5	125	13 (0.001)	70 (24-88)	91 (90-93)
		Antegrade	5	125	13 (0.001)	70 (24-88)	91 (90-93)
		Retrograde	0	N.A.	N.A.	N.A.	N.A.
	Plate		10	242	158 (<0.001)	94 (91-96)	92 (91-94)
		ORPO	7	163	127 (<0.001)	95 (92-97)	93 (92-95)
		MIPO	3	79	30 (<0.001)	93 (84-97)	91 (89-94)
MEPI[b] 10, 11, 60, 66, 79, 107, 115, 118, 121, 123, 127, 131, 146, 151, 153, 172, 183	**Nonoperative**		0	N.A.	N.A.	N.A.	N.A.
	IMN		6	487	949 (<0.001)	99 (99-100)	95 (92-98)
		Antegrade	5	442	928 (<0.001)	100 (99-100)	95 (91-98)
		Retrograde	1	N.A.	N.A.	N.A.	N.A.
	Plate		23	914	2087 (<0.001)	99 (99-99)	94 (93-96)
		ORPO	14	520	369 (<0.001)	96 (95-97)	95 (94-96)
		MIPO	9	394	453 (<0.001)	98 (98-99)	95 (91-98)
Pain (VAS)[c] 161, 183, 184, 192	**Nonoperative**		0	N.A.	N.A.	N.A.	N.A.
	IMN		3	69	119 (<0.001)	98 (97-99)	2 (0-4)
		Antegrade	3	69	119 (<0.001)	98 (97-99)	2 (0-4)
		Retrograde	0	N.A.	N.A.	N.A.	N.A.
	Plate		3	107	485 (<0.001)	100 (99-100)	2 (0-5)
		ORPO	2	77	5 (0.025)	80 (14-95)	1 (0-1)
		MIPO	1	30	N.A.	N.A.	N.A.

95% CI 95% Confidence interval, ASES American Shoulder and Elbow Surgeons, IMN Intramedullary nailing, MEPI Mayo Elbow Performance Index, MIPO Minimally invasive plate osteosynthesis, N.A. not applicable, ORPO Open reduction plate osteosynthesis, VAS Visual Analog Scale

[a] The American Shoulder and Elbow Surgeons (ASES) score ranges from 0 to100 points, with a higher score representing better outcome[200]

[b] The Mayo Elbow Performance Index (MEPI) ranges from 5 to 100 points, with a higher score representing better outcome[201]

[c] The level of pain was measured with a Visual Analog Scale (VAS), ranging from 0 to 10 points, with a higher score representing more pain

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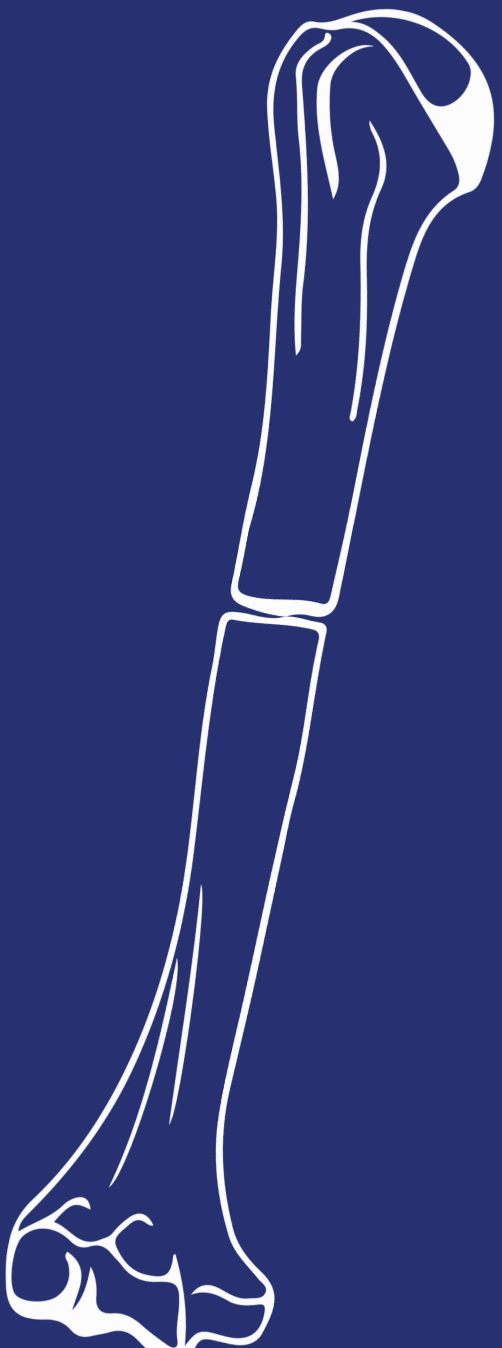

PART 3

Functional and clinical outcomes

Chapter 3
Functional and clinical outcome after operative versus nonoperative treatment of a humeral shaft fracture (HUMMER): results of a multicenter prospective cohort study
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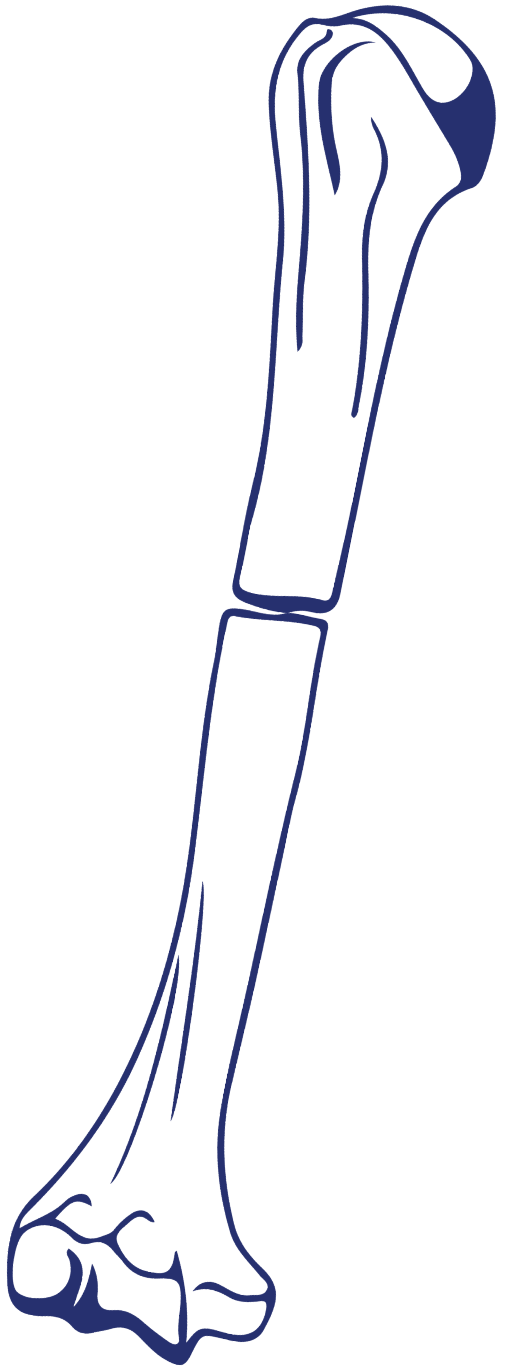
Journal of Shoulder and Elbow Surgery International



CHAPTER 3

Functional and clinical outcome after operative versus nonoperative treatment of a humeral shaft fracture (HUMMER): results of a multicenter prospective cohort study

European Journal of Trauma and Emergency Surgery 2022

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ABSTRACT

Purpose: The best treatment of humeral shaft fractures in adults is still under debate. This study aimed to compare functional and clinical outcome of operative versus nonoperative treatment in adult patients with a humeral shaft fracture. We hypothesized that operative treatment would result in earlier functional recovery.

Methods: From October 23, 2012 to October 03, 2018, adults with a humeral shaft fracture AO type 12A or 12B were enrolled in a prospective cohort study in 29 hospitals. Patients were treated operatively or nonoperatively. Outcome measures were the Disabilities of the Arm, Shoulder, and Hand score (DASH; primary outcome), Constant–Murley score, pain (Visual Analog Score, VAS), health-related quality of life (Short Form-36 (SF-36) and EuroQoL-5D-3L (EQ-5D)), activity resumption (Numeric Rating Scale, NRS), range of motion (ROM) of the shoulder and elbow joint, radiologic healing, and complications. Patients were followed for one year. Repeated measure analysis was done with correction for age, gender, and fracture type.

Results: Of the 390 included patients, 245 underwent osteosynthesis and 145 were primarily treated nonoperatively. Patients in the operative group were younger (median 53 versus 62 years; $p < 0.001$) and less frequently female (54.3% versus 64.8%; $p = 0.044$). Superior results in favor of the operative group were noted until six months follow-up for the DASH, Constant–Murley, abduction, anteflexion, and external rotation of the shoulder, and flexion and extension of the elbow. The EQ-US, and pronation and supination showed superior results for the operative group until six weeks follow-up. Malalignment occurred only in the nonoperative group ($N = 14$; 9.7%). In 19 patients with implant-related complications ($N = 26$; 10.6%) the implant was exchanged or removed. Nonunion occurred more often in the nonoperative group (26.3% versus 10.10% in the operative group; $p < 0.001$).

Conclusion: Primary osteosynthesis of a humeral shaft fracture (AO type 12A and 12B) in adults is safe and superior to nonoperative treatment, and should therefore be the treatment of choice. It is associated with a more than twofold reduced risk of nonunion, earlier functional recovery and a better range of motion of the shoulder and elbow joint than nonoperative treatment. Even after including the implant-

related complications, the overall rate of complications as well as secondary surgical interventions was highest in the nonoperative group.

Trial registration: NTR3617 (registration date 18-SEP-2012).

BACKGROUND

Humeral shaft fractures account for 1–3% of all fractures.[1] The incidence rate is 14.5 per 100,000 persons per year with a gradually increasing age-specific incidence from the fifth decade, reaching almost 60/100,000 per year in the ninth decade.[1]

Last decade, the optimal treatment for humeral shaft fractures was subject to debate. A recent meta-analysis shows that satisfactory results can be achieved with both nonoperative and operative management.[2] The meta-analysis of data from randomized controlled trials (RCTs) in their review showed no statistically significant differences in favor of either one of the treatment options. Operative and nonoperative treatment each have their individual advantages and disadvantages. Surgical treatment is mostly performed using intramedullary nailing or plating, and the mostly used nonoperative treatment is immobilization with a functional (Sarmiento) brace or a cast.[3] Fracture fixation allows for early mobilization, and is aimed to achieve earlier functional recovery. A disadvantage is the risk of surgical complications.[4] Nonoperative treatment is aimed to achieve secondary bone healing by temporary immobilization of the arm. This initially results in functional impairment and may delay functional recovery. Moreover, the indirect fracture stabilization and risk of inadequate fracture alignment may increase the risk of malunion and nonunion.[5, 6] Nonunion occurs in up to 10% of patients treated operatively and in up to 23% of patients treated nonoperatively.[2, 5, 6] A complication that may occur after a humeral shaft fracture is radial nerve palsy. A systematic review reported an average radial nerve palsy rate at presentation of 11.8% in 4517 patients.[7] The reported rate of radial nerve palsy due to surgery was 3.5%.[2]

The finding that the rate of surgical treatment was approximately 50% across all AO fracture subtypes indicates that consensus on the best treatment strategy for humeral shaft fractures was lacking at the time the study was designed.[8] Lack of confirmative evidence about the best treatment strategy was also concluded in a Cochrane review.[9] A survey among members of the British Elbow and Shoulder Society in 2021 concluded that the management preference for humeral shaft fractures among surgeons is highly variable, and that this may be partly attributed to the sparsity of high-quality evidence. They proposed that well-designed prospective cohort studies or randomized trials may guide further management of these injuries.[10] The current study was designed to provide such high-quality evidence. We hypothesized that operative treatment would result in earlier functional recovery.

The primary objective of this study was to examine the effect of operative versus nonoperative treatment on the Disabilities of the Arm, Shoulder, and Hand (DASH) score, reflecting functional outcome and pain of the upper extremity, in adult patients who sustained a humeral shaft fracture. Secondary aims were to examine the effect of treatment on functional outcome (Constant–Murley) score, level of pain, range of motion of the shoulder and elbow joint, occurrence of complications with associated interventions, health-related quality of life, and the time to resumption of work and activities of daily living in these patients.

METHODS

Setting and participants

The HUMMER study was a multicenter, parallel group cohort study, conducted in 29 hospitals in The Netherlands. All persons aged 18 years or older presenting to the Emergency Department (ED) with a humeral shaft fracture (AO type 12A or 12B on plain radiographs) were eligible for inclusion.[11] Primary osteosynthesis had to be performed within 14 days after presentation to the ED. Patients were excluded if they had (1) concomitant injuries affecting treatment and rehabilitation of the affected arm; (2) a humeral fracture treated with an external fixator; (3) a pathological, recurrent, or open humeral shaft fracture; (4) neurovascular injuries requiring immediate surgery (excluding radial nerve palsy); (5) additional traumatic injuries of the affected arm that would influence upper extremity function; (6) an impaired upper extremity function prior to the injury; (7) retained hardware around the affected humerus; (8) rheumatoid arthritis; or (9) a bone disorder which would impair bone healing (excluding osteoporosis). Patients with expected problems in maintaining follow-up or with insufficient Dutch language proficiency were also excluded. Exclusion of a patient because of enrollment in another drug or surgical intervention trial was left to the discretion of the attending surgeon on a case-by-case basis. The study was exempted by the Medical Research Ethics Committees and Local Ethics Boards of all participating centers. The study protocol is available online.[12]

Treatment allocation and masking

Eligible patients were informed about the study after presentation to the ED and could be enrolled until their first outpatient department visit 14 days after trauma. Patients were treated operatively or nonoperatively, as per decision of the patient and treating surgeon. All surgeons were certified (orthopedic) trauma surgeons with extensive experience in fracture care. Plaster casts or braces were applied by experienced orthopedic or plaster technicians.

Masking participants or investigators for treatment was not possible. To reduce bias, the follow-up measurements were standardized. Radiographs were evaluated independently by two assessors (IB and DDH). In case of disagreement, consensus was reached after discussion.

Intervention

If a surgeon decided to perform osteosynthesis, the approach for fracture reduction (open or closed), fixation (antegrade or retrograde nailing, or open or minimally invasive plate osteosynthesis), the type and brand of the materials as well as the use of cerclage wires and other add-ons were left to the surgeon. Critical elements of this treatment (*e.g.*, type of implant, surgical approach, operative delay, and duration of surgery) were recorded.

The type of nonoperative treatment was also left to the attending surgeon. Usually it consisted of a splint, collar and cuff or (hanging) cast for 1–2 weeks, followed by a Sarmiento brace for 4–6 weeks. Critical elements of this treatment were also recorded.

Due to a lack of evidence favoring a particular approach, the physical therapy and rehabilitation program was recorded but not standardized.

Assessments and follow-up

Follow-up data were obtained during outpatient visits at two weeks (7–21 days window), six weeks (4–8 weeks window), three months (11–15 weeks window), six months (6–7 months window), and 12 months (12–14 months window) after start of treatment. At each visit, the investigators recorded clinical data from the patient files (*e.g.*, complications and treatment) and measured the range of motion of the shoulder and elbow. At each visit, patients were asked to complete a set questionnaires on their level of pain, functional recovery, activity resumption, and health-related quality of life (HR-QoL). From six weeks onwards, the investigators determined the Constant–Murley score. As part of routine care, anterior–posterior and lateral radiographs of the humerus were made at the time of hospital presentation, after reduction, and at each subsequent hospital visit.

The primary outcome measure was the Disabilities of the Arm, Shoulder and Hand (DASH) score.[13, 14] Secondary outcome measures were the Constant–Murley score[15], level of pain (Visual Analog Scale, VAS), analgesic drugs used, Range of Motion (ROM) of the shoulder and elbow joint, time to resumption of work, resumption of activities of daily living (Numeric Rating Scale, NRS), health-related quality of life (Short Form-36 Physical Component Summary (SF-36 PCS) and Mental Component Summary (SF-36 MCS), and EuroQoL-5D-3L Utility Score (EQ-5D US) and Visual Analog Scale (EQ-5D VAS))[16-18], the occurrence of complications with associated secondary interventions, and radiologic healing. Nonunion is defined as a failure to heal at 26 weeks post fracture with no progress toward healing seen on the most recent radiographs.[19] This was determined from radiographs by two experienced trauma surgeons independently. ROM was measured by trained research physicians or research assistants using a goniometer and a standardized protocol. The patient-reported outcome measures were all available in Dutch and were proven reliable, valid, and responsive in the studied population.[20,21] A detailed description of these questionnaires can be found in the published study protocol.[12]

At baseline, patient characteristics, such as age, gender, American Society of Anesthesiologists' (ASA) classification, smoking, comorbidities, dominant side, medication use, and work and sports participation pre-trauma, were collected. Also, injury-related variables (such as the affected side, mechanism of injury, and fracture classification (according to the AO classification system)[11], and additional injuries) were recorded.

Statistical analysis

Sample size calculation for the primary analysis was based on the assumption that the mean DASH in the nonoperative group would be 16, with a Standard Deviation

(SD) of 16.[22] We expected a DASH score of 10 (SD 10) in the operative group at three months.[22] A two-sided test with an α level of 0.05 and a β level of 0.2 required 78 patients in both treatment groups. To account for loss of patients due to mortality (10%) and loss to follow-up (10% anticipated based upon previous studies by the research team), a sample size of 95 patients per group would suffice. To allow for subgroup analysis for the most common AO fracture subtypes, 400 patients were targeted. This was based on the relative occurrences of the AO fracture subtypes as found in a retrospective study.[8]

Analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 25. Analysis was by intention to treat and all statistical tests were two-sided. The study is registered at the Netherlands Trial Register (NTR3617). Missing data were not imputed. Normality of continuous data was assessed using the Shapiro–Wilk test, and homogeneity of variances across groups was tested with the Levene's test. Chi-squared analysis was used for statistical testing of categorical data. Continuous data were analyzed using a Mann–Whitney *U* test. P values < 0.05 were regarded as statistically significant.

Continuous outcomes that were repeatedly measured over time were compared between treatment groups using linear mixed-effects regression models. These multilevel models included random effects for the intercepts of the model and time coefficient of individual patients. Since the outcome measures were not linearly related with time, the time points were entered as factor. The models included fixed effects for treatment group, age, gender, and the individual fracture types. The effect of a fracture at the dominant side, smoking, and radial nerve palsy at trauma was non-significant in all models and these covariates were therefore not included. As most participating hospitals used both treatment strategies, study site was also not included in the model. The interaction between treatment group and time was included in the model to test for differences between the groups over time. For each follow-up moment, the estimated marginal mean was computed per treatment group and compared post hoc using a Bonferroni test to correct for multiple testing. Absence of overlap in the 95% confidence interval around the marginal means was regarded as significant at $p < 0.05$.

RESULTS

Patient and injury characteristics

Between October 23, 2012 and October 03, 2018, 466 patients were screened for eligibility, of whom 390 were included. Main exclusion reasons were an impaired arm function before trauma (*N* = 9), expected problems with follow-up (*N* = 7), and rheumatoid arthritis (*N* = 7). Twenty patients declined to participate, and 23 were screened too late and were thus recorded as missed. Of the included patients, 245 were operated and 145 underwent nonoperative treatment (Fig. 1). All patients received the allocated treatment. Twenty patients were lost to follow-up due to mortality (*N* = 4) or withdrawal of consent (nine in the operative group and seven in the nonoperative group). Thirty-five in the operative group and 20 patients in the nonoperative group did not show up at least one follow-up visit (Fig.1).

The two treatment groups had similar baseline and injury characteristics, except for a relative underrepresentation of females (*N* = 133 (54.3%) versus *N* = 94 (64.8%); $p = 0.044$) and patients with osteoporosis or osteopenia (*N* = 1 (0.4%) versus *N* = 5 (3.4%); $p = 0.028$), and a lower median age (53 (P_{25}–P_{75} 35–66) versus 62 (P_{25}–P_{75} 49–71) years; $p < 0.001$) in the operative group (Table 1). Fractures in the operative group were less often A1 (*N* = 57 (23.3%) versus *N* = 51 (35.2%)) or B1 (*N* = 51 (20.8%) versus *N* = 42 (29.0%)), and more often A3 (*N* = 71 (29.0%) versus *N* = 18 (12.4%); $p = 0.002$).

Treatment details and hospital admission

Osteosynthesis was performed by 121 surgeons, with 74 surgeons performing only one operation, and seven surgeons performing between five and 13 operations. Surgery was performed after a median of 6 (P_{25}–P_{75} 2–9) days, with a median duration of surgery of 81 (P_{25}–P_{75} 65–112) minutes. Intramedullary nailing was used in most patients (*N* = 169; 69.0%). In 158 (93.5%) of them, an antegrade nail was used. Seventy-six (31.0%) patients were treated using plate fixation. After a median stay of 2 (P_{25}–P_{75} 2–4) days, the vast majority of operated patients (*N* = 235; 95.6%) were discharged home.

Fracture immobilization in the nonoperative group was performed using a brace (N=68; 46.9%) or cast (N=21; 14.5%). In 56 (38.6%), only a sling or collar and cuff were used. Twenty-six (17.9%) patients required hospital admission (Table 1). After a median stay of 2 (P_{25}–P_{75} 2–3) days, most patients (N=23; 88.5%) were discharged home. Hospital stay and subsequent stay in a nursing home, care hotel, elderly care facility, or rehabilitation center did not differ significantly between the two treatment groups. Likewise, patient in both groups had a similar number of physical therapy sessions; 217 (88.6%) and 120 (82.8%) patients in the operative and nonoperative group had physical therapy, respectively.

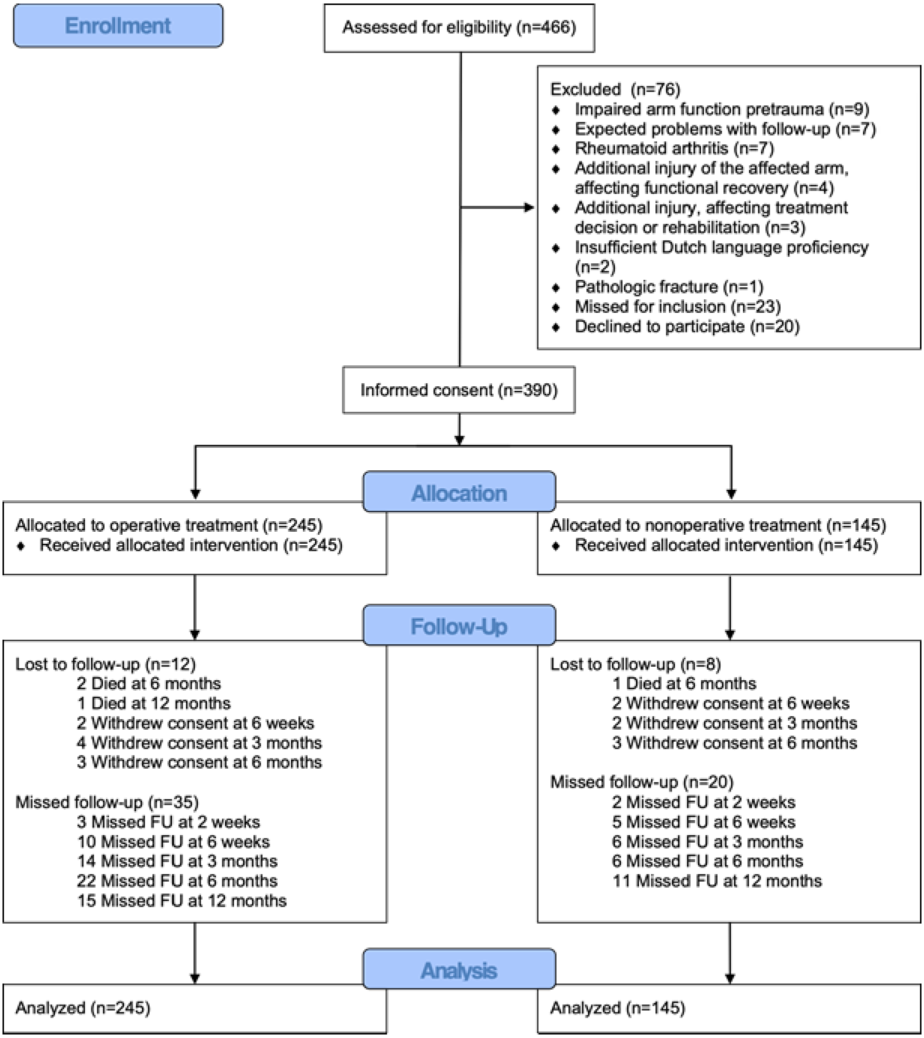

Fig. 1 Flow chart of the study

Table 1. Patient, injury, treatment, and admission details of study participants by treatment group

	*N**	**All (*N*=390)**	*N**	**Operative (*N*=245)**	*N**	**Nonoperative (*N*=145)**	***P* value**
Patient characteristics							
Female	390	227 (58.2%)	245	133 (54.3%)	145	94 (64.8%)	**0.044**
Age (year)	390	57 (40-68)	245	53 (35-66)	145	62 (49-71)	**< 0.001**
BMI (kg/m^2)	387	26.0 (23.4-29.7)	244	26.1 (23.4-29.9)	143	25.8 (23.4-29.6)	0.928
Smoking	390	81 (20.8%)	245	55 (22.4%)	145	26 (17.9%)	0.304
ASA 3 or 4	390	25 (6.4%)	245	13 (5.3%)	145	12 (8.3%)	0.286
Comorbidities							
Any	390	198 (50.8%)	245	115 (46.9%)	145	83 (57.2%)	0.059
Diabetes	390	30 (7.7%)	245	18 (7.3%)	145	12 (8.3%)	0.844
Osteoarthritis	390	32 (8.2%)	245	15 (6.1%)	145	17 (11.7%)	0.058
Osteoporosis/osteopenia	390	6 (1.5%)	245	1 (0.4%)	145	5 (3.4%)	**0.028**
Medication use	390	208 (53.3%)	245	127 (51.8%)	145	81 (55.9%)	0.463
Number of medications	208	3 (1-5)	127	2 (1-4)	81	3 (1-5)	0.225
Injury characteristics							
Dominant side affected	390	189 (48.5%)	245	116 (47.3%)	145	73 (50.3%)	0.601
Fracture classification							
A1	390	108 (27.7%)	245	57 (23.3%)	145	51 (35.2%)	**0.002**
A2		66 (16.9%)		43 (17.6%)		23 (15.9%)	
A3		89 (22.8%)		71 (29.0%)		18 (12.4%)	
B1		93 (23.8%)		51 (20.8%)		42 (29.0%)	
B2		15 (3.8%)		10 (4.1%)		5 (3.4%)	
B3		19 (4.9%)		13 (5.3%)		6 (4.1%)	
Radial nerve palsy at presentation	390	16 (4.1%)	245	13 (5.3%)	145	3 (2.1%)	0.185
Additional injuries	390	37 (9.5%)	245	26 (10.6%)	145	11 (7.6%)	0.374
Ipsilateral arm	390	7 (1.8%)	245	6 (2.4%)	145	1 (0.7%)	0.266
Contralateral arm	390	5 (1.3%)	245	4 (1.6%)	145	1 (0.7%)	0.655

Admission and follow-up characteristics							
Hospital							
Admission	390	271 (69.5%)	245	245 (100.0%)	145	26 (17.9%)	**< 0.001**
LOS (days)	271	2 (2-4)	245	2 (2-4)	26	2 (2-3)	0.830
Discharge disposition							
Home	271	258 (95.2%)	245	235 (95.9%)	26	23 (88.5%)	0.093
Care hotel		8 (3.0%)		6 (2.4%)		2 (7.7%)	
Elderly care facility		2 (0.7%)		1 (0.4%)		1 (3.8%)	
Rehabilitation center		3 (1.1%)		3 (1.2%)		0 (0.0%)	
Other care facility admission	390	13 (3.3%)	245	8 (3.3%)	145	5 (3.4%)	1.000
Nursing home, LOS (days)	1	30 (30-30)	1	30 (30-30)	0	N.A.	N.A.
Care hotel, LOS (days)	7	10 (5-30)	4	8 (5-25)	3	21 (3-21)	0.721
Elderly care facility, LOS (days)	4	35 (23-84)	1	21 (21-21)	3	42 (28-42)	0.180
Rehabilitation clinic, LOS (days)	3	25 (24-25)	3	25 (24-25)	0	N.A.	N.A.
Physical therapy (number of sessions)	337	24 (12-45)	217	25 (13-48)	120	22 (12-42)	0.307

P-values <0.05 are shown in boldface

Data are presented as *N* (%) or median (P_{25}–P_{75})

ASA American Society of Anesthesiologists' classification, *BMI* body mass index, *LOS* length of stay

**N* represents the number of patients for whom data were available per follow-up moment

CHAPTER 3

Patient-reported functional outcome, pain, and activity resumption

The DASH (primary outcome measure), Constant–Murley, pain scores, and ability to perform daily activities improved over time in both the operative and nonoperative group (Fig. 2). Table 2 shows the results of the multilevel model, *i.e.*, the statistical significance of treatment effect and the estimated marginal means at three months; at that time a difference between the groups was expected. Supplemental Table S1 shows the original, unadjusted values (median, P_{25}–P_{75}, and univariate *p*-value) as well as the adjusted values (estimated marginal means with 95% CI) for all follow-up visits. The mean DASH score diminished from 48.2 points at two weeks to 11.0 points at 12 months in the operative group, and from 56.9 to 8.8 points in the nonoperative group (Fig. 2A). Patients in the operative group reported statistically significantly lower levels of disability until three months follow-up than patients in the nonoperative group. The interaction between treatment and time was also significant ($p_{interaction} < 0.001$); this reflects a difference in recovery speed between the two groups and the overlap in DASH values from three months onwards.

Similar as for the DASH, the Constant–Murley score also showed a significant treatment effect in favor of the operative group ($p_{treatment} < 0.001$). Patients in this group also recovered faster ($p_{interaction} < 0.001$; Fig. 2B and Table 2). Scores for the affected side increased from 42 points at six weeks to 72 points at 12 months in the operative group and from 25 to 74 points in the nonoperative group (Fig. 2B). Significantly higher scores for the affected side were noted in the operative group at 6 weeks (42 versus 25 points) and three months (54 versus 42), but not at later time points. The values at the contralateral side stayed consistently between 74 and 83 in both groups.

The course of pain was not significantly associated with treatment ($p_{treatment} = 0.479$; Fig. 2C). The total reduction in pain level was, however, slightly more pronounced in the nonoperative group ($p_{interaction} = 0.003$). Patients reported no pain at the contralateral side.

Patients in the operative group reported a better ability to participate in activities like sports and hobbies at six weeks (4.9 versus 4.0 in the nonoperative group) and three months (6.7 versus 5.7), yet both groups reported 9.0 at 12 months. This resulted in a significant interaction ($p_{interaction} < 0.001$), but the overall treatment effect was non-significant ($p_{treatment} = 0.056$).

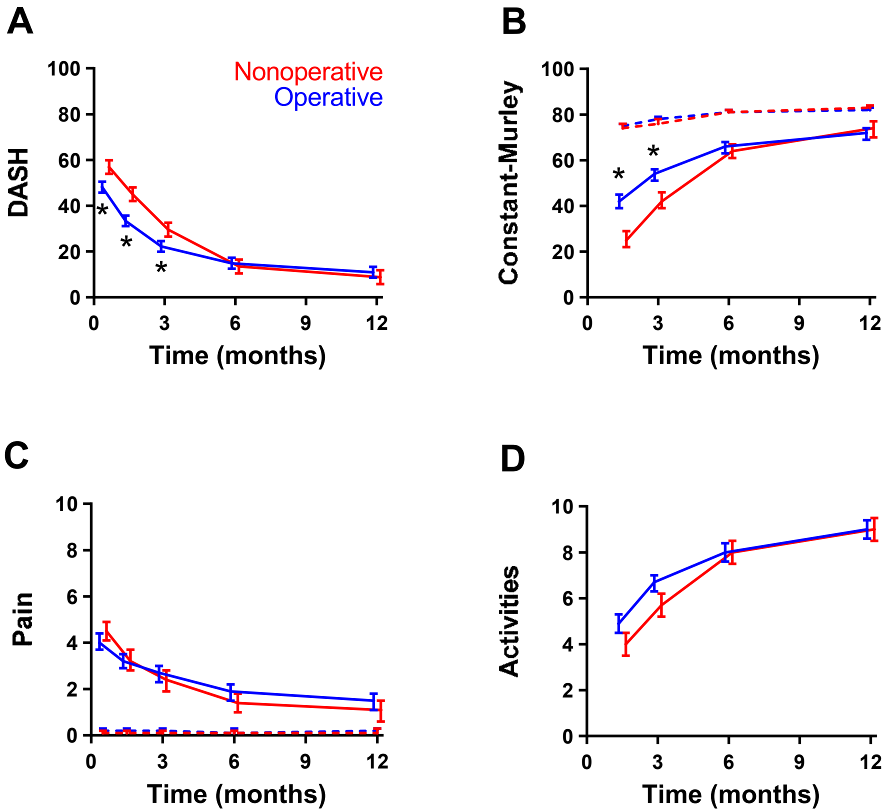

Fig. 2 Changes in functional outcome scores, pain, and activity resumption over time by treatment group.

A Disabilities of the Arm, Shoulder, and Hand (DASH) score, **B** Constant–Murley score of the affected arm, **C** pain (VAS, Visual Analog Scale) of the affected side, **D** the extent to which patients resumed their activities at the pre-trauma level (Numeric Rating Scale, NRS) over time. Higher scores represent more disability (DASH), a better function (Constant-Murley), more pain (VAS), and level of activity resumption (NRS, Numeric Rating Scale). Data are shown as estimated marginal mean with the corresponding 95% confidence interval, adjusted for age, gender, and fracture type, as emerging from the multivariable analysis. Blue lines represent the operative group; red lines represent the nonoperative group. In panel **C**, the dashed lines represent the contralateral side. *$p < 0.05$ (Bonferroni test)

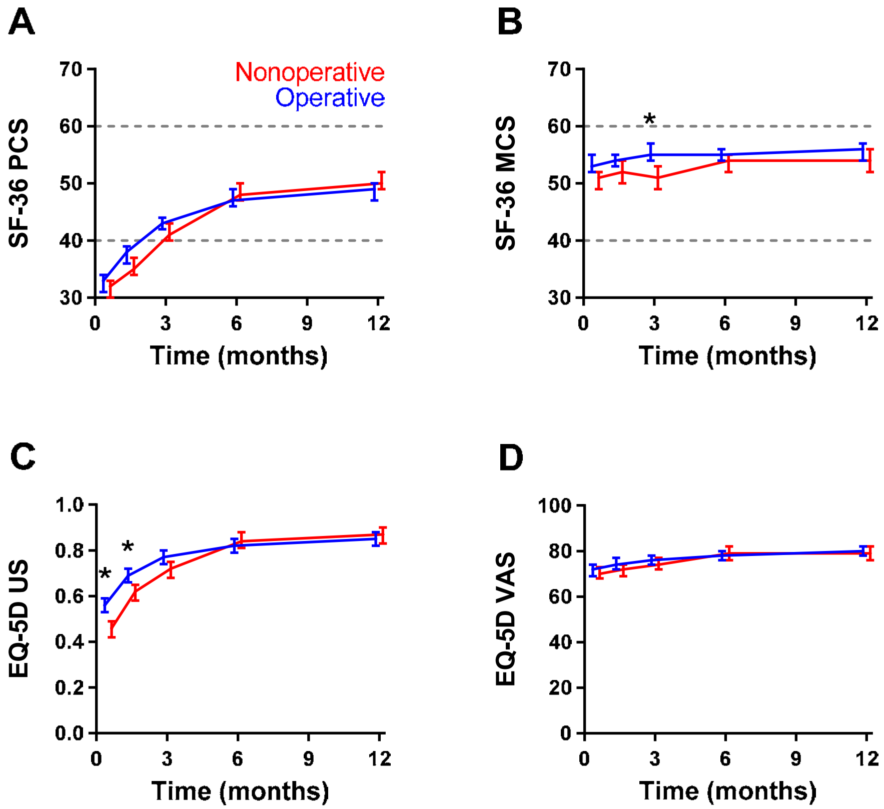

Fig. 3 Changes in health-related quality of life over time by treatment group. **A** Short Form-36 (SF-36) Physical Component Summary (SF-36 PCS), **B** SF-36 Mental Component Summary (SF-36 MCS), **C** EuroQoL-5D-3L (EQ-5D) utility score (EQ-5D US), and **D** EQ-5D Visual Analog Scale (EQ-5D VAS) over time. Higher scores represent better quality of life. Data are shown as estimated marginal mean with the corresponding 95% confidence interval, adjusted for age, gender, and fracture type, as emerging from the multivariable analysis. Blue lines represent the operative group; red lines represent the nonoperative group. In panels **A** and **B**, the dashed lines represent the mean ± SD (50 ± 10) that was used for normalizing the data. *$p < 0.05$ (Bonferroni test)

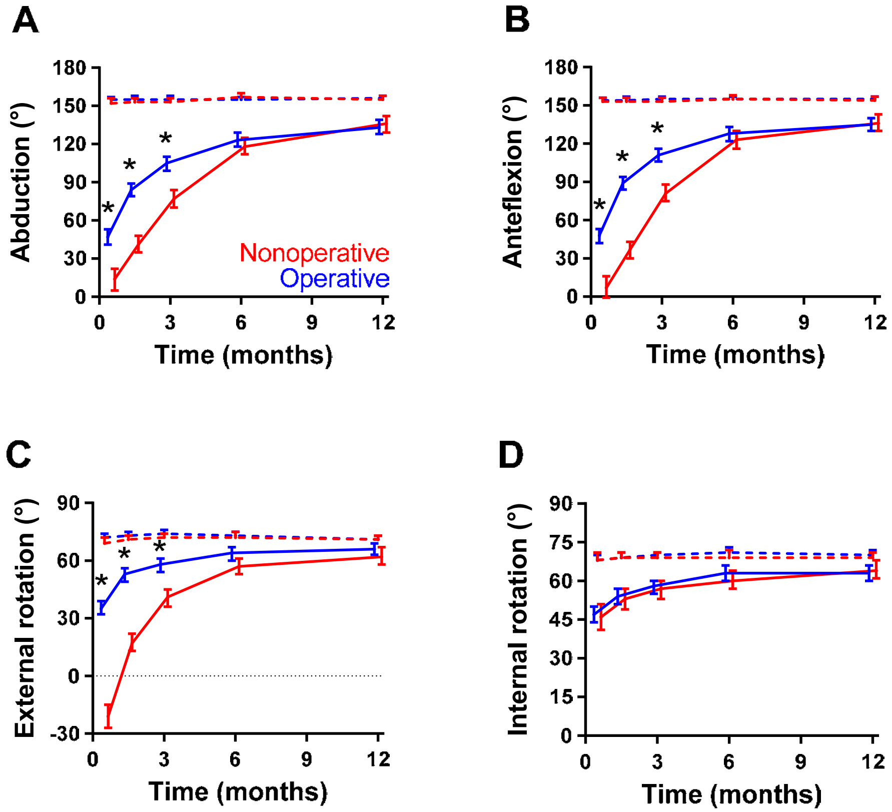

Fig. 4 Changes in range of motion of the shoulder over time by treatment group. **A** Abduction, **B** anteflexion, **C** external rotation, and **D** internal rotation of the shoulder over time. Higher scores represent better range of motion (ROM). Data are shown as estimated marginal mean with the corresponding 95% confidence interval, adjusted for age, gender, and fracture type, as emerging from the multivariable analysis. Blue lines represent the operative group; red lines represent the nonoperative group. Dashed lines represent the contralateral side. *$p < 0.05$ (Bonferroni test)

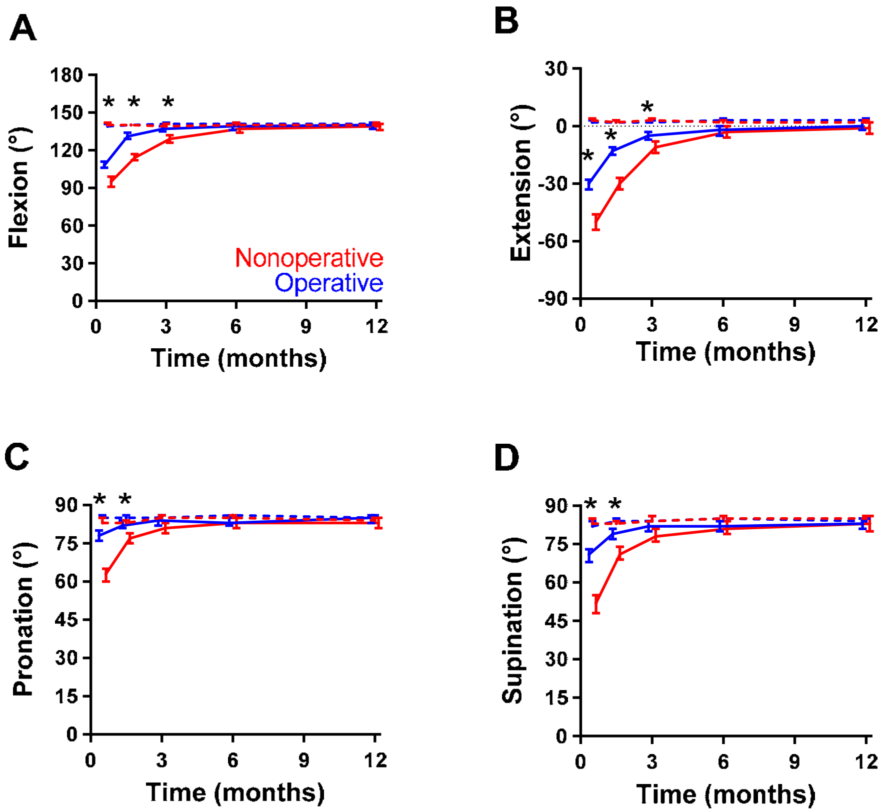

Fig. 5 Changes in range of motion of the elbow over time by treatment group. **A** Flexion, **B** extension, **C** pronation, and **D** supination of the elbow over time. Higher scores represent better range of motion (ROM). Data are shown as estimated marginal mean with the corresponding 95% confidence interval, adjusted for age, gender, and fracture type, as emerging from the multivariable analysis. Blue lines represent the operative group; red lines represent the nonoperative group. *$p < 0.05$ (Bonferroni test)

Table 2. Treatment effect over time and outcome at three months follow-up by treatment group

	Effect		Outcome at three months follow-up	
	F ($p_{treatment}$)	F ($p_{interaction}$)	Operative (N=245)	Nonoperative (N=145)
Patient reported outcome measures				
DASH	11.79 (**0.001**)	27.30 (< **0.001**)	**22.3 (19.9-24.6)**	**29.6 (26.6-32.6)**
Constant-Murley	19.45 (< **0.001**)	44.23 (< **0.001**)	**54 (51-56)**	**42 (39-46)**
Pain	0.50 (0.479)	3.98 (**0.003**)	2.7 (2.3-3.0)	2.4 (1.9-2.8)
Activity resumption	3.69 (0.056)	7.79 (< **0.001**)	**6.7 (6.3-7.0)**	**5.7 (5.2-6.2)**
HR-QoL				
SF-36	0.49 (0.484)	7.36 (< **0.001**)	43 (42-44)	41 (40-43)
PCS				
MCS	7.80 (**0.005**)	1.80 (0.126)	55 (54-57)	51 (49-53)
EQ-5D	6.04 (**0.014**)	10.97 (< **0.001**)	0.77 (0.74-0.80)	0.72 (0.68-0.75)
US				
VAS	0.96 (0.328)	1.73 (0.141)	76 (74-78)	74 (72-77)
Shoulder range of motion (°)				
Abduction	45.79 (< **0.001**)	43.01 (< **0.001**)	**105 (99-110)**	**77 (70-84)**
Anteflexion	67.27 (< **0.001**)	70.32 (< **0.001**)	**111 (106-116)**	**81 (75-88)**
Exernal rotation	156.03 (< **0.001**)	81.58 (< **0.001**)	**58 (54-61)**	**41 (36-45)**
Internal rotation	0.32 (0.570)	0.64 (0.636)	58 (55-60)	57 (53-60)
Elbow range of motion (°)				
Flexion	52.86 (< **0.001**)	21.11 (< **0.001**)	**137 (135-139)**	**129 (126-132)**
Extension deficit	56.41 (< **0.001**)	27.60 (< **0.001**)	**-5 (-7- to -3)**	**-11 (-14- to -8)**
Pronation	42.88 (< **0.001**)	16.99 (< **0.001**)	84 (82-85)	81 (79-83)
Supination	28.64 (< **0.001**)	22.68 (< **0.001**)	82 (80-84)	78 (76-881)

Changes in recovery pattern were assessed in the multilevel model. Results are shown by the F value for treatment and for the interaction term in the model (treatment * follow-up moment), with their corresponding p value in parenthesis.

DASH Disabilities of the Arm, Shoulder, and Hand, *EQ-5D* EuroQoL-5D, *HR-QoL* Health-Related Quality of Life, *MCS* Mental Component Summary, *Mo* month, *NRS* Numerical Rating Scale, *PCS* Physical Component Summary, *SF-36* Short Form-36; *US* Utility Score, *VAS* Visual Analog Scale, *We* week

Data of the outcome at three months are shown as the estimated marginal mean with 95% confidence interval after three months follow-up adjusted for age, gender, and fracture type. If the intervals did not overlap, this is indicated in bold face. The Constant-Murley score, pain score, and ranges of motion of the shoulder and arm are shown for the affected side. Bold face indicates that the 95% confidence interval of the two treatment groups did not overlap (p<0.05, Bonferroni test)

Health-related quality of life

Figure 3 shows changes in HR-QoL over time. The corresponding estimated marginal means at three months and results of the multilevel models are shown in Table 2 and Supplemental Table S1. The SF-36 PCS improved at similar speed over time in both groups, from 32 at two weeks to 50 at 12 months in the nonoperative group and from 33 to 49 in the operative group. From three months onwards, it was within the normal range of 50 ± 10 points. The SF-36 MCS was consistently within the normal range throughout the entire follow-up period, with the entire curve of the operative group being just above that of the nonoperative group ($p_{treatment}$ = 0.005).

The EQ-5D US was significantly higher in the operative group at two and six weeks (0.56 and 0.69) than in the nonoperative group (0.46 and 0.62) and showed a significant treatment effect and interaction with time ($p_{treatment} = 0.014$ and $p_{interaction} < 0.001$). The EQ-VAS, on the other hand, was unaffected by the type of treatment and hardly improved over time ($p_{treatment} = 0.328$ and $p_{interaction}$ = 0.141).

Range of motion

Changes in ROM of the shoulder are shown in Figure 4, Table 2, and Supplemental Table S1. Abduction, anteflexion, and external rotation of the shoulder all showed a significant treatment effect and interaction with time ($p_{treatment} < 0.001$ and $p_{interaction} < 0.001$). For all three motions, the values were between 33 and 56° higher in the operative group than in the nonoperative group. The largest difference was seen for external rotation at two weeks; 35° in the operative group versus − 21° in the nonoperative group. The difference reduced over time but remained statistically significant until three months follow-up. Treatment had no significant effect on internal rotation ($p_{treatment} = 0.571$ and $p_{interaction}$ = 0.636).

Changes in ROM of the elbow are shown in Figure 5, Table 2 and Supplemental Table S1. All measured ranges of motion of the elbow were statistically significantly better for the operated patients than for the nonoperated patients until six weeks follow-up (pronation and supination) or three months follow-up (flexion and extension). All ranges of motion of the elbow recovered to about the same values as the contralateral side and showed a significant treatment effect and interaction with time ($p_{treatment} < 0.001$ and $p_{interaction} < 0.001$).

Resumption of work and sports

Table 3 shows the patients' participation and resumption of work and sports. About half of the patients ($N = 198$) had a paid job prior to their injury. Paid work was significantly more common in the operative group ($N = 136$; 55.5%) than in the nonoperative group ($N = 62$; 42.8%; $p = 0.016$). These patients also worked more hours per week (38 versus 32; $p = 0.016$). The exertional level was similar in both groups. Work absenteeism post-injury was reported by more than 90% of patients. Although the operative group resumed work seven work days earlier (26 days versus 33 in the nonoperative group), this did not reach statistical significance ($p = 0.253$).

Overall, 378 (98.5%) patients participated in sports or hobbies pre-trauma, for a median of 17h per week, all but one patient resumed sports and hobbies during follow-up. No significant differences were noted between the two treatment groups.

Complications and secondary surgical interventions

Complications were more common in the nonoperative group ($N = 50$; 34.5%) than in the operative group ($N = 58$; 23.7%; $p = 0.026$; Table 4). As a consequence, secondary surgical interventions were also done more frequently in the nonoperative group ($N = 37$ (25.5%) versus $N = 20$ (12.2%); $p = 0.001$). Malalignment occurred only in the nonoperative group ($N = 14$; 9.7%); 11 of these patients were operated. In the operative group, implant-related complications were most common ($N = 26$; 10.6%). This included nail protrusion ($N = 13$), screw protrusion ($N = 8$), screw cutout ($N = 2$), inadequate implant size ($N = 1$) or implant type ($N = 1$), or chronic pain ($N = 1$). These complications resulted in implant exchange or removal in three and 16 patients, respectively. Five nonoperatively treated patients developed disproportionate pain, resulting in secondary osteosynthesis. Postoperative or persistent radial nerve palsy, which occurred in nine (3.7%) patients of the operative group and three (2.1%) patients of the nonoperative group, fully recovered in 86% and 67% of patients, respectively ($p = 0.437$). Nonunion occurred significantly more often in the nonoperative group ($N = 30$; 26.3%) than in the operative group ($N = 19$; 10.1%; $p < 0.001$). Twenty of these 30 and 10 of the 19 patients underwent (revision) osteosynthesis within a year after injury.

Table 3. Work and sports participation pretrauma and post-trauma resumption of study participants by treatment group

	*N**	All (*N*=390)	*N**	Operative (*N*=245)	*N**	Nonoperative (*N*=145)	*P* value
Work							
Paid work (*N* patients)	390	198 (50.8%)	245	136 (55.5%)	145	62 (42.8%)	**0.016**
Hours per week	194	36 (27-40)	134	38 (32-40)	60	32 (21-40)	**0.016**
Exertional level							
Light, mainly sedentary	198	88 (44.4%)	136	64 (47.1%)	62	24 (38.7%)	0.304
Medium work		71 (35.9%)		49 (36.0%)		22 (35.5%)	
Heavy or very heavy work		39 (19.7%)		23 (16.9%)		16 (25.8%)	
Work absence	196	179 (91.3%)	134	123 (91.8%)	62	56 (90.3%)	0.787
Work days missed	196	30 (13-54)	134	26 (12-49)	62	33 (15-59)	0.253
Sports or hobby							
Sports or hobby (*N* patients)	390	384 (98.5%)	245	242 (98.8%)	145	142 (97.9%)	0.675
Hours per week	378	17 (9-31)	240	16 (9-30)	138	19 (9-32)	0.115
Resumption at 12 months	241	340 (99.7%)	215	214 (99.5%)	126	126 (100.0%)	1.000

P-values <0.05 are shown in boldface

Data are presented as *N* (%) or median (P_{25}–P_{75})

*N** represents the number of patients for whom data were available per follow-up moment

Table 4. Complications and secondary surgical intervention by treatment group

	*N**	All (*N*=390)	*N**	Operative (*N*=245)	*N**	Nonoperative (*N*=145)	*P* value
Any complication	390	108 (27.7%)	245	58 (23.7%)	145	50 (34.5%)	**0.026**
Any surgical reintervention	390	67 (17.2%)	245	30 (12.2%)	145	37 (25.5%)	**0.001**
Malalignment	390	14 (3.6%)	245	0 (0.0%)	145	14 (9.7%)	**< 0.001**
Osteosynthesis		11		N.A.		11	N.A.
Cuff pathology	390	3 (0.8%)	245	3 (1.2%)	145	0 (0.0%)	0.298
Superficial infection	390	6 (1.5%)	245	5 (2.0%)	145	1 (0.7%)	0.419
Deep infection	390	1 (0.3%)	245	1 (0.4%)	145	0 (0.0%)	1.000
Drainage and implant removal		1		1		N.A.	N.A.
Implant-related complication	390	26 (6.7%)	245	26 (10.6%)	145	0 (0.0%)	**< 0.001**
Nail protrusion		13		13		N.A.	
Screw protrusion		8		8		N.A.	
Screw cutout		2		2		N.A.	
Inadequate implant size		1		1		N.A.	
Inadequate implant type		1		1		N.A.	
Chronic pain		1		1		N.A.	
Insufficient fixation		3		3		N.A.	
Inadequate implant size		22		22		N.A.	
Chronic pain		1		1		N.A.	
Implant exchange		3		3		N.A.	N.A.
Implant removal		16		16		N.A.	N.A.
Disproportional pain and disability	390	5 (1.3%)	245	0 (0.0%)	145	5 (3.4%)	**0.007**
Osteoynthesis		5		N.A.		5	N.A.
Post-operative or persistent radial nerve apraxia	390	12 (3.3%)	245	9 (3.7%)	145	3 (2.1%)	N.A.
Osteosynthesis		1		0		1	N.A.
Osteosynthesis and nerve grafting		1		0		1	N.A.
Malunion	390	3 (0.8%)	245	0 (0.0%)	145	3 (2.1%)	0.051
Nonunion	302	49 (16.2%)	188	19 (10.1%)	114	30 (26.3%)	**< 0.001**
(Revision) osteosynthesis		30		10		20	

P-values <0.05 are shown in boldface

Data are presented as number (%) or as median (P_{25}–P_{75}) and were analyzed using a Chi-squared test and Mann-Whitney *U* test, respectively

*N** represents the number of patients for whom data were available per follow-up moment

DISCUSSION

Data from the current multicenter prospective study demonstrate that adult patients with a closed humeral shaft fracture AO type 12A or 12B treated operatively have a better outcome until six months than patients treated nonoperatively in terms of a lower DASH score, higher Constant–Murley score, improved shoulder and elbow ROM, and a higher health-related quality of life (EQ-5D US). In addition, the operated group had fewer complications and surgical re-interventions. Given the multicenter design, the findings of this study can be generalized and therefore will apply to all different levels of trauma centers.

The statistically significant difference in DASH score in the first six months after trauma of 8.8 points or more in favor of the operative group is in line with previous RCTs which show a mean difference of 18.0 and 6.0 points at six months.[23,24] In addition, the FISH trial also shows superior DASH scores until six month follow-up.[25] The differences are larger than the minimally important change for the DASH (6.7 points) in the study population, confirming that our findings are statistically as well as clinically significant.[20] Quick-DASH correlates highly with function and patient satisfaction, and is considered a suitable tool for evaluating adult humeral shaft outcomes.[26]

Similar as the DASH, the Constant–Murley score also showed superior upper extremity function in the operative group until six months after trauma. This was also shown in the FISH trial[25], however, another RCT by Matsunaga et al. found no significant difference in score during a 12 month follow-up period.[24] It is not clear if this lack of difference can be attributed to a lower mean age, lower proportion of females, and inclusion of 12% of patients with an AO type 12C fractures in the nonoperative group in their study.

With regards to complications, both the current data and a meta-analysis show that pain, infection, and radial nerve palsy are no contributing factors in the decision-making for humeral shaft fractures.[2] Both operatively and nonoperatively treated patients in the current study reported a similar level and decrease of pain during the 12 month follow-up. Similar findings have previously also been reported.[24] Rämö et al., on the other hand, reported slightly, yet statistically significant, less pain in the operative group until six weeks after trauma, but the difference in pain was less than the threshold for clinical relevance.[25] In any case, pain per se is no contra-indication for operative management. In fact, five (3.4%) patients in the nonoperative group of the current study were operated due to disproportional pain.

Six patients out of 245 operated patients in our study had an infection (2.4%), of which five were only superficial according to the CDC classification. This is slightly less than the 3.1% out of 611 operated patients as reported in a recent meta-analysis.[2]

Sixteen (4.1%) patients presented with radial nerve palsy after trauma, which is a much lower rate than the 15.6% (201/1,289) reported in a meta-analysis.[2] The postoperative radial nerve palsy rate in their study was 3.6%, with a full recovery rate (at follow-up ranging from 6 to 72 months) of 96.4%. In our study, nine of out 232 (3.9%) patients developed a postoperative radial nerve palsy, of whom eight showed full recovery within the 12 month follow-up. This implies that the risk of persistent radial nerve palsy due to surgery at 12 months is 0.4% (*i.e.*, 1/232), and this minimal risk should be no reason to avoid surgery.

An inherent disadvantage of operative management is the risk of implant-related complications. Implant removal was performed due to nail or screw protrusion or chronic pain in 16/245 (6.9%) patients who were all treated with an IMN. For the same indication, hardware removal was reported in 10/156 (6.4%) patients in one RCT and three observational studies.[23, 27-29]

To achieve early functional recovery, treatment should focus on timely fracture healing and preventing malalignment. In this study, malalignment only occurred after nonoperative treatment, with 11 out of 14 patients requiring revision surgery. This rate of 9.7% is in line with 11.0% as calculated from one RCT and three observational studies.[24, 27, 28, 30] The risk of nonunion in our study was 2.6-fold higher after nonoperative treatment than after operative treatment (*i.e.*¸ 26.3% versus 10.1%). Analogous to our data, another RCT and two observational studies show a 2–2.5-fold higher nonunion rate after nonoperative treatment.[23, 31, 32] The effect was even stronger in two RCTs, which show 15 and 25% nonunion in the nonoperative group versus none at all after surgery.[24, 25] With data supporting that nonunion can, to a large extent, be prevented by immediate surgery, surgery should be the first option for the treatment of humeral shaft fractures.

Strengths and limitation

The main strength of this prospective, multicenter study is that it is the largest series of patients with a humeral shaft fracture to date. The sample size was much higher than 47 to 110 patients in the most recent prospective studies on this topic.[24-26, 33, 34] Combined with the participation of 29 hospitals across the country, including level 1, 2, and 3 trauma centers, it therewith represents current practice. Furthermore, treatment heterogeneity across participating hospitals caused by not standardizing treatment or rehabilitation will improve generalization of the results. The higher prevalence of females and higher median age in the nonoperative group in this study is in line with published data.[2] This may also explain the higher prevalence of osteoporosis/osteopenia in the nonoperative group. Overall, this indicates that selection bias due to the study design is unlikely, based on these patient characteristics.

A benefit of the observational design, allowing surgeon to decide on treatment, surgical approach, and implant, is that surgeons could use the (operative) technique they felt was best for the individual patient in their hands. This in contrast to a randomized design where randomization could result in the (operative) technique where the surgeon would feel less comfortable with or had less experience in. Another strength is that dedicated researchers performed the follow-up measurements of all patients. This centralized coordination allowed hospitals with insufficient research resources to participate. In a previous study it was shown that data quality and completeness can benefit from central study coordination.[35]

As commonly seen in observational studies, some imbalance in baseline data was noted between the two treatment groups. Although this may be considered as a limitation, we were able to correct for this in the mixed-linear models. When designing the study, we considered a RCT not feasible. The rationale, which includes strong patient and surgeon preference and early termination of RCTs at that time due to enrollment issues, is elaborated on the published study protocol.[12] Another limitation could be that some participating hospitals enrolled < 5 patients, suggesting that not all patients were screened for participation. Overall, 46 patients were missed for screening or declined participation. Consequently, the study sample was not consecutive. As this study did not interfere with treatment decision, it is unlikely that this has introduced selection bias or affected validity of the results. On the other hand, despite great efforts of the researchers, some bias due to missed follow-up visits and consent withdrawal cannot be ruled out. As this was the case in 19% of patients in both treatment arms, this is unlikely to be differential.

CONCLUSION

Primary osteosynthesis of a humeral shaft fracture (AO type 12A and 12B) in adults is safe and superior to nonoperative treatment, and should therefore be the treatment of choice. It is associated with a more than twofold reduced risk of nonunion, earlier functional recovery and a better range of motion of the shoulder and elbow joint than nonoperative treatment. Even after including the implant-related complications, the overall rate of complications as well as secondary surgical interventions was highest in the nonoperative group.

Supplemental Table S1. Functional outcome and range of motion of the shoulder and elbow over time by treatment group, based upon univariate and multivariable repeated measure analysis

			Univariate analysis						Multivariable, repeated measure analysis	
	Time	*N**	All (*N*=390)	*N**	Operative (*N*=245)	*N**	Nonoperative (*N*=145)	*P* value	Operative (*N*=245)	Nonoperative (*N*=145)
DASH	2 we	360	51.7 (37.7-63.3)	227	48.3 (33.9-58.3)	133	59.2 (48.3-67.5)	**< 0.001**	**48.2 (45.8-50.5)**	**56.9 (53.9-59.9)**
	6 we	366	35.8 (21.7-52.5)	229	29.2 (17.5-43.3)	137	48.3 (33.3-58.8)	**< 0.001**	**33.4 (31.1-35.7)**	**45.0 (42.1-48.0)**
	3 mo	348	20.8 (10.1-34.9)	220	17.5 (7.5-30.6)	128	26.3 (15.2-43.3)	**< 0.001**	**22.3 (19.9-24.6)**	**29.6 (26.6-32.6)**
	6 mo	337	8.3 (2.5-20.3)	209	8.3 (2.5-18.3)	128	9.6 (1.7-22.3)	0.468	14.9 (12.5-17.3)	13.5 (10.5-16.5)
	12 mo	344	3.3 (0.0-14.2)	217	3.3 (0.0-14.2)	127	3.3 (0.0-12.5)	0.855	11.0 (8.6-13.3)	8.8 (5.8-11.8)
Constant-Murley	2 we	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
	6 we	339	33 (21-52)	220	41 (27-58)	119	21 (14-31)	**< 0.001**	**42 (39-45)**	**25 (22-29)**
	3 mo	344	51 (35-65)	218	55 (39-72)	126	40 (24-57)	**< 0.001**	**54 (51-56)**	**42 (39-46)**
	6 mo	331	69 (55-79)	205	70 (56-82)	126	66 (50-76)	**0.007**	66 (63-68)	64 (61-67)
	12 mo	339	77 (65-83)	213	77 (65-84)	126	77 (67-82)	0.553	72 (69-74)	74 (70-77)
Pain (VAS)	2 we	359	3.7 (1.9-6.4)	226	3.4 (1.9-5.7)	133	4.4 (2.1-6.9)	0.082	4.0 (3.7-4.4)	4.5 (4.1-4.9)
	6 we	364	2.6 (1.1-4.8)	228	2.3 (0.9-5.0)	136	3.0 (1.6-4.7)	0.144	3.2 (2.9-3.5)	3.2 (2.8-3.7)
	3 mo	346	1.7 (0.5-4.0)	220	1.5 (0.2-4.4)	126	1.9 (0.8-3.6)	0.393	2.7 (2.3-3.0)	2.4 (1.9-2.8)
	6 mo	336	0.8 (0.0-2.1)	208	0.9 (0.0-2.1)	128	0.5 (0.0-1.9)	0.199	1.9 (1.5-2.2)	1.4 (1.0-1.8)
	12 mo	344	0.0 (0.0-1.5)	217	0.0 (0.0-1.7)	127	0.0 (0.0-1.3)	0.649	1.5 (1.1-1.8)	1.1 (0.6-1.5)
Activity resumption (NRS)	2 we	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
	6 we	361	5 (3-7)	228	5 (3-8)	133	4 (2-6)	**0.007**	**4.9 (4.5-5.3)**	**4.0 (3.5-4.5)**
	3 mo	348	7 (5-9)	217	8 (5-9)	131	6 (3-9)	**0.015**	**6.7 (6.3-7.0)**	**5.7 (5.2-6.2)**
	6 mo	333	9 (7-10)	207	9 (7-10)	126	9 (7-10)	0.549	8.0 (7.6-8.4)	8.0 (7.5-8.5)
	12 mo	336	10 (9-10)	211	10 (9-10)	125	10 (9-10)	0.084	9.0 (8.6-9.4)	9.0 (8.5-9.5)
SF-36 PCS	2 we	334	33 (28-37)	214	34 (30-38)	120	30 (25-37)	**0.001**	33 (31-34)	32 (30-33)
	6 we	339	37 (32-42)	210	38 (33-43)	129	34 (29-39)	**< 0.001**	38 (36-39)	35 (34-37)
	3 mo	322	43 (36-50)	207	44 (38-51)	115	41 (36-47)	**0.002**	43 (42-44)	41 (40-43)
	6 mo	319	50 (43-55)	196	51 (43-55)	123	50 (42-55)	0.541	47 (46-49)	48 (47-50)
	12 mo	333	53 (45-57)	211	52 (45-57)	122	53 (44-56)	0.989	49 (47-50)	50 (49-52)
SF-36 MCS	2 we	334	54 (46-61)	214	55 (47-61)	120	52 (45-60)	0.202	53 (52-55)	51 (49-52)
	6 we	339	56 (48-61)	210	57 (49-61)	129	54 (47-60)	0.104	54 (53-55)	52 (50-54)
	3 mo	322	57 (49-61)	207	58 (54-61)	115	55 (44-60)	**0.002**	**55 (54-57)**	**51 (49-53)**
	6 mo	319	57 (53-60)	196	57 (54-60)	123	56 (50-61)	0.449	55 (54-56)	54 (52-55)
	12 mo	333	58 (53-60)	211	58 (53-60)	122	57 (51-60)	0.198	56 (54-57)	54 (52-56)
EQ-5D US	2 we	361	0.55 (0.40-0.73)	228	0.67 (0.43-0.73)	133	0.43 (0.31-0.67)	**< 0.001**	**0.56 (0.53-0.59)**	**0.46 (0.42-0.49)**
	6 we	364	0.73 (0.56-0.81)	228	0.73 (0.61-0.84)	136	0.69 (0.47-0.73)	**< 0.001**	**0.69 (0.66-0.72)**	**0.62 (0.58-0.65)**
	3 mo	348	0.81 (0.69-0.90)	220	0.81 (0.73-0.90)	128	0.73 (0.61-0.84)	**< 0.001**	0.77 (0.74-0.80)	0.72 (0.68-0.75)
	6 mo	336	0.84 (0.78-1.00)	209	0.84 (0.78-1.00)	127	0.84 (0.78-1.00)	0.886	0.82 (0.79-0.85)	0.84 (0.81-0.88)
	12 mo	342	1.00 (0.81-1.00)	215	1.00 (0.81-1.00)	127	1.00 (0.81-1.00)	0.984	0.85 (0.82-0.88)	0.87 (0.83-0.90)
EQ-5D VAS	2 we	359	70 (60-80)	226	75 (65-80)	133	70 (60-80)	0.082	72 (69-74)	70 (68-73)
	6 we	367	75 (65-80)	231	75 (70-80)	136	70 (60-80)	**0.003**	74 (72-77)	72 (69-74)
	3 mo	348	80 (70-85)	219	80 (70-85)	129	75 (70-83)	0.053	76 (74-78)	74 (72-77)
	6 mo	337	80 (70-90)	209	80 (75-90)	128	80 (70-90)	0.920	78 (76-80)	79 (76-82)
	12 mo	344	80 (75-90)	217	80 (75-90)	127	80 (70-90)	0.174	80 (78-82)	79 (76-82)

Shoulder abduction (º)	2 we	218	40 (10-74)	161	55 (30-80)	57	0 (0-30)	**< 0.001**	**47 (41-53)**	**14 (5-22)**
	6 we	361	60 (40-100)	232	80 (50-125)	129	40 (19-55)	**< 0.001**	**84 (79-89)**	**41 (35-48)**
	3 mo	350	90 (60-135)	220	105 (73-145)	130	70 (45-95)	**< 0.001**	**105 (99-110)**	**77 (70-84)**
	6 mo	334	130 (95-155)	207	140 (105-160)	127	125 (90-150)	**0.002**	123 (118-129)	118 (112-125)
	12 mo	341	150 (115-160)	215	150 (115-165)	126	145 (114-155)	0.099	133 (128-139)	136 (129-141)
Shoulder anteflexion (º)	2 we	213	40 (5-75)	158	53 (25-85)	55	0 (0-15)	**< 0.001**	**48 (42-53)**	**7 (-1-16)**
	6 we	360	70 (30-114)	232	90 (56-130)	128	28 (10-55)	**< 0.001**	**89 (84-94)**	**37 (30-43)**
	3 mo	350	105 (70-135)	220	118 (90-145)	130	80 (47-120)	**< 0.001**	**111 (106-116)**	**81 (75-88)**
	6 mo	334	135 (109-155)	207	140 (110-155)	127	125 (100-145)	**0.001**	128 (122-133)	123 (116-130)
	12 mo	341	145 (125-160)	215	150 (125-160)	126	140 (120-155)	0.060	135 (130-140)	136 (130-143)
Shoulder external rotation (º)	2 we	210	25 (0-53)	156	40 (15-60)	54	-30 (-50-0)	**< 0.001**	**35 (32-39)**	**-21 (-27- -15)**
	6 we	356	45 (20-65)	231	60 (40-70)	125	20 (0-38)	**< 0.001**	**53 (49-56)**	**17 (13-22)**
	3 mo	347	52 (40-70)	220	60 (45-75)	127	45 (25-60)	**< 0.001**	**58 (54-61)**	**41 (36-45)**
	6 mo	334	60 (50-75)	207	65 (55-80)	127	60 (45-70)	**< 0.001**	64 (60-67)	57 (53-61)
	12 mo	341	65 (55-79)	215	70 (55-80)	126	65 (50-75)	**0.016**	66 (63-69)	62 (58-67)
Shoulder internal rotation (º)	2 we	204	53 (30-70)	149	60 (38-70)	55	50 (25-60)	0.264	47 (44-50)	46 (41-51)
	6 we	350	60 (45-70)	228	60 (45-70)	122	60 (40-65)	0.214	54 (51-57)	53 (49-57)
	3 mo	344	60 (45-70)	218	60 (45-70)	126	60 (45-70)	0.114	58 (55-60)	57 (53-60)
	6 mo	333	65 (50-70)	207	65 (55-75)	126	60 (50-70)	**0.007**	63 (60-66)	60 (57-64)
	12 mo	340	65 (50-75)	215	65 (50-75)	125	65 (50-75)	0.592	63 (60-66)	64 (61-68)
Elbow flexion (º)	2 we	204	105 (90-124)	153	110 (90-125)	51	90 (90-110)	**< 0.001**	**108 (106-111)**	**95 (91-99)**
	6 we	359	130 (120-140)	230	135 (125-140)	129	120 (100-130)	**< 0.001**	**131 (129-134)**	**114 (112-117)**
	3 mo	348	135 (130-140)	220	140 (133-141)	128	135 (120-140)	**< 0.001**	**137 (135-139)**	**129 (126-132)**
	6 mo	334	140 (135-145)	207	140 (135-145)	127	140 (130-145)	0.112	139 (136-141)	137 (134-140)
	12 mo	341	140 (135-145)	215	140 (135-145)	126	140 (135-145)	1.000	140 (137-142)	139 (136-141)
Elbow extension (º)	2 we	204	-30 (-45- -15)	153	-25 (-40- -15)	51	-50 (-75- -30)	**< 0.001**	-30 (-33- -28)	-50 (-54- -46)
	6 we	359	-10 (-30- -5)	230	-6 (-20-0)	129	-25 (-45- -15)	**< 0.001**	-13 (-15- -11)	-30 (-33- -27)
	3 mo	349	-5 (-15-0)	220	0 (-10-5)	129	-10 (-18-0)	**< 0.001**	-5 (-7- -3)	-11 (-14- -8)
	6 mo	334	0 (-5-5)	207	0 (-5-5)	127	0 (-5-0)	**0.001**	-2 (-5-0)	-3 (-6-0)
	12 mo	341	0 (0-5)	215	0 (0-5)	126	0 (-5-5)	**0.009**	0 (-2-3)	-1 (-4-2)
Elbow pronation (º)	2 we	222	80 (75-85)	162	83 (75-85)	60	75 (60-80)	**< 0.001**	**78 (76-80)**	**63 (60-65)**
	6 we	364	85 (80-85)	232	85 (80-85)	132	80 (75-85)	**< 0.001**	**82 (81-84)**	**77 (75-79)**
	3 mo	351	85 (80-90)	221	85 (80-90)	130	80 (80-85)	**< 0.001**	84 (82-85)	81 (79-83)
	6 mo	334	85 (80-90)	207	85 (80-90)	127	85 (80-85)	0.052	83 (82-85)	83 (81-85)
	12 mo	341	85 (80-90)	215	85 (84-90)	126	85 (80-86)	**0.004**	85 (83-86)	83 (81-85)
Elbow supination (º)	2 we	222	75 (60-85)	162	77 (69-85)	60	60 (33-75)	**< 0.001**	**71 (68-73)**	**52 (48-55)**
	6 we	364	80 (71-85)	232	85 (75-87)	132	75 (62-85)	**< 0.001**	**79 (77-81)**	**71 (69-74)**
	3 mo	351	85 (80-85)	221	85 (80-90)	130	80 (75-85)	**< 0.001**	82 (80-84)	78 (76-81)
	6 mo	334	85 (80-90)	207	85 (80-90)	127	85 (80-90)	0.083	82 (80-84)	81 (79-84)
	12 mo	341	85 (80-90)	215	85 (80-90)	126	85 (80-89)	**0.025**	83 (81-85)	83 (80-86)

Data for the univariate analysis are presented as median (P_{25}-P_{75}), data for the repeated measure multivariable analysis are shown as estimated marginal mean with 95% confidence interval

DASH Disabilities of the Arm, Shoulder, and Hand, *EQ-5D* EuroQoL-5D, *MCS* Mental Component Summary, *Mo* month, *NRS* Numerical Rating Scale, *PCS* Physical Component Summary, *SF-36*, Short Form-36, *US* Utility Score, *VAS* Visual Analog Scale, *We* week

*N** represents the number of patients for whom data were available per follow-up moment

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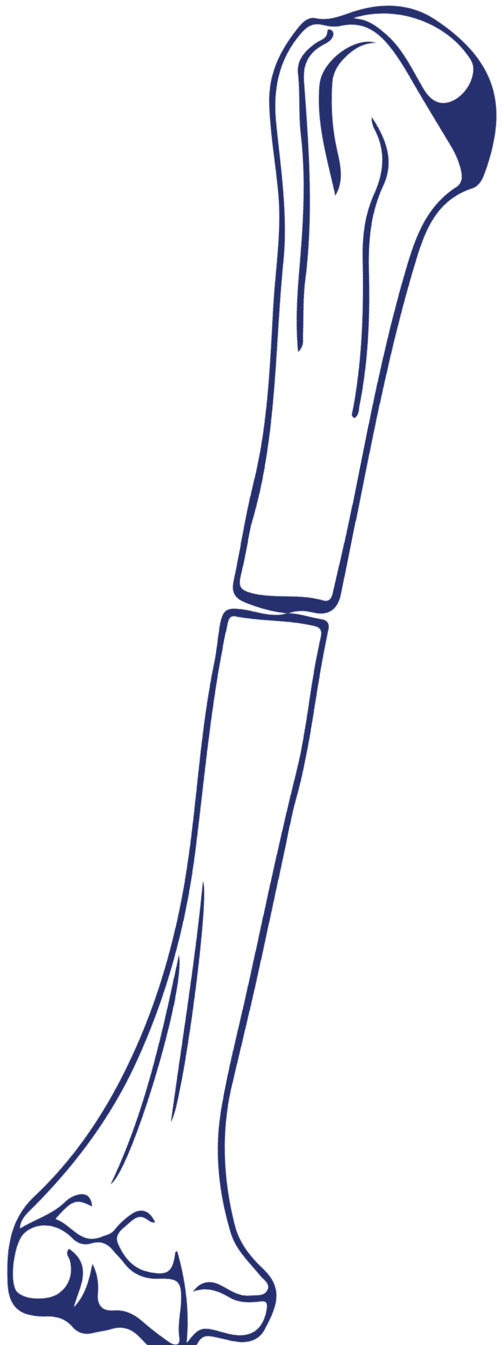

CHAPTER 4

Functional and clinical outcomes after plate osteosynthesis versus intramedullary nailing of a humeral shaft fracture: the results of the HUMMER multicenter, prospective cohort study

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ABSTRACT

Background: Plate osteosynthesis (referred to throughout as plating) and intramedullary nailing (referred to throughout as nailing) are the most common operative strategies for humeral shaft fractures. However, it is undecided which treatment is more effective. This study aimed to compare functional and clinical outcomes of these treatment strategies. We hypothesized that plating would result in an earlier recovery of shoulder function and fewer complications.

Methods: From October 23, 2012, to October 3, 2018, adults with a humeral shaft fracture, OTA/AO type 12A or 12B, were enrolled in a multicenter, prospective cohort study. Patients were treated with plating or nailing. Outcome measures included the Disabilities of the Arm, Shoulder and Hand (DASH) score, Constant-Murley score, ranges of motion of the shoulder and elbow, radiographic healing, and complications until 1 year. Repeated-measure analysis was done with correction for age, sex, and fracture type.

Results: Of the 245 included patients, 76 were treated with plating and 169 were treated with nailing. Patients in the plating group were younger, with a median age of 43 years compared with 57 years for the nailing group ($p < 0.001$). The mean DASH score after plating improved faster over time, but did not differ significantly from the score after nailing at 12 months (11.7 points [95% confidence interval (CI), 7.6 to 15.7 points]) for plating and 11.2 points [95% CI, 8.3 to 14.0 points] for nailing). The Constant-Murley score and shoulder abduction, flexion, external rotation, and internal rotation displayed a significant treatment effect ($p_{treatment} \leq 0.001$), in favor of plating. The plating group had 2 implant-related complications, whereas the nailing group had 24, including 13 nail protrusions and 8 screw protrusions. Plating resulted in more postoperative temporary radial nerve palsy (8 patients [10.5%] compared with 1 patient [0.6%]; $p < 0.001$) and a trend toward fewer nonunions (3 patients [5.7%] compared with 16 patients [11.9%]; $p = 0.285$) than nailing.

Conclusions: Plating of a humeral shaft fracture in adults results in faster recovery, especially of shoulder function. Plating was associated with more temporary nerve palsies, but fewer implant-related complications and surgical reinterventions, than

nailing. Despite heterogeneity in implants and surgical approach, plating seems to be the preferred treatment option for these fractures.

INTRODUCTION

The best operative treatment for humeral shaft fractures remains subject to debate. The treatment options are intramedullary nailing (referred to throughout as nailing) and plate osteosynthesis (referred to throughout as plating), each with their advantages and disadvantages. Nailing is less invasive and may require less surgical time, but may be associated with rotator cuff symptoms. Plating allows anatomic reduction and fracture compression, but the more extensive surgical approach has a potential risk of radial nerve injury. Three meta-analyses reported ranges of pooled rates for both superficial and deep infections (1.6% to 2.3% after nailing compared with 1.7% to 7.7% after plating), secondary nerve palsy (2.5% to 6.4% after nailing compared with 2.9% to 6.9% after plating), and nonunion (3.6% to 9.2% after nailing compared with 1.1% to 8.6% after plating).[1–3]

Although some studies showed no significant effect of treatment on functional shoulder scores[4–6], both Li et al.[7] and Yuan et al.[8] showed higher Constant-Murley scores after plating than after nailing.

Because of heterogeneity in methodology, patient population, fracture type, and outcome measures across previous studies, it is undecided which treatment is more effective. Plating allows for anatomic reduction and fracture compression and avoids complications involving the rotator cuff, so we hypothesized that plating would result in earlier functional recovery and a lower complication risk compared with nailing. The aims of this study were to examine the effect of plating compared with that of nailing on functional recovery and complications in adults with a humeral shaft fracture.

MATERIALS AND METHODS

Settings and Participants

This study used data from the operative treatment group of the HUMMER (HUMeral Shaft Fractures: Measuring Recovery after Operative versus Non-operative Treatment) study.[9] Twenty-eight hospitals that participated in this multicenter, parallel-group cohort study provided patients for the operatively treated group. The decision about surgical treatment was left to the discretion of the treating surgeon. All patients who were ≥18 years of age, had a humeral shaft fracture (OTA/AO type 12A or 12B, confirmed by radiography), and underwent a surgical procedure <14 days after hospital presentation were included after they provided written informed consent.[10] Patients with pre-trauma disability or additional trauma to the arm that could affect the outcome or with expected problems with maintaining follow-up were excluded. A full list of eligibility criteria is available in the published study protocol.[11] The local Medical Research Ethics Committee at each site exempted the study (no. MEC-2012-396).

Treatment Allocation and Masking

The decision about which implant to use was left to the discretion of the treating surgeon. Participants and investigators were not blinded to the treatment. To reduce bias, follow-up measurements were standardized. Two assessors (I.B. and D.D.H.) independently evaluated the radiographs. Consensus was reached after discussion.

Intervention

Treatment was provided on the basis of local protocols, and the surgical procedure was performed by certified, experienced, orthopaedic trauma surgeons. There were no study-specific requirements with regard to fracture reduction (open or closed), plating (open or minimally invasive), nailing (antegrade or retrograde), type and brand of the devices, and other elements of the surgical procedure, among others. With no evidence favoring a specific approach, the physical therapy and rehabilitation programs were also not standardized. Critical elements of treatment were recorded.

Assessments and Follow-up

The follow-up visits took place at 2 weeks (range, 7 to 21 days), 6 weeks (range, 4 to 8 weeks), 3 months (range, 11 to 15 weeks), 6 months (range, 6 to 7 months), and 12 months (range, 12 to 14 months) after the surgical procedure.[11] At each visit, clinical data were collected from the patients' medical files. Also, shoulder and elbow ranges of motion were measured using a goniometer, and patients were asked to complete questionnaires on the level of pain, functional recovery, activity resumption, and health-related quality of life. The Constant-Murley score was determined at 6 weeks and subsequent visits. Anteroposterior and lateral radiographs of the humerus were made at presentation, after the operation, and at each study visit.

The Disabilities of the Arm, Shoulder and Hand (DASH) score served as the primary outcome measure.[12,13] The secondary outcome measures were the Constant-Murley score[14], level of pain (on a visual analog scale [VAS]), analgesic drugs used, shoulder and elbow ranges of motion, time to resumption of work, resumption of activities of daily living (on a numeric rating scale [NRS]), health-related quality of life (Short Form-36 [SF-36] and EuroQol-5 Dimensions-3 Levels [EQ-5D-3L])[15–17], the occurrence of complications and associated secondary interventions, and radiographic healing.[11] Nonunion was defined as a failure to heal at 6 months postoperatively with no progress toward healing seen on radiographs.[18] The patient-reported outcome measures have been proven to be reliable, valid, and responsive in the studied population and were available in Dutch.[19,20] The outcome measures are detailed in the published study protocol.[11]

Patient characteristics, injury-related details, and the number of physical therapy sessions were recorded.[11]

Statistical Analysis

The HUMMER study was powered for detecting a 6-point difference in DASH score between the operatively treated group and the nonoperatively treated group, for which 95 patients per group were sufficient.[11] In order to allow for subgroup analysis and more advanced statistical modeling, a total of 400 patients were targeted. This analysis used only the operatively treated group.

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 25 (IBM). All statistical tests were 2-sided, and analysis was by intention to treat. The HUMMER study is registered at the Netherlands Trial Register (NTR3617). Missing data were not imputed. Categorical data were analyzed using the chi-square test. Continuous data, which were all non-normally distributed according to the Shapiro-Wilk test, were analyzed using the Mann-Whitney U test. Significance was set at $p < 0.05$.

Continuous outcomes that were repeatedly measured over time were compared between treatment groups using linear mixed-effects regression models.[9] These multilevel models included fixed effects for the treatment group, age, sex, and fracture type and random effects for the intercepts of the model and time coefficient of individual patients. Explorative analyses showed that fracture location on the dominant side, smoking, radial nerve palsy at the time of the injury, and hospital were nonsignificant in all models; therefore, these covariates were not included in the final models. Finally, time was included as a factor because the outcome measures did not change linearly over time. The interaction between time and treatment group was included in the model in order to test for differences between the groups that varied over time. The estimated marginal mean with the 95% confidence interval (CI) at each follow-up time was computed for each treatment group. The means were compared post hoc using a Bonferroni correction for multiple testing. The absence of overlap of the 95% CIs around the marginal means was regarded as significant at $p < 0.05$.

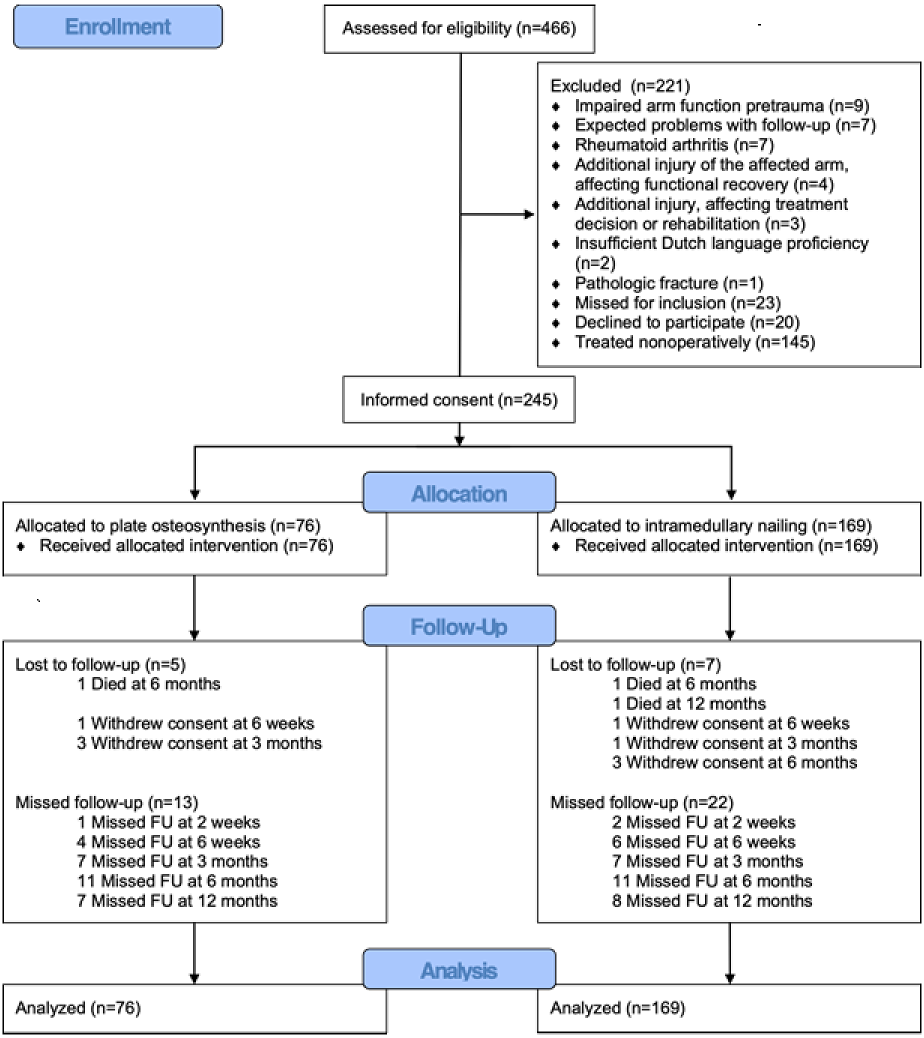
Source of Funding

This study was supported by a grant from the Osteosynthesis and Trauma Care Foundation (number 2013-DHEL), which had no role in the conduct of the study.

RESULTS

Patient and Injury Characteristics

Between October 23, 2012, and October 3, 2018, 245 patients of the HUMMER study underwent a surgical procedure: 76 patients (31.0%) underwent plating, and 169 patients (69.0%) underwent nailing (Fig. 1). Twelve patients were lost to follow-up due to mortality (n = 3) or withdrawal of consent.



FU = Follow-up

Fig. 1 Flowchart for the study

The plating group had a younger median age at 43 years (P_{25} to P_{75}, 25 to 61 years) than the nailing group at 57 years (P_{25} to P_{75}, 40 to 68 years) ($p < 0.001$); the plating group also had a lower median body mass index (BMI) at 24.8 kg/m^2 (P_{25} to P_{75}, 22.5 to 28.3 kg/m^2) than the nailing group at 26.3 kg/m^2 (P_{25} to P_{75}, 23.9 to 30.1 kg/m^2) ($p = 0.024$) (Table I). Radial nerve palsy at presentation was more common after plating (10 patients [13.2%]) than after nailing (3 patients [1.8%]) ($p = 0.001$).

Treatment Details and Hospital admission

A total of 121 surgeons operated on ≥1 patients: plating was performed by 47 surgeons and nailing was performed by 94 surgeons. All patients in the plating group were treated with a locking plate. The majority of patients in the nailing group (158 [93.5%]) were treated with an antegrade nail. Of the nails, 36 were an Expert Humeral Nail (DePuy Synthes); 44, a MultiLoc Humeral Nail (DePuy Synthes); 88, a T2 Humeral Nailing System (Stryker); and 1, a Titanic Elastic Nail (DePuy Synthes). The median duration of the surgical procedure was significantly longer ($p < 0.001$) after plating (113 minutes [P_{25} to P_{75}, 84 to 134 minutes]) than after nailing (81 minutes [P_{25} to P_{75}, 57 to 89 minutes]) (Table I). The other admission and follow-up characteristics, including the number of physical therapy sessions, were similar in both groups.

Patient-Reported Functional Outcome, Pain, Activity Resumption

The DASH score, Constant-Murley score, pain level, and ability to perform daily activities all improved over time in both treatment groups (Fig 2, Table II; see also Appendix Supplemental Table S1). Table III provides the results of the multilevel model (i.e., the significance of treatment effects and estimated marginal means at 3 months, which was the time that a difference between the treatment groups was expected). Appendix Supplemental Table S1 shows the crude, unadjusted, values (median, P_{25} to P_{75}, and univariate p value) and the adjusted values (i.e., estimated marginal means with 95% CIs) by follow-up time. The mean DASH score diminished from 48.9 points at 2 weeks to 11.7 points (95% CI, 7.6 to 15.7 points) at 12 months in the plating group and from 48.3 points at 2 weeks to 11.2 points (95% CI, 8.3 to 14.0 points) at 12 months in the nailing group (Fig. 2-A). Although treatment overall had no significant effect on the DASH score ($p = 0.479$), patients in the nailing group showed a faster functional recovery ($p = 0.008$) (Table II).

Similar to the DASH score, the Constant-Murley score showed a significant treatment effect in favor of the plating group ($p_{treatment} < 0.001$ and $p_{interaction} = 0.002$) (Fig. 2-B, Table II; see also Appendix Supplemental Table S1). Scores for the affected side increased from 52 points at 6 weeks to 76 points at 12 months in the plating group and from 38 points at 6 weeks to 70 points at 12 months in the nailing group. Significantly higher scores for the involved side were noted in the plating group at 6 weeks (52 compared with 38 points; $p < 0.001$) and 3 months (61 compared with 51 points; $p < 0.001$).

The plating group reported less pain ($p_{treatment} = 0.007$ and $p_{interaction} = 0.003$) (Fig. 2-C, Table II). The effect was most prominent at 6 weeks (2.2 after plating compared with 3.7 after nailing).

Treatment had no significant effect on activity resumption ($p_{treatment} = 0.162$ and $p_{interaction} = 0.135$) (Fig. 2-D, Table II). The resumption of work and sports activities was unaffected by treatment (see Appendix Supplemental Table S2). Treatment also had no significant effect on the health-related quality of life, except for the SF-36 Mental Component Summary (MCS) ($p_{treatment} = 0.014$ and $p_{interaction} = 0.482$) (Fig. 3, Table II; see also Appendix Supplemental Table S1).

Table I - Patient, injury, treatment, and admission details of study participants by treatment group*

	All (N=245)		Plating group (N=76)		Nailing group (N=169)		P Value‡
	Patients with Available Data	Value†	Patients with Available Data	Value†	Patients with Available Data	Value†	
Patient characteristics							
Female	245	133 (54.3%)	76	38 (50.0%)	169	95 (56.2%)	0.407
Age *(yr)*	245	53 (35, 66)	76	43 (25, 61)	169	57 (40-68)	**<0.001**
BMI *(kg/m²)*	244	26.1 (23.4, 29.9)	76	24.8 (22.5, 28.3)	168	26.3 (23.9, 30.1)	**0.024**
Smoking	245	55 (22.4%)	76	17 (22.4%)	169	38 (22.5%)	1.000
ASA 3 or 4	245	13 (5.3%)	76	1 (1.3%)	169	12 (7.1%)	0.070
Comorbidities	245	115 (46.9%)	76	28 (36.8%)	169	87 (51.5%)	**0.038**
Any							
Diabetes	245	18 (7.3%)	76	4 (5.3%)	169	14 (8.3%)	0.597
Arthritis and/or arthrosis	245	15 (6.1%)	76	3 (3.9%)	169	12 (7.1%)	0.404
Osteoporosis or osteopenia	245	1 (0.4%)	76	0 (0.0%)	169	1 (0.6%)	1.000
Medication use	245	127 (51.8%)	76	32 (42.1%)	169	95 (56.2%)	0.053
No. of medications	128	2 (1, 4)	32	2 (1, 4)	96	3 (1, 5)	0.166
Injury characteristics							
Dominant side affected	245	116 (47.3%)	76	34 (44.7%)	169	82 (48.5%)	0.678
Fracture classification							
A1	245	57 (23.3%)	76	20 (26.3%)	169	37 (21.9%)	0.334
A2		43 (17.6%)		13 (17.1%)		30 (17.8%)	
A3		71 (29.0%)		16 (21.1%)		55 (32.5%)	
B1		51 (20.8%)		19 (25.0%)		32 (18.9%)	
B2		10 (4.1%)		2 (2.6%)		8 (4.7%)	
B3		13 (5.3%)		6 (7.9%)		7 (4.1%)	
Radial nerve palsy at presentation	245	13 (5.3%)	76	10 (13.2%)	169	3 (1.8%)	**0.001**
Additional injuries	245	26 (10.6%)	76	5 (6.6%)	169	21 (12.4%)	0.188
Ipsilateral arm	245	6 (2.4%)	76	1 (1.3%)	169	5 (3.0%)	0.669
Contralateral arm	245	4 (1.6%)	76	1 (1.3%)	169	3 (1.8%)	1.000

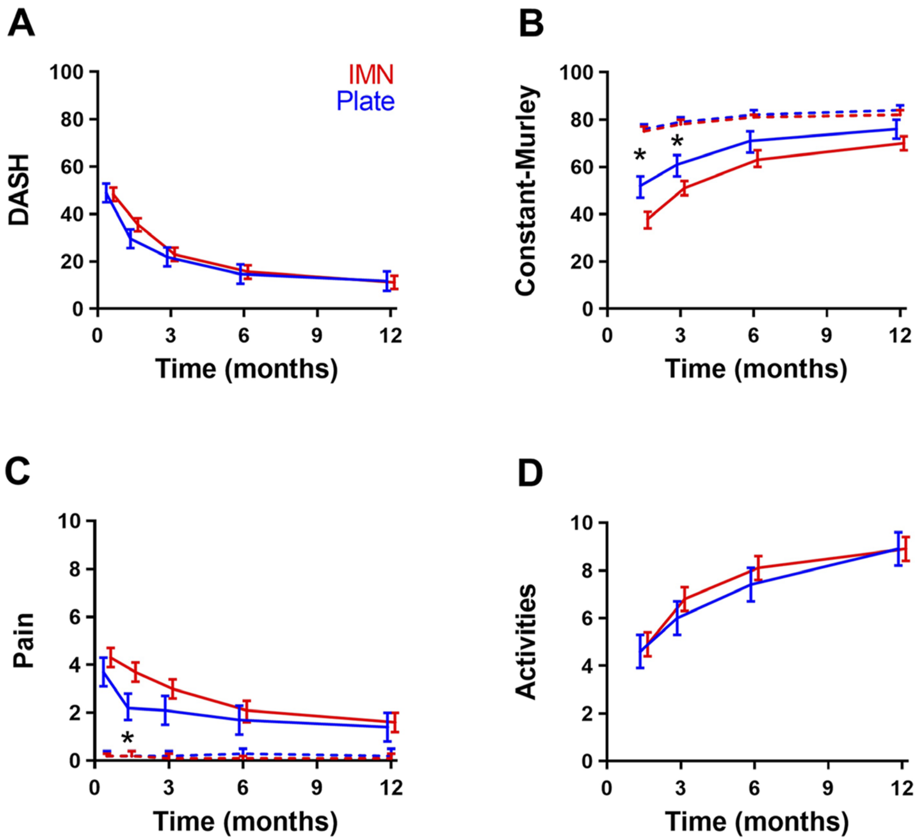
Admission and follow-up characteristics							
Surgical delay *(day)*	245	6 (2, 9)	76	6 (2, 9)	169	5 (2-9)	0.499
Duration of surgery *(min)*	245	81 (65, 112)	76	113 (84, 134)	169	81 (57, 89)	**<0.001**
HLOS *(day)*	245	2 (2, 4)	76	3 (2, 4)	169	2 (2, 4)	0.054
Discharge disposition							
Home	245	235 (95.9%)	76	76 (100.0%)	169	159 (94.1%)	0.196
Care hotel		6 (2.4%)		0 (0.0%)		6 (3.6%)	
Elderly care facility		1 (0.4%)		0 (0.0%)		1 (0.6%)	
Rehabilitation center		3 (1.2%)		0 (0.0%)		3 (1.8%)	
Other care facility admission	245	8 (3.3%)	76	0 (0.0%)	169	8 (4.7%)	0.061
Nursing home *(day)*	1	30 (30, 30)	0	N.A.	1	30 (30, 30)	N.A.
Care hotel *(day)*	4	8 (5, 25)	0	N.A.	4	8 (5, 25)	N.A.
Elderly care facility *(day)*	1	21 (21, 21)	0	N.A.	1	21 (21, 21)	N.A.
Rehabilitation clinic *(day)*	3	25 (24, 25)	0	N.A.	3	25 (24, 25)	N.A.
Physical therapy							
No. of sessions	217	25 (13, 48)	64	25 (8, 39)	153	26 (14, 51)	0.086

* ASA = American Society of Anesthesiologists, and NA = not applicable. † The values are given as the number of patients, with the percentage in parentheses, or as the median, with the P_{25} to P_{75} in parentheses. ‡ Bold represents significance

Table II - Treatment effect over time and outcome at the 3-month follow-up by treatment group*

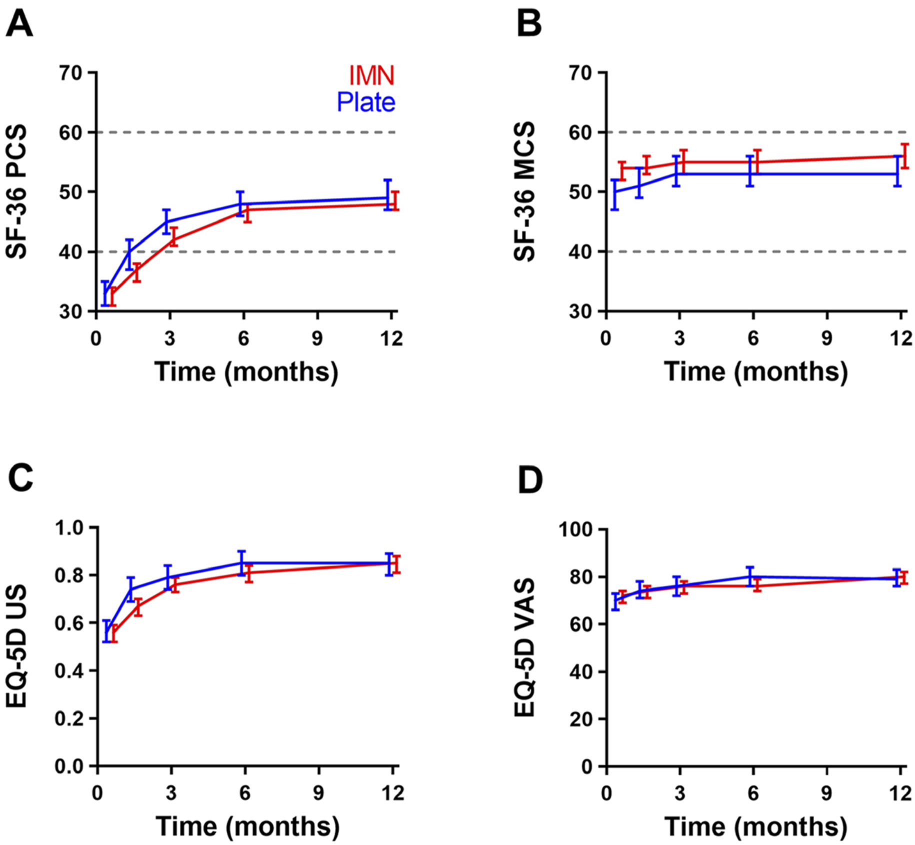
	Effect†‡				Outcome at the 3-month follow-up§	
	Treatment		Interaction			
	F Value	P Value	F Value	P Value	Plating Group (N=76)	Nailing group (N=169)
Patient reported outcome measures						
DASH score	0.50	0.479	3.45	**0.008**	21.9 (17.9 to 25.9)	23.0 (20.2 to 25.8)
Constant-Murley score#	20.43	**<0.001**	4.88	**0.002**	61 (56 to 65)**	51 (48 to 54)**
VAS pain score#	7.53	**0.007**	4.09	**0.003**	2.1 (1.5 to 2.7)	3.0 (2.6 to 3.4)
Activity resumption	1.97	0.162	1.86	0.135	6.0 (5.3 to 6.7)	6.8 (6.3 to 7.3)
Health-related quality of life						
SF-36 PCS	2.61	0.108	1.04	0.386	45 (43 to 47)	42 (41 to 44)
SF-36 MCS	6.13	0.014	0.87	0.482	53 (51 to 56)	55 (53 to 57)
EQ-5D US	1.97	0.162	2.17	0.071	0.79 (0.74 to 0.84)	0.76 (0.73 to 0.79)
VAS pain	0.06	0.802	2.00	0.092	76 (72 to 80)	76 (73 to 78)
Shoulder range of motion# *(deg)*						
Abduction	35.66	**<0.001**	7.89	**<0.001**	122 (114 to 131)**	97 (91 to 103)**
Flexion	34.06	**<0.001**	7.68	**<0.001**	125 (117 to 134)**	104 (98 to 110)**
External rotation	16.36	**<0.001**	8.18	**<0.001**	63 (58 to 69)	56 (52 to 59)
Internal rotation	11.25	**0.001**	0.32	0865	63 (58 to 68)	56 (53 to 60)
Elbow range of motion# *(deg)*						
Flexion-extension arc	0.32	0.572	1.05	0.380	131 (125 to 136)	133 (129 to 137)
Pronation-supination arc	0.14	0.712	1.73	0.141	165 (160 to 170)	166 (163 to 170)

* MCS = Mental Component Summary, PCS = Physical Component Summary, and US = Utility Score. † Changes in recovery pattern were assessed in the multilevel model. ‡ Results are shown by the F-value for treatment and for the interaction term in the model (treatment × follow-up time), with their corresponding p-value; significant p values are shown in bold. § Data of the outcomes at 3 months are shown as the estimated marginal mean, with the 95% CI in parentheses, after the 3-month follow-up adjusted for age, gender, and fracture type. # For the involved side. ** The 95% CIs of the 2 treatment groups did not overlap ($p < 0.05$, per the Bonferroni test).



Figs. 2-A through 2-D Changes in functional outcome scores, pain and activity resumption over time by treatment group.

Higher scores represent more disability (DASH), a better function (Constant-Murley), more pain (VAS), and a higher level of activity resumption (NRS). Data are shown as estimated marginal mean with the corresponding 95% CI (shown as error bars), adjusted for age, gender, and fracture type, as calculated in the multivariable analysis. Blue lines represent the plate group; red lines represent the intramedullary nailing (IMN) group. Dashed lines represent the values of the contralateral side. * $P < 0.05$ (Bonferroni test). **Fig. 2-A** The DASH overall score. **Fig. 2-B** The Constant-Murley score of the affected arm. **Fig. 2-C** Pain (VAS) on the affected side. **Fig. 2-D** The extent to which patients resumed their activities at pretrauma level (NRS) over time.



Figs 3-A through 3-D Changes in health-related quality of life over time by treatment group.

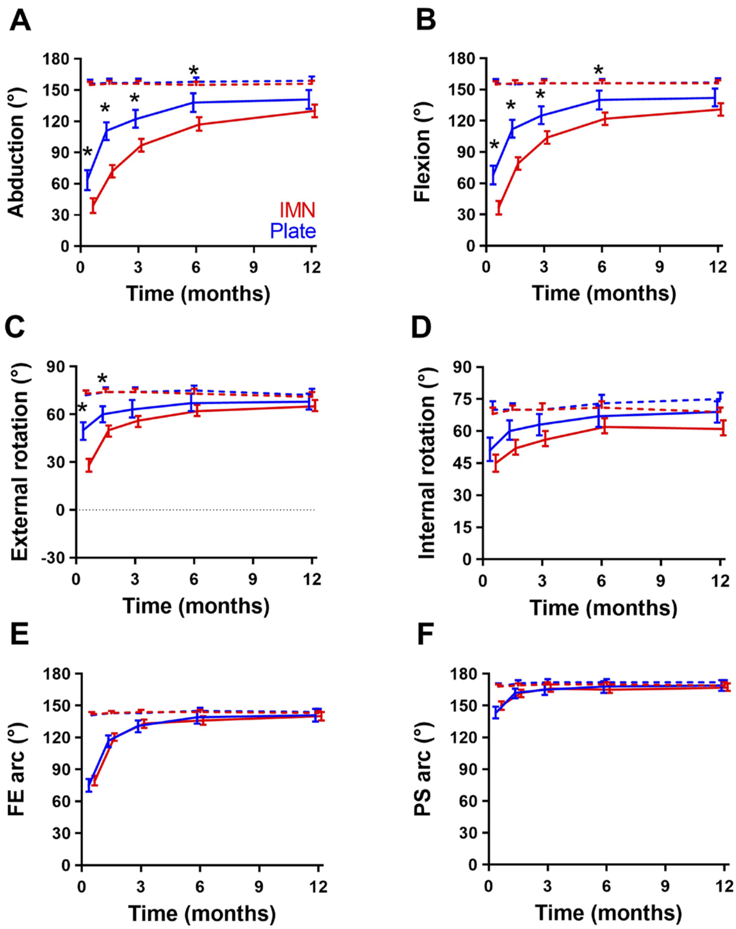
Higher scores represent better quality of life. Data are shown as estimated marginal mean with the corresponding 95% CI (shown as error bars), adjusted for age, gender, and fracture type, as calculated in the multivariable analysis. Blue lines represent the plate group; red lines represent the intramedullary nailing (IMN) group. **Fig. 3-A** SF-36 Physical Component Summary (PCS); the dashed lines represent the mean and the standard deviation (50 ± 10) that was used for normalizing the data. **Fig. 3-B** SF-36 Mental Component Summary (MCS); the dashed lines represent the mean and the standard deviation (50 ± 10) that was used for normalizing the data. **Fig. 3-C** EQ-5D utility score (EQ-US). **Fig. 3-D** EQ-VAS over time.

Shoulder and Elbow Ranges of Motion

Changes in range of motion are shown in Figure 4, Table II, and Appendix Supplemental Table S1. Shoulder range of motion showed a significant treatment effect in favor of plating ($p_{treatment} < 0.001$) (Figs. 4-A through 4-D). Abduction, flexion, and external rotation also showed a significant interaction with time ($p < 0.001$). Treatment had no significant effect on elbow range of motion (Figs. 4-E and 4-F).

Complications and Secondary Surgical Interventions

Complications (in 58 patients [23.7%]) did not differ significantly ($p = 0.417$) between the plating group (19.7%) and the nailing group (25.4%) (Table III). Complications were unrelated to the type of intramedullary nail. In 30 patients, the complication required secondary surgical intervention, primarily in the nailing group (28 patients, compared with 2 in the plating group; $p < 0.001$). One deep infection occurred in the nailing group. After irrigation and debridement, the intramedullary nail was removed. Two patients in the plating group had implant-related complications. One patient had screw cutout that did not require treatment. In the second patient, the plate was not long enough to span the fracture plane and was replaced. The vast majority of implant-related complications occurred in the nailing group. These were mostly nail protrusion ($n = 13$) or screw protrusion ($n = 8$), but screw cutout ($n = 1$), an inadequate implant type ($n = 1$), and chronic pain ($n = 1$) also occurred. In 16 patients in the nailing group, the nail was removed, and, in 2 other patients, the implant was replaced. Postoperative radial nerve palsy without preoperative symptoms was more prevalent after plating (8 patients [10.5%]) than after nailing (1 patient [0.6%]) ($p < 0.001$); it fully recovered in 83.3% of patients after plating and 100% of patients after nailing ($p = 1.000$). Nonunion rates did not differ between the plating group (3 patients [5.7%]) and the nailing group (16 patients [11.9%]) ($p = 0.285$). Revision surgery due to nonunion was performed in 1 patient in the plating group and 9 patients in the nailing group.



Figs. 4-A through 4-F Changes in ranges of motion of the shoulder and elbow over time by treatment group.

Higher scores represent better range of motion. Data are shown as the estimated marginal mean with the corresponding 95% CI (shown as error bars), adjusted for age, sex, and fracture type, as calculated in the multivariable analysis. Blue line represent the plating group; red lines represent the intramedullary nailing (IMN) group. Dashed lines represent the values of the contralateral side. * P <0.05 (Bonferroni test). FE = flexion-extension, and PS = pronation-supination. The graphs show abduction (**Fig. 4-A**), flexion (**Fig. 4-B**), external rotation (**Fig. 4-C**), and internal rotation of the shoulder (**Fig. 4-D**), and flexion-extensino arc (**Fig. 4-E**) and pronation-supination arc of the elbow over time (**Fig. 4-F**).

Table III – Complications and secondary interventions by treatment group*

	All (N=245)		Plate (N=76)		IMN (N=169)		P
	Patients with Available Data	**Value†**	**Patients with Available Data**	**Value†**	**Patients with Available Data**	**Value†**	**Value‡**
Any complication	245	58 (23.7%)	76	15 (19.7%)	169	43 (25.4%)	0.417
Any surgical reintervention	245	30 (12.2%)	76	2 (2.6%)	169	28 (16.6%)	**0.001**
Cuff pathology	245	3 (1.2%)	76	0 (0.0%)	169	3 (1.8%)	0.554
Superficial infection	245	5 (2.0%)	76	3 (3.9%)	169	2 (1.2%)	0.175
Deep infection	245	1 (0.4%)	76	0 (0.0%)	169	1 (0.6%)	1.000
Drainage and implant removal		1		NA		1	NA
Implant-related complication	245	26 (10.6%)	76	2 (2.6%)	169	24 (14.2%)	**0.006**
Screw cutout		2		1		1	
Inadequate implant type		1		0		1	
Nail protrusion		13		0		13	
Screw protrusion		8		0		8	
Inadequate implant size		1		1		0	
Chronic pain		1		0		1	
Implant exchange		3		1		2	
Implant removal		16		0		16	
Post-operative radial nerve apraxia	245	9 (3.7%)	76	8 (10.5%)	169	1 (0.6%)	**<0.001**
Full recovery	21	18 (85.7%)	18	15 (83.3%)	3	3 (100.0%)	1.000
Nonunion	188	19 (10.1%)	53	3 (5.7%)	135	16 (11.9%)	0.285
Revision osteosynthesis		10		1		9	

* NA = not applicable. † The values are given as number of patients, with or without the percentage in parentheses. ‡ Chi-square test for categorical variables or Mann Whitney U test for continuous variables. Bold p values are significant.

DISCUSSION

This study showed faster functional recovery, as measured by the DASH score, after plating, but the plating and nailing groups had similar DASH scores at 12 months. The plating group showed superior Constant-Murley scores and shoulder range of motion after plating until 6 months after trauma. Significantly more surgical reinterventions were needed in the nailing group, which also showed more implant-related complications.

A previous randomized controlled trial showed superior Constant-Murley scores for minimally invasive plate osteosynthesis (MIPO) at 95.3 points compared with intramedullary nailing at 89.0 points at 12 months.[7] The difference at 12 months in the current study is within the same range. Superior scores for plating after 2 years were reported in a large cohort study of >400 participants: 90.3 points compared with 82.1 points.[8] In other studies, with a follow-up of 1 to 2 years, the University of California Los Angeles (UCLA) shoulder score and the American Shoulder and Elbow Surgeons (ASES) score did not differ between plating and nailing.[4–6] This lack of significance may be due to the sample size of <25 per group.

Similar to the Constant-Murley score, shoulder abduction, flexion, and external rotation improved faster after plating than after nailing. This may be the consequence of introducing an intramedullary nail through the supraspinatus tendon. Three recent meta-analyses[1–3] mentioned only 1 study that showed superior shoulder abduction after MIPO.[21]

The current study showed a 6.4-fold greater reintervention rate and a 5.5-fold greater implant-related complication rate in the nailing group. The risk of a technical error seems higher after nailing. The main indication for revision surgery in this group was nail protrusion, which may explain the inferior shoulder function (i.e., Constant-Murley score and shoulder range of motion) in this group. The literature has been inconclusive, with 1 meta-analysis showing a significantly higher revision rate after nailing (odds ratio [OR], 0.29; p = 0.02) and 2 reporting no significant difference (risk ratio [RR], 0.40, and OR, 1.21; p > 0.05).[1–3]

Only 6 (2.4%) of 245 patients developed a postoperative infection, with no meaningful difference between the treatment groups. Previous meta-analyses, all with <5% infection rates, showed either no effect of treatment or a higher infection rate after nailing or plating than in our data.[1,22]

The current study showed no significant difference in nonunion rates between plating (5.7%) and nailing (11.9%), although the study may have been underpowered for this outcome. This was in line with 2 recent meta-analyses[1,3], in which rates for plating were reported to be 3.0% and 5.6% and rates for nailing were reported to be 4.3% and 6.9%. The nonunion rate of 9.0% after nailing reported by van de Wall et al.[2] was in line with our study. However, the low nonunion rate in the plating group in their meta-analysis (1.2%) resulted in a significantly lower risk of nonunion in the MIPO group than in the nailing group (OR, 0.18; p = 0.002).[2]

Secondary radial nerve palsy was observed more commonly after plating (10.5%) than after nailing (0.6%) (p < 0.001). The lower risk of palsy after nailing than after plating was in line with a meta-analysis of 26 studies (2.5% compared with 6.9%; OR, 0.44; p < 0.001).[1] Other recent meta-analyses showed no effect of osteosynthesis (MIPO compared with nailing and MIPO or open reduction plate osteosynthesis [ORPO] compared with nailing) on secondary radial nerve palsy.[2,3] Nerve function recovered spontaneously during follow-up in all but 3 patients in the plating group, leading to a 1-year risk of nerve palsy of 3.9% in this group.

Strength and Limitations

A strength of this prospective, multicenter study is the large sample size. The study was designed to achieve the best possible outcome for either treatment group by allowing surgeons to treat individual patients according to the operative procedure with which they had extensive experience. Moreover, the treatment heterogeneity across participating hospitals that resulted from not standardizing perioperative care or rehabilitation will have increased the generalizability of the results. However, lack of standardization may have caused an unknown bias in the results. Nevertheless, given the number of sites and therefore the differences in implants and surgical approaches used, it is unlikely that a specific technique has either caused or masked a significant difference between the treatment groups. This is also supported by the fact that 85% of the participating surgeons used only 1 type of implant.

A limitation inherent to observational studies was that some imbalance in baseline data across the treatment groups was noted. However, we were able to correct for this in the linear mixed-effects models. Furthermore, despite our efforts, some bias due to missed follow-up visits could not be ruled out. The rates of loss to follow-up were 7% after plating and 4.1% after nailing, which are low and unlikely to represent an important differential.

CONCLUSION

The plating of a humeral shaft fracture in adults results in faster functional recovery, especially of shoulder function. Plating was associated with more temporary nerve palsies, but fewer implant-related complications and surgical reinterventions, than nailing. Despite heterogeneity in implants and surgical approach, plating seems to be the preferred treatment option for these fractures.

Supplemental Table S1. Functional outcome and range of motion of the shoulder and elbow over time by treatment group, based upon univariate and multivariable repeated measure analysis

	Time	Univariate analysis							Multivariable, repeated measure analysis	
		N*	All (N=245)	N*	Plate (N=76)	N*	IMN (N=169)	P-value	Plate (N=76)	IMN (N=169)
DASH	2 we	227	48.3 (33.9-58.3)	69	48.3 (32.5-59.6)	158	47.5 (35.0-58.3)	0.880	48.9 (45.0-52.9)	48.3 (45.5-51.1)
	6 we	229	29.2 (17.5-43.3)	68	22.1 (12.5-40.4)	161	31.7 (20.4-44.6)	**0.001**	29.6 (25.6-33.5)	35.5 (32.7-38.3)
	3 mo	220	17.5 (7.5-30.6)	63	11.7 (3.3-29.2)	157	18.3 (9.2-30.9)	0.068	21.9 (17.9-25.9)	23.0 (20.2-25.8)
	6 mo	209	8.3 (2.5-18.3)	60	5.8 (1.9-17.1)	149	9.2 (2.5-20.0)	0.266	14.7 (10.6-18.8)	15.6 (12.7-18.4)
	12 mo	217	3.3 (0.0-14.2)	64	2.5 (0.0-12.3)	153	3.3 (0.0-15.0)	0.718	11.7 (7.6-15.7)	11.2 (8.3-14.0)
Constant-Murley	2 we	NA	NA	NA	NA	NA	NA	NA	NA	NA
	6 we	220	41 (27-58)	68	58 (39-71)	152	36 (25-51)	**<0.001**	**52 (47-56)**	**38 (34-41)**
	3 mo	218	55 (39-72)	63	68 (50-78)	155	52 (37-65)	**<0.001**	**61 (56-65)**	**51 (48-54)**
	6 mo	205	70 (56-82)	59	77 (64-84)	146	69 (55-78)	**0.002**	71 (66-75)	63 (60-67)
	12 mo	213	77 (65-84)	63	82 (74-87)	150	75 (62-83)	**0.001**	76 (72-80)	70 (67-73)
Pain (VAS)	2 we	226	3.4 (1.9-5.7)	69	2.6 (1.6-5.0)	157	3.9 (1.9-6.0)	**0.049**	3.7 (3.1-4.3)	4.3 (3.9-4.7)
	6 we	228	2.3 (0.9-5.0)	68	1.0 (0.0-3.0)	160	3.0 (1.3-5.6)	**<0.001**	**2.2 (1.7-2.8)**	**3.7 (3.3-4.1)**
	3 mo	220	1.5 (0.2-4.4)	63	0.9 (0.0-2.9)	157	1.7 (0.6-4.9)	**0.001**	2.1 (1.5-2.7)	3.0 (2.6-3.4)
	6 mo	208	0.9 (0.0-2.1)	60	0.7 (0.0-1.5)	148	1.0 (0.0-2.3)	0.128	1.7 (1.1-2.3)	2.1 (1.6-2.5)
	12 mo	217	0.0 (0.0-1.7)	64	0.0 (0.0-1.4)	153	0.0 (0.0-1.8)	0.667	1.4 (0.8-2.0)	1.6 (1.2-2.0)
Activity resumption (NRS)	2 we	NA	NA	NA	NA	NA	NA	NA	NA	NA
	6 we	228	5 (3-8)	79	5 (0-8)	158	5 (3-7)	0.434	4.6 (3.9-5.3)	4.9 (4.4-5.4)
	3 mo	217	8 (5-9)	63	7 (4-9)	155	8 (5-9)	0.061	6.0 (5.3-6.7)	6.8 (6.3-7.3)
	6 mo	207	9 (7-10)	60	9 (6-10)	147	9 (7-10)	0.107	7.4 (6.7-8.1)	8.1 (7.6-8.6)
	12 mo	211	10 (9-10)	63	10 (9-10)	148	10 (9-10)	0.227	8.9 (8.2-9.6)	8.9 (8.4-9.4)
SF-36 PCS	2 we	214	34 (30-38)	64	34 (31-39)	150	34 (29-37)	0.176	33 (31-35)	33 (31-34)
	6 we	210	38 (33-43)	62	41 (37-45)	148	36 (33-43)	**0.003**	40 (37-42)	37 (35-38)
	3 mo	207	44 (38-51)	62	48 (40-53)	145	43 (36-50)	**0.004**	45 (43-47)	42 (41-44)
	6 mo	196	51 (43-55)	58	51 (46-55)	138	51 (42-55)	0.356	48 (46-50)	47 (45-48)
	12 mo	211	52 (45-57)	62	54 (48-48)	149	52 (44-57)	0.113	49 (47-52)	48 (47-50)
SF-36 MCS	2 we	214	55 (47-61)	64	52 (43-58)	150	56 (49-62)	**0.005**	50 (47-52)	54 (52-55)
	6 we	210	57 (49-61)	62	55 (46-61)	148	57 (50-61)	0.099	51 (49-54)	54 (53-56)
	3 mo	207	58 (54-61)	62	57 (52-60)	145	59 (54-62)	**0.036**	53 (51-56)	55 (53-57)
	6 mo	196	57 (54-60)	58	57 (52-59)	138	58 (54-60)	0.170	53 (51-56)	55 (53-57)
	12 mo	211	58 (53-60)	62	57 (52-59)	149	58 (55-61)	**0.018**	53 (51-56)	56 (54-58)

EQ-5D-US	2 we	228	0.67 (0.43-0.73)	69	0.61 (0.43-0.81)	159	0.68 (0.43-0.73)	0.334	0.56 (0.52-0.61)	0.56 (0.52-0.59)
	6 we	228	0.73 (0.61-0.84)	68	0.81 (0.70-0.90)	160	0.73 (0.61-0.81)	**0.001**	0.74 (0.69-0.79)	0.67 (0.63-0.70)
	3 mo	220	0.81 (0.73-0.90)	63	0.84 (0.81-1.00)	157	0.81 (0.72-0.90)	**0.027**	0.79 (0.74-0.84)	0.76 (0.73-0.79)
	6 mo	209	0.84 (0.78-1.00)	60	0.90 (0.81-1.00)	149	0.84 (0.76-1.00)	**0.042**	0.85 (0.80-0.90)	0.81 (0.77-0.84)
	12 mo	215	1.00 (0.81-1.00)	64	1.00 (0.81-1.00)	151	0.90 (0.81-1.00)	0.593	0.85 (0.80-0.89)	0.85 (0.81-0.88)
EQ-5D-VAS	2 we	226	75 (65-80)	68	75 (62-80)	158	75 (65-80)	0.971	70 (66-73)	72 (69-74)
	6 we	231	75 (70-80)	69	80 (70-80)	162	75 (70-81)	0.426	74 (71-78)	74 (71-76)
	3 mo	219	80 (70-85)	63	80 (70-90)	156	80 (70-85)	0.453	76 (72-80)	76 (73-78)
	6 mo	209	80 (75-90)	60	80 (78-90)	149	80 (70-90)	0.073	80 (76-84)	76 (74-79)
	12 mo	217	80 (75-90)	64	80 (75-90)	153	80 (75-90)	0.995	79 (76-83)	80 (77-82)
Shoulder abduction (º)	2 we	161	55 (30-80)	54	78 (49-95)	107	45 (24-65)	**<0.001**	**64 (54-73)**	**39 (32-46)**
	6 we	232	80 (50-125)	70	133 (85-155)	162	65 (45-95)	**<0.001**	**111 (102-119)**	**72 (66-78)**
	3 mo	220	105 (73-145)	63	140 (90-160)	157	95 (65-133)	**<0.001**	**122 (114-131)**	**97 (91-103)**
	6 mo	207	140 (105-160)	59	155 (140-165)	148	130 (95-155)	**<0.001**	**138 (129-147)**	**117 (111-124)**
	12 mo	215	150 (115-165)	64	160 (136-165)	151	150 (110-160)	**<0.001**	141 (132-150)	130 (124-136)
Shoulder flexion (º)	2 we	158	53 (25-85)	54	83 (58-106)	104	40 (20-65)	**<0.001**	**68 (59-77)**	**37 (30-43)**
	6 we	232	90 (56-130)	70	130 (95-155)	162	80 (50-115)	**<0.001**	**112 (104-121)**	**79 (73-85)**
	3 mo	220	118 (90-145)	63	135 (115-155)	157	110 (80-135)	**<0.001**	**125 (117-134)**	**104 (98-110)**
	6 mo	207	140 (110-155)	59	155 (140-160)	148	130 (105-155)	**<0.001**	**140 (131-149)**	**122 (116-128)**
	12 mo	215	150 (125-160)	64	158 (141-165)	151	145 (115-155)	**<0.001**	142 (134-151)	131 (125-137)
Shoulder external rotation (º)	2 we	156	40 (15-60)	52	60 (40-75)	104	30 (10-45)	**<0.001**	**50 (44-55)**	**28 (24-32)**
	6 we	231	60 (40-70)	70	65 (54-80)	161	50 (35-65)	**<0.001**	**60 (55-65)**	**50 (46-53)**
	3 mo	220	60 (45-75)	63	65 (50-85)	157	55 (45-70)	**0.001**	63 (58-69)	56 (52-59)
	6 mo	207	65 (55-80)	59	70 (60-85)	148	65 (51-75)	**0.042**	67 (62-73)	62 (59-66)
	12 mo	215	70 (55-80)	64	70 (60-80)	151	65 (55-80)	0.103	68 (63-73)	65 (62-69)
Shoulder internal rotation (º)	2 we	149	60 (38-70)	51	60 (40-70)	98	50 (29-66)	0.105	51 (46-57)	45 (41-49)
	6 we	228	60 (45-70)	69	65 (50-70)	159	60 (40-65)	**<0.001**	60 (56-65)	52 (49-56)
	3 mo	218	60 (45-70)	63	70 (50-75)	155	60 (43-70)	**0.002**	63 (58-68)	56 (53-60)
	6 mo	207	65 (55-75)	59	70 (60-80)	148	65 (55-70)	**0.020**	67 (62-72)	62 (59-66)
	12 mo	215	65 (50-75)	64	70 (60-85)	151	60 (45-75)	**<0.001**	69 (64-74)	61 (58-65)
Elbow flexion-extension arc (º)	2 we	153	75 (55-105)	51	75 (55-95)	102	80 (55-110)	0.283	75 (69-81)	79 (75-84)
	6 we	230	125 (110-135)	70	125 (99-134)	160	125 (111-135)	0.267	117 (111-122)	120 (117-124)
	3 mo	220	135 (125-145)	63	135 (125-145)	157	135 (125-145)	0.955	131 (125-136)	133 (129-137)
	6 mo	207	140 (130-145)	59	140 (135-145)	148	140 (130-145)	0.674	139 (133-145)	136 (132-140)
	12 mo	215	145 (135-148)	64	145 (135-145)	151	145 (135-148)	0.816	141 (135-147)	140 (136-144)

Supplemental Table S1. Functional outcome and range of motion of the shoulder and elbow over time by treatment group, based upon univariate and multivariable repeated measure analysis

	Time	Univariate analysis							Multivariable, repeated measure analysis	
		N*	All (N=245)	N*	Plate (N=76)	N*	IMN (N=169)	P-value	Plate (N=76)	IMN (N=169)
Elbow pronation-supination arc (º)	2 we	162	160 (144-170)	53	160 (135-170)	109	160 (150-170)	0 459	143 (138-149)	150 (146-154)
	6 we	232	165 (156-170)	70	165 (155-175)	162	165 (159-170)	0.693	162 (157-166)	162 (158-165)
	3 mo	221	170 (160-175)	63	170 (165-175)	158	170 (160-175)	0.336	165 (160-170)	166 (163-170)
	6 mo	207	170 (165-175)	59	170 (165-180)	148	170 (160-175)	0.334	168 (162-173)	165 (162-169)
	12 mo	215	170 (164-175)	64	170 (165-180)	151	170 (160-175)	0.302	169 (164-174)	167 (164-171)

Data for the univariate analysis are presented as median (P_{25} to P_{75}), data for the repeated measure multivariable analysis are shown as estimated marginal mean with 95% confidence interval.

N* represents the number of patients for whom data were available per follow-up moment.

DASH, Disabilities of the Arm, Shoulder, and Hand; EQ-5D, EuroQoL-5D; IMN, Intramedullary nail; MCS, Mental Component Summary; Mo, month; NRS, Numerical Rating Scale, PCS, Physical Component Summary; SF-36, Short Form-36; US, Utility Score; VAS, Visual Analog Scale; We, week.

Supplemental Table S2. Work and sports participation pretrauma and post-trauma resumption of study participants by treatment group

		N*	All (N=245)	N*	Plate (N=76)	N*	IMN (N=169)	P-value
Work								
Paid work (N patients)		245	136 (55.5%)	76	46 (60.5%)	169	90 (53.3%)	0.331
	Hours per week	134	38 (32-40)	45	36 (26-40)	89	40 (32-40)	0.348
Exertional level								
	Light, mainly sedentary	136	64 (47.1%)	46	22 (47.8%)	90	42 (46.7%)	0.359
	Medium work		49 (36.0%)		19 (41.3%)		30 (33.3%)	
	Heavy or very heavy work		23 (16.9%)		5 (10.9%)		18 (20.0%)	
Work absence		134	123 (91.8%)	45	41 (91.1%)	89	82 (92.1%)	1.000
Work days missed		134	26 (12-49)	45	24 (14-35)	89	28 (12-63)	0.372
Sports or hobby								
Sports or hobby (N patients)		245	242 (98.8%)	76	76 (100.0%)	169	166 (98.2%)	0.554
	Hours per week	240	16 (9-30)	76	14 (8-25)	164	18 (10-30)	0.137
	Resumption at 12 months	215	214 (99.5%)	63	63 (100.0%)	152	151 (99.3%)	1.000

Data are presented as N (%) or median (P_{25} to P_{75}) and were analyzed using a Chi-squared test and Mann-Whitney U-test, respectively.

N* represents the number of patients for whom data were available per follow-up moment.

IMN, Intramedullary nail.

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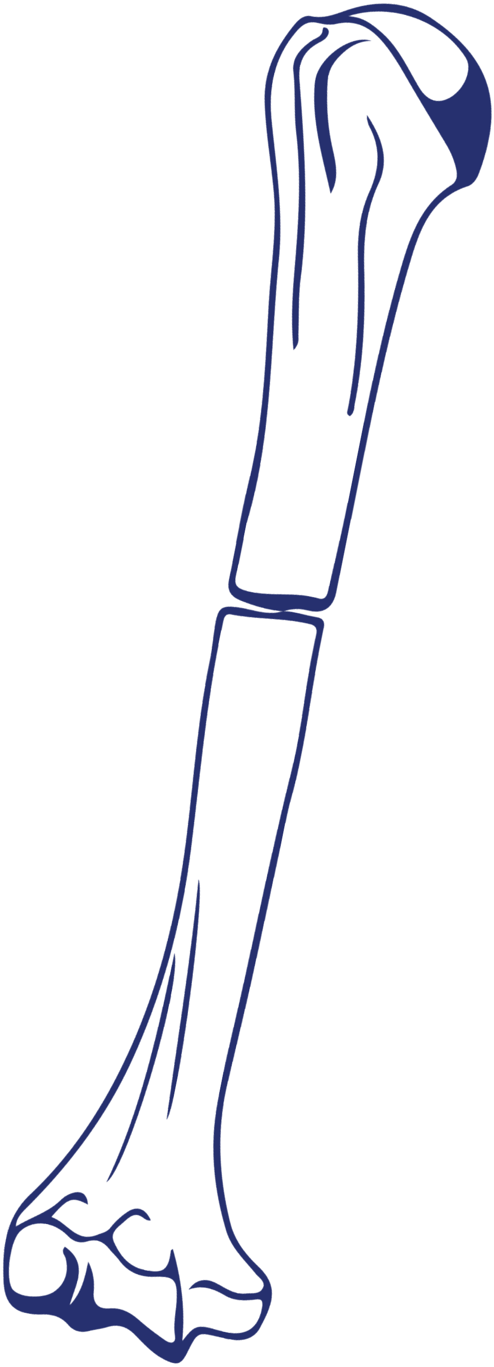

CHAPTER 5

Recovery and functional outcome after radial nerve palsy in adults with a humeral shaft fracture: a multicenter prospective case series

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ABSTRACT

Background: The consequences of radial nerve palsy associated with a humeral shaft fracture are unclear. The aim of this study was to examine the functional recovery of radial nerve palsy, at presentation or postoperatively, in patients with a humeral shaft fracture.

Methods: Data from patients who participated in the HUMeral shaft fractures: measuring recovery after operative versus non-operative treatment (HUMMER) study, a multicenter prospective cohort study including adults with a closed humeral shaft fracture Arbeitsgemeinschaft für Osteosynthesefragen (AO) type 12A or 12B, and had radial nerve palsy at presentation or postoperatively, were extracted from the HUMMER database. The primary outcome measure was clinically assessed recovery of motor function of the radial nerve. Secondary outcomes consisted of treatment, functional outcome (Disabilities of the Arm, Shoulder, and Hand and Constant-Murley Score), pain level, quality of life (Short Form-36 and EuroQoL-5D-3L), activity resumption, and range of motion of the shoulder and elbow joint at 12 months after trauma.

Results: Three of the 145 nonoperatively treated patients had radial nerve palsy at presentation. One recovered spontaneously and 1 after osteosynthesis. Despite multiple surgical interventions, the third patient had no recovery after entrapment between fracture fragments. Thirteen of the 245 operatively treated patients had radial nerve palsy at presentation; all recovered. Nine other patients had post-operative radial nerve palsy; 8 recovered. One had ongoing recovery at the last follow-up, after nerve release and suture repair due to entrapment under the plate. At 12 months, the functional outcome scores of all patients suggested full recovery regarding functional outcome, pain, quality of life, activity resumption, and range of motion.

Conclusion: Radial nerve palsy in patients with a humeral shaft fracture at presentation or post-operatively functionally recovers in 94% and 89%, respectively.

BACKGROUND

Radial nerve palsy is associated with humeral shaft fractures, whether primary due to the initial trauma or secondary as a consequence of treatment.[5, 8, 11, 13, 15, 19, 24, 31] The radial nerve is at risk due to its complex course, winding around the humeral shaft, and its close relationship to surrounding structures.[8, 11, 15, 19, 31] As the radial nerve provides motor and sensory function to the arm, nerve damage can result in inability to extend and stabilize the wrist, also known as a wrist drop. Damage to the radial nerve causes difficulties in daily life as it severely compromises function and hand use.[15, 21]

The reported rate of radial nerve palsy at presentation is approximately 10%.[11] Reported rates of postoperative radial nerve palsy range from 3%-7%.[2, 5, 11, 29] Postoperative radial nerve palsy can be caused by manipulation and reposition, leading to neurapraxia, entrapment in the fracture site or compression by hardware, causing severe partial or complete lesions.[15] Even though plate osteosynthesis with open reduction and internal fixation allows for direct visualization of the radial nerve, the implant placement, soft tissue preparation, and intraoperative nerve exploration increase the risk of iatrogenic radial nerve damage.[5, 20] Inherent to the treatment with intramedullary nailing (IMN), a risk of injuring the radial nerve arises due to manipulation of the fracture and the placement of distal screws nearby the radial nerve's circuitous course around the distal humeral bone.[10, 16, 20, 27, 32] A literature review, comparing plate osteosynthesis and IMN, has found similar rates of postoperative radial nerve palsy in both treatments.[35]

The influence of an existing or potential radial nerve palsy on the choice of the treatment of a humeral shaft fracture is not straightforward. The majority of palsies (88%-100%) will recover spontaneously in weeks to months after trauma.[2, 11, 23] Therefore, Bishop and Ring concluded that there is no reason to solely operate on closed humeral shaft fractures because radial nerve palsy is present after trauma, and clinical monitoring is initially the best option.[3] If signs of nerve recovery remain absent (after 4 months) or ultrasonography shows nerve damage, treatment is indicated. This can either be done with nonoperative treatment, such as bracing, rehabilitation, and electrostimulation, or surgical treatment, consisting of exploration, suture repair, and nerve and tendon transfer.[15, 22, 31] However, the optimal treatment of radial nerve palsy and its influence on the choice of treatment of a humeral shaft fracture is currently controversial in clinical practice.

This prospective multicenter case series was performed as a secondary analysis to a large prospective cohort study of 390 patients with a closed humeral shaft fracture and reflects routine clinical practice. The aim of this study was to examine the consequences of a radial nerve palsy, at presentation and postoperatively, for patients with a closed humeral shaft fracture in terms of recovery and functional outcome in routine clinical practice.

METHODS

Setting and participants

This case series was performed as a secondary analysis of the HUMeral shaft fractures: measuring recovery after operative versus non-operative treatment (HUMMER) study, a multicenter prospective cohort study conducted at 29 hospitals. The study design, methods, and primary outcome have been reported elsewhere.[7, 17] The HUMMER study was exempted by the local Medical Research Ethics Committee (no. MEC-2012-296) and recruited patients between October 23, 2012, and October 03, 2018. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting of observational studies were followed.[30] All patients gave written informed consent.

All patients aged 18 years or older with a closed humeral shaft fracture (Arbeitsgemeinschaft für Osteosynthesefragen [AO] type 12A or 12B; confirmed on X-ray) included in the HUMMER study, who either had radial nerve palsy at presentation or postoperatively, were included in this case series.

Assessments and follow-up

Baseline patient characteristics (ie, age, gender, and dominance of the affected arm) and injury-related variables known to be associated with radial nerve palsy (ie, mechanism of injury, fracture location, and classification (according to the AO/Orthopaedic Trauma Association classification system) were extracted.[9] The approach of fracture reduction (open or closed) and choice of treatment of the humeral shaft fracture was left up to the treating physician and was not dictated by the presence of radial nerve palsy at presentation.

The primary outcome measure was clinically assessed recovery of the radial nerve at 12 months follow-up. Recovery was defined as full recovery of motor function, including grip strength and wrist extension. Recovery of the radial nerve palsy was recorded during follow-up in the HUMMER study and based upon documented clinical assessment of recovery of motor function, as mentioned in the Dutch guidelines.[28]

Secondary outcomes extracted were the Disabilities of the Arm, Shoulder, and Hand (DASH) (ranging from 0-100 points, with a lower score representing less disability) and the Constant-Murley score (ranging from 0-100 points, with a higher score representing better outcome) at 12 months follow-up.[1, 6, 12] Furthermore, pain (Visual Analog Score [VAS]; ranging from 0-10 points, with a higher score representing more pain), health-related quality of life (Short Form-36 [SF-36] and EuroQoL-5D-3L [EQ-5D], with a higher score representing better quality of life), activity resumption (Numeric Rating Scale [NRS]; the extent to which patients resumed their activities at the pretrauma level), and range of motion of the shoulder and elbow joints, at 12 months follow-up were extracted.[4, 33, 34] Quality of life scores were compared with published population norms (EQ-5D) or standardized combined scores (SF-36, mean of 50 ± 10 standard deviation [SD]).[14, 26] Range of motion of the shoulder and elbow joint were compared with reference values.[25]

Statistical analysis

Analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 25 (SPSS, Armonk, NY, USA). Normality of continuous data was tested with the Shapiro-Wilk test. Descriptive statistics were used to report the data. Continuous data are shown as median and percentiles (P_{25}-P_{75}; nonparametric). Categorical data are reported as N (%). The rates of radial nerve palsy at presentation and postoperatively are reported with 95% confidence intervals (95% CI). The secondary outcomes were extracted from the HUMMER database after comparison between treatment groups using linear mixed-effects regression models, as described before.[7]

RESULTS

Patient and injury characteristics

Twenty-five patients with a radial nerve palsy were included (Fig. 1 and Table I). Three patients were lost to follow-up, however, clinical documentation of treatment and recovery was retrieved locally. Out of the 390 patients, 16 (4.1% [95% CI 2.4-6.6]) presented with radial nerve palsy after trauma, of whom 13 were operated for their humeral shaft fracture. The group of patients with radial nerve palsy at presentation consisted of 9 men (56%) and had a median age of 49 years (P_{25}-P_{75} 36–61). The mechanism of injury was frequently low energy trauma (N=11; 69%). The fractures were often spiral (N=8; 50%) and most often located in the middle of the humeral shaft (N=14; 88%).

In 13 of the 245 operatively treated patients, postoperative radial nerve palsy could not be assessed, as they were already diagnosed with radial nerve palsy at presentation. Nine out of remaining 232 (3.9% [95% CI 1.8-7.2]) operatively treated patients showed a postoperative radial nerve palsy, of which 5 men (56%) and a median age of 32 years (P_{25}-P_{75} 30–63). Eight (89%) of these patients were treated with plate osteosynthesis and 1 (11%) with IMN. The mechanism of injury was frequently low energy trauma (N=7; 78%). Six (67%) out of 9 patients had a spiral fracture. The fractures were located in the distal (N=4; 44%), middle (N=4; 44%), and proximal (N=1; 12%) third of the humeral shaft.

Treatment and recovery of radial nerve palsy at presentation

Three nonoperatively treated patients had radial nerve palsy at presentation, of whom 2 (67%) recovered. One (33%) recovered spontaneously. The other one (33%) recovered after secondary osteosynthesis with open plating 16 days post-trauma, with reported identification of an intact radial nerve, and postoperative treatment with a cock-up splint. The third (33%) patient did not regain radial nerve function. A secondary osteosynthesis with a retrograde IMN, 18 days post-trauma, without identification of the radial nerve was performed. An explorative revision surgery, 71 days post-trauma, showed a crushed radial nerve entrapped between fracture fragments. Subsequent nerve grafting, 7 months post-trauma, did not result in signs of improvement of function and further treatment including (cock-up) bracing and hand therapy, did not result in recovery of the radial nerve function either. The following tendon transfer also failed to restore wrist extension.

Ten (77%) of the 13 operatively treated patients with radial nerve palsy at presentation were treated with plate osteosynthesis and 3 (23%) with IMN. During surgery, the radial nerve was reported as identified in 9 (69%) out of the 13 patients. The identified radial nerve showed no macroscopic damage in 7 cases (77%) and a partial nerve lesion due to trauma in 2 cases (23%). Lesions were not addressed at the time of surgery. All operatively treated patients with radial nerve palsy at presentation spontaneously recovered after monitoring (N=10; 77%) or treatment with a brace (cock-up; N=3; 23%) or hand therapy (N=1; 8%).

Treatment and recovery of postoperative radial nerve palsy

Eight (89%) of the 9 patients with postoperative radial nerve palsy were treated for their humeral shaft fracture with plate osteosynthesis and 1 (11%) with IMN. During surgery in 6 (67%) patients, the radial nerve was reported as identified and a partial macroscopic lesion was reported in 3 (50%) patients. The possible cause of the lesions was unknown. Lesions were not addressed at the time of surgery.

Postoperative radial nerve palsy recovered spontaneously without an additional surgical intervention for the nerve in 8 (89%) patients. Three (33%) patients were solely monitored and 5 (56%) were treated nonoperatively with bracing (cock-up; N=6) or rehabilitation (hand therapy; N=1). Absence of full recovery of postoperative radial nerve palsy occurred in 1 (11%) patient, after plate osteosynthesis with a Philos plate without identification of the radial nerve. An explorative revision surgery, performed 2 days later, indicated nerve release and suture repair due to entrapment under the plate. This resulted in signs of improvement and ongoing recovery at the last follow-up.

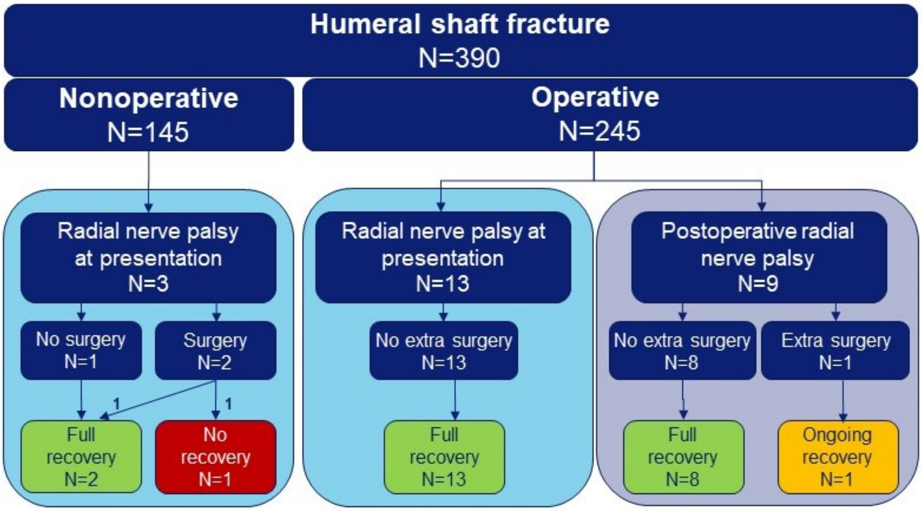

Figure 1 Flowchart of patients with radial nerve palsy in the study.

Functional outcome after radial nerve palsy

At 12 months, the mean levels of functional outcome scores of patients with a radial nerve palsy, either at presentation or postoperatively, suggested full functional recovery regarding arm function (median DASH 8.3 [P_{25}-P_{75} 7.4-11.1] and Constant-Murley 74 [P_{25}-P_{75} 72-78]; Table II). Mean pain score was 1 (P_{25}-P_{75} 1-2) and activities were resumed at pre-trauma level (mean NRS of 9 [P_{25}-P_{75} 9-9]). Health-related quality of life measured with the EQ-5D (EuroQol-5D-US [EQ-5D-US] 0.87 [P_{25}-P_{75} 0.85-0.90] and EQ-5D-VAS 81 [P_{25}-P_{75} 79-83]) were similar to the population norms (EQ-5D-US 0.89 and EQ-5D-VAS 81). The SF-36 scores (SF-36 Physical Component Summary [PCS] 50 [P_{25}-P_{75} 48-52], SF-36 Mental Component Summary [MCS] 55 [P_{25}-P_{75} 55-57]) were comparable with the standardized combined scores (SF-36 PCS 50; SF-36 MCS 50). Furthermore, functional levels of range of motion were achieved.

Table I. Patient, injury, treatment, and recovery details of radial nerve palsy in study participants.

Patient	Moment of diagnosis	Age (year)	Sex	AO classification	Location (third)	Dominant arm affected	Trauma mechanism	Treatment	Nerve identification	Macroscopic nerve lesion	Treatment of radial nerve palsy	Recovery 12 mo
1	Presentation	61	M	A1	Middle	Yes	HET	Brace	N.A.	N.A.	Secondary osteosynthesis (plate), Brace (cock-up)	Full
2	Presentation	69	M	A1	Middle	Yes	LET	Brace	N.A.	N.A.	Secondary osteosynthesis (IMN), nerve graft, brace (cock-up), hand therapy (N=40), tendon transfer	No
3	Presentation	33	M	B1	Middle	Yes	LET	Brace	N.A.	N.A.	None	Full
4	Presentation	63	F	A1	Middle	Yes	LET	IMN	N.A.	N.A.	None	Full
5	Presentation	42	M	B2	Middle	No	HET	IMN	N.A.	N.A.	None	Full
6	Presentation	74	M	A3	Middle	Yes	LET	IMN	N.A.	N.A.	None	Full
7	Presentation	52	F	A1	Middle	No	LET	Plate	Yes	No	None	Full
8	Presentation	31	F	A2	Middle	Yes	LET	Plate	Yes	No	None	Full
9	Presentation	34	F	A3	Middle	No	LET	Plate	Yes	Partial	None	Full
10	Presentation	44	F	B2	Middle	No	HET	Plate	Yes	No	None	Full
11	Presentation	53	F	B1	Distal	Yes	LET	Plate	Yes	Partial	Brace (cock-up)	Full
12	Presentation	61	M	A3	Middle	No	LET	Plate	Yes	No	None	Full
13	Presentation	20	M	B1	Distal	No	HET	Plate	Yes	No	None	Full
14	Presentation	40	M	B1	Middle	Yes	LET	Plate	Yes	No	Brace (cock-up)	Full
15	Presentation	59	M	A2	Middle	Yes	LET	Plate	No	N.A.	None	Full
16	Presentation	46	F	A3	Middle	Yes	HET	Plate	Yes	No	Brace (cock-up), hand therapy (N=13)	Full
17	Postoperative	57	M	A3	Middle	Yes	HET	IMN	No	N.A.	None	Full
18	Postoperative	65	F	B1	Middle	No	LET	Plate	Yes	Partial	None	Full
19	Postoperative	25	M	B1	Distal	Yes	LET	Plate	Yes	No	Brace (cock-up)	Full
20	Postoperative	32	F	A1	Distal	No	LET	Plate	No	N.A.	None	Full
21	Postoperative	30	M	B1	Distal	Yes	LET	Plate	Yes	Partial	Brace (cock-up)	Full
22	Postoperative	32	F	A1	Distal	No	LET	Plate	Yes	No	Brace (cock-up)	Full
23	Postoperative	62	M	A1	Middle	Yes	LET	Plate	Yes	Partial	Brace (cock-up)	Full
24	Postoperative	31	M	B2	Middle	Yes	HET	Plate	Yes	No	Brace (cock-up), hand therapy (N=6)	Full
25	Postoperative	63	F	B3	Proximal	No	LET	Plate	No	N.A.	Nerve suture repair, brace (cock-up)	Ongoing

AO, Arbeitsgemeinschaft für Osteosynthesefragen; *F*, Female; *HET*, High energy trauma; *IMN*, Intramedullary nailing; *LET*, Low energy trauma; *M*, Male; *Mo*, months.

Table II. Functional outcome and range of motion of patients with radial nerve palsy at 12 months after trauma

	All (N=25)	**Nonoperative treatment (N=3)**	**Operative treatment (N=22)**	
		Radial nerve palsy at presentation (N=3)	**Radial nerve palsy at presentation (N=13)**	**Postoperative radial nerve palsy (N=9)**
DASH	8.3 (7.4-11.1)	7.3 (2.5-8.7)	9.5 (7.8-11.7)	8.2 (5.7-11.8)
Constant-Murley	74 (72-78)	76 (74-82)	73 (70-77)	76 (71-80)
Pain (VAS)	1 (1-2)	1 (0-1)	1 (1-2)	1 (1-1)
Activity resumption (NRS)	9 (9-9)	9 (9-10)	9 (9-9)	9 (9-9)
SF-36 PCS	50 (48-52)	50 (49-54)	50 (48-51)	51 (48-52)
SF-36 MCS	55 (55-57)	55 (55-55)	55 (55-57)	56 (54-57)
EQ-5D-US	0.87 (0.85-0.90)	0.89 (0.87-0.93)	0.87 (0.85-0.89)	0.88 (0.84-0.91)
EQ-5D-VAS	81 (79-83)	78 (77-83)	81 (79-83)	81 (80-84)
Shoulder abduction (º)	138 (132-154)	138 (132-155)	136 (132-148)	143 (131-156)
Shoulder anteflexion (º)	140 (135-154)	140 (135-153)	138 (135-148)	145 (132-156)
Shoulder exorotation (º)	67 (64-73)	64 (62-69)	67 (65-71)	73 (63-74)
Shoulder endorotation (º)	63 (59-68)	59 (57-68)	65 (60-70)	63 (59-68)
Elbow flexion (º)	138 (137-139)	137 (135-137)	139 (138-140)	138 (137-140)
Elbow extension (º)	0 (0-2)	-4 (-4-0)	1 (0-3)	1 (0-2)
Elbow pronation (º)	85 (84-86)	82 (81-84)	85 (84-86)	85 (84-86)
Elbow supination (º)	83 (82-86)	80 (78-83)	84 (82-87)	84 (82-86)

DASH, Disabilities of the Arm, Shoulder, and Hand; *EQ-5D*, EuroQoL-5D; *MCS*, Mental Component Summary; *NRS*, Numerical Rating Scale; *PCS*, Physical Component Summary; *SF-36*, Short Form-36; *US*, Utility Score; *VAS*, Visual Analog Scale.

Data are presented as median (P_{25}-P_{75}).

The Constant-Murley score, pain score, and ranges of motion of the shoulder and elbow joint are shown for the affected side.

DISCUSSION

The results of this study indicate that almost all radial nerve palsies spontaneously reach full recovery and the rate of persistent complaints due to radial nerve palsy at presentation in the HUMMER study is 0.3% (N=1, ie, 1/390) and due to postoperative radial nerve palsy is 0.4% (N=1, ie, 1/232). This study reports lower rates of radial nerve palsy at presentation (4.1% [95% CI 2.4-6.6]) than previously reported in a similar population (10%, ie, 88/922).[11] Postoperative radial nerve palsy rates (3.9% [95% CI 1.8-7.2]) were similar as reported previously (ranging from 3%-7%).[5, 11, 29] Recovery rates of radial nerve palsy at presentation (N=15; 94%) and postoperatively (N=8; 89%) were comparable with earlier cited literature (94% and 94%, respectively).[11]

Even though a higher DASH score may be expected as specific upper extremity functionalities rated in the DASH may be compromised if patients experience loss of extension due to radial nerve palsy, the DASH scores of patients with radial nerve palsy (8.3), were comparable with the level of all HUMMER patients at the 12-month follow-up (11.0 for the nonoperative and 8.8 for the operative group).[7] Furthermore, the Constant-Murley Score, pain, activity resumption, and health-related quality of life scores were similar to those of the whole patient group, even though wrist drop can impact multiple aspects of these measures.[7] All in all, the minimal risk of an impaired radial nerve function should be explained in shared decision making; however, it should be stressed that this is most often temporary.

Considering range of motion, a possible difference was expected in elbow extension and supination, as these movements are initiated by muscles (partly) innervated by the motor branch of the radial nerve (distal of a humeral shaft fracture; m. anconeus, m. brachialis, m. extensor carpi radialis longus, and m. supinator). However, the patients with radial nerve palsy achieved functional levels of range of motion, if compared with reference values and all HUMMER patients, suggesting that radial nerve palsy did not affect range of motion or disability was compensated by other muscles (eg, m. triceps for elbow extension and m. biceps for supination).[7, 25] In future research, range of motion of the wrist (flexion, extension, radial deviation, and ulnar deviation) should be assessed to examine all motor functions of the radial nerve.

This current data suggest that radial nerve palsy at presentation is no indication for operative exploration as almost all palsies recovered spontaneously without a secondary intervention. The HUMMER study showed that there was no tendency to treat patients with radial nerve palsy at presentation operatively.[7] Nerve identification during secondary surgical procedures showed very few partial and no complete macroscopic lesions of the radial nerve, suggesting that radial nerve palsy is mostly caused by temporary neurapraxia. However, if entrapment of the nerve by fracture fragments is suspected, the use of ultrasound as a diagnostic modality is indicated, given its noninvasive nature and its ability to accurately diagnose entrapment or lesions of the radial nerve with a sensitivity and specificity of 89% and 95%, respectively.[18] In case of entrapment or lesions, immediate nerve exploration, release and suture repair is indicated to allow for recovery of nerve function.

It should be conveyed that, since postoperative radial nerve palsy is rare and almost always spontaneously recovers, persistent postoperative radial nerve palsy should be no discouragement for operative treatment of humeral shaft fractures. However, safe surgical procedures are only possible with careful nerve exploration and identification, which is most feasible during open plate osteosynthesis. Written and visual confirmation of the safe position of the radial nerve relative to the implant are desired to facilitate shared decision making in the case of persistent palsy in order to rule out the possibility of entrapment. Only if radial nerve palsy is persistent, surgical documentation is incomplete, and ultrasound implies a complete lesion or entrapment, secondary surgical exploration is indicated.

Strengths and limitations

The main strength of this case series is that the prospective design allows for generalizable and clinically relevant results. A limitation of this study is that the study design did not include a protocol for the assessment and treatment of radial nerve palsy, resulting in heterogeneity in the choice of diagnostic instruments and management strategies. Since years of experience is not included in the HUMMER database, it is unclear if the occurrence of iatrogenic radial nerve palsy in operatively treated patients could be attributed to experience of the surgeon. Furthermore, the relatively low number of cases can be critiqued, however, cannot be avoided due to the low prevalence of radial nerve palsy associated with humeral shaft fractures.

CONCLUSIONS

Radial nerve palsy in patients with a humeral shaft fracture at presentation or postoperatively functionally recovers in 94% and 89%, respectively.

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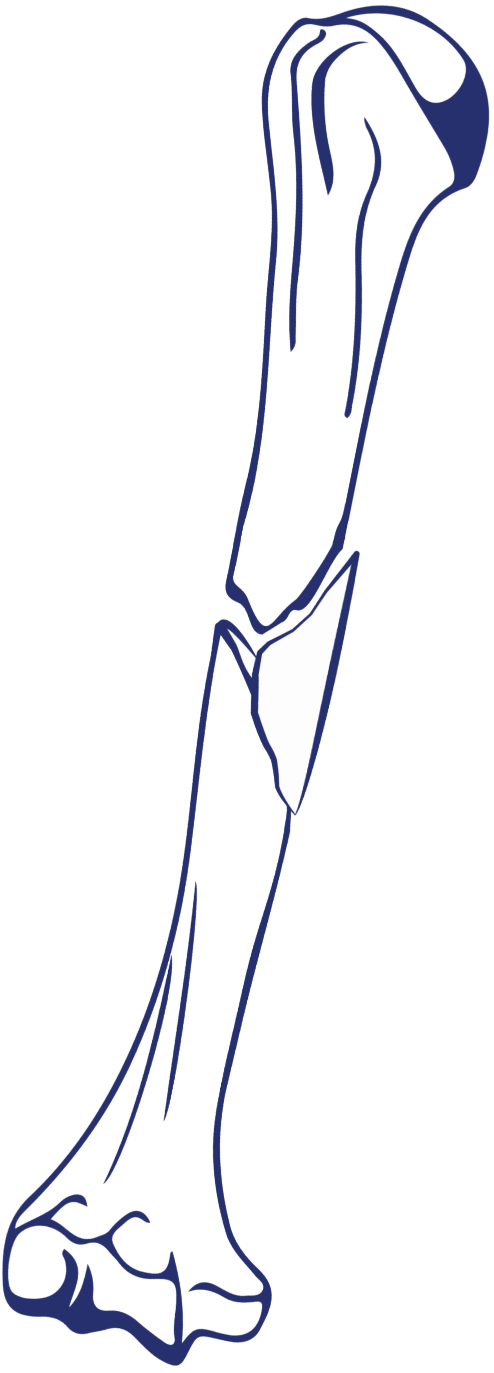
PART 4

Societal burden

Chapter 6
Economic evaluation of operative versus nonoperative treatment of a humeral shaft fracture: economic analyses alongside a multicenter prospective cohort study (HUMMER)
European Journal of Trauma and Emergency Surgery



CHAPTER 6

Economic evaluation of operative versus nonoperative treatment of a humeral shaft fracture: economic analyses alongside a multicenter prospective cohort study (HUMMER)

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ABSTRACT

Purpose: Operative treatment of a humeral shaft fracture results in faster recovery than nonoperative treatment. The cost-effectiveness, in terms of costs per Quality-Adjusted Life Year (QALY) gained (Dutch threshold €20,000-€80,000) or minimal important change (MIC) in disability reduced (DASH 6.7), is unknown. The aim of this study was to determine cost-utility and cost-effectiveness of operative versus nonoperative treatment in adults with a humeral shaft fracture type 12A or 12B.

Methods: This study was performed alongside a multicenter prospective cohort study. Costs for health care and lost productivity until one year after trauma were calculated. The incremental cost-utility ratio (ICUR) was reported in costs per QALY (based on the EuroQoL-5D-3L (EQ-5D)) gained. The incremental cost-effectiveness ratio (ICER) was reported in costs per MIC (based on the DASH score at three months) reduced.

Results: Overall, 245 patients were treated operatively and 145 nonoperatively. In the operative group, the mean total costs per patient (€11,925 versus €8793; $p < 0.001$) and QALYs (0.806 versus 0.778; $p < 0.001$) were higher. The ICUR of operative treatment was €111,860 per QALY gained (*i.e.*, €3132/0.028). The DASH was 7.3 points ($p < 0.001$) lower in the operative group. The ICER of operative treatment was €2880 per MIC in disability reduced (*i.e.*, €3132/7.3*6.7).

Conclusion: Due to the limited effect of treatment on quality of life measured with the EQ-5D, the ICUR of operative treatment (€111,860 per QALY gained) exceeds the threshold. However, the incremental costs of €2880 per clinically meaningful difference in DASH are much lower and suggest that operative treatment for a humeral shaft fracture is cost-effective.

BACKGROUND

In an era of budget restraints on health care costs, efficient resource use is crucial and data on cost-effectiveness of treatment are gaining importance in health care budget allocation.[1-3] In the Netherlands, costs of injuries account for 5% of the total health care budget and 8% of the indirect costs resulting from all diseases.[3] However, there seems to be a paucity of evidence in the area of cost-utility and cost-effectiveness of treatment of orthopedic trauma injuries.[2] Multiple studies have shown that long bone fractures are costly in terms of direct medical costs and lost productivity.[4, 5] The burden on society of long bone fractures can be attributed to the costs of surgery, possible reinterventions, and the physical rehabilitation of patients.[5] When comparing upper extremity injuries, upper arm fractures resulted in the highest costs per case (€4440) in the Netherlands.[6] Cumulative medical costs in the Netherlands of patients, admitted due to a humeral shaft fracture only, added up to €10.6 million in 2012.[7]

Humeral shaft fractures pose a burden on society as they make up 3% of all orthopedic injuries.[8] In the Netherlands, the overall incidence rate of patients admitted for a humeral fracture per year has risen by 132% to 7.2 per 100,000 person years from 1986 to 2012, partly attributable to an aging population.[7] Incidence rate is characterized by a bimodal age distribution, affecting both young and elderly patients, which influences the pattern of health care costs.[7, 9] Fractures in young employed persons can induce high costs due to the absence of work and lost productivity.[4] Furthermore, it is established that especially medical costs of humeral shaft fractures in elderly women are substantial due to extended nursing home admission or homecare.[7, 9]

Humeral shaft fractures can be managed operatively or nonoperatively, with both treatments resulting in high union rates and excellent results.[8] Nonoperative treatment is mostly performed using a functional brace.[10] Operative treatment mostly includes plate osteosynthesis, intramedullary nailing (IMN), or external fixation for limited indications.[8] The primary results of the HUMMER study indicate, based on functional and clinical outcomes, that operative treatment should be the preferred treatment option for these fractures, as it is associated with faster functional recovery and fewer complications such as nonunion than nonoperative treatment.[11]

These findings are not yet supported by data on health care consumption and costs.[12] Policy-makers need the detailed information provided by cost-utility (CUA) and cost-effectiveness analyses (CEA) to adequately balance costs and effects with suitable thresholds of efficiency in order to provide well-informed advice on health care budget allocation.[9, 13-15] Therefore, the aim of this study was to determine cost-utility and cost-effectiveness of operative versus nonoperative treatment of adult patients with a humeral shaft fracture. The hypothesized was that operative treatment would be cost-effective, due to earlier functional recovery and lower costs for follow-up and lost productivity outweighing higher costs for initial treatment.

METHODS

Setting and participants

These economic analyses were performed alongside the observational HUMMER study.[16] The study was exempted by the local Medical Research Ethics Committee (no. MEC-2012–296) and registered at the Netherlands Trial Register (NTR3617). Patients were eligible if they (1) were aged 18 years and older (with no upper limit), (2) had a closed fracture of the humeral shaft (AO type 12A or 12B; confirmed on X-ray), (3) had provided written informed consent, and if operatively treated, (4) had an operation within 14 days after presentation to the Emergency Department.[17] Patients were excluded if they had sustained other traumatic injuries or were known to have pre-existing disorders that were expected to affect bone healing, treatment, or rehabilitation of the affected arm (*e.g.*, polytrauma, open fractures, pathological fractures, bone disorders (excluding osteoporosis), rheumatoid arthritis, or pre-existing impaired upper extremity function). Furthermore, patients with expected problems with follow-up (*e.g.,* no fixed address or cognitive impairment) or insufficient comprehension of the Dutch language were excluded. Full details on inclusion and exclusion criteria are available in the published study protocol.[16]

Treatment was left to the treating physician and consisted either of operative treatment with plate osteosynthesis or IMN, or nonoperative treatment with a splint, plaster, collar and cuff, or hanging cast, followed by a Sarmiento brace.

Outcomes measures

The effect measure for the CUA was the Quality-Adjusted Life Years (QALYs). The mean increase in QALYs during one year was calculated using the EuroQol-5D-3L (EQ-5D), a validated questionnaire recommended for assessing quality of life in trauma patients, especially for economic assessments.[18-20] Participants completed the EQ-5D at two and six weeks and three, six, and 12 months after initiation of treatment. The EQ-5D descriptive system consists of five health domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with three answer levels (no problem, moderate problem, or severe problem). Utility scores were calculated to express the health status descriptions ranging from zero to one, in which zero is death and one is full health.

The effect measure for the CEA was the Disabilities of the Arm, Shoulder, and Hand (DASH) score at three months, as at that time, a clinical difference was expected.[21] The DASH is a validated, 30-item (scored 1–5), self-report questionnaire with an overall score ranging from 0 (no disability) to 100 (severe disability), reflecting functional outcome and pain of the upper extremity.[22, 23] The minimal important change (MIC) of the DASH is 6.7 points.[21]

Health care consumption and productivity loss measurement

These economic analyses were performed from a societal perspective, following Dutch guidelines.[24, 25] Data on health care consumption and work absenteeism were collected at each scheduled follow-up contact using a custommade questionnaire based upon the Medical Consumption Questionnaire (iMCQ) and the iMTA Productivity Cost Questionnaire (iPCQ).[26, 27] Data were gathered until one year after trauma. Health care consumption included intramural and extramural medical care directly associated with diagnosis, treatment, and rehabilitation of the patient with a humeral shaft fracture. Missing data of hospital care consumption were collected during the close-out visits at each hospital.

Cost calculation

Reference prices of health care resources were derived from the Dutch manual for costing in economic evaluations where possible (Supplemental Table S1-2).[28] Other reference prices for cost categories were calculated based on data derived from the participating academic and non-academic hospitals, surgical equipment and implant firms, the NZa (Nederlandse Zorgautoriteit; Dutch Healthcare Authority), the CVZ (College voor Zorgverzekeringen; Health Care Insurance Board), or obtained from home care firms.[24, 29] Reference unit costs for 2020 (€) were used or adjusted to 2020 (€) costs with the national consumer price index.[30] Inflation was taken into account. Costs were calculated by multiplying the frequency of resource use by the unit prices per cost category. Comparison with US costs was done after applying the exchange rate (€1 = US$1.21).[31]

Indirect societal costs due to work absence were calculated using the friction cost method.[18] Costs for lost productivity were defined as the costs associated with production loss and replacement due to illness, disability, and premature death.[32] Costs for lost productivity were calculated by multiplying the cumulative duration of work absence in hours within the first 85 days after injury with the costs related to work absenteeism for different five-year age groups for employed persons aged 18–68 years (Supplemental Table S1).[33]

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences version 25 (SPSS, Chicago, Ill., USA). Missing data were not imputed. Data were averaged for patients for whom data were available. Analysis was performed according to intention to treat and all statistical tests were two-sided. Chi-squared analysis was used for statistical testing of categorical data. Functional outcomes that were repeatedly measured over time were compared between treatment groups using linear mixed-effects regression models, as described before.[11] The models included fixed effects for treatment group, age, gender, and the individual fracture types. Continuous data were analyzed using a Mann–Whitney *U* test. For the pairwise comparison of the mean costs, the bootstrap 95% confidence interval (95% CI) was computed based on 1000 replications. Since the time horizon was one year, no discounting was required for costs and health utilities. Results were reported following the CHEERS Checklist for reporting economic health evaluations.[34] A p value < 0.05 was taken as a threshold for statistical significance in all statistical tests.

The incremental cost-utility ratio (ICUR), comparing operative versus nonoperative treatment, was expressed in terms of incremental mean total costs per mean QALY gained and calculated by dividing the difference of the mean total costs by the difference of the mean increase in QALYs over 12 months. The Dutch threshold of maximum costs per QALY was used (ranging from €20,000 up to €80,000 per QALY).[9, 13-15, 35]

The incremental cost-effectiveness ratio (ICER), comparing operative treatment versus nonoperative treatment, was reported in terms of incremental costs for a clinically meaningful difference (6.7 DASH points reduced at the three months' time point). The ICER was calculated by dividing the difference of the mean total costs of the two interventions by the difference of the mean DASH score at three months and multiplied by 6.7. This ratio, with a different time interval used in the numerator and denominator, was chosen in order to compare clinical expected differences to the total costs of treatment, as a difference in DASH score was expected at three months and treatment of a humeral shaft fracture usually does not exceed one year.[16]

RESULTS

Patient characteristics and employment details

Between October 23, 2012 and October 3, 2018, 390 patients were included of whom 245 (62.8%) were treated operatively and 145 (37.2%) nonoperatively. Compared with the nonoperative group, patients in the operative group were younger (median age of 53 (P_{25}–P_{75} 35–66) versus 62 (P_{25}–P_{75} 49–71) years; $p < 0.001$) and more often male (45.6% versus 35.2%; $p = 0.044$) (Table 1). Furthermore, patients in the operative group were significantly more often employed (55.5% versus 42.8% in the nonoperative group; $p = 0.016$) and worked more hours per week (38 versus 32 h in the nonoperative group; $p = 0.016$). Twenty patients were lost to follow-up due to mortality ($N = 4$) or withdrawal of consent ($N = 16$). The total number of patients available for follow-up varied per follow-up moment, as 55 patients did not show up at least one follow-up visit.

QALY and DASH

The mean increase in QALYs during one year was 0.028 higher after operative treatment (mean of 0.806 (95% CI 0.801–0.811) versus 0.778 (95% CI 0.771–0.784) in the nonoperative group; $p < 0.001$), which was mostly attributable to a faster increase in health-related quality of life in the first six months.

There was a significant and clinically meaningful difference in DASH score of 7.3 points between the operative and nonoperative group at three months follow-up, in favor of the operative group (mean of 22.3 (95% CI 19.9–24.6) versus 29.6 (95% CI 26.6–32.6) in the nonoperative group; $p = 0.001$).

Health care consumption and work absence

An overview of the mean health care consumption and work absenteeism per patient is shown in Table 2. Patients in the operative group were all admitted to the hospital ($N = 145$, 100%) for a median stay of 2 (P_{25}–P_{75} 2–4) days. In the nonoperative group, 26 (17.9%) patients were admitted for a median stay of 2 (P_{25}–P_{75} 2–3) days. Patients in the operative group had significantly more medical imaging units during their primary stay compared to the nonoperative group (median 4 (P_{25}–P_{75} 2–4) versus 2 (P_{25}–P_{75} 2–2) units; $p < 0.001$). During follow-up, patients in the nonoperative group had significantly more medical imaging, used more devices for immobilization, and had more outpatient clinic visits. Besides that, compared with the operative group, a doubling of surgical reinterventions was found in the nonoperative group (12.2% ($N = 30$) versus 25.5% ($N = 37$); $p < 0.001$). Reinterventions in the operative group ($N = 30$) were performed due to implant-related complications ($N = 19$), nonunion ($N = 10$), and a deep infection ($N = 1$). Surgical interventions in the nonoperative group ($N = 37$) consisted of conversions to osteosynthesis of the humeral shaft fracture due to nonunion ($N = 20$), malunion ($N = 11$), pain ($N = 5$), and persistent radial nerve apraxia ($N = 2$).

Although the operative group resumed work seven days earlier (26 versus 33 days in the nonoperative group), there was no significant difference in work absence in days ($p = 0.253$).

Health care costs and costs for lost productivity

An overview of the mean health care costs per patient is shown in Table 3. The mean total costs were significantly higher in the operative group (€11,925 versus €8793 in the nonoperative group; $p < 0.001$) (Table 3). In addition, the mean total hospital costs per patient of primary stay were significantly higher in the operative group (€5159 versus €1093; $p < 0.001$). The mean costs of surgery attributed to almost half of the costs of primary stay (€2434). The mean follow-up costs per person were significantly lower in the operative group (€1377 versus €2306; $p < 0.001$). The mean costs for ambulance transport, medical imaging (primary stay), initial treatment, and hospital admission days (primary stay) were significantly higher in the operative group. The mean costs of devices for immobilization (initial treatment), medical imaging (follow-up), and mean costs related to revision surgery and consequent hospital admission days were significantly lower in the operative group

Table 1. Patient characteristics and employment details

	All (*N* = 390)		**Operative (*N* = 245)**		**Nonoperative (*N* = *145*)**		***P* value**
	N*		***N****		***N****		
Patient characteristics							
Female	390	227 (58.2%)	245	133 (54.3%)	145	94 (64.8%)	**0.044**
Age (year)	390	57 (40-68)	245	53 (35-66)	145	62 (49-71)	**<0.001**
Work							
Employed	390	198 (50.8%)	245	136 (55.5%)	145	62 (42.8%)	**0.016**
Hours per week	194	36 (27-40)	134	38 (32-40)	60	32 (21-40)	**0.016**

P values < 0.05 are shown in boldface

Data are presented as *N* (%) or median (P_{25}–P_{75})

*N** represents the number of patients for whom data were available per follow-up moment

Table 2. Mean health care consumption and work absenteeism by treatment group

		All (*N*=390)		**Operative (*N*=245)**		**Nonoperative (*N*=145)**		***P* value**
		N*		***N****		***N****		
Health care consumption - primary stay								
Ambulance transport	Rides	390	1 (0-1)	245	1 (1-1)	145	1 (1-1)	1.000
Emergency department	Visits	390	1 (1-1)	245	1 (1-1)	145	1 (1-1)	1.000
Medical imaging	Visits	390	2 (2-4)	245	4 (2-4)	145	2 (2-2)	**<0.001**
Initial treatment								
Operation time (including anesthesia)	Minutes	194	120 (96-152)	194	120 (96-152)	N.A.	N.A.	N.A.
Operation time (in theater)	Minutes	224	81 (65-112)	224	81 (65-112)	N.A.	N.A.	N.A.
Devices for immobilization	Units	390	1 (1-1)	244	1 (1-1)	145	1 (1-2)	1.000
Admission and follow-up characteristics								
Hospital	Admission	390	271 (69.5%)	245	245 (100.0%)	145	26 (17.9%)	**<0.001**
	LOS (days)	271	2 (2-4)	245	2 (2-4)	26	2 (2-3)	0.830
Health care consumption – follow-up								
Medical imaging	Units	390	11 (8-14)	245	10 (8-12)	145	12 (10-15)	**<0.001**
Devices for immobilization	Units	390	0 (0-0)	245	0 (0-0)	145	0 (0-0)	**<0.001**
Outpatient clinic	Visits	390	5 (3-6)	390	4 (3-6)	390	5 (4-7)	**<0.001**
General practitioner	Visits	318	0 (0-1)	201	0 (0-1)	117	0 (0-1)	0.341
Emergency department	Visits	318	0 (0-0)	201	0 (0-0)	117	0 (0-0)	0.970
Adverse events								
Any surgical reintervention	Number	390	67 (17.2%)	245	30 (12.2%)	145	37 (25.5%)	**0.001**
Operation time (including anesthesia)	Minutes	56	86 (43-130)	23	50 (27-99)	33	93 (69-153)	0.103
Operation time (in theatre)	Minutes	64	118 (77-172)	27	86 (52-162)	37	125 (102-192)	0.311
Hospital admission	LOS (days)	46	1 (1-3)	12	2 (1-4)	34	1 (1-3)	0.988

Discharge disposition resulting in changes in living situation								
Nursing home	LOS (days)	1	30 (30-30)	1	30 (30-30)	0	N.A.	N.A.
Care hotel	LOS (days)	7	10 (5-30)	4	8 (5-25)	3	21 (3-21)	0.721
Elderly care facility	LOS (days)	4	35 (23-84)	1	21 (21-21)	3	42 (28-42)	0.180
Rehabilitation clinic	LOS (days)	3	25 (24-25)	3	25 (24-25)	0	N.A.	N.A.
Health care consumption related to rehabilitation								
Physical therapy	Number of sessions	343	22 (10-45)	217	25 (12-48)	125	20 (10-40)	0.392
Home care	Hours	318	0 (0-0)	201	0 (0-0)	117	0 (0-0)	0.506
Other rehabilitation therapy	Number of sessions	318	0 (0-0)	201	0 (0-0)	117	0 (0-0)	0.084
Work								
Work absence	% of employed patients	196	179 (91.3%)	134	123 (91.8%)	62	56 (90.3%)	0.787
Work days missed	Days	196	30 (13-54)	134	26 (12-49)	62	33 (15-59)	0.253

P values < 0.05 are shown in boldface

Data are presented as *N* (%) or median (P_{25}–P_{75})

*N** represents the number of patients for whom data were available per follow-up moment

LOS, Length of Stay

Table 3. The mean costs (2020) (€) by treatment group

	All (*N*=390)		Operative (*N*=245)		Nonoperative (*N*=145)		Mean difference in costs	*P* value
	N*		N*		N*			
Hospital costs – primary stay								
Ambulance transport	390	391 (355-427)	245	435 (387-480)	145	317 (256-377)	118 (23 to 201)	**0.018**
Emergency department visit	390	280 (280-280)	245	280 (280-280)	145	280 (280-280)	0 (0 to 0)	-
Medical imaging	390	211 (200-222)	245	244 (231-257)	145	155 (139-174)	89 (71 to 115)	**0.001**
Initial treatment								
Surgical costs	335	1380 (1234-1520)	190	2434 (2337-2532)	N.A.	N.A.	2434 (2265 to 2526)	**0.001**
Immobilization	390	41 (36-46)	245	12 (10-15)	145	90 (82-98)	-78 (-85 to -69)	**0.001**
Hospital admission days	390	1188 (1041-1330)	245	1742 (1566-1935)	145	251 (154-350)	1491 (1336 to 1677)	**0.001**
Total hospital costs – primary stay	335	3399 (3130-3672)	190	5159 (4901-5441)	145	1093 (974-1219)	4066 (3577 to 4268)	**0.001**
Hospital costs – follow-up								
Medical imaging	390	683 (659-708)	245	636 (609-668)	145	761 (720-799)	-125 (-163 to –55)	**0.001**
Outpatient clinic visits	390	419 (387-454)	245	396 (356-445)	145	458 (420-494)	-62 (-130 to 10)	0.095
General practitioner visits	318	18 (15-21)	201	18 (14-23)	117	16 (11-22)	2 (-5 to 10)	0.462
Emergency department visits	318	11 (5-17)	201	10 (3-18)	117	12 (2-24)	-2 (-16 to 12)	0.825
Medication	390	84 (66-102)	245	82 (60-107)	145	89 (61-124)	-7 (-67 to 20)	0.302
Immobilization	390	4 (2-6)	245	2 (1-4)	145	6 (3-11)	-4 (-5 to 1)	0.192
Adverse events								
Revision surgery	378	363 (265-470)	238	159 (91-237)	140	708 (508-93)	-549 (-742 to -268)	**0.001**
Hospital admission days	390	124 (85-165)	245	61 (20-114)	145	229 (145-330)	-168 (-260 to -35)	**0.020**
Total hospital costs – follow-up	306	1717 (1548-1900)	194	1377 (1229-1551)	112	2306 (1935-2685)	-929 (-1250 to -444)	**0.001**

Costs related to rehabilitation / changes in living situation								
Discharge disposition	318	501 (220-855)	201	553 (171-1074)	117	413 (83-864)	140 (-289 to 1175)	0.203
Home care	318	836 (505-1201)	201	593 (303-970)	117	1250 (568-2123)	-657 (-1584 to 13)	0.099
Rehabilitation therapy								
Physical therapy	343	1087 (971-1199)	217	1148 (1014-1288)	125	981 (828-1143)	167 (-63 to 424)	0.134
Other rehabilitation therapy	318	18 (7-32)	201	21 (8-38)	117	14 (0-42)	7 (-21 to 42)	0.563
Total costs related to rehabilitation/ changes in living situation	318	2473 (1942-3023)	201	2324 (1765-2982)	117	2731 (1913-3736)	-407 (-1388 to 1085)	0.818
Indirect costs								
Costs for lost productivity	318	2894 (2471-3338)	201	3007 (2449-3623)	117	2702 (1986-3422)	305 (-849 to 1266)	0.692
Total costs	263	10,615 (9681-11,531)	153	11,925 (10,791-13,153)	110	8793 (7584-10,140)	3132 (1325 to 4940)	**0.001**

The exchange rate was €1 = US$1.21[31]

P values < 0.05 are shown in boldface

Data are presented as a mean with a bootstrap 95% CI

*N** represents the number of patients for whom data were available per follow-up moment

The main cost drivers for operative treatment were costs for lost productivity (25%), surgery (20%), hospital admission (primary stay) (15%), and physical therapy (10%) (Table 3 and Fig. 1). The main cost drivers for nonoperative treatment were costs for lost productivity (31%), home care (14%), physical therapy (11%), and revision surgery (8%).

Cost-utility analysis

Operative treatment resulted in higher mean total costs per person until 12 months of €3132 (95% CI €1325–€4940; $p < 0.001$). The mean change in QALYs until 12 months was 0.028 ($p < 0.001$) higher in the operative group. Hence, this resulted in incremental costs for operative treatment of €111,857 (*i.e.*, €3132/0.028) per QALY gained.

Cost-effectiveness analysis

The mean difference in DASH score was 7.3 points ($p < 0.001$) in favor of operative treatment, resulting in incremental costs for operative treatment of €2880 (*i.e.*, €3132/7.3*6.7) for a meaningful change in disability.

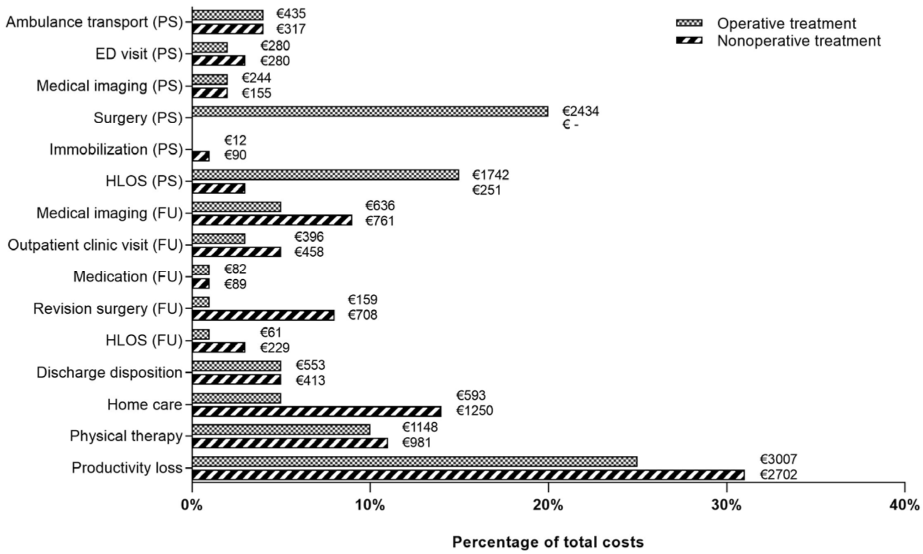

Fig. 1 The relative contribution of various cost categories

The exchange rate was €1.00 = US$1.21.[31]

Only cost categories representing more than 1% of the total costs are shown.

ED Emergency department, *FU* Follow-up, *HLOS* Hospital length of stay, *PS* Primary stay

DISCUSSION

This study showed that operative treatment of a humeral shaft fracture results in higher mean costs per person over one year of €3132 (95% CI €1325–€4940; $p < 0.001$) than nonoperative treatment. The mean difference in QALYs (0.028; $p < 0.001$) during one year in favor of the operative group demonstrates that operative treatment results in a higher health-related quality of life during the first year after trauma. This difference is statistically significant but small, therefore incremental costs per QALY gained are high (€111,857; *i.e.*, €3132/0.028). The clinical and statistically significant difference of 7.3 DASH points ($p < 0.001$) in favor of the operative group exceeds the MIC and results in incremental costs for operative treatment of €2880 for a measurable change in disability.

The different measures of efficacy used in these economic analyses should be carefully weighted in the decision-making process. Economic evaluations with QALYs may be preferred in order to allow for comparison across populations with different medical conditions. However, a humeral shaft fracture does not necessarily affect a patient's self-reported health-related quality of life as the injury may have little effect on some of the measured domains of the EQ-5D (*i.e.,* anxiety and depression), resulting in marginal differences in QALYs gained.[21] Due to the limited effect of a humeral shaft fracture on quality of life, the costs per QALY (€111,857) exceed the threshold set by society. The difference in functional outcome measured by the DASH score was shown to be more specific than the health-related quality of life measured in QALYs.[21] An ICER calculated with the DASH score cannot be compared to other injuries, but it does show the relatively low incremental costs of operative treatment for a clinically meaningful difference and suggests that operative treatment for a humeral shaft fracture is cost-effective.

The results of the cost calculations are comparable with results from previous research. Polinder *et al*. (2013) described comparable direct health care costs of upper arm fractures of €4440 per case (versus €5116 in this study), taking into account inflation and the more detailed health care resource use described in this study.[6] Bonafede *et al*. (2013) determined higher direct health care costs (US$10,842 (≈ €8960) versus €7589) and higher costs for lost productivity (US$4868 (≈ €4023 versus €2894 in this study) per humeral fracture.[4] However, costs were calculated by multiplying the total number of hours reported absent multiplied by an average rate per hour (human capital approach) instead of assuming that productivity costs are only incurred during the period until the moment the employee is replaced, the so-called friction period.[4, 32] Meerding *et al*. (2006) described similar total costs of humeral shaft fractures in the Netherlands, namely €9430 per patient, with also hospital care costs and costs for lost productivity as main cost drivers.[36]

Patients' preferences shape clinical decision-making which therefore could be influenced by employment status. It is desirable that employed patients return to work as soon as possible, especially knowing that costs for lost productivity account for more than a quarter of the total costs of treatment of a humeral shaft fracture and added up to €5.4 million in the Netherlands for admitted patients alone in 2012.[7] Hendy *et al.* (2020) identified no advantage for faster return to work after operative or nonoperative treatment of humeral shaft fractures.[37] This study showed that employed patients were treated operatively more often, but there was no significant difference in work absence in days or costs for lost productivity between treatment groups. However, the underlying differences between the treatment groups, specifically the male predominance, younger median age, and overrepresentation of employed patients, who also worked significantly more hours per week, in the operative treatment group, result in an underestimation of the advantage of their earlier return to work in terms of costs for lost productivity.

Strengths and limitations

The strengths of this study include a large multicenter prospective cohort methodology measuring health utility, a formal economic costing approach, and a societal perspective for costs. Furthermore, this study design ensures great external validity by allowing for variation between hospitals (*e.g.*, differing policies on follow-up procedures and allocation of resources).

A limitation of these cost analyses is that both groups included multiple treatment strategies with different costs of material (Supplemental Table S1). Moreover, costs were based on Dutch prices and practices and therefore may vary depending on the health care system used. Furthermore, the follow-up duration of 12 months did not take into account the late complications of nonunion or the need for revision surgery after more than one year. Lastly, the lack of an upper age limit for age inclusion may have (slightly) skewed the results, based on life expectancy and working situation.

CONCLUSION

This study showed that operative treatment of a humeral shaft fracture is more expensive than nonoperative treatment, but results in a higher health-related quality of life and significantly less disability. Due to the limited effect of a humeral shaft fracture on quality of life measured with the EQ-5D, the cost-effectiveness of operative treatment in terms of costs per QALY (€111,857) exceeds the acceptability limit. However, the incremental costs of €2880 per clinically meaningful difference in DASH are much lower and suggest that operative treatment for a humeral shaft fracture is cost-effective.

Supplemental Table S1. Sources and unit costs of health care resources in 2020 (€)

Cost category	Unit	Source of consumption data	Source of value	Unit price (€)
Hospital costs – primary stay				
Ambulance transport	Ride	Hospital registry	NZa[1]	730
Emergency department visit	Visit	Hospital registry	Cost manual[2]	280
Medical imaging				
Laboratory tests	Test	Hospital registry	NZa[1]	22[a]/28[b]
X-ray upper extremity	X-ray	Hospital registry	NZa[1]	59
CT-scan upper extremity	CT-scan	Hospital registry	NZa[1]	157
MRI scan upper extremity	MRI scan	Hospital registry	NZa[1]	232
EMG	EMG	Hospital registry	Hospital/industry data[3]	160
Ultrasound	Ultrasound	Hospital registry	NZa[1]	94
Arthrography	Arthrogram	Hospital registry	Hospital/industry data[3]	134
Hospital admission days	Day	Hospital registry	Cost manual[2]	694[a]/479[b]
Medication*	Dose per day	Hospital registry/ Patient questionnaire[§]	CVZ[4]	Variable
Operative treatment				
Surgeon	Hour	Hospital registry	Cost manual[2]	85[a]/88[b]
Operating room**	Hour	Hospital registry	Hospital/industry data[3]	600[a]/708[b]
Equipment and implants	Unit	Hospital registry	Hospital/industry data[3]	Variable
Depuy Synthes MultiLoc IMN***				478
MultiLoc IMN endcap				38
MultiLoc IMN screw[c]				65
MultiLoc IMN 4.5mm screw				76
MultiLoc IMN locking screw				54
T2 Stryker IMN****				302
T2 Stryker endcap				35
T2 Stryker screw				31
Depuy Synthes Titanium Elastic Nail (TEN)***				97
Depuy Synthes Expert Humeral Nail (EHN)***				357
EHN endcap				36
EHN spiral blade				301
EHN screw				46
Stryker AxSOS humeral plate****				527
Stryker AxSOS locking screw				59
Depuy Synthes Philos proximal humeral plate***				699
Depuy Synthes femur plate***				507

Depuy Synthes metaphyseal plate***				304
Depuy Synthes distal extra-articular***				841
Depuy Synthes screw[c]				29
Depuy Synthes locking screw				34
Depuy Synthes cortex screw				25
Devices for immobilization	Unit	Hospital registry	Variable	Variable
Sling or collar and cuff			Mean of tracked prices[5]	8
Splint			Mean of tracked prices[5]	33
Brace			Hospital/industry data[3]	103
Hanging cast			Hospital/industry data[3]	53
Pressure bandage			Mean of tracked prices[5]	2
Gilchrist			Mean of tracked prices[5]	28
Tubigrip			Mean of tracked prices[5]	8
Nonoperative treatment				
Devices for immobilization				Variable
Hospital costs – follow-up				
Medical imaging				Variable
Medication*				Variable
General practitioner	Visit	Patient questionnaire[§]	Cost manual[2]	36
Outpatient clinic visits	Visit	Hospital registry/ Patient questionnaire[§]	Cost manual[2]	
Surgeon				79
Rehabilitation doctor				98
Neurologist				107
Anesthetist				98
Geriatrician				98
Rheumatologist				98
Wound care nurse				34
Plaster cast nurse				34
Adverse events				
Emergency department visit				280
Hospital admission days				694[a]/479[b]
Medication*				Variable
Revision surgery				
Surgeon				85[a]/88[b]
Operating room**				600[a]/708[b]

Supplemental Table S1. Sources and unit costs of health care resources in 2020 (€)

Cost category	Unit	Source of consumption data	Source of value	Unit price (€)
Equipment and implants				Variable
Implant removal	Operation	Hospital registry	Hospital/industry data[3]	- [a]/- [b]
Radial nerve grafting	Operation	Hospital registry	Hospital/industry data[3]	67[a]/191[b]
Incision and drainage	Operation	Hospital registry	Hospital/industry data[3]	41[a]/191[b]
Costs related to rehabilitation / changes in living situation				
Discharge disposition				
Care hotel	Days	Patient questionnaire[§]	Cost manual[2]	178
Elderly home	Days	Patient questionnaire[§]	Cost manual[2]	182
Nursing home	Days	Patient questionnaire[§]	Cost manual[2]	182
Rehabilitation center	Days	Patient questionnaire[§]	Cost manual[2]	497
Home care (household support/nursing care)	Hours	Patient questionnaire[§]	Cost manual[2]	79
Rehabilitation therapy				
Physical therapy	Session	Patient questionnaire[§]	Cost manual[2]	36
Other rehabilitation therapy				
Edema therapy	Session	Patient questionnaire[§]	Cost manual[2]	42
Occupational therapy	Session	Patient questionnaire[§]	Cost manual[2]	36
Hand therapy	Session	Patient questionnaire[§]	Cost manual[2]	37
Chiropractic therapy	Session	Patient questionnaire[§]	Cost manual[2]	58
Massage therapy	Session	Patient questionnaire[§]	Cost manual[2]	59
Manual therapy	Session	Patient questionnaire[§]	Cost manual[2]	46
Acupuncture therapy	Session	Patient questionnaire[§]	Cost manual[2]	88
Work absence				
age 18-20	Hours	Patient questionnaire[§]	CBS[6]	7
age 20-25	Hours	Patient questionnaire[§]	CBS[6]	13
age 25-30	Hours	Patient questionnaire[§]	CBS[6]	18
age 30-35	Hours	Patient questionnaire[§]	CBS[6]	22
age 35-40	Hours	Patient questionnaire[§]	CBS[6]	25
age 40-45	Hours	Patient questionnaire[§]	CBS[6]	27
age 45-50	Hours	Patient questionnaire[§]	CBS[6]	28
age 50-55	Hours	Patient questionnaire[§]	CBS[6]	28
age 55-60	Hours	Patient questionnaire[§]	CBS[6]	28
age 60-65	Hours	Patient questionnaire[§]	CBS[6]	28
age 65-68	Hours	Patient questionnaire[§]	CBS[6]	25

The exchange rate was: €1 = US$ 1.21[31]

* Humeral shaft fracture related medication only (see Supplemental Table S2 for details).

** Including operating room personnel, anesthesia, surgical equipment, and overhead costs.

*** Depuy Synthes (Companies, Raynham, Massachusetts, United States).

**** Stryker Corporation (Kalamazoo, Michigan, United States).

[§] Patient questionnaire; Customized version.

[1] NZa; Nederlandse Zorgautoriteit (Dutch Healthcare Authority) standard costs.[24]

[2] Cost manual; Manual on cost research, methods, and standard costs in economic healthcare evaluations, version 2015.[28]

[3] Hospital/industry data; costs were requested from one academic hospital, one non-academic hospital, and one surgical equipment and implant firm. Means were calculated and used as an estimation of the costs in all participating hospitals.

[4] CVZ; Standard prices were used as described by the CVZ (Supplemental Table S2).[29]

[5] Mean of tracked prices; costs of aids were presented online by home care firms. These costs were used as an estimation of the real costs in all participating patients.

[6] CBS; Costs of work absence 2020 (€) were used as described by the CBS.[33]

[a] Academic hospital, [b] Non-academic hospital, [c] Average screw prices were used when screw specifics were not attained.

CBS, Centraal Bureau voor de Statistiek (Statistics Netherlands); CVZ, College voor Zorgverzekeringen (Health Care Insurance Board); CT, Computed tomography; EHN, Expert humeral nail; IMN, Intramedullary nail; MRI, Magnetic resonance imaging; NZa, Nederlandse Zorgautoriteit (Dutch Healthcare Authority); TEN, Titanium elastic nail.

Supplemental Table S2. Sources and unit costs of health care resources in 2020 (€)

Medication name	Dose	ATC code*	Unit price (€)
Amoxicillin	625 mg	J01CR02	0.65
Aspirin	80 mg	N02BA01	0.05
Cefazolin	1 g	J01DB04	2.90
Ciprofloxacin	500 mg	J01MA02	0.11
Clindamycin	300 mg	J01FF01	0.39
Diclofenac/Voltaren	50 mg	M01AB05	3.18
	75 mg	M01AB05	4.77
	100 mg	M01AB05	6.36
	75 mg	M01AB55	0.50
Etoricoxib	60 mg	M01AH05	0.33
	90 mg	M01AH05	0.27
Fentanyl (transdermal)	12 microg/hour	N02AB03	0.02
	25 microg/hour	N02AB03	0.03
Fraxiparine	9,500 IE anti-Xa/ml, 0.3ml	B01AB06	1.84
Ibuprofen	200 mg	M01AE01	0.05
	400 mg	M01AE01	0.10
	600 mg	M01AE01	0.08
	800 mg	M01AE01	0.13
Morphine (solution)	5 mg/ml	N02AA01	0.16
Morphine (injection)	10 mg/ml	N02AA01	11.30
Morphine (tablet)	10 mg	N02AA01	0.32
	15 mg	N02AA01	0.38
Naproxen	250 mg	M01AE02	0.07
	500 mg	M01AE02	0.11
Omeprazole	10 mg	A02BC01	0.06
	20 mg	A02BC01	0.05
	40 mg	A02BC01	0.06
Oxycodone	5 mg	N02AA05	0.12
Oxycontin	5 mg	N02AA05	0.22
	10 mg	N02AA05	0.33
Oxynorm	5 mg	N02AA05	0.45
	10 mg	N02AA05	0.76
	20 mg	N02AA05	0.60
	30 mg	N02AA05	2.16
Pantoprazole	20 mg	A02BC02	0.05
	40 mg	A02BC02	0.08

Medication name	Dose	ATC code*	Unit price (€)
Paracetamol	500 mg	N02BE01	0.03
	1 g	N02BE01	0.09
Paracetamol/codeine	500 mg/10 mg	N02BE51	0.05
	500 mg/20 mg	N02BE51	0.07
Piritramide	10 mg/ml, 2 ml	N02AC03	1.85
Tramadol	50 mg	N02AX02	0.05
Triamcinolonacetonide	10 mg/ml	H02AB08	1.68
Paracetamol, tramadol/Zaldiar	325 mg/37.5 mg	N02AJ13	0.17

The exchange rate was: €1 = US$1.21[31]

Standard prices were used as described by the CVZ (College voor Zorgverzekeringen; Health Care Insurance Board), online available on www.medicijnkosten.nl.[29]

ATC code; Anatomical Therapeutic Chemical Classification System; CVZ, College voor Zorgverzekeringen (Health Care Insurance Board).

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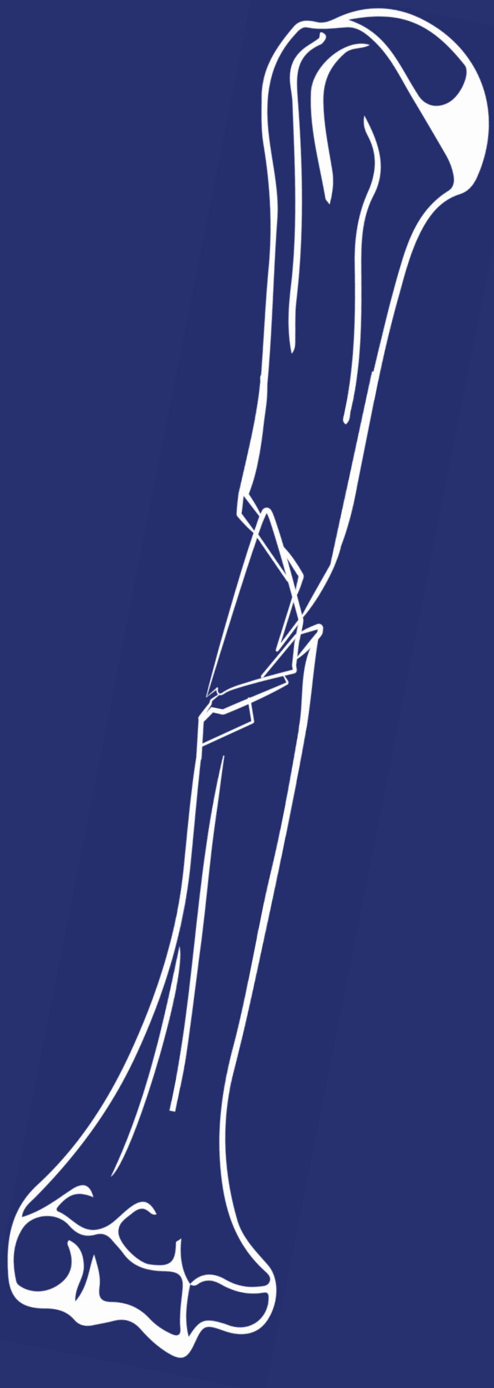
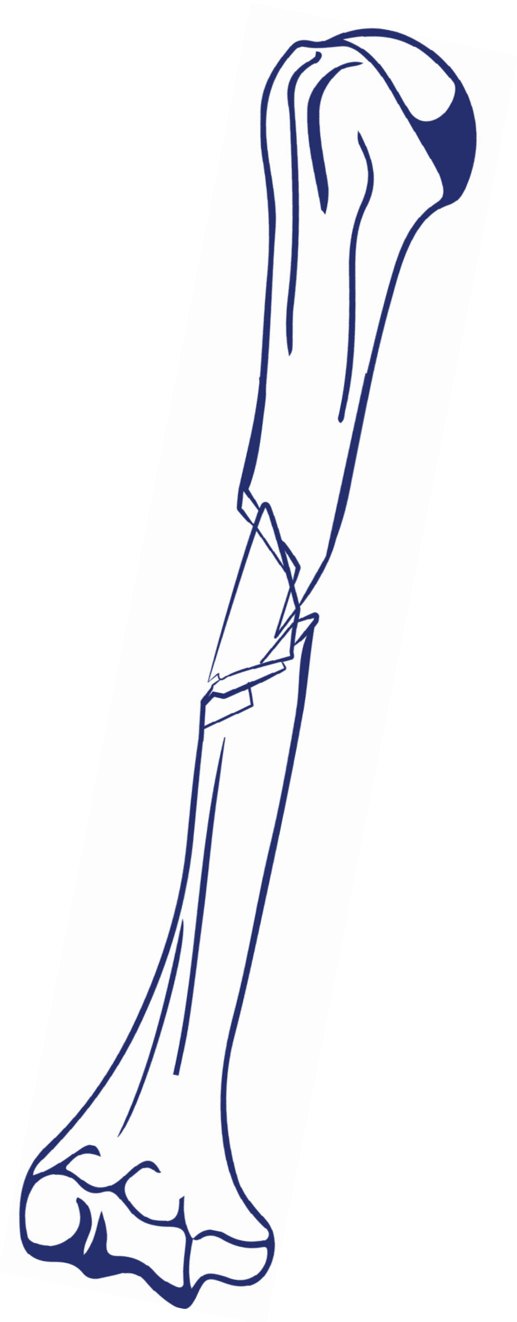


PART 5

Polytrauma

Chapter 7
Fracture type, treatment, and outcome of humeral shaft fractures in polytrauma patients: a case series
Submitted



CHAPTER 7

Fracture type, treatment, and outcome of a humeral shaft fractures in polytrauma patients: a case series

Submitted

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Dennis Den Hartog
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Michael H.J. Verhofstad

ABSTRACT

Purpose: Since most clinical studies on humeral shaft fractures exclude polytraumatized patients, the epidemiology in this population is largely unknown. The aim of this study was to describe the fracture type, treatment, and outcome of humeral shaft fractures in adult polytraumatized patients.

Methods: A case series with a single follow-up questionnaire was performed in patients aged 16 years or older with a humeral shaft fracture and an injury severity score of 16 or higher, admitted to a level 1 trauma center between January 1, 2007, and July 31, 2021. Details on injuries, treatment, and clinical outcome were collected from the national trauma registry and medical records. Patients were asked to complete the Disabilities of the Arm, Shoulder, and Hand (DASH), EuroQol-5D (EQ-5D), and Short Form-36 (SF-36).

Results: Twenty-nine patients were included. The median age was 41 years and 18 (62%) were male. Most fractures were type A (N=19; 66%). Most patients were treated operatively (N=26; 90%) within three days. Radial nerve palsy at presentation was reported in five (20%) patients. Infection occurred in one (4%) patient and nonunion in six (27%) patients. The patient-reported outcome measures were as follows (median; quartiles): DASH 20.0 (P_{25}-P_{75} 5.6-35.2), EQ utility score 0.75 (P_{25}-P_{75} 0.58-0.88), EQ visual analog score 0.80 (P_{25}-P_{75} 71-95), SF-36 physical component summary 49 (P_{25}-P_{75} 43-55), and SF-36 mental component summary 58 (P_{25}-P_{75} 47-61).

Conclusions: Humeral shaft fractures in adult polytraumatized patients were most often AO-type A and treated operatively. Radial nerve palsy at presentation and nonunion rates were high. Patients still reported upper extremity disability at approximately five years post trauma.

BACKGROUND

Many studies have reported on the fracture type, treatment, and outcome of isolated humeral shaft fractures.[1-5] However, even though it has been described that 49% of patients with a humeral shaft fracture had an injury severity score (ISS) ≥16, most clinical studies on humeral shaft fractures exclude polytraumatized patients.[5-9] In general, patients with an isolated humeral shaft fracture have good or excellent clinical outcomes. Outcomes may become less favorable in polytraumatized patient population.[10-13] However, since most studies exclude polytraumatized patients, the epidemiology and outcome of humeral shaft fractures in polytraumatized populations is largely unknown.

Given the higher level of energy causing the injury, it is possible that humeral shaft fractures in polytraumatized patients are more often comminuted and accompanied by more extensive soft tissue damage. The fracture location and pattern are of interest, since they may influence treatment, risk of complications, and long-term functional recovery.[2] Furthermore, the presence of other (more life-threatening) injuries may have an effect on the (timing of) treatment, complication risk, and (long-term) recovery of the humeral shaft fracture.[14] Clinical and patient-reported outcomes are valuable for evaluating the long-term consequences in terms of disability and health-related quality-of-life.

The relative lack of research directed at understanding the impact of polytrauma on the epidemiology and outcome of a humeral shaft fracture results in the need for an overview of this diverse population and insight into the long-term consequences. The aim of this study was to describe the fracture type, treatment, and outcome of humeral shaft fractures in adult polytraumatized patients.

METHODS

Study design

This case series enrolled adult polytraumatized patients (age 16 years or older with an ISS ≥16) with a radiologically confirmed humeral shaft fracture, who were admitted to a level 1 trauma center between January 1, 2007, and July 31, 2021, and provided informed consent. Patients were identified from the national trauma registry (NTR). Radiographic imaging (X-ray or CT-scan) was assessed to determine the eligibility (SHVB and DDH). Patients were excluded if they had 1) insufficient cognitive function to comprehend the study documents; 2) insufficient comprehension of the Dutch language; 3) unknown contact details; or 4) deceased during follow-up. The study was exempted by the local Medical Research Ethics Committee (No. MEC-2018-1231 and No. MEC-2022-0371).

Data collection

The following patient characteristics and details of admission and additional traumatic injuries were extracted from the NTR: age, sex, hospital length of stay (HLOS), admission to the intensive care unit (ICU), and ICU length of stay (ICU LOS). Details on additional traumatic injuries were extracted and described using the nine separate Abbreviated Injury Scale (AIS) regions. Upper extremity injuries were described using the AIS type of injury. Upper extremity fractures were described based on fracture location. The AIS coding used for patients admitted before January 1, 2015, was the AIS 1990 (update 1998).[15] The AIS 2005 (update 2008) was used for patients admitted after January 1, 2015.[16]

Details on the humeral shaft fracture were collected from the patient's medical records, *i.e.,* AO/OTA classification, presence of radial nerve palsy at presentation, treatment strategy (nonoperative treatment, *i.e.*, functional bracing, or operative treatment, *i.e.*, intramedullary nailing (IMN), plate osteosynthesis, or an external fixator), and time to operative treatment.[17] Furthermore, data were collected on infection at the humeral shaft fracture site occurring within 30 days after hospital presentation requiring surgical intervention and nonunion (defined as a failure to heal at six months post fracture with no progress towards healing seen on the most recent radiographic imaging). Radiographic imaging (X-ray or CT-scan) was reviewed for determining the fracture type and identify nonunion (SHVB and DDH).

Eligible patients were invited by regular mail to complete three validated patient-reported outcome measures (PROMs; the Disabilities of the Arm, Shoulder, and Hand (DASH), EuroQol-5D (EQ-5D-5L), and Short Form-36 version 2 (SF-36-v2)).[18-24]

The DASH is a 30-item (scored 1-5) instrument with an overall score ranging from zero (no disability) to 100 (severe disability), reflecting disability and pain of the upper extremity.[18-20] The EQ-5D-5L is a 5-item instrument for measuring health-related quality-of-life, consisting of a utility score (EQ-US) and a visual analog scale (EQ-VAS), both ranging from zero (death) to 100 (perfect health).[21-23] The SF-36 is a 36-item instrument for measuring health-related quality-of-life, representing eight health domains that are combined into a Physical Component Summary (PCS) and a Mental Component Summary (MCS) score.[24] Normalized scores range from zero to 100 points for each domain, with higher scores indicating better quality-of-life. Scores were converted to a norm-based score and compared with United States general population (1998) norms, in which each scale was scored to have the same average (50) and standard deviation (SD; 10).[25]

Data analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 28 (SPSS®, Chicago, Ill., USA). The Shapiro-Wilk test was used to test normality of continuous data. Continuous data, which were all non-parametric, are reported as a median with percentiles (P_{25}-P_{75}). Categorical data are reported as number with percentages (N; %).

RESULTS

Baseline patient and injury characteristics

Sixty-one polytraumatized patients had a confirmed humeral shaft fracture based on radiographic imaging (Figure 1). Of these, 38 were eligible and were invited to complete the questionnaires. Twenty-nine of these completed the questionnaire, resulting in a response rate of 76%.

The median age at trauma was 41 (P_{25}-P_{75} 26-51) years and 18 (62%) patients were male (Table 1). The median ISS was 29 (P_{25}-P_{75} 22-43). Nineteen (66%) type A, seven (24%) type B, and three (10%) type C fractures were identified. Type A3 (N=9; 31%) and A2 (N=7; 24%) fractures were the most common fracture types. Five (20%) of the 25 patients in whom radial nerve function was assessed, had radial nerve palsy at presentation. Radial nerve function was undocumented in one patient, unevaluable due to tetraplegia in one patient, and unknown due to transfers to other hospitals in two patients.

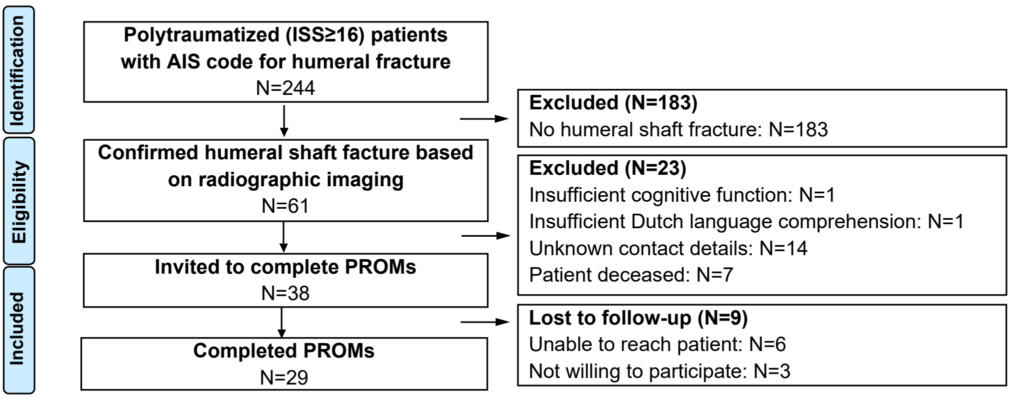

Fig. 1 Flow chart of the study

AIS, Abbreviated Injury Score; ISS, Injury Severity Score; PROMs, Patient Reported Outcome Measures.

Table 1: Baseline patient characteristics, injury, and treatment details

Characteristic		N*	Total population (N=29)
Patient characteristics			
Age at trauma (years)		29	41 (26-51)
Male		29	18 (62%)
Injury Severity Score		29	29 (22-43)
Injury characteristics			
Fracture type	A1	29	3 (10%)
	A2		7 (24%)
	A3		9 (31%)
	B1		3 (10%)
	B2		4 (14%)
	B3		0 (0%)
	C1		1 (3%)
	C2		1 (3%)
	C3		1 (3%)
Radial nerve palsy at presentation		25	5 (20%)
Treatment details			
HLOS (days)		29	14 (9-47)
ICU admission		29	20 (69%)
ICU LOS (days)		20	5 (2-15)
Index treatment	Nonoperative	29	3 (10%)
	Operative		26 (90%)
Nonoperative treatment	Functional brace	3	3 (100%)
Operative treatment	Intramedullary nailing	25	12 (48%)
	Plate osteosynthesis		10 (40%)
	External fixator		3 (12%)
Time to operative treatment		24	3 (1-6)
Complications			
Infection		25	1 (4%)
Nonunion		22	6 (27%)
Survey at follow-up			
Upper extremity treatment since hospital discharge		27	3 (11%)
	Infection (near plate)	3	1 (33%)
	Cartilage repair		1 (33%)
	Surgery for muscle spasms		1 (33%)

Data are presented as median (P_{25}-P_{75}) of n (%).

N* represents the number of patients for whom data were available.

ICU, Intensive Care Unit; ICU LOS, ICU length of stay; HLOS, Hospital length of stay

Treatment and complications

The median HLOS was 14 (P_{25}-P_{75} 9-47) days (Table 1). Twenty (69%) patients were admitted to the ICU for a median of five (P_{25}-P_{75} 2-15) days. Three (10%) patients were treated nonoperatively. Twenty-six (90%) patients were treated operatively. The median time to surgery was 3 (P_{25}-P_{75} 1-6) days (N=24). The time to surgery in two patients was unknown due to transfers to other hospitals. The type of operative treatment consisted of IMN in 12 (48%) patients, plate osteosynthesis in 10 (40%) patients, and an external fixator in three (12%) patients. One patient had two humeral shaft fractures and was treated on one side with an IMN and on the other side with plate osteosynthesis, and was therefore not included in the abovementioned calculations.

Data on infection and nonunion was unavailable in three and seven patients, respectively, due to transfer to other hospitals (N=4) and lack of radiographic imaging (N=3). One (4%) patient had an infection at the fracture site requiring surgical intervention. Six of the 22 patients with available radiographic imaging (27%) had a nonunion. All patients with an infection or nonunion were treated operatively.

Traumatic injury details

The 29 included patients had a total of 82 upper extremity injuries (Table 2). Sixty-five (79%) of these were fractures, the next most prominent injuries were superficial soft tissue injuries (N=6; 7%), muscle/tendon/ligament injuries (N=4; 5%), and vascular injuries (N=4; 5%). Fourteen (48%) patients had two or more upper extremity fractures. The most common fracture location was the humerus (N=30; 46%), followed by the (meta)carpus (N=8; 12%), ulna (N=8; 12%), and radius (N=7; 11%).

Additional injuries were most often located to the thorax (N=23; 79%), head (N=19; 66%), and lower extremities (N=16; 55%; Table 3). Severe injuries occurred most often to the thorax (N=22; 76%), head (N=16; 55%), and upper extremities (N=11; 38%).

Table 2: Type of upper extremity injuries and location of upper extremity fractures

Type of injury	N injuries (N=82)	N patients (N=29)	N patients with 1 up to 10 injuries					
			1	2	3	4	5	10
Soft tissue	6 (7%)	5 (17%)	4	1				
Muscle/tendon/ligaments	4 (5%)	3 (10%)	2	1				
Nerves	1 (1%)	1 (3%)	1					
Vascular	4 (5%)	3 (10%)	2	1				
Joints	2 (2%)	2 (7%)	2					
Fracture	65 (79%)	29 (100%)	15	5	4	2	2	1
Type of fracture	**N fractures (N=65)**	**N patients (N=29)**	**N patients with 1 up to 3 fractures**					
			1	**2**	**3**			
Clavicle	5 (8%)	5 (17%)	5					
Scapula	6 (9%)	6 (21%)	6					
Humerus	30 (46%)	29 (100%)	28	1				
Radius	7 (11%)	6 (21%)	5	1				
Ulna	8 (12%)	6 (21%)	5		1			
Hand	0 (0%)	0 (0%))						
Carpus/metacarpus	8 (12%)	6 (21%)	4	2				
Finger	1 (2%)	1 (3%)	1					

Data are shown as n (%).

Table 3: Overview of the location and severity of injuries for the nine anatomical regions

Body region	Any injury (AIS≥1) (N=29)	Severe injury (AIS≥3) (N=29)
Head	19 (66 %)	16 (55%)
Face	9 (31%)	2 (7%)
Neck	0 (0%)	0 (0%)
Thorax	23 (79%)	22 (76%)
Abdomen	13 (45%)	5 (17%)
Spine	13 (45%)	8 (28%)
Upper extremity	29 (100%)	11 (38%)
Lower extremity	16 (55%)	10 (34%)
External	3 (10%)	0 (0%)

Data are shown as n (%).

AIS, Abbreviated injury scale.

Patient-reported outcome measures

The median time from trauma to the completion of the follow-up questionnaires was 55 (P_{25}-P_{75} 37-85) months. The median DASH score was 20.0 (P_{25}-P_{75} 5.6-35.2; Table 4). The EQ-US and EQ-VAS were 0.75 (P_{25}-P_{75} 0.58-0.88) and 80 (P_{25}-P_{75} 71-95), respectively. The proportion of patients with a certain level of problems in each of the domains of the EQ-5D-5L survey is shown in Figure 2. Few patients reported extreme problems or inability to do one of the activities; however, more than half of the patients reported extreme to mild problems with walking, daily activities, or pain. The median SF-36 PCS and SF-36 MCS scores were 49 (P_{25}-P_{75} 43-55) and 58 (P_{25}-P_{75} 47-61), respectively (Figure 3). Scores were lowest for the domains physical functioning (45; P_{25}-P_{75} 33-54), role limitations due to physical health (43; P_{25}-P_{75} 36-55), and general health perceptions (49; P_{25}-P_{75} 39-58).

Table 4: Patient-reported outcome measures

Outcome measure		**N***	**Total population (N=29)**
DASH		28	20.0 (5.6-35.2)
EQ-5D-5L	US	24	0.75 (0.58-0.88)
	VAS	24	80 (71-95)
SF-36	PCS	19	49 (43-55)
	MCS	23	58 (47-61)
	Physical functioning	28	45 (33-54)
	Role limitations due to physical health	28	43 (36-55)
	Bodily pain	28	51 (43-60)
	General health perceptions	28	49 (39-58)
	Vitality, energy, or fatigue	28	48 (40-60)
	Social functioning	28	52 (41-57)
	Role limitations due to emotional problems	28	48 (41-56)
	General mental health	28	50 (40-61)

Data are presented as median (P_{25}-P_{75}).

N* represents the number of patients for whom data were available.

DASH, Disabilities of the Arm, Shoulder, and Hand; EQ-5D-5L, EuroQol-5D five level; MCS, Mental Component Summary; PCS, Physical Component Summary; SF-36, Short Form-36; US, Utility score; VAS, Visual Analog Scale.

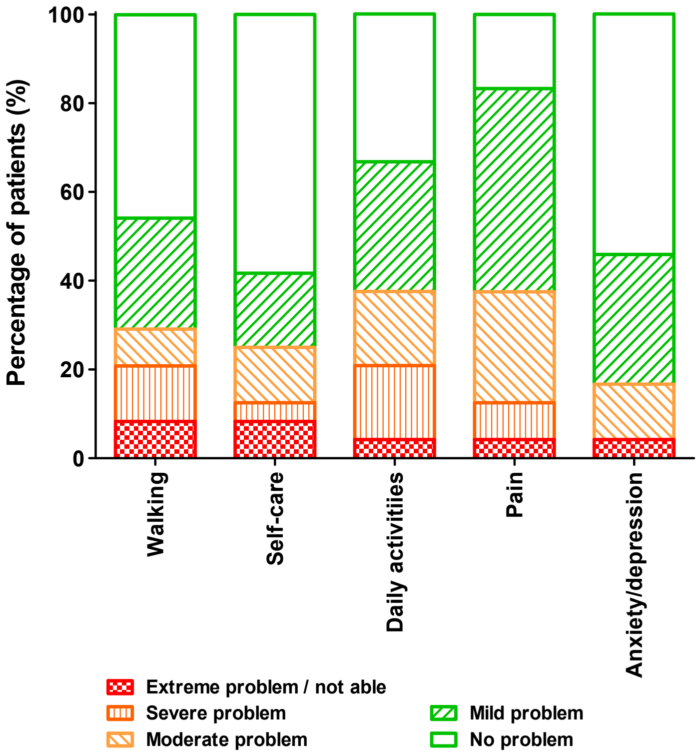

Figure 2: Level of problems in the domains of the EQ-5D-5L survey reported by polytraumatized patients with a humeral shaft fracture

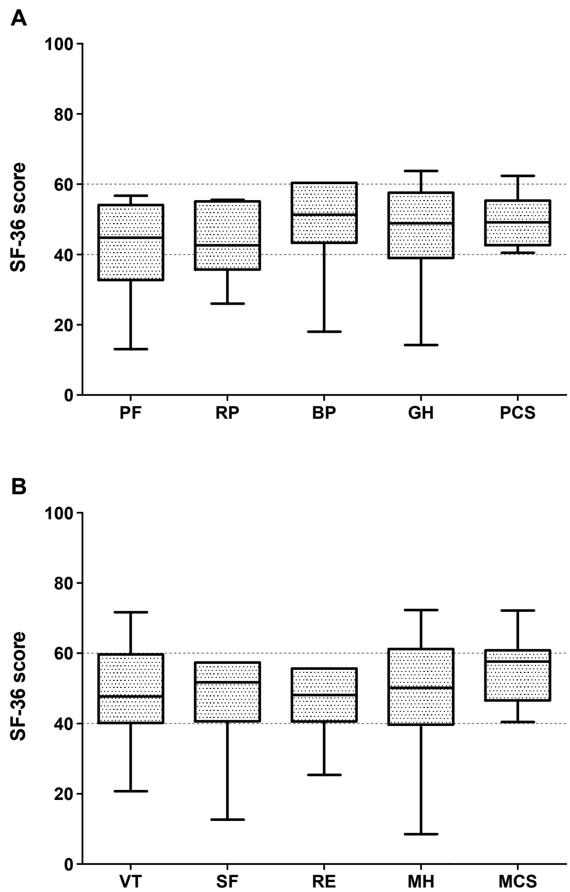

Figure 3: SF-36 scores for the domains of the SF-36 survery reported by polytraumatized patients with a humeral shaft fracture

Data are shown as box-whisker plots, in which the horizontal lines within boxes, boxes and whiskers indicate the median, 1st and 3rd quartile, and minimum and maximum observed value. Horizontal dotted lines represent United States general population (1998) norm-based scores (mean of 50 ± 10 SD).

BP, bodily pain; GH, general health perceptions; MCS, Mental Component Summary; MH, general mental health; PCS, Physical Component Summary; PF, physical functioning; RE, role limitations due to emotional problems; RP, role limitations due to physical health; SF, social functioning; SF-36, Short Form-36; VT, vitality, energy, or fatigue.

DISCUSSION

This study provides a detailed description of adult polytraumatized patients with a humeral shaft fracture admitted to a level 1 trauma center during a 15-year period. Humeral shaft fractures in adult polytraumatized patients were most often AO-type A (66%) and treated operatively (90%). Rates of radial nerve palsy at presentation (20%) and nonunion were high (27%). Approximately five years post trauma, disregarding the EQ-US, patient reported levels of quality-of-life comparable to the population norms and standardized combined scores. However, the DASH score indicated that patients still experience upper-extremity disability in the long term.

Type A2 and A3 fractures comprised more than half of the humeral shaft fractures (24 and 31%, respectively) in contrast to populations with an isolated humeral shaft fractures in which type A1 fractures were most common (19 and 28%).[2-5] This is possibly due to the high energy trauma mechanism causing direct trauma to the arm instead of transmitted rotational or axial loading forces caused by a fall. More complex fractures (type C) could have been expected, considering the high energy trauma mechanism, but were seldom reported and comparable with a population with an isolated humeral shaft fracture (9 versus 10%).[2]

The polytraumatized population was younger and more often male than a population with an isolated humeral shaft fracture.[2, 5, 7] These patients have possible larger physiological reserves, resulting in better outcomes.[26] However, this study found that the presence of multiple traumatic injuries is associated with a longer HLOS and higher rate of ICU admission than a population with an isolated humeral shaft fracture (14 versus 2 days, 69 versus 0%, respectively).[5] It is unclear if the longer HLOS was attributable to the impaired arm function restricting self-care or to other injuries prolonging the need for monitoring and rehabilitation.

A high proportion of this polytraumatized population was treated operatively (90%), with a median time to surgery of 3 days. This is in accordance with studies emphasizing the relevance of initial and timely surgical treatment.[27-30] Upper extremity function is necessary for personal hygiene, use of crutches, and daily activities, especially when additional injuries of the (ipsilateral) upper extremity are present.[14] (Relative) stability provided by operative treatment can be considered desirable as this can shorten bedridden immobilization, improve independence, and enable patients to start rehabilitation at an earlier time-point.

Radial nerve palsy at presentation was more often seen than described in a population with an isolated humeral shaft fracture (20 versus 4 and 6%), as expected with high energy trauma and contusion of the soft tissues.[5, 7, 31] The nonunion rate in the current study was higher than reported in a population with an isolated humeral shaft fracture (27 versus 16%).[5] The higher nonunion rate might be explained with the Diamond concept, which describes that fracture healing is regulated by the nature and extent of the trauma, the stability of fracture fixation, and biological bone healing processes.[32] This suggests that the fracture environment is less favorable in a polytraumatized patient than in a patient with an isolated fracture, due to more extensive injuries to the surrounding (neurovascular) structures.

Patient-reported outcome measures can provide insight into the magnitude of the impact of the trauma on function and quality of life. The DASH score indicates more disability of the upper extremity in this polytraumatized population than in patients with an isolated humeral shaft fracture (20.0 versus 3.3).[5] This is of importance, as upper-extremity disability can result in work absence and prolonged home care, increasing not only the individual but also the societal burden.[11, 33] Furthermore, it should be noted that the level of disability might be underestimated as, due to the lack of objective measurement of function (strength and range of motion), no distinction can be made between adaptation to disability and actual disability. The EQ-US were lower than the population norm (0.75 versus 0.89).[22] The EQ-VAS, SF-36 PCS, and SF-36 MCS were comparable to the population norms and standardized combined scores (EQ-VAS 80 versus 81; PCS 49 versus

50; MCS 58 versus 50).[22, 23] This suggests that even though physical limitations are present, they do not greatly impact the patient's perception of their general health-related quality-of-life at approximately five years post-trauma.

The most prominent drawbacks of this study are the retrospective and single center design, and single follow-up measurement at a random time-point, giving little insight into the course of recovery of the humeral shaft fracture.

CONCLUSION

Humeral shaft fractures in adult polytraumatized patients were most often AO-type A (66%) and treated operatively (90%). High rates of radial nerve palsy at presentation (20%) and nonunion (27%) were found. Approximately five years post trauma, patients reported levels of quality-of-life comparable to the population norms and standardized combined scores, but still experienced upper extremity disability.

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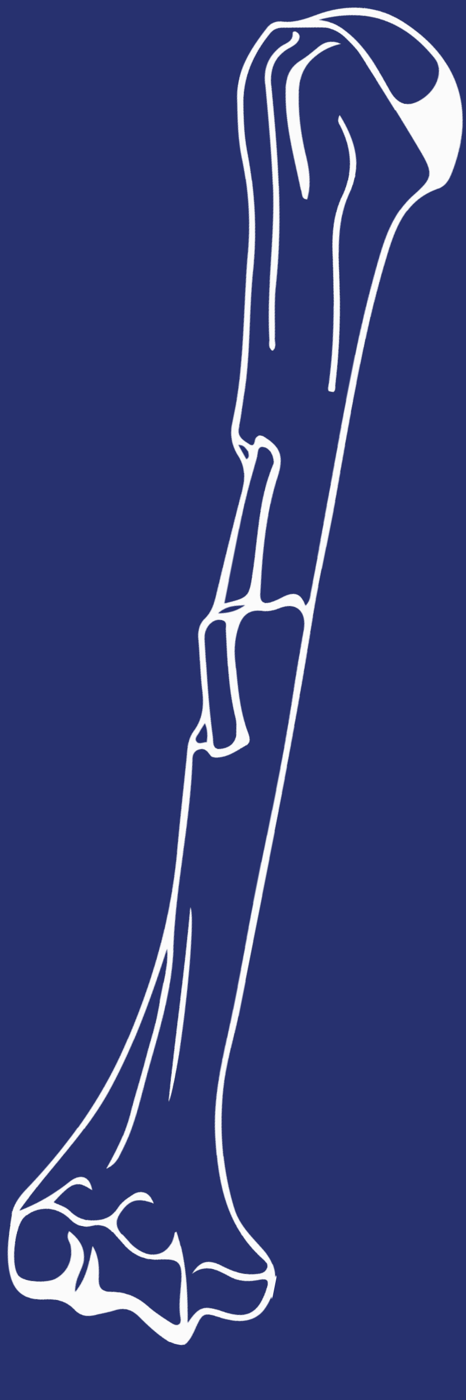


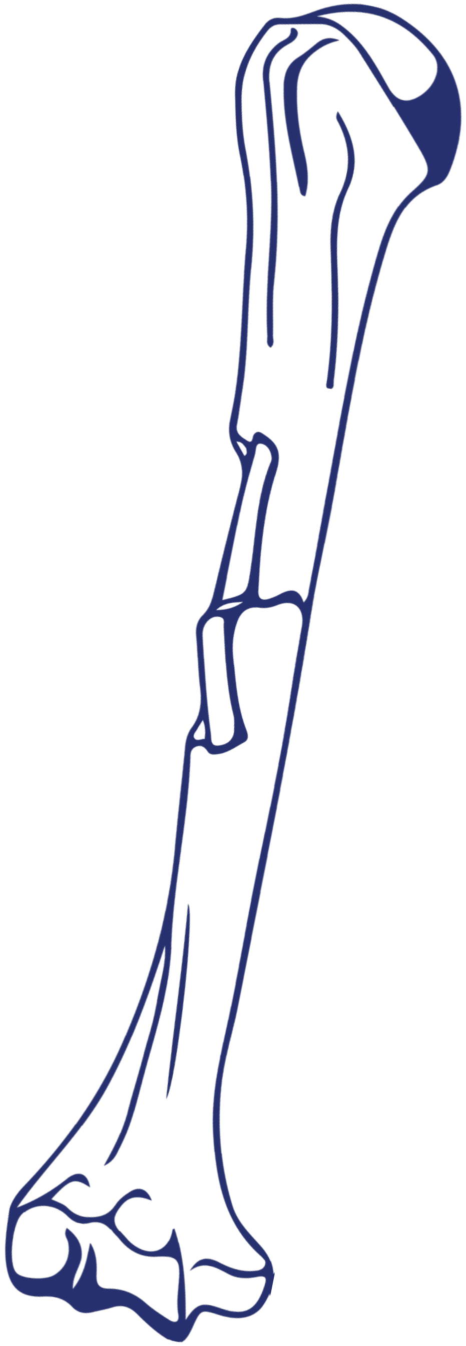
PART 6

General discussion, future perspectives, and summary

Chapter 8
General discussion and future perspectives

Chapter 9
Summary and conclusions

Chapter 10
Nederlandse samenvatting en conclusions



CHAPTER 8

General discussion and future perspectives

GENERAL DISCUSSION

In this general discussion, the research questions as described in the outline of this thesis and the results are put into perspective. Subsequently, this chapter argues the added value of the results to the pre-existing knowledge on the topic and addresses methodological considerations. Finally, the implications for shared decision-making are outlined and recommendations for future research are made.

What is known?

The scientific base for some (surgical) treatment options for humeral shaft fractures is not always solid. The systematic review and meta-analysis in **Chapter 2** compared fracture healing, complications, and functional outcome after nonoperative and operative treatment of a humeral shaft fracture. The results suggest that all regular treatment modalities result in satisfactory outcomes. However, if contraindications are absent, operative treatment, and specifically plate osteosynthesis, should be considered the preferred treatment as it results in the most favorable fracture healing rates, least complications, and best functional outcomes.

This conclusion can be derived from multiple aspects of recovery after a humeral shaft fracture. The Diamond concept of fracture healing underlines the importance of both the biological and the mechanical fracture environment.[1] This includes adequate stability, facilitating successful bone repair. Stability can be achieved in time with fracture healing, but also immediately by relative or absolute surgical stabilization. Instability, especially due to delayed fracture healing, may cause prolonged pain and function loss. Operative treatment enables some level of early recovery since it provides (relative) stability, even if the fracture fails to heal and results in a nonunion. In line with previous systematic reviews, the results of this systematic review indicate that nonunion is more common after nonoperative treatment (11%) than after IMN (6%) and plating (3%).[2-4] As a nonunion represents a disabling pathological condition which is difficult to treat, such percentages call for early surgical treatment of a humeral shaft fracture. On the other hand, the number needed to treat to prevent one nonunion is nine. This makes treatment of a humerus shaft fracture an ideal condition for a shared-decision making process. Quantitative data on risks and benefits of each therapeutic option are needed for a reliable treatment decision.

As with any traumatic injury, adverse events and complications can be difficult to prevent. A feared complication of the treatment of a humeral shaft fracture is (secondary) radial nerve palsy. The current systematic review shows this was relatively rare (1, 3, and 7% in the nonoperative, IMN, and plating group, respectively). However, questions about the rate of persistent radial nerve palsy and associated disability could not be addressed due to the heterogeneity in reporting.

Apart from secondary radial nerve palsy, other complications have been reported. Compared with plating, IMN was associated with higher reported rates of intraoperative, implant-, and shoulder-related complications. Those outcomes are in line with findings of other reviews, mentioning lower complication rates in the plating group than in the IMN group.[5-7] Besides uneventful fracture healing, recovery of function is desired. Each treatment strategy resulted in satisfactory functional outcomes after one year, indicating that a good functional outcome can be achieved irrespective of the treatment modality. However, plate osteosynthesis resulted in a slight advantage of functional recovery considering the DASH, Constant-Murley, and UCLA shoulder score, which might be explained by the higher rates of complications and shoulder-related problems in the IMN group.

Despite the complete analysis of current literature and the direction of the outcomes, the results of this study should be interpreted with care given the methodological differences and clinical heterogeneity of the included studies. It can be argued that well-designed and correctly performed systematic reviews and meta-analyses can provide definitive answers regarding the choice of treatment as they are considered the highest level of evidence. The advantages include low (administrative) costs, less time-consuming methods, and the summarization of the findings of all relevant individual studies, thereby making the evidence more accessible to decision makers. However, systematic reviews and meta-analyses are only as good as the data in the included studies. The low methodological quality of the included studies in this systematic review indicate the need for a properly powered prospective study with clearly defined outcomes, validated questionnaires, and robust statistical methods, to allow for more evidence-based decision making in the treatment of a humeral shaft fracture.

Functional and clinical outcomes

The HUMMER study was designed to meet these needs. Results from this multicenter prospective study outlined in **Chapter 3** demonstrate that adult patients with a closed humeral shaft fracture AO type 12A or B treated operatively have a better outcome until six months after trauma than patients treated nonoperatively. This was shown by a lower rate of complications, superior upper extremity function (lower DASH and higher Constant-Murley score) and shoulder and elbow range of motion, and a better health-related quality of life (EQ-5D US).

As described before, the main goal of treatment is to achieve timely fracture stability to facilitate bone healing. Re-alignment in upper-extremity fractures is partly facilitated by gravity, but at risk when relative stability is absent. Especially rotation-instability can result in dislocation, shortening, and angulation which consequently interferes with the fracture healing processes. In order words, the degree of motion between fracture fragments is the key for fracture healing.[8] The circumferential pressure of a functional brace results in relative immobilization when used correctly. Functional brace treatment can be demanding, putting noncompliant patients at a marked risk of nonunion.[9] Noncompliance can lead to excessive movement at the level of the fracture fragments, resulting in alteration of the reparative processes and consequently, nonunion.[10] Besides that, if soft tissues are too thick, it is challenging to provide a well-fitted brace. Operative treatment with nailing provides intramedullary stability but cannot prevent rotation-instability. If the movement within the fracture does not decrease over time, no consolidation can be expected which results in a nonunion. However, fracture fixation with plate osteosynthesis counteracts dislocating forces providing absolute stability and therefore allowing for fracture healing with stable fixation and biomechanical stimulation.

The risk of nonunion in the HUMMER study was 2.6-fold higher after nonoperative treatment than after operative treatment (N=30 (26%) versus N=19 (10%); $p<0.001$). Overall, the results show a significantly higher number of complications in the nonoperative group (N=50; 35%) than in the operative group (N=58 (24%); $p=0.026$). In addition, the risk of any surgical (re)intervention was 2.1-fold higher after nonoperative treatment than after operative treatment (26% versus 12%). This is in line with the results of this systematic review, which show that, apart from complications specific to surgery, all complications occurred more often in the nonoperative group. All things considered, this data supports that initial operative treatment provides a more predictable course of recovery than nonoperative treatment, which is associated with complications in one out of four patients.

Nowadays, focus is shifting from achieving bone union and avoiding complications to achieving excellent functional outcomes. The difference in DASH score is statistically significant as well as clinically relevant until three months, as the differences are larger than the minimally important change for the DASH (6.7 points) in the study population.[11] In terms of upper extremity function, the Constant-Murley score was higher in the operative group until six months after trauma. These findings correspond with the FISH RCT, including 82 adult patients with a closed humeral shaft fracture, which also showed superior DASH and Constant-Murley scores in the operative group until six months follow-up.[12] Regarding range of motion, shoulder abduction, forward flexion, external rotation, and elbow flexion and extension were all statistically significantly better in the operative group than in the nonoperative group until three months follow-up. These results are important for shared decision-making on treatment.

A secondary analysis of the HUMMER data, concerning the comparison of the two main surgical approaches of a humeral shaft fracture, IMN versus plate osteosynthesis (**Chapter 4**), showed superior Constant-Murley scores and shoulder range of motion after plating during the first six months after trauma. Significantly more surgical reinterventions were needed in the IMN group, which also showed more implant-related complications.

An inherent disadvantage of both operative strategies is the risk of implant-related complications and subsequent revisions, which were 5.5-fold and 6.4-fold higher in the IMN group compared with the plate group. All implant removals performed were due to implant-related complications in patients treated with an IMN (N=16; 7%) and mostly due to nail and screw protrusion. The lower rate of implant-related complications and revisions in the plate group exceeds the advantages of IMN such as shorter operation time, less blood loss, and smaller incisions.

The inferior functional outcome scores and range of motion in the IMN group can possibly be explained by the problems that may arise as a consequence of introducing an IMN through the rotator cuff muscles and associated complications. These findings are in line with the pooled analyses, which indicated a slight advantage of functional recovery after operative treatment with plate osteosynthesis and lower rates of shoulder dysfunction, intraoperative, and implant-related complications compared than in the IMN group.

The choice of treatment can possibly be influenced by existing or potential radial nerve palsy. Results of an analysis of HUMMER patients with radial nerve palsy (**Chapter 5**) indicate that the rate of persistent complaints due to radial nerve palsy at presentation and postoperative radial nerve palsy is very low (0.3% and 0.4%, respectively) and suggests radial nerve palsy is mostly caused by temporary neurapraxia. Postoperative radial nerve palsy was observed more often after plating (11%) than after nailing (1%; **Chapter 4**). Nonetheless, the burden of a temporary restricted range of motion due to radial nerve palsy and the unpredictable course of recovery should be acknowledged. In this secondary analysis, functional outcomes (DASH, Constant-Murley, pain, range of motion, activity resumption, and health-related quality of life) were analysed at 12 months after trauma, possibly resulting in an underestimation of the extensive burden of transient radial nerve palsy. Furthermore, it could be argued that even though wrist drop can impact multiple aspects of these measures, they do not adequately capture the disability caused by the radial nerve palsy. Unfortunately, due to the lack of objective measurement of radial nerve function (range of motion of the wrist, grip strength, and electromyography), no distinction can be made between adaptation to disability and actual disability.

Although persistent postoperative radial nerve palsy is rare, it should not be discouraging for operative treatment of a humeral shaft fracture. Intra-operative nerve exploration and identification is important. This can best be achieved with exploration of the radial nerve with full visibility, which is most feasible during plate osteosynthesis. As one of the two persistent palsies reported was a result of entrapment of the nerve under the plate, it could be argued that this should only be performed or supervised by an experienced and skilled surgeon.

Societal burden

The societal impact of a humeral shaft fracture is high. It is not necessarily expressed in years of life lost, but in the loss of economically productive time, medical costs, and possible consequences for personal life. The economic evaluation of the HUMMER study (**Chapter 6**) showed that operative treatment of a humeral shaft fracture is associated with €3,130 higher mean costs per person over one year than nonoperative treatment. This difference in costs was mainly due to the hospital costs for the primary stay, including surgery and hospital admission. However, hospital costs for the follow-up were higher in the nonoperative group, mainly due to a higher need for secondary surgery and consequent hospital admission days. There was also a trend toward higher costs related to rehabilitation and changes in housing situation in the nonoperative group, however, this difference was not significant.

In economic evaluations, the higher mean costs for operative treatment can be justified if the treatment also results in more favorable outcomes. The results show that both treatments result in a consistent improvement during one year in favor of the operative group. This difference was mostly attributable to the faster recovery of operatively treated patients in the first six months. The EQ-5D may not adequately capture this effect as sustaining a humeral shaft fracture does not necessarily affect a patient's general health perception, resulting in small effects measured in some of the domains of the EQ-5D (*e.g.,* anxiety and depression).[14] Therefore, the effect of treatment might not be adequately captured with this instrument, resulting in statistically significant, but marginal differences in QALYs. Even though the absolute difference in costs is low, the division by the small denominator results in high incremental costs per QALY gained (€111,860; €3,130/0.028), which exceed the Dutch threshold for costs per QALY (€20,000-€80,000). The effectiveness of the treatment of humeral shaft fractures is more specifically captured with the DASH score. Although the incremental cost-effectiveness ratio calculated with the DASH score cannot be compared with other injuries, the low incremental costs of operative treatment (€2,880) for a clinically meaningful difference suggest that operative treatment of a humeral shaft fracture is cost-effective.

Besides effect measures of health-related quality of life and functional recovery, patient's preference should also be taken into account in clinical decision-making. Employment status can influence the choice of treatment, as patients may want to return to work as soon as possible. Cost for lost productivity were a main driver of costs, both in the operative (25%; €3,010/€11,930) and nonoperative

(31%; €2,700/€8,790) group. However, the younger men and overrepresentation of employed patients in the operative group suggest a possible preference for operative treatment for employed patients.

Reflecting on the HUMMER study

The main strength of the HUMMER study (**Chapter 3, 4,** and **5**) is that it evaluated multiple aspects of the treatment of a humeral shaft fracture through a multidimensional approach. In order to do so, it generated data on the largest sample of patients with a humeral shaft fracture to date.[12, 13, 15-17] The multicenter design with almost 30 participating hospitals in the Netherlands, including level 1, 2, and 3 trauma centers, ensures greater external validity by allowing for treatment heterogeneity between hospitals. The prospective design allowed for accurate collection of relevant data such as injury characteristics, description of treatment and recovery, improvement of function, and micro-costing in routine clinical practice.

Another benefit of the observational design is that surgeons could use the treatment strategy they had experience with and felt was best for the individual patient so they could reach the best possible result. This in contrast to RCTs where randomization could result in the (operative) technique where the surgeon would feel less comfortable with and patients refraining from or withdrawing consent if the allocated treatment is not their preferred treatment. This could cause problems of low recruitment and high drop-out rates, which is observed in surgical trials comparing surgical and nonoperative treatment.[18] Prolonged inclusion periods due to slow accrual of a sufficient numbers of participants lead to a longer study duration and higher costs, and can possibly outbalance the potential advantages of RCTs.[19, 20] This results in a delicate trade-off between the time and money needed for planning and conducting a properly powered multicenter RCT and the benefits of a more highly valued scientific method. The few orthopedic trauma RCTs with similar research questions that have mastered the art of riding dead horses, do not necessarily result in more valid observations.[21] Some studies have shown that observational studies, where physicians can use the technique they have most experience with and best fit patient's preferences, lead to similar outcomes without the limitations of randomization which may in practice decrease the validity of the outcomes in clinical practice.[22, 23]

As can be expected from a prospective observational cohort, the chosen treatment was not completely random, and some imbalance in baseline data was noted between the treatment groups. Linear mixed-effects regression models with intercepts of the model and time coefficient were used to statistically correct for this imbalance and mitigate this limitation. Another limitation could be that the expected inclusion rate of 10 patients per month was not achieved (actual rate of 5.5 patients per month, *i.e.*, 390 patients in 71 months) and some participating hospitals enrolled fewer patients than expected, suggesting that not all patients were screened for participation and therefore the study sample was not consecutive.

Other limitations include the lack of a protocol for the assessment of radial nerve palsy, resulting in heterogeneity in the documentation of function, rehabilitation, and recovery. Lastly, considering the economic analyses, the follow-up duration of 12 months did not take into account continuing health care use beyond one year.[24]

Polytrauma

Although approximately 50% of patients with a humeral shaft fracture has an injury severity score (ISS) >16, little is known about the fracture type, optimal treatment strategy, and outcomes of these fractures in polytraumatized patients.[25] Ideally, the influence of additional injuries on the functional outcome of a humeral shaft fracture would be examined in a prospective comparative study comparing a group of patients with an isolated humeral shaft fracture with a matched polytraumatized group with a humeral shaft fracture. If functional outcome would be reported by the DASH score at the three months' time-point, calculation of the required sample size would be based on the assumption that the mean DASH would be 20 (SD 20) in the isolated fracture group and 30 (SD 30) in the polytraumatized group (**Chapter 3** and **7**). A two-sided test with an α level of 0.05 and a β level of 0.2 would result in a requirement of 63 patients in every group. In order to account for loss of patients due to mortality (10%) and loss-to-FU (10%), 79 patients per group would be required. The sample size of 61 polytraumatized patients enrolled in 15 years in a single level I trauma center supports that a monocentric prospective study would be unfeasible. Furthermore, these sample size calculations do not cover for distinguishing between operative and nonoperative treatment, which would result in even larger required sample sizes.

Shared decision-making

The ultimate aim of this thesis was to answer scientific questions in the ongoing debate on the treatment of a humeral shaft fracture and therewith improve care for patients. The obtained insight in clinical and functional outcomes can facilitate informed shared decision-making by shedding light on the optimal treatment of a humeral shaft fracture and possible complications. Although these outcomes give some helpful directions, it might be difficult for patients to weigh the potential risks and benefits of each treatment method when considering the possible treatment options. Patients may tend to overestimate potential burdens early after trauma (such as postoperative radial nerve palsy, wound infection, and surgical anxiety), but underestimate issues that may arise later during rehabilitation (such as nonunion, malalignment, implant-related complications, secondary interventions, and inferior function and range of motion). In our opinion, the benefits of fast recovery and low rates of late complications of operative treatment should be stressed. However, the different values and preferences of patients should be appreciated.

FUTURE PERSPECTIVES

This thesis provided answers regarding functional recovery, complications, and cost-effectiveness of treatment of a humeral shaft fracture in different settings but gave rise to many new questions. Partly, the main question remains: what is the best treatment for an individual patient with a humeral shaft fracture? The best treatment is generally known at a population-level, but it remains unclear which patient and injury characteristics determine the optimal approach. The data from the HUMMER study can possibly facilitate identifying those likely to fail nonoperative treatment with baseline predictors. Furthermore, it can possibly enable answering questions on the effect of the quality of surgery on the outcomes. Besides that, the cost-effectiveness of plate osteosynthesis versus intramedullary nailing can be calculated. The HUMMER study can also be a good start for investigating the long-term effects of operative versus nonoperative treatment of a humeral shaft fracture. Lastly, cooperation with other level 1 trauma centers could enable prospective research on polytraumatized patients with a humeral shaft fracture.

In considering the future, optimized patient-centered care might be realized by using Artificial Intelligence to classify fractures and combine patient and injury characteristics with known outcomes in order to decide on the best treatment strategy. Furthermore, more awareness of the climate-impact of the different treatment modalities is warranted in future orthopedic trauma research.

Finally, it should be noted that the emotional, physical, and societal impact of trauma is high, but financial contribution for trauma research is often insufficient. Raising money for research on humeral shaft fractures with extraordinary endeavors may not sound very appealing, as the recovery of a humeral shaft fracture does not particularly have the X-factor, but I do hope this thesis shows that research contributes to elevating the burden caused by this injury.[26, 27]

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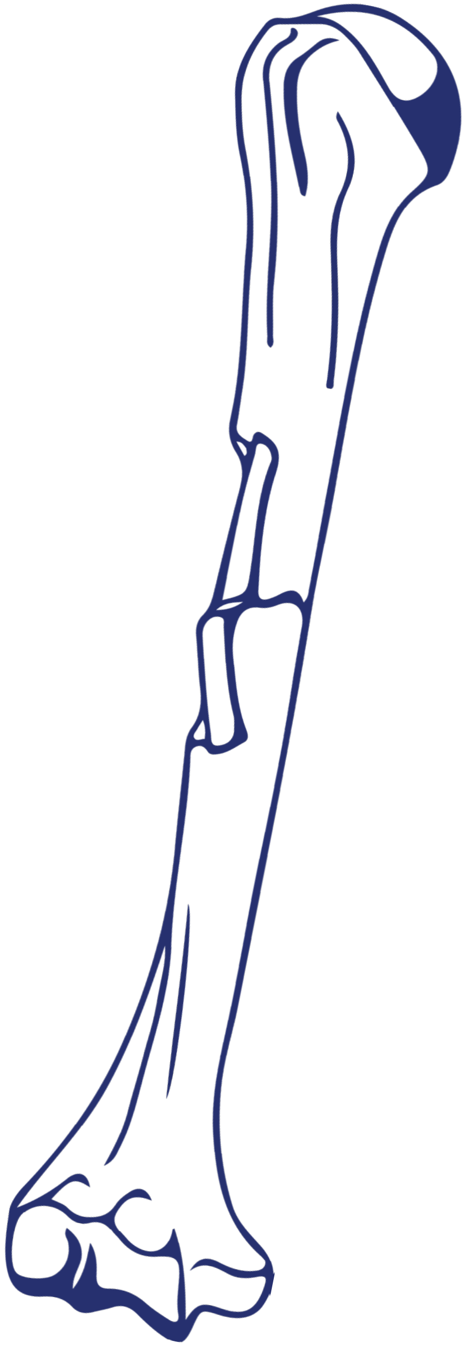


CHAPTER 9

Summary and conclusions

SUMMARY AND CONCLUSIONS

Chapter 1 is an introduction of this thesis. It outlines the epidemiological and anatomical aspects of humeral shaft fractures and gives insight into the treatment, outcomes, and complications. Furthermore, it describes the societal burden of humeral shaft fractures in polytraumatized patients.

Chapter 2 describes a systematic literature review and pooled analysis of the fracture healing rates, functional outcome, and complications of nonoperative and operative treatment of humeral shaft fractures. A total of 173 studies, reporting the results of 11,868 patients, were included. The fracture healing rate for the nonoperative group was 89% (95% CI 84-92%), 94% (95% CI 92-95%) for the IMN group, and 96% (95% CI 95-97%) for the plating group. The rate of secondary radial nerve palsies was 1% in the nonoperative group, 3% in the IMN group, and 6% in the plating group. Intraoperative complications and implant failures occurred more frequently in the IMN group than in the plating group. The DASH score ranged from 23 (95% CI 17-29) in the (antegrade) IMN group to 7 (95% CI 1-13) in the minimally invasive plate osteosynthesis group. The Constant-Murley score in the IMN group was 90 (95% CI 85-95) and 93 (95% CI 92-95) in the plating group. The UCLA shoulder score in the IMN group was 28 (95% CI 22-34) and 33 (95% CI 32-33) in the plating group.

Conclusion

- These findings suggest that even though all treatment modalities result in satisfactory outcomes, plate osteosynthesis seems to result in the most favorable outcomes.

Chapter 3 to **6** describe the results of the HUMMER study, a multicenter prospective cohort study with 29 participating centers designed to compare operative and nonoperative treatment of a closed humeral shaft fracture AO type 12A and B.

A comparison of functional and clinical outcome of operative versus nonoperative treatment in adult patients with a humeral shaft fracture is presented in **Chapter 3**. Of the 390 included patients, 245 were operated and 145 were treated nonoperatively. Patients in the operative group were younger (median 53 versus 62 years; p<0.001) and less frequently female (N=133 (54.3%) versus N=94 (64.8%); p=0.044). Superior results in favor of the operative group were noted until six months follow-up for the DASH, Constant-Murley, shoulder abduction, anteflexion, and exorotation, and elbow flexion and extension. The EQ-US and elbow pronation and supination showed superior results for the operative group until six weeks follow-up. Malalignment occurred only in the nonoperative group (N=14; 9.7%) and implant-related complications only in the operative group (N=26; 10.6%, of whom 19 required implant exchange or removal). Nonunion occurred more often in the nonoperative group (N=30 (26.3%) versus N=19 (10.1%) in the operative group; p<0.001).

Conclusions

- Operative treatment is associated with a more than twofold reduced risk of nonunion, earlier functional recovery, and a better range of motion of the shoulder and elbow joint than nonoperative treatment.
- The rate of complications as well as secondary surgical interventions was higher in the nonoperative group.

Chapter 4 examines functional and clinical outcome after operative treatment with IMN or plate osteosynthesis in adults with a closed humeral shaft fracture included in the HUMMER study**.** Of the 245 included patients, 169 were treated with IMN and 76 with plate osteosynthesis. Patients in the plate group were younger (median 43 versus 57 years; p<0.001). The Constant-Murley score and shoulder abduction, flexion, external rotation, and internal rotation showed a significant treatment effect with a $p_{treatment} \leq 0.001$, in favor of plating. The plate group had only two implant-related complications, whereas the IMN group showed 13 nail protrusions and eight screw protrusions. Post-operative temporary radial nerve palsy was more common after plating (N=8; 10.5% versus N=1; 0.6%; $p<0.001$). Nonunion occurred less frequently after plating (N=3; 5.7%) than after nailing (N=16; 11.9%; $p=0.285$).

Conclusions

- Plate osteosynthesis of a humeral shaft fracture in adults results in faster recovery, especially of the shoulder function.
- Plate osteosynthesis was associated with fewer implant-related complications and surgical reinterventions than nailing.
- Plate osteosynthesis should be the preferred operative treatment strategy for humeral shaft fractures AO type 12 A and B.

Chapter 5 examines the consequences of radial nerve palsy at presentation and postoperative radial nerve palsy in patients with a closed humeral shaft fracture. Three out of the 145 initially nonoperatively treated patients had radial nerve palsy at presentation, of whom one recovered spontaneously and one after osteosynthesis. Despite multiple surgical interventions, one patient had no recovery of radial nerve function within the 12 months follow-up period after nerve entrapment between fracture fragments. Of the 245 operatively treated patients, 13 had radial nerve palsy at presentation, who all showed full recovery. Nine patients suffered from postoperative radial nerve palsy of which eight healed uneventfully. In one patient recovery was still ongoing at the last follow-up, after nerve release and suture repair due to nerve entrapment under the plate were performed. One year after trauma, the functional outcome scores of patients with radial nerve palsy, either at presentation or postoperatively, suggested full functional recovery regarding arm function (DASH and Constant-Murley score), pain, and activity resumption. The quality of life scores corresponded to standardized population norms and functional levels of range of motion were achieved.

Conclusions

- Radial nerve palsy in humeral shaft fractures, either at presentation or postoperative, has a low occurrence rate and a high rate of spontaneous functional recovery.
- Treatment of humeral shaft fractures should not be guided by the presence of radial nerve palsy at presentation or risk of postoperative radial nerve palsy.

Chapter 6 analyzes the cost-utility and cost-effectiveness of operative versus nonoperative treatment in patients with a humeral shaft fracture. The mean total costs were €3,140 (95% CI €1,330-€4,940; $p<0.001$) higher in operatively treated patients. The mean difference in QALY at one year was 0.028 ($p<0.001$) in favor of operative treatment, resulting in an incremental cost-utility ratio for operative treatment of €111,860 per QALY gained, which exceeds the Dutch threshold of costs per QALY (ranging from €20,000 to €80,000). The mean difference in DASH score was 7.3 ($p<0.001$) in favor of operative treatment, resulting in an incremental cost-effectiveness ratio of €2,880 for a minimal important change in disability (6.7 DASH points reduced).

Conclusions

- Due to the limited effect of the treatment a humeral shaft fracture on quality of life measured with the EQ-5D, the cost-effectiveness in terms of costs per QALY (€111,860) exceeds the acceptability limit.
- The incremental costs of €2,880 per meaningful difference in DASH are well below this limit and suggest that operative treatment for a humeral shaft fracture is cost-effective.

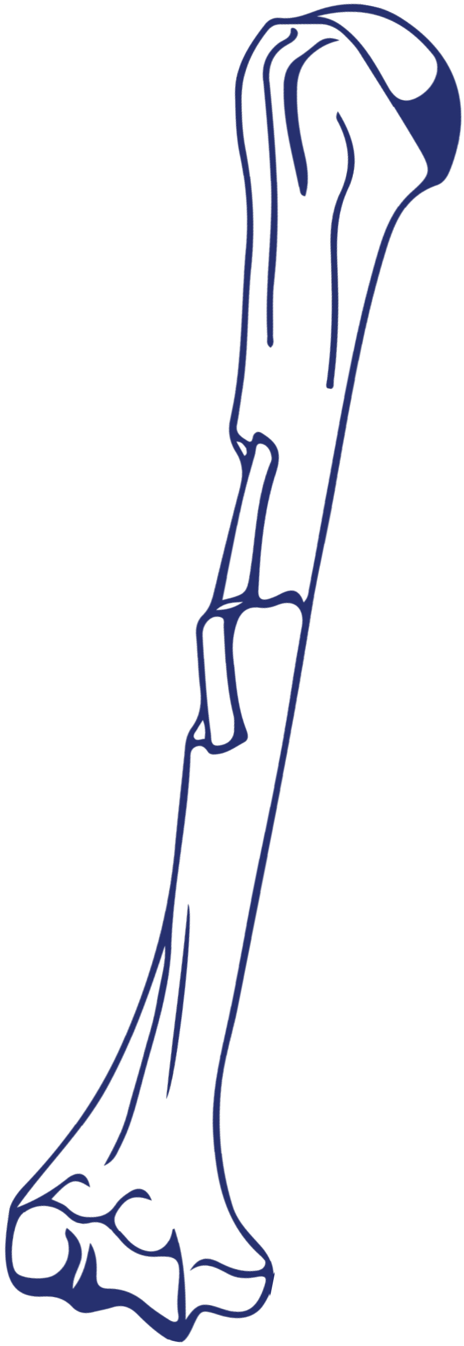
Chapter 7 examines the fracture type, treatment, and outcome of humeral shaft fractures in adult polytraumatized patients. Twenty-nine patients with a humeral shaft fracture and an injury severity score of 16 or higher were included in a case series with a single follow-up questionnaire approximately five years post trauma.

The median age was 41 years and 18 (62%) were male. Most fractures were type A (N=19; 66%). Most patients were treated operatively (N=26; 90%) within a median of three days. Radial nerve palsy at presentation occurred in five (20%) patients, infection in one (4%), and nonunion in six (27%). The median DASH score was 20.0 (P_{25}-P_{75} 5.6-35.2), EQ utility score 0.75 (P_{25}-P_{75} 0.58-0.88), EQ visual analog score 0.80 (P_{25}-P_{75} 71-95), SF-36 physical component summary 49 (P_{25}-P_{75} 43-55), and SF-36 mental component summary 58 (P_{25}-P_{75} 47-61).

Conclusions

- Humeral shaft fractures in adult polytraumatized patients were most often AO-type A and treated operatively.
- Radial nerve palsy at presentation and nonunion rates were relatively high.
- Patients still reported upper extremity disability at approximately five years post trauma.

Finally, the general discussion and future perspectives are discussed in **Chapter 8**.



CHAPTER 10

Nederlandse samenvatting en conclusies

NEDERLANDSE SAMENVATTING EN CONCLUSIES

Hoofdstuk 1 is de introductie van dit proefschrift. Het beschrijft de epidemiologische en anatomische aspecten en geeft inzicht in de verschillende behandelopties van humerusschachtfracturen en de resultaten hiervan. Daarnaast beschrijft het de maatschappelijke last van humerusschachtfracturen in polytrauma patiënten.

In **Hoofdstuk 2** worden de resultaten van een systematisch literatuuroverzicht en gepoolde analyse van de klinische uitkomsten en complicaties van de niet-operatieve en operatieve behandeling van humerusschachtfracturen gepresenteerd. In totaal werden 173 studies, die 11.868 patiënten beschreven, geïncludeerd. Het consolidatiepercentage voor de niet-operatieve groep was 89% (95% betrouwbaarheidsinterval (BI) 84-92%), 94% (95% BI 92-95%) in de intramedullaire pen-groep en 96% (95% BI 95-97%) in de plaat-groep. De gepoolde analyse toonde dat de prevalentie van nervus radialis uitval 1% was in de niet-operatieve groep, 3% in de intramedullaire pen-groep en 6% in de plaat-groep. In de intramedullaire pen-groep kwamen intra-operatieve complicaties en implantaat falen vaker voor dan in de plaat-groep. De DASH score varieerde van 23 (95% BI 17-29) in de (antegrade) intramedullaire pen-groep tot 7 (95% BI 1-13) in de minimaal invasieve plaatosteosynthese-groep. De Constant-Murley score was 90 (95% BI 85-95) in de intramedullaire pen-groep en 93 (95% BI 92-95) in de plaat-groep. De UCLA schouder score was 28 (95% BI 22-34) in de intramedullaire pen groep en 33 (95% BI 32-33) in de plaat-groep.

Conclusie

- Alle behandelopties leiden tot een acceptabel resultaat, maar een operatieve behandeling, en specifiek plaatosteosynthese, resulteert in de meest gunstige uitkomsten.

Hoofdstuk 3 tot **6** beschreven de resultaten van de HUMMER studie, een prospectieve cohortstudie met 29 deelnemende centra waarin de operatieve versus niet-operatieve behandeling van gesloten humerusschachtfracturen, AO type 12A en B, werden onderzocht.

Hoofdstuk 3 vergeleek de functionele en klinische uitkomsten van operatief versus niet-operatief behandelde volwassen patiënten met een humerusschachtfractuur. Van de 390 geïncludeerde patiënten, waren 245 operatief en 145 niet-operatief behandeld. Patiënten in de operatieve groep waren jonger (mediaan 53 versus 62 jaar; p<0,001) en minder vaak vrouw (N=133 (54,3%) versus N=94 (64,8%); p=0,044). De operatieve groep toonde superieure resultaten voor de DASH, Constant-Murley, schouder abductie, anteflexie en exorotatie en elleboog flexie en extensie tot zes maanden na het trauma. Daarnaast resulteerde operatieve behandeling in superieure resultaten van de EQ-US en elleboog pronatie en supinatie tot zes weken na trauma**.** Niet-anatomisch geheelde fracturen werden enkel gezien in de niet-operatieve groep (N=14; 9,7%) en implantaat-gerelateerde complicaties alleen in de operatieve groep (N=26; 10,6%, waarvan het voor 19 patiënten nodig was om het implantaat te verwijderen of vervangen). Consolidatie faalde vaker in de niet-operatieve groep (N=30 (26,3%) versus N=19 (10,1%) in de operatieve groep; p<0,001).

Conclusies

- Operatieve behandeling resulteert in een halvering van het risico op nonunion, sneller functioneel herstel en een beter bewegingsbereik van de schouder en elleboog vergeleken met niet-operatieve behandeling.
- Niet-operatieve behandeling resulteert in meer in complicaties en secundaire interventies dan de operatieve groep.

Hoofdstuk 4 onderzocht de functionele en klinische uitkomsten van operatieve behandeling, met een intramedullaire pen of plaatosteosynthese, van humerusschachtfracturen. Van de 245 geïncludeerde patiënten, waren 169 behandeld met een intramedullaire pen en 76 met plaatosteosynthese. Patiënten in de plaat-groep waren jonger (mediaan 43 versus 57 jaar; p<0,001). De Constant-

Murley score en schouder abductie, flexie, exorotatie en endorotatie waren significant beter in de plaat-groep ($p_{behandeling} \leq 0{,}001$). De plaat-groep had maar twee implantaat-gerelateerde complicaties, terwijl dit aantal in de intramedullaire pen-groep 21 bedroeg. Tijdelijk postoperatief zenuwletsel van de nervus radialis kwam vaker voor in de plaat-groep (N=8; 10,5% versus N=1; 0,6%; p<0,001). Falen van consolidatie kwam vaker voor na het plaatsen van een intramedullaire pen (N=16; 11,9%) dan na plaatosteosynthese (N=3; 5,7%; p=0,285), maar dit verschil was niet significant.

Conclusies

- Plaatosteosynthese resulteert in sneller herstel, met name van de schouderfunctie.
- Plaatosteosynthese is geassocieerd met minder implantaat-gerelateerde complicaties en secundaire interventies dan behandeling met een intramedullaire pen.
- Plaatosteosynthese zou de voorkeur moeten hebben als operatieve behandeling van humerusschachtfracturen, AO type 12 A en B.

In **hoofdstuk 5** zijn de gevolgen van uitval van de nervus radialis geassocieerd met een humerusschachtfractuur beschreven op basis van functieherstel. Drie van de 145 niet-operatief behandelde patiënten had radialisletsel bij presentatie, waarvan één spontaan herstelde en één na osteosynthese. Ondanks meerdere chirurgische interventies, trad bij een patiënt geen functieherstel van radialisletsel op binnen de 12 maanden follow-up periode na zenuwbeknelling tussen de fractuurfragmenten. Van de 245 operatief behandelde patiënten, hadden dertien radialisletsel bij presentatie, welke allemaal volledig herstelde binnen twaalf maanden. Negen patiënten hadden postoperatief radialisletsel, waarvan acht spontaan herstelde. Bij een patiënt werd, na re-exploratie en hechten van de zenuw vanwege zenuwbeknelling onder de plaat, na twaalf maanden nog steeds functieverbetering gezien. Een jaar na het ongeval duidden de uitkomsten van het cohort, op basis van bewegingsbereik, dagelijks gebruik en kwaliteit van leven, op een volledig herstel van de radialisfunctie. De meetwaarden, wat betreft functionele uitkomsten, pijn, gezondheid-gerelateerde kwaliteit van leven, mate van hervatten van activiteiten en bewegingsbereik van de schouder en elleboog, van alle patiënten kwamen overeen met de populatienorm.

Conclusies

- De prevalentie van nervus radialisuitval (primair en secundair) is laag en het spontaan functioneel herstel is goed tot excellent.
- De keuze van de techniek voor de behandeling van humerusschachtfracturen zou niet moeten worden beïnvloed door de aanwezigheid van radialisletsel bij presentatie of het risico op postoperatief radialisletsel.

Hoofdstuk 6 analyseerde de kostenutiliteit en kosteneffectiviteit van de operatieve versus niet-operatieve behandeling van humerusschachtfracturen. De gemiddelde totale kosten waren €3.140 (95% BI €1.330-€4.940; p<0,001) hoger in de operatief behandelde patiënten. Het verschil in QALYs na een jaar was 0,028 (p<0,001) hoger in de operatieve groep, resulterend in een incrementele kostenutiliteitsratio van €111.860 per QALY voor de operatieve groep, welke het Nederlandse aanvaardbaarheidslimiet van kosten per QALY overschrijdt (variërend van €20,000 tot €80,000). De DASH score was 7,3 lager in de operatieve groep na drie maanden, resulterend in een incrementele kosteneffectiviteitsratio van €2.880 voor een klinisch meetbaar verschil in effectiviteit.

Conclusies

- Door het beperkte effect van de behandeling van een humerusschachtfractuur op de kwaliteit van leven gemeten met de ED-5D, overschrijdt de incrementele kosten-utiliteitsratio van een operatieve behandeling (€111,860) de aanvaardbaardheidslimiet van de kosten per QALY.
- De incrementele kosten van €2.880 per klinisch meetbaar verschil in effectiviteit gemeten met de DASH liggen ver onder dit limiet en suggereren dat een

operatieve behandeling van een humerusschachtfractuur kosteneffectief is.

Hoofdstuk 7 beoogde om het fractuurtype, de behandeling en uitkomsten van humerusschachtfracturen in polytrauma patiënten te beschrijven. Er werden 29 patiënten met een humerusschachtfractuur en een totale letselscore van 16 of hoger geïncludeerd in deze patiëntenserie waarbij eenmalig een vragenlijst werd afgenomen. De mediane leeftijd was 41 jaar en 18 (62%) patiënten waren man. Het meest voorkomende fractuurtype was type A (N=19; 66%). De meeste patiënten waren operatief behandeld (N=26; 90%) binnen drie dagen (mediaan). Nervus radialisletsel was gerapporteerd in vijf (20%) patiënten, infectie in één (4%) en falen van de consolidatie van de humerusschachtfractuur in zes (27%). De mediane DASH score was 20.0 (P_{25}-P_{75} 5.6-35.2), EQ utility score 0.75 (P_{25}-P_{75} 0.58-0.88), EQ visual analog score 0.80 (P_{25}-P_{75} 71-95), SF-36 physical component summary 49 (P_{25}-P_{75} 43-55), en SF-36 mental component summary 58 (P_{25}-P_{75} 47-61).

Conclusies

- Humerusschachtfracturen in volwassen polytrauma patiënten zijn het vaakst AO-type A en worden overwegend operatief behandeld.
- Nervus radialisletsel en falen van consolidatie kwam relatief vaak voor.
- Patiënten rapporteerden ongeveer vijf jaar na het trauma nog steeds beperkingen van de bovenste extremiteiten.

Tot slot worden de algemene discussie en toekomstperspectieven besproken in **Hoofdstuk 8**.

APPENDICES

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List of publications

PhD portfolio

Dankwoord

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LIST OF PUBLICATIONS

Humeral shaft fracture: systematic review of non-operative and operative treatment
Van Bergen SH, Mahabier KC, Van Lieshout EMM, Van der Torre T, Notenboom CAW, Jawahier PC, Verhofstad MHJ, Den Hartog D
Archives of Orthopaedic and Trauma Surgery 2023

Functional and clinical outcome after operative versus nonoperative treatment of a humeral shaft fracture (HUMMER): results of a prospective multicenter cohort study
Den Hartog D, Van Bergen SH, Mahabier KC, Verhofstad MHJ, Van Lieshout EMM, on behalf of the HUMMER investigators
European Journal of Trauma and Emergency Surgery 2022

Functional and clinical outcomes after plate osteosynthesis versus intramedullary nailing of a humeral shaft fracture: the results of the HUMMER multicenter, prospective cohort study
Den Hartog D, Mahabier KC, Van Bergen SH, Verhofstad MHJ, Van Lieshout EMM, on behalf of the HUMMER investigators
The Journal of Bone and Joint Surgery 2023

Recovery and functional outcome after radial nerve palsy in adults with a humeral shaft fracture: a multicenter prospective case series
Van Bergen SH, Van Lieshout EMM, Verhofstad MHJ, Den Hartog D, on behalf of the HUMMER investigators
Journal of Shoulder and Elbow Surgery International 2023

Economic evaluation of operative versus nonoperative treatment of a humeral shaft fracture: economic analyses alongside a multicenter prospective cohort study (HUMMER)

Van Bergen SH, Van Lieshout EMM, Mahabier KC, Geraerds AJLM, Polinder S, Den Hartog D, Verhofstad MHJ, on behalf of the HUMMER investigators

European Journal of Trauma and Emergency Surgery 2022

Fracture type, treatment, and outcome of humeral shaft fractures in polytrauma patients: a case series

Van Bergen SH, Den Hartog D, Zeelenberg ML, Van Lieshout EMM, Verhofstad MHJ

Submitted

PHD PORTFOLIO

Name PhD student:	Saskia H. Van Bergen
PhD period:	Jun 2021 - Feb 2024
Promotors:	Prof. dr. M.H.J. Verhofstad
Co-promotors:	dr. D. Den Hartog and dr. E.M.M. Van Lieshout
Erasmus MC Department:	Trauma Research Unit, Department of Surgery

PhD Training	**Year**	**ECTS**
Courses		
Core competence exam	2022	1.0
Scientific Integrity, Erasmus MC, Rotterdam	2022	0.3
Junior Basiskwalificatie Onderwijs	2022	5.0
Seminars, workshops, and master classes		
Scientific Publications, Erasmus MC, Rotterdam	2021	0.3
Visual Communication, Erasmus MC, Rotterdam	2021	0.3
Conflict Mediation, Erasmus MC, Rotterdam	2022	0.3
PhD intervision sessions, Erasmus MC, Rotterdam	2021-22	0.3
Oral presentations		
Economic evaluation of treatment of a humeral shaft fracture		
EFORT Congress, *Lisbon, Portugal*	2022	1.0
IOTA Traumadagen, *Amsterdam, The Netherlands*	2022	1.0
Radial nerve palsy in humeral shaft fractures		
Assistentensymposium, *Rotterdam, The Netherlands*	2023	1.0
Awarded prof. dr. G.J. Heijmans-prijs		
ECTES, *Ljubljana, Slovenia*	2023	1.0
Traumadagen, *Amsterdam, The Netherlands*	2023	1.0

PhD Training	Year	ECTS
Systematic review of humeral shaft fractures		
Chirurgendagen, *Veldhoven, The Netherlands*	2023	1.0
Fracture type, treatment and outcome of a humeral shaft fracture in polytrauma patients		
Traumadagen, *Amsterdam, The Netherlands*	2023	1.0
Poster presentations		
Functional and clinical outcome after plate osteosynthesis versus intramedullary nailing of humeral shaft fractures		
ECTES, *Ljubljana, Slovenia*	2023	1.0
Radial nerve palsy in humeral shaft fractures		
IOTA Traumadagen, *Amsterdam, The Netherlands*	2022	1.0
OTA, Seattle, *Washington, United States of America*	2023	1.0
Submitted by NVT as best poster presentation		
Other attended conferences		
Assistentensymposium, *Amersfoort, The Netherlands*	2019	1.0
Traumadagen, *Amsterdam, The Netherlands*	2021	1.0
International conference on Disaster and Military Medicine, *Düsseldorf, Germany*	2021	1.0
Asisstentensymposium, *online*	2022	1.0
Chirurgendagen, *The Hague, The Netherlands*	2022	1.0

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Saskia Heleen Van Bergen was born on November 28th, 1996 in Eindhoven, the Netherlands. After graduating grammar school cum laude at the Lorentz Casimir Lyceum in 2014, she started a Bachelor of Arts, consisting of multiple social sciences such as anthropology and philosophy, at the Victoria University of Wellington in New Zealand.

After a year abroad, she returned to the Netherlands and started medical school at the Erasmus University of Rotterdam. After obtaining a bachelor in Medicine, during which she gratefully joined the Honours Class, she started the NIHES Research Master Clinical Research to develop the necessary scientific skills to conduct high-quality research. The master consisted of multiple epidemiological courses and an 18 month research internship at the Trauma Research Unit, Erasmus MC, Rotterdam. Throughout this period, her interest in trauma surgery and research grew into the ambition to pursue her research as a PhD candidate.

As a person, she has always had the adage that curiosity is the base of gaining knowledge and aimed to develop herself both academically and as a person. During her studies she did so by doing an additional master in Health Economic, Policy and Law, as well as enriching her knowledge as a student assistant and teacher at the Department of Anatomy and Neuroscience. She volunteered her time amongst others as an organizer of events for fellow students (IFMSA, MFVR, EARP, RSC/RVSV, Co-Raad) and multiple charities (Rijden tegen Kanker (KWF), Hartstichting, Kids Run Free, Kletsmaatje, VoorleesExpress).

Most enlighting was her work at Defensity College, consisting of military training, personal self-development courses, and internships at multiple disciplines of the the Netherlands Armed Forces. Lastly, her multiple committee and (advisory) board positions enhanced her ability of problem solving, working efficiently in a team, and professional responsibility.

Currently, she is finishing her medical internships and will aim to pursue her dream to become a trauma surgeon at the Netherlands Armed Forces.