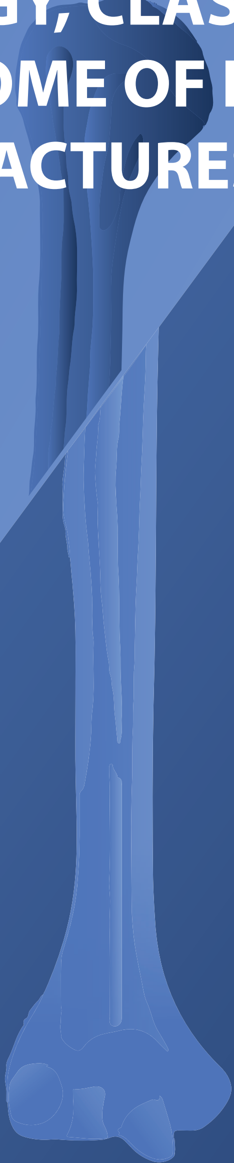
EPIDEMIOLOGY, CLASSIFICATION AND OUTCOME OF HUMERUS FRACTURES



Kiran C. Mahabier

Epidemiology, Classification and Outcome of Humerus Fractures

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Epidemiology, Classification and Outcome of Humerus Fractures

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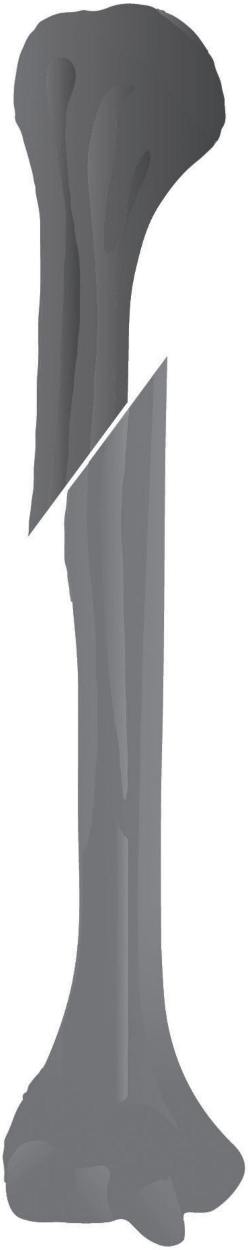

PART I

GENERAL INTRODUCTION

Chapter 1

General introduction, aim and outline of the thesis

GENERAL INTRODUCTION

Epidemiology and societal burden

Between 1986 and 2008, over 3.7 million persons presented to an Emergency Department (ED) of a Dutch hospital with an upper extremity injury. This comprised 42% of all ED visits in The Netherlands.[1] The incidence rate of upper extremity injuries overall increased by 13%, from 970 in 1986 to 1,098 per 100,000 person years in 2008. Fractures of the humerus have an incidence rate of 122 per 100,000 persons per year.[2] Proximal fractures account for 50% these. Proximal humerus fractures are the third most common fractures after hip fractures and distal radius fractures.[3] Humeral shaft fractures have an incidence rate of 14 - 19 per 100,000 per year.[2, 4] They account for 3% of all fractures and for 20% of fractures of the humerus. The incidence shows a peak in the third decade of life and especially an increase in elderly patients.[4, 5] Distal humerus fractures have an incidence rate of 43 per 100,000 persons per year and with a peak in children aged 5-9 years.[2]

Fractures of the humerus are associated with a profound temporary and sometimes even permanent, impairment of independence and quality of life. The societal burden associated with these injuries is high and causes high costs for health care and lost productivity.[6-10]

Anatomy

The proximal and the distal segments of long bones are defined by a square whose sides have the same length as the widest part of the epiphysis (Figure 1).[11] The proximal humerus consists of a head, a greater and a lesser tubercle and a neck. Attached to de greater tubercle are the three of the four muscles of the rotator cuff, *i.e.* the supraspinatus, infraspinatus and teres minor. The fourth rotator cuff muscle is the subscapularis and attaches to the lesser tubercle. The proximal humerus articulates with the glenoid fossa of the scapula forming the shoulder joint. The humeral shaft is the site of attachment for various muscles. Anteriorly the coracobrachialis, deltoid, brachialis and brachioradialis are attached to the shaft and posteriorly the medial and lateral heads of the triceps. The radial nerve runs closely from proximal at the posterior side of the humerus to the lateral side at the mid shaft position, continuing to the distal humerus at the anterior side. Because of this close relation a fracture of the shaft can cause injury to the nerve. The trochlea and capitellum of the distal humerus form the elbow joint with the ulna and radius.

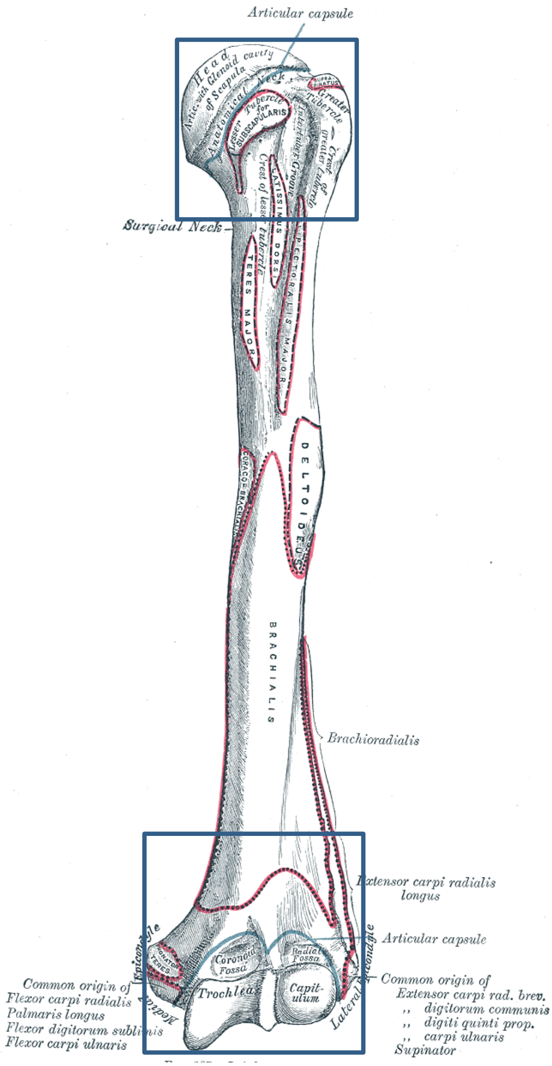

Figure 1. Humerus

Gray's Anatomy of the Human Body (1918) (Copyright free). The blue squares mark the proximal and distal parts of the humerus. The area in between is the humeral shaft.

Clinical presentation

Humerus fractures are mostly caused by direct trauma to the arm or shoulder, rotational forces or axial loading forces transmitted though the elbow. The most common trauma mechanism is a fall from standing height. Falling causes 88% of all humerus fractures.[2] Patients present with pain, swelling, and hematoma at the fracture site. Moreover, often there is an inability to use the arm. Humeral shaft fractures are associated with radial nerve palsy, so careful neurological examination and documentation is important. Motor testing should include extension of the wrist and metacarpophalangeal joints as well as abduction and extension of the thumb. The median and ulnar nerves are rarely affected by humeral shaft fractures.

Fracture classification

A fracture classification system should not only provide a reliable and reproducible means of communication between physicians, but also provide for repeated viewings of the same material.[12] Ideally it should assist in managing fractures, have a prognostic value for the outcome of patients, and facilitate documentation and research.[13] Such classification systems need validation to provide a basis for reliable documentation and evaluation of patient care. Only then the gateway to evidence-based procedures and healthcare can be opened in the coming years.[14]

For proximal humerus fractures different classification systems are used. Classification of proximal humerus fractures is especially important for comminuted fractures. Most fractures are treated non-operatively, but comminuted fractures often require surgical treatment.[15, 16] A valid classification system can guide treatment decisions and comparison of functional outcome. The most widely used systems are the Neer and Hertel classifications.

The Neer classification is based on the existence of displacements of one or more of the major segments of the proximal humerus: the articular surface, the greater and the lesser tuberosity, and the shaft (Figure 2). Displacement is defined as at least 1-cm distance and/or 45° angle between fragments.[17, 18]

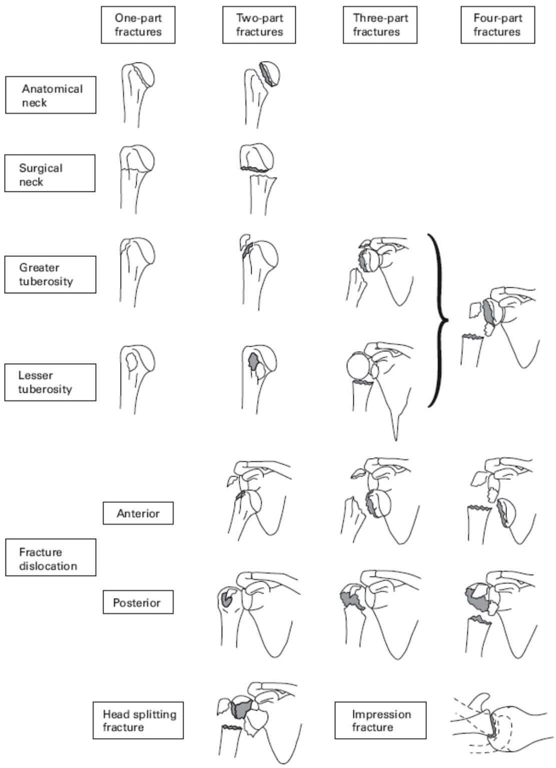

Figure 2. Neer classification of proximal humeral fractures
(Reprinted with permission from Neer CS, 2nd. Four-segment classification of proximal humeral fractures: purpose and reliable use. J Shoulder Elbow Surg. 2002 Jul-Aug;11(4):389-400.)[17]

The Hertel classification is based upon Codman's traditional four-part concept (Figure 3).[19] It provides a precise description of the fracture pattern by means of five basic fracture planes. These fracture planes lie between the greater tuberosity and the humeral head, the greater tuberosity and the shaft, the lesser tuberosity and the head, the lesser tuberosity and the shaft, and the lesser tuberosity and the greater tuberosity. There are six possible fractures dividing the humerus into two fragments, five possible fractures dividing the humerus into three fragments, and a single fracture dividing the humerus into four fragments.[20, 21]

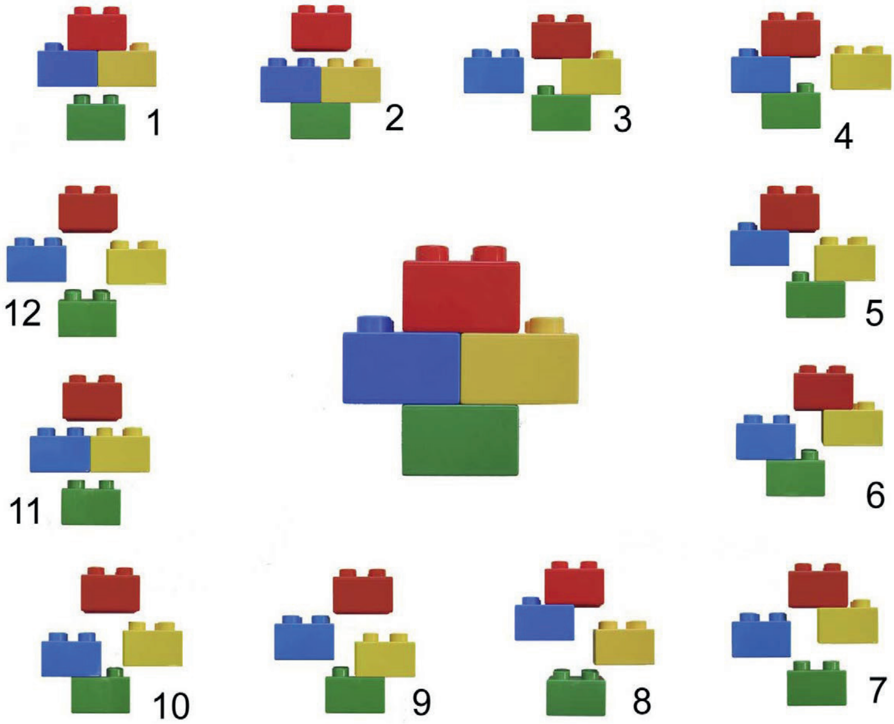

Figure 3. Hertel classification of proximal humeral fractures
Combining the fracture planes between the head (red), the greater (blue) and lesser (yellow) tuberosity and the shaft (green) results in 12 possible fracture patterns. (Reprinted with permission from Hertel R, Hempfing A, Stiehler M, Leunig M. Predictors of humeral head ischemia after intracapsular fracture of the proximal humerus. J Shoulder Elbow Surg 2004;13:427-33.)[20, 21]

Humeral shaft fractures are most widely classified using the AO/OTA classification system.[12, 22] In the AO/OTA classification, the first number stands for the long bone (humerus = 1). The second number characterizes the segment (diaphyseal = 2). As shown in Figure 4, three types of fractures are defined and coded with letters: type A consists of simple fractures, type B of wedge-type fractures, and type C of complex fractures. Each of these three types can be further subdivided into groups 1, 2, or 3. Overall, the AO/OTA classification system for humeral shaft fractures has nine groups (12-A1/2/3, 12-B1/2/3, 12-C1/2/3). Despite the widespread use of this classification the inter- and intra-observer variability for humeral shaft fractures is not yet know.

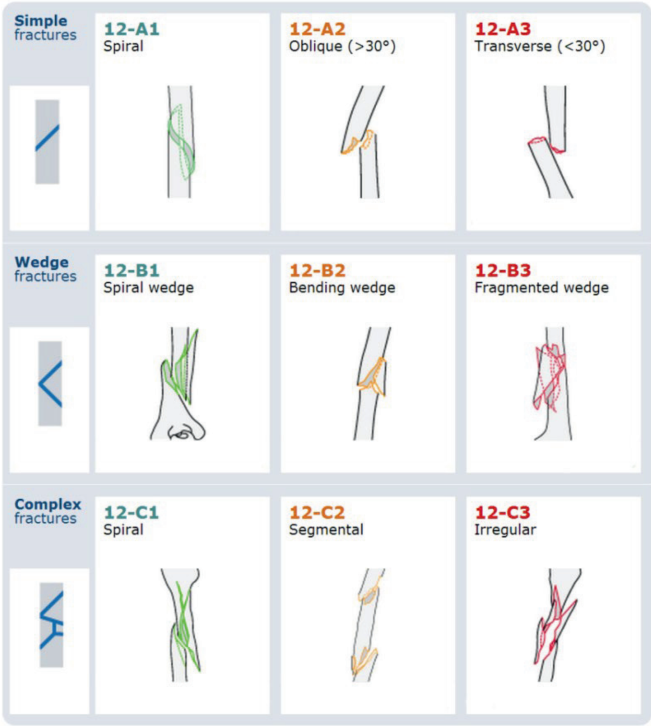

Figure 4. AO/OTA classification for humeral shaft fractures
(Reprinted with permission from the AO and OTA foundations).[12, 13]

Treatment

The treatment and clinical outcome in this thesis focuses on humeral shaft fractures in particular. Humeral shaft fractures can be treated non-operatively or operatively. The optimal management is the subject of clinical and scientific debate.[23] Operative and non-operative treatment strategies both have their pros and cons. Operative fracture fixation aims for early mobilization, which may lead to earlier functional recovery and reduced pain. However, surgical complications and fixation failure may occur.[24] Non-operative treatment may be associated with more pain and discomfort in the first weeks and may be associated with a higher malunion risk due to the lack of fracture re-alignment.[25, 26] Longer immobilization may delay functional recovery. Non-union occurs in 15-30% after operative treatment versus 2-23% after non-operative treatment (for which most patients require secondary surgical treatment).[24, 25]

Non-operative treatment starts with a collar-and-cuff sling or coaptation splint. As soon as the swelling of the upper arm is decreased a functional brace is applied. This functional brace was introduced by dr. Sarmiento in 1977 and is thus also often called a Sarmiento brace.[25] The brace encircles the arm and has two adjustable Velcro straps. Ideally the brace extends from approximately two to three centimeters distal to the axilla to one centimeter proximal to the medial epicondyle.[7] The Velcro straps allow the patients to adjust and tighten the brace when swelling decreases. The brace gives relative immobilization of the fracture by offering circumferential soft tissue compression.[27] In the first weeks the brace needs to be accompanied with a collar and cuff. Gravity facilitates alignment of the fracture, so patients must be instructed not to lean on their elbow and to sleep upright. A sling is not advised because it cause compression of the fracture fragments. Because the adjacent joints (*i.e.*, shoulder and elbow joints) are not immobilized, patients are able to start pendulum exercises of the shoulder and passive and active exercises of the elbow in an early stage. Active elevation and abduction of the shoulder are not allowed at that stage, as these motions can cause angular deformity. Once clinical consolidation is achieved these motions are permitted again. Despite the possibility of early mobilization of the shoulder and elbow joints, impairment of range of motion (ROM) of especially the shoulder joint should be anticipated.[28, 29]

Options for operative treatment are of an intramedullary nail (IMN), plate osteosynthesis, and an external fixator. The use of an external fixator as a definitive treatment strategy of humeral shaft fractures is limited, as it is used in damaged control surgery and open fractures with extensive soft tissue injury and is not further discussed in this thesis. An IMN is placed in the medullary cavity of the humerus and is thus in line with the mechanical axis of the humerus. Preferably, a closed fracture reduction is performed when using an IMN. This preserves the periosteal blood supply and minimizes the disruption of the biological healing response. The incisions are small and IMN require less soft tissue stripping than plate osteosynthesis.[7] However, shoulder-related complaints caused by impingement and cuff pathology are frequently reported.[30] In traditional plate osteosynthesis the fracture is opened. It offers direct visualization and anatomic reduction, but has potential disadvantages, such as a iatrogenic radial nerve injury. Since this form of plate osteosynthesis also requires extensive soft-tissue stripping vascularization of the bone might be destroyed.[31] In minimally invasive plate osteosynthesis (MIPO) less soft tissue is dissected. This avoids iatrogenic loss of viability and the need to expose the radial nerve.[32] The development of these different surgical techniques and implant designs has expanded the number of surgical indications.[33, 34] Since the year 2002 an increased number of plate osteosynthesis is observed.[35, 36] Nevertheless, the best surgical treatment of humeral shaft fractures is still unclear. Although IMN has conceptual benefits over plate osteosynthesis, no differences in functional recovery or complications between IMN and plating have yet been observed so far.[37-40]

Radial nerve palsy

An important complication of a humeral shaft fracture is radial nerve palsy. This palsy can be caused by the trauma or from treatment. A systematic review of 4,517 patients reported a prevalence of 12% after a humeral shaft fracture. Although 70% recovered spontaneously, the palsy was permanent in 12% of cases accounting for a substantial impairment and costs. Holstein and Lewis believed that a simple spiral fracture in the distal third of the humeral shaft poses a greater risk of radial nerve palsies.[41] In this distal part the radial nerve comes through the lateral intermuscular septum and is in direct contact with the humerus. This causes the radial nerve to have limited mobility. A fracture at this level results in laceration or entrapment of the radial nerve between the two fragments. This was confirmed by Ekholm *et al.* in a study showing a significantly increased risk of radial nerve palsies in patients with a AO/OTA type 12A1.3 fracture.[42, 43] A primary radial nerve palsy is no absolute indication for surgical exploration. No differences in final results were shown between early exploration and initial observation.[43]

Patient-reported outcome

Patient-reported outcome measures (PROMs) are becoming increasingly important instruments to evaluate clinical outcome and functional recovery from the patient's perspective.[44] PROMs measure patient perceptions of specified aspects of their own health that either cannot be directly observed (*e.g.*, pain) or that are not practical or feasible to directly observe (*e.g.*, performance of daily activities).[45] An advantage of generic quality of life PROMs, like the Short Form 36 (SF-36) and EuroQoL-5D (EQ-5D), is that they allow comparison across populations with different medical conditions. Region-specific instruments give insight in disabilities, pain, and problems caused by a specific disease or condition. Some instruments combine a patient-reported part with a clinician-reported part. Effects of treatment can be monitored over time with all three types of instruments, and they can be used to compare different treatment strategies. Instruments should only be used if proven reliable and valid.

AIM OF THIS THESIS

The general aim of this thesis was to improve care for patients with a humerus fracture. First by giving insight into the changes in incidence and associated costs. Secondly, the reliability of fracture classification systems used to guide treatment are evaluated. Furthermore, instruments used to measure outcome of treatment in patients with a humeral shaft fracture are validated. And finally, functional outcome and complications of operative and non-operative treatment of patients with humeral shaft fractures are compared.

OUTLINE OF THIS THESIS

General introduction

Chapter 1 provides a general introduction to the subject of this thesis. It elucidates the epidemiological aspects of humerus fractures and gives insight into the treatment and outcome of humeral shaft fractures. Furthermore it describes the aim of this thesis.

Epidemiology

Chapter 2 describes long-term population-based trends in the incidence rate of patients with a humeral fracture admitted to a hospital in the Netherlands from 1986 to 2012 and gives a detailed overview of the associated costs for health care and lost productivity.

Fracture classification

In **Chapter 3** the inter-observer reliability and intra-observer reproducibility of the Hertel with the Neer classification for comminuted proximal humeral fractures are examined. **Chapter 4** describes the inter-observer reliability and intra-observer reproducibility of the AO/OTA classification for humeral shaft fractures.

Outcome

Chapter 5 describes the validity, reliability, responsiveness, and Minimal Important Change (MIC) of the Disabilities of the Arm, Shoulder and Hand (DASH) and Constant-Murley scores for patients with a humeral shaft fracture. In **Chapter 6** outcome after operative versus non-operative treatment of humeral shaft fractures is retrospectively examined, by comparing the time to radiological union and the rates of delayed union and complications. **Chapter 7** describes a systematic literature review and pooled analysis comparing clinical outcome and complications between non-operative and operative treatment of humeral shaft fractures. This study focuses, besides consolidation and complications of treatment, also on functional outcome scores and range of motion. **Chapter 8** describes the protocol of a multicenter prospective study (HUMMER study) to examine the effect of operative versus non-operative treatment on the DASH score, functional outcome, the level of pain, range of motion of the shoulder and elbow joint, the rate of complications and associated secondary interventions, the time to resumption of work and activities of daily living, health-related quality of life, costs, and cost-effectiveness.

General discussion and future perspectives

Chapter 9 presents a general discussion of the performed research. Furthermore, the author hypothesizes on future perspectives of research in this field with an emphasis on outcome of the treatment of humeral shaft fractures. **Chapter 10** summarizes the performed research in English and **Chapter 11** in Dutch.

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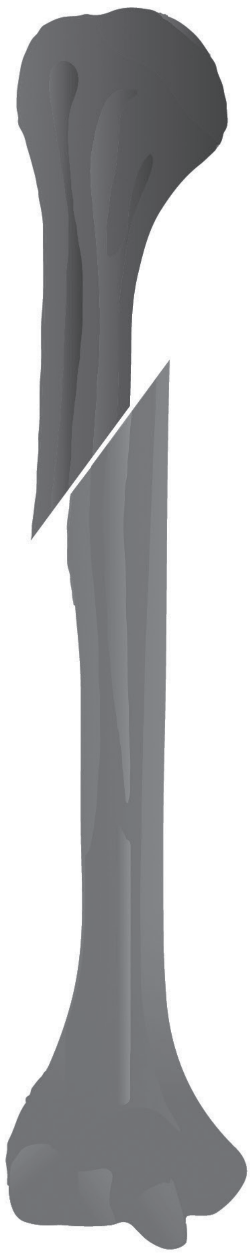

PART II

Epidemiology

Chapter 2 Trends in incidence rate, health care consumption, and costs for patients admitted with a humeral fracture in The Netherlands between 1986 and 2012
Injury 2015;46:1930–1937

Chapter 2

Trends in incidence rate, health care consumption, and costs for patients admitted with a humeral fracture in The Netherlands between 1986 and 2012

Injury 2015;46:1930–1937

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ABSTRACT

Introduction: This study aimed to examine long-term population-based trends in the incidence of patients with a humeral fracture admitted to a hospital in the Netherlands from 1986 to 2012 and to give a detailed overview of the health care consumption and productivity loss with associated costs.

Materials and methods: Age and gender-standardized incidence rates of hospital admissions for patients with a proximal, shaft, or distal humeral fracture were calculated for each year (1986-2012). Injury cases, length of hospital stay (LOS), trauma mechanism, and operation rate were extracted from the National Medical Registration. An incidence-based cost model was applied to calculate costs for direct health care and lost productivity in 2012.

Results: Between 1986 and 2012 112,910 patients were admitted for a humeral fracture. The incidence rate increased from 17.8 in 1986 to 40.0 per 100,000 person years in 2012. Incidence rates of proximal fractures increased the most, especially in elderly women. Operation rates decreased in patients aged 70 years or older. The mean LOS decreased from nine days in 1997 to five days in 2012. The cumulative LOS of all patients in 2012 was 28,880 days of which 73% were caused by women and 81% were caused by patients aged 50 years or older. Cumulative medical costs in 2012 were M€55.4, of which M€43.4 was spent on women. Costs increased with age. Costs for hospital care contributed most to the overall costs per case until 70 years of age. From 70 years onwards, the main cost determinants were hospital care, rehabilitation/nursing care, and home care. Cumulative costs due to lost productivity were M€23.5 in 2012. Costs per case increased with age in all anatomic regions.

Conclusions: The crude number of patients admitted for a humeral fracture increased 124% in 27 years, and was associated with age and gender. Proximal fractures in elderly women accounted most significantly for this increase and most of the costs. The main cost determinants were hospital care and productivity loss.

INTRODUCTION

Between 1986 and 2008, over 3.7 million persons presented to an Emergency Department (ED) of a Dutch hospital with an upper extremity injury; this comprised 42% of all ED visits in The Netherlands.[1] The incidence rate of upper extremity injuries overall increased by 13%, from 970 in 1986 to 1,098 per 100,000 person years in 2008, showing these injuries put an increasing pressure to resources. Incidence rates and health care use were related both to age and gender. In 2007, the total health care costs of upper extremity injuries in The Netherlands amounted €290 million. Fractures were the most expensive injuries to treat among upper extremity injuries, as 76% of the overall costs of the treatment were spent on the treatment of fracture patients.[1]

Given the sometimes permanent, disabling effect of humeral fractures, the societal burden associated with these injuries can be high.[2-4] Trauma affects persons of all ages and fractures in employed patients cause high costs for health care and lost productivity.[5, 6] In current economic distress, insight into trends in incidence and costs of individual patient groups is highly relevant. Population-based knowledge of trends in incidence gives directions for the allocation of health care services and for preventive measures. Age and gender dependency of humeral fractures at the proximal end versus the shaft versus the distal end have not been described in detail yet. Likewise, detailed evaluations of costs, gaining insight in the parameters that contribute most to the overall costs, such as costs for hospital stay, physical therapy and rehabilitation, nursing care and costs due to productivity loss are not available. Due to budgetary restraints and increasing health care costs, such economic analyses are gaining importance.

Therefore, this study aimed to examine long-term population-based trends in the incidence rate of patients with a humeral fracture admitted to a hospital in the Netherlands from 1986 to 2012 and to give a detailed overview of the associated costs for health care and lost productivity.

METHODS

Data source

For this retrospective, epidemiological study data were collected for patients admitted to a hospital in The Netherlands with a humeral fracture in the period 1986-2012. In 2012 the Netherlands had 16.7 million inhabitants.[7] Injury cases were extracted from the National Medical Registration (LMR) of the Dutch Hospital Database (DHD), Utrecht, The Netherlands. The DHD collects hospital data of all hospitals in The Netherlands with a uniform classification system and has an almost complete national coverage (missing values <5%, except in 2007 12%). These figures were extrapolated by the Consumer and Safety Institute to full national coverage for each year. An extrapolation factor was estimated by comparing the adherence population of the participating hospitals with the total Dutch population in each year using the population data obtained from Statistics Netherlands.[7, 8] Patients are included in the LMR for their main diagnosis at discharge, defined by the International Classification of Diseases (ICD) 9th and (since 2010) 10th revision.[9] Codes for humeral fractures are presented in Table 1. Injuries include both traumatic and pathologic fractures.

The study was exempted by the local Medical Research Ethics Committee Erasmus MC (No. MEC-2014-120).

Calculation of incidence rates

Age- and gender-specific incidence rates were calculated in 5-year age groups for each year of the study. In order to adjust for differences in the demographic composition over time, incidence rates were standardized for age (in 5-year age groups) and gender using a direct standardization method, as previously described.[1] In short, the age- and gender-specific incidence rates per 100,000 person years were calculated based upon the Dutch mid-year standard population (calculated using the formula $((N_{1986} + N_{2012})/2)$).

Table 1. Humeral fractures classified in ICD-9 and ICD-10

Fracture region	Fracture closed or open	ICD-9	ICD-10
Proximal	Fracture of upper end of humerus closed	812.0	S42.2
	Fracture of upper end of humerus open	812.1	S42.2
Shaft	Closed fracture of shaft or unspecified part of humerus	812.2	S42.3
	Fracture of shaft or unspecified part of humerus open	812.3	S42.3
Distal	Fracture of lower end of humerus closed	812.4	S42.4
	Fracture of lower end of humerus open	812.5	S42.4

Hospital length of stay, trauma mechanism, and surgical intervention

Data regarding hospital length of stay (LOS), trauma mechanism, and operation rate were extracted from the LMR database for 10-year age categories. In order to assess trends in LOS and trauma mechanism over time, mean LOS and percentage of trauma mechanisms were averaged over 5-year intervals from 1993 to 2012. For operation rates, data were averaged over a 5-year interval 2008-2012, as earlier data were not available.

Direct and indirect health care costs

The incidence-based Dutch Burden of Injury Model was used in order to measure and describe direct and indirect health care costs.[1, 10-12] Patient numbers, health care consumption and related costs and costs for lost productivity were calculated using the LMR database and a patient follow-up survey on health care use.[13] Costs were measured from a societal perspective. Patients were followed until two years after trauma. Medical costs included ambulance care, in-hospital care, general practitioner (G.P.) care, home care, physical therapy, and rehabilitation/nursing care. Health care costs were calculated by multiplying incidence and health care volumes with unit costs (*e.g.*, costs per day in hospital). Unit costs were estimated according to national guidelines for health care costing.[14] Costs for lost productivity were determined as described before.[12] Productivity costs were defined as the costs associated with production loss and replacement due to illness, disability, and premature death.[15] The absenteeism model was used in order to estimate costs for productivity loss for all patients aged 15-64 years. The friction cost method was used because health care needs are most substantial in the first year after injury for the majority of injuries.[16] Age-specific costs are presented in 10-year (medical costs) or 5-year (lost productivity) age groups for men and women separately. Data were averaged over 5-year intervals; 2002-2007 2008-2012, as earlier data were not available. Inflation has been taken into account.

RESULTS

Incidence rates

During the study period 112,910 patients were admitted for a humeral fracture. The crude number of patients per year increased by 124% ; from 2,790 in 1986 to 6,250 in 2012. The overall incidence rate increased from 17.8 per 100,000 person years (py) in 1986 to 40.0 per 100,000 py in 2012. The increase in incidence rate was largest for proximal fractures (20.0/100,000 py in 2012; +277%), but was also noted for shaft fractures (7.2/100,000 py in 2012; + 132%) and distal fractures (12.8/100,000 py in 2012; +36%; Fig. 1A). The largest increase was seen for proximal fractures in women since the year 2002.

The incidence rates showed a bimodal distribution, with a clear peak at 5-9 years of age for both genders and a gradual increase from 50 years onwards in women and from 65 years onwards in men (Fig. 1B-C). Whereas the peak at 5-9 years has remained fairly stable during the study period (83.0/100,000 py for boys and 97.8/100,000 py for girls in 2012), the increase in the elderly has become more pronounced after the year 2002.

Fig. 1D and E show incidence rates for the different age groups and anatomical regions in 2012 for men and women separately. Until 15 years of age, humeral fractures were mainly located at the distal end both in boys (40.3/100,000 py or 83% of total) and girls (47.2/100,000 py or 86% of total). From 50 years onwards, incidence rates of proximal, shaft, and distal fractures increased, especially in women. From 65 years, proximal fractures (33.1/100,00 py in men versus 119.1/100,000 py in women) clearly outnumbered fractures at the shaft (9.7 versus 37.6/100,000 py) and distal end (6.5 versus 23.0/100,000 py).

Trauma mechanism

Throughout the study period, falling was the dominant trauma mechanism at all ages. In 2012, falling caused 71% of proximal, 69% of shaft, and 79% of distal fractures in men. In women, these percentages were 82%, 81%, and 80%. The second most common mechanism was a traffic accident (22%, 20%, and 14% in men, and 15%, 13%, and 17% in women, respectively).

Operative treatment

In 2012, operation rates for men and women of all ages combined were 62% for proximal, 67% for shaft, and 80% for distal fractures (Fig. 2). For both genders, operation rates were fairly stable until 70 years, and decreased at older age. Overall, 73% of proximal fractures were operated in patients aged <70 years. At older age, operation rates decreased to 22% (24% in men, 22% in women) in the >90 age group. Of the shaft fractures, 72% were operated in patients aged <70 years, and decreased to 47% (50% in men, 46% in women) in the oldest old. Distal fractures were operated most frequently; 81% in patients aged <70 years, decreasing to 48% (25% in men, 52% in women) in the oldest old.

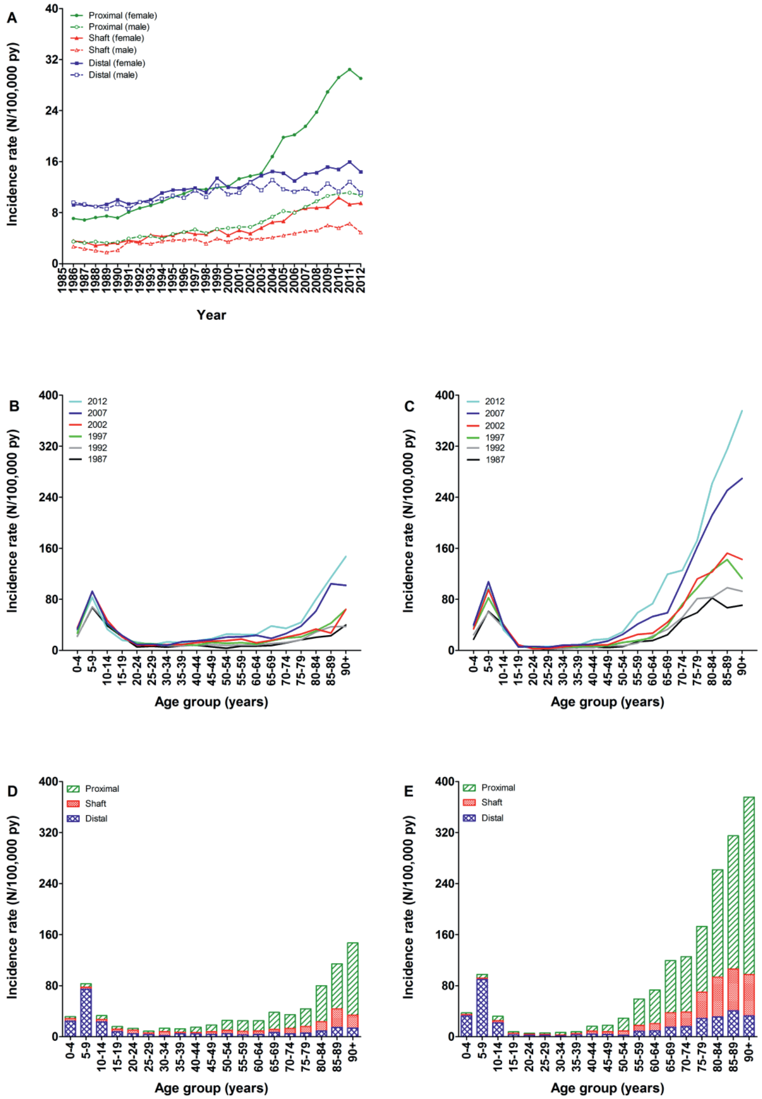

Figure 1. Age-related incidence rates (per 100,000 person years) of humeral fractures overall (A), in males (B, D), and in females (C, E)

Data are shown by anatomical region (A, D, E) and year (B, C). D and E show data for 2012.

Length of hospital stay

The cumulative hospital LOS decreased from 34,050 days in 1997 to 28,880 days in 2012. In four consecutive 5-year periods, the mean LOS per case increased with age, most significantly after 70 years (Fig. 3A and B). Over time the mean LOS per case decreased in all age groups from nine days in 1997 to five days in 2012. The mean LOS per case in men and women admitted with a proximal fracture in 2012 was five days (4 days in patients <70 years and 7 days in patients aged 70 or older; Fig. 3C and D). For patients with a shaft fracture mean LOS per case was five days (4 days at < 70 years and 8 days at >70). For patients with a distal fractures, mean LOS per case was three days (2 and 8 days, respectively). LOS per case seemed unrelated to gender. The cumulative LOS in 2012 for men and women combined was 28,880 days, of which 73% were caused by women (Fig. 3E and F). Of these hospital days 81% were caused by patients aged 50 years or older. Proximal fractures accounted for the largest part of the total LOS; 16,810 days versus 6,150 days for shaft and 5,920 days for distal fractures.

Costs for health care consumption

The cumulative medical costs for admitted patients increased from 47.8 million euro (M€) in 2007 to M€ 55.4 in 2012, of which approximately 75% were caused by women (Table 2). The proximal humeral fractures accounted for the major part of the total costs (M€35.0 in 2012), while shaft and distal fractures were less expensive (M€10.6 and M€9.7, respectively). Costs per case were €11,224 for proximal, €9,430 for shaft, and €4,858 for distal fractures. In addition to costs per case being higher in women than in men (€10,383 versus €5,796 in 2012 for all fractures and age groups combined, see Table 2), costs consistently increased with age (Fig. 4).

For each anatomic region, costs for hospital care contributed most to the overall costs per case until 70 years of age. From 70 years onwards, the main cost determinants were hospital care, rehabilitation/nursing care, and (most significantly in women) home care. For proximal fractures, overall costs per case until 70 years were €6,111 (€5,207 for men versus €6,620 for women), of which 60% (68% versus 56%) were spent on hospital care. At ages >70 years, mean costs per case were €17,119 (€15,144 versus €17,483), of which 39% (47% versus 38%) were spent on hospital care, 30% (30% versus 30%) on rehabilitation/nursing care, and 25% (16% versus 26%) on home care. For shaft fractures, overall costs per case until 70 years were €5,260 (€4,556 versus €5,870 for women), of which 66% (74% in men versus 61% in women) were spent on hospital care. At ages >70 years, mean costs per case were €15,163 (€12,039 versus €15,750), of which 33% (40% versus 32%) were spent on hospital care, 35% (36% versus 35%) on rehabilitation/nursing care, and 26% (17% versus 27%) on home care. For distal fractures, overall costs per case until 70 years were €3,393 (€3,233 for men versus €3,540 for women), of which 83% (87% in men versus 79% in women) were spent on hospital care. At ages >70 years, mean costs per case were €13,771 (€11,908 versus €14,092), of which 35% (41% versus 34%) were spent on hospital care, 35% (37% versus 35%) on rehabilitation/nursing care, and 26% (17% versus 27%) on home care.

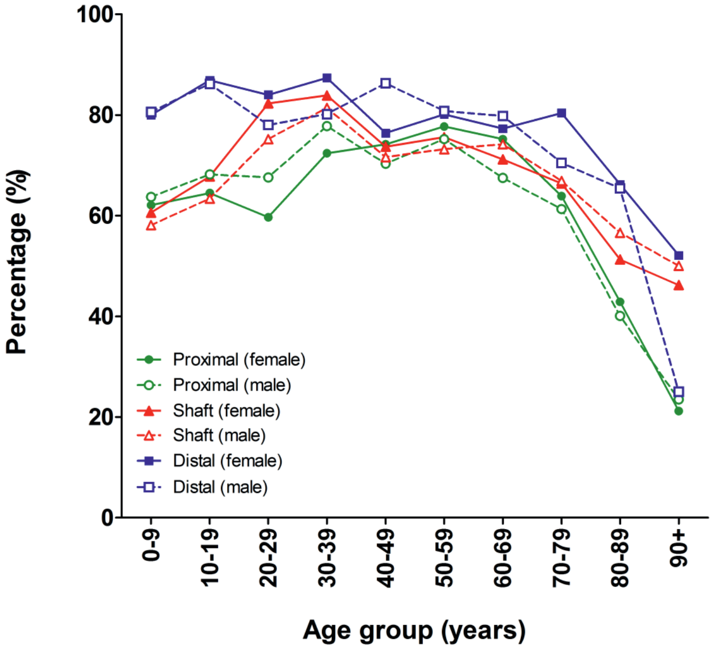

Figure 2. Age-related percentage of patients undergoing surgical treatment in males and females

Data are shown by anatomical region for 2012.

Costs for lost productivity

For each anatomic region, >90% of patients had to take time off from work due to their humeral fracture, with no clear difference between men and women or across age groups. The cumulative number of days off work were 70,900 days in 2012 and were higher for proximal fractures (39,000 days) than for shaft (16,950 days) or distal (14,950 days) fractures. The associated cumulative costs for lost productivity were M€23.5 (M€13.5, M€5.4, and M€4.6, respectively), with consistently higher total costs as well as costs per case for men (Table 3). The costs per case gradually increased with age in all anatomic regions to more than €25,000 in men and more than €19,000 in women aged 60 years or older (Fig. 5A and B). Due to differences in incidence rates, cumulative costs were highest for patients with a proximal fracture, with a peak for men aged 50-54 years (M€1.5) and women aged 55-59 years (M€2.1).

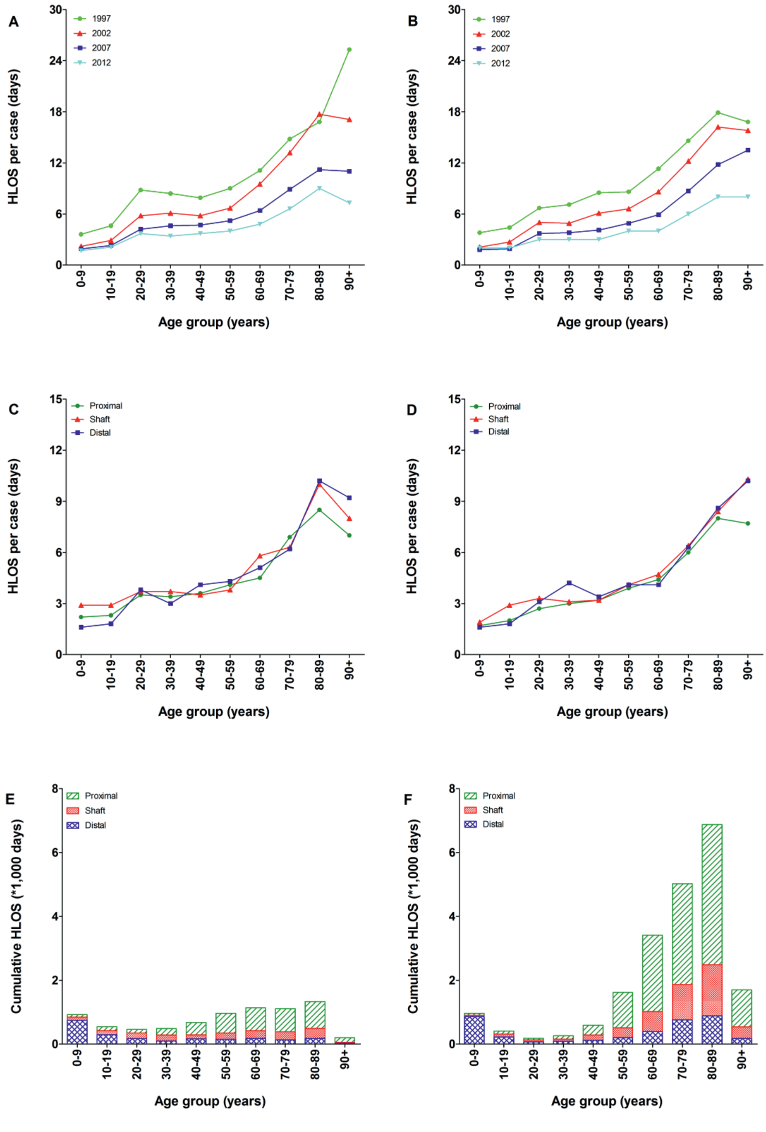

Figure 3. Hospital length of stay in males (A, C, E) and females (B, D, F)

A and B show data of the entire humerus for four different time periods. C to F show data by anatomical region for 2012.

Table 2. Medical costs per case and cumulative costs by anatomical region and gender in 2012

	Proximal	Shaft	Distal	Total
Men				
N	828	378	861	2,067
Costs/case (€)	7,913	6,043	3,650	5,796
Total costs (M€)	6.6	2.3	3.1	12.0
Women				
N	2,293	749	1,136	4,179
Costs/case (€)	12,420	11,140	5,773	10,383
Total costs (M€)	28.5	8.3	6.6	43.4
Overall (men + women)				
N	3,121	1,128	1,997	6,246
Costs/case (€)	11,224	9,430	4,858	8,864
Total costs (M€)	35.0	10.6	9.7	55.4

Table 3. Absenteeism and associated costs for lost productivity by anatomical region and gender in 2012

	Proximal	Shaft	Distal	Total
Men				
Employed[a]	343 (78)	174 (75)	159 (75)	676 (76)
Costs/case (€)	22,383	19,256	19,464	20,890
Total costs (M€)	7.1	3.1	2.9	13.1
Women				
Employed[a]	369 (54)	139 (61)	109 (59)	317 (56)
Costs/case (€)	18,506	17,681	17,339	18,114
Total costs (M€)	6.3	2.3	1.8	10.4
Overall (men + women)				
Employed[a]	712 (63)	313 (68)	269 (68)	1,293 (65)
Costs/case (€)	20,374	18,558	18,598	19,566
Total costs (M€)	13.5	5.4	4.6	23.5

[a] Data are shown as number (%).

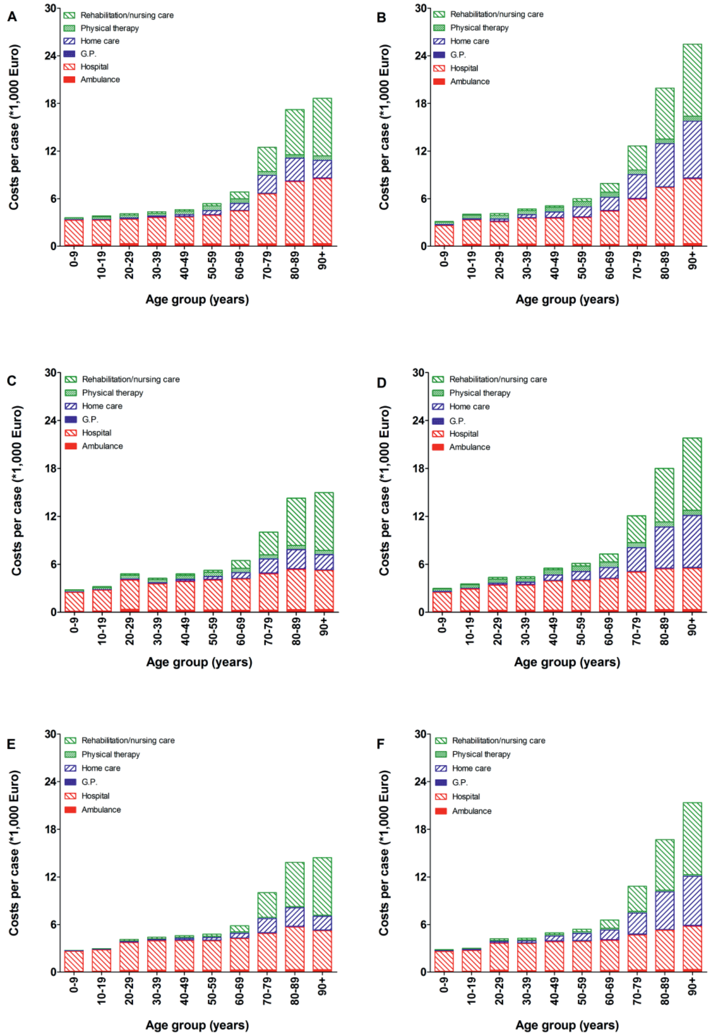

Figure 4. Age-related costs per case due to humeral fractures in males (A, C, E) and females (B, D, F) in proximal (A, B), shaft (C, D) and distal (E, F) humeral fractures in 2012

Costs are separated in different cost determinants.

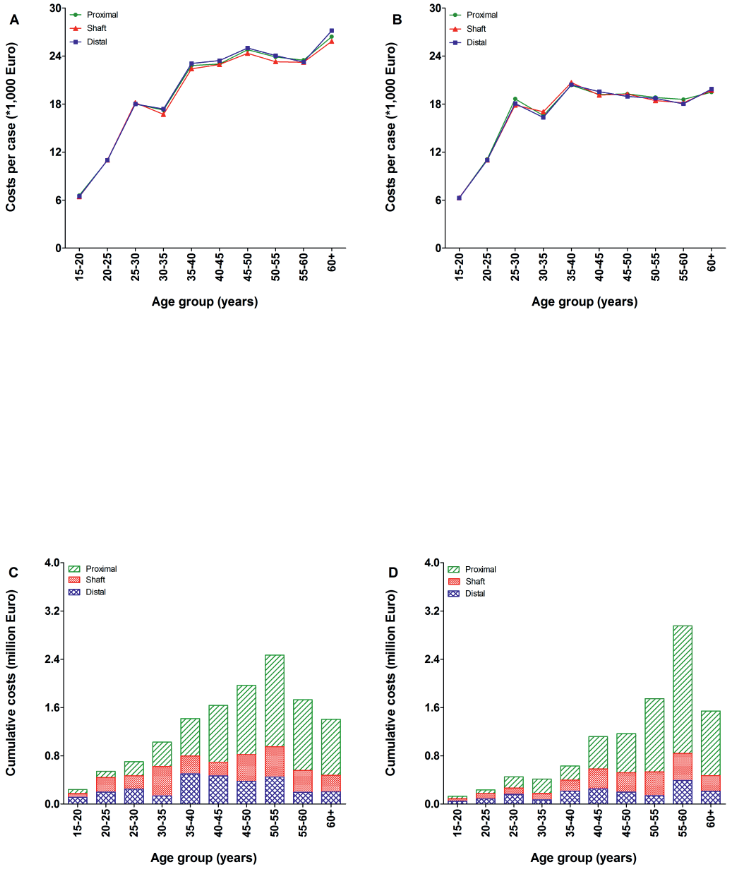

Figure 5. Age-related costs for lost productivity in males (A, C) and females (B, D) in 2012

Data are shown by age group and anatomical region. The upper panels show information about costs per case, the lower panels show cumulative costs for the entire study population.

DISCUSSION

In the 27 year study period, the crude number of patients increased by 124%; in total 112,910 patients were admitted. Incidence rates, health care consumption, and direct and indirect costs were all associated with anatomic region, age, and gender.

The increase in humeral fractures over time in general may be attributable to population ageing, with increasing numbers of elderly (women) being at risk for fractures due to osteoporosis.[17] The incidence rate of proximal humeral fractures of 20.0/100,000 person years in 2012 is somewhat lower than published[18], although that study included patients from the age of 15 years. The incidence rate of proximal fractures increased mostly in women, similar to studies from Finland and Austria.[19-21] The even faster increase in clinical admissions since 2002 may also be attributable to introduction of new and development of existing locking plates resulting in new technologies and techniques. Increased operation rates since 2002 has been described before in a single-center study from the US and, especially for women, also in a Finnish population study.[22, 23]

Similarly, development of new plating options may explain the increase in admissions of patients with shaft fractures, which was also reported for the Finnish population.[24] These new options may have resulted in operative treatment of patients that would previously have been treated non-operatively, not requiring hospitalization. Both in their and our study, this effect was most noticeable in women and the older age groups. The incidence rate for humeral shaft fractures of seven per 100,000 person years is in line with published data.[18] The current data also confirm the known bimodal age distribution, with a peak in the age group 20-24 and a gradual increase from 50 years onwards.[25, 26] In the current study, however, the peak in young adult women was less pronounced.

Distal humeral fractures account for the biggest share of humeral fractures in children, with a peak in the age groups 5-9. This is in line with the reported average age of 6.8 years.[27] The incidence rate (13/100,000 person years) in the current study was slightly higher than the 9/100,000 person years published for patients aged 15 years or older.[18]

As reported before, falling was the dominant trauma mechanism for all three types of humeral fractures.[25, 26, 28, 29] This supports the relevance of fall prevention strategies as a measure to reduce the number of fractures.[30]

Since 1993 LOS decreased from nine to five days per case. Previous data (13.8 days in 1989 and 9.3 days in 2013) seem to support this trend.[31, 32] The 9.3 days was reported for patients admitted to a regional trauma center only, which may explain their seemingly longer hospital stay.[31] Although this decrease is most likely due to changing hospital protocols and care pathways (aimed at earlier transfer to nursing or rehabilitation facilities), current data are not suitable to confirm this. Despite increasing incidence rates, the decrease in LOS per case was paralleled by a decrease in the cumulative LOS over time. Elderly women with a proximal humeral fracture contributed most significantly to the cumulative LOS. As costs for hospital stay are only a part of the total medical costs, reduced LOS did not cause a reduction in medical costs.

Current data showed that medical costs increased with age. This has not been reported before. Main cost determinants were hospital care, rehabilitation/nursing care, and home care. The finding that especially elderly women need more home care might reflect that women tend to outlive their partners and elderly are more prone to losing their independence after sustaining an injury. Polinder *et al.* reported lower costs per case for upper arm fractures in 2007 (€4,440) than the current study in 2012 (€8,644).[1] However, that study also included non-admitted patients. Previous studies reported total costs without providing the cost components as done in the current study.[1, 10]

A strength of our study is that it is population-based, offering long-term trends. National registry data are more reliable in representing true health care problems than extrapolating data from a single study or hospital. In addition, as the rate of missing data was fairly stable over time, trends noted are unlikely due to changes in coding and documentation. Data are reported for humeral fractures as a whole, but also for specific anatomical regions. Moreover, age and gender-dependent trends were evaluated. This study presented detailed information on health care and lost productivity costs in patients admitted for a humeral fracture. To the best of our knowledge, this has not been previously described.

We acknowledge limitations, the most obvious being that this study only included admitted patients. The LMR database only contains information about admitted patients. A national database that records all Emergency Department attendances exists, but there is no unique code for extracting the data for humeral fractures as a whole, nor per anatomical region. In that database humeral fractures are pooled together with fractures of the clavicle and scapula. In addition, the ICD coding system is the same for traumatic and pathological fractures, making it impossible to exclude the pathological fractures. Also, as patients are recorded based on the main injury at discharge underreporting might occurred in patients with multiple injuries.

CONCLUSIONS

This study showed an increase of 124% in absolute numbers of patients admitted for humeral fractures in the last 27 years. This increase was associated with age and gender. Proximal fractures in elderly women accounted most significantly for this increase and most of the costs. This insight in direct and indirect medical costs and costs for lost productivity offers tools for cost reduction and give direction to future demands.

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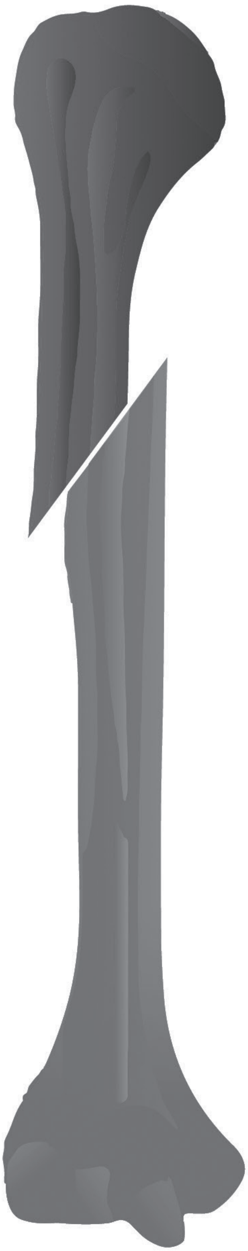

PART III

Fracture classification

Chapter 3

The reliability and reproducibility of the Hertel classification for comminuted proximal humeral fractures compared with the Neer classification

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ABSTRACT

Introduction: The Neer classification is the most commonly used fracture classification system for proximal humeral fractures. Inter- and intra-observer agreement is limited, especially for comminuted fractures. A possibly more straightforward and reliable classification system is the Hertel classification. The aim of this study was to compare the inter- and intra-observer variability of the Hertel with the Neer classification in comminuted proximal humeral fractures.

Materials and Methods: Four observers evaluated blinded radiographic images (X-rays, CT-scans, and CT-scans with 3D-reconstructions) of 60 patients. After at least two months classification was repeated.

Results: Inter-observer agreement on plain X-rays was fair for both Hertel (κ=0.39; 95% CI 0.23-0.62) and Neer (κ=0.29; 0.09-0.42). Inter-observer agreement on CT-scans was substantial (κ=0.63; 0.56-0.72) for Hertel and moderate for Neer (κ=0.51; 0.29-0.68). Inter-observer agreement on 3D-reconstructions was moderate for both Hertel (κ=0.60; 0.53-0.72) and Neer (κ=0.51; 0.39-0.58).

Intra-observer agreement on plain X-rays was fair for both Hertel (κ=0.38; 0.27–0.59) and Neer (κ=0.40; 0.15-0.52). Intra-observer agreement on CT-scans was moderate for both Hertel (κ=0.50; 0.38-0.66) and Neer (κ=0.42; 0.35-0.52). Intra-observer agreement on 3D-reconstructions was moderate for Hertel (κ=0.55; 0.45-0.64) and substantial for Neer (κ=0.63; 0.48-0.79).

Conclusions: The Hertel and Neer classifications showed a fair to substantial inter- and intra-observer agreement on the three diagnostic modalities used. Although inter-observer agreement was highest for Hertel classification on CT-scans, Neer classification had the highest intra-observer agreement on 3D-reconstructions. Data of this study do not confirm superiority of either classification system for the classification of comminuted proximal humeral fractures.

INTRODUCTION

The incidence of fractures of the proximal humerus is 106 per 100,000 person years and a triplication of this number is expected by the year 2030.[1] Besides the impact of these fractures on health and quality of life, they also impose an economic burden on the society.[2-6] The most important determinants for treatment choice include age, co-morbidities, functional demand, surgical expertise, and the personality of the fracture.[7] Approximately eighty percent of the proximal humeral fractures are minimal or non-displaced fractures which can be treated conservatively. However, comminuted fractures (*i.e.*, three-part, four–part, and head-split fractures) often require surgical treatment.[8, 9]

Since most clinical studies include only specific fracture classes, a reliable and reproducible classification is needed for adequate patient selection. The most frequently used classification systems for the proximal humeral fractures are the Neer and the AO (Arbeitsgemeinschaft für Osteosynthesefragen) classifications.[10] Unfortunately both classifications showed disappointing inter- and intra-observer agreement with kappa values below 0.40 for classifying comminuted proximal humeral fractures.[11-14] The Neer classification defines fracture displacement as a 1-cm distance and/or a 45° angle between fragments.[15] Exact measurements of the displacement and angulation make this system difficult to apply in clinical practice. Therefore, a classification system with better reliability and reproducibility for comminuted proximal humeral fractures is warranted. Such a classification system may guide treatment and evaluation of results.[16, 17] A classification system that potentially meets these criteria is the Hertel classification. This classification is also known as the Lego-system, which is based upon the four-part concept of Codman.[18, 19]

The aim of this study was to compare the inter-observer reliability and intra-observer reproducibility of the Hertel with the Neer classification for comminuted proximal humeral fractures.

MATERIALS AND METHODS

Radiographs

Radiographic images were selected from hospital records and from the radiology system PACS (Picture Archiving and Communication System) of two Level 1 trauma centers using a unique identifying code for diagnosis and treatment of all consecutive proximal humerus and humeral shaft fractures (Diagnose Behandel Combinatie, DBC, 207), or based upon the Abbreviated Injury Score (AIS90; 752600.2 Humerus - fracture NFS, 752602.2 Humerus - fracture - closed/undisplaced, 752604.3 Humerus - fracture - open/displaced/comminuted, 752606.3 Humerus - fracture - with radial nerve involvement).

All consecutive adult patients diagnosed with a comminuted (three- and four part and head-split fractures) fracture of the proximal humerus between January 1 2003 and October 15 2010 of whom plain X-rays and CT-scans were available, were found eligible. Pathological and recurrent fractures were excluded. The principal investigator (GITI) was adequately trained and had sufficient experience to select the radiographic images meeting the criterion of representing a comminuted fracture. The first eligible 60 patients were selected. Comminuted fractures were defined as three-part, four-part, and head-split fractures according to Hertel.

Radiographs obtained from the standard trauma series were used. This series at least had to include anteroposterior and lateral views. Radiographs accepted for clinical decision making were regarded of sufficient quality for inclusion. Two X-rays were available for 50 patients, three for seven patients and four for three patients. The 3D-volume rendering reconstructions were made using an open-source program (OsiriX version 3.9.2, Geneva, Switzerland).[20] The reconstructions could be rotated over both X- and Y-axis and consisted of 40 images per axis. All X-rays and CT-scans were collected and blinded by the principal investigator, who did not participate in the classification of the images. In order to guarantee identical viewing conditions all observers evaluated all images with the same open-source viewer (ClearCanvas Workstation version 2.0, Toronto, Canada). For every observer the cases were presented in a different, random order.

Hertel classification

The Hertel classification is based upon Codman's traditional four-part concept (Figure 1).[21] It provides a precise description of the fracture pattern by means of five basic fracture planes. These fracture planes lie between the greater tuberosity and the humeral head, the greater tuberosity and the shaft, the lesser tuberosity and the head, the lesser tuberosity and the shaft, and the lesser tuberosity and the greater tuberosity. There are six possible fractures dividing the humerus into two fragments, five possible fractures dividing the humerus into three fragments, and a single fracture dividing the humerus into four fragments.[18, 19] The comminuted (*i.e.*, 3- and 4-part and head-split fractures) are marked with red boxes.

Neer classification

The Neer classification is based on the existence of displacements of one or more of the major segments of the proximal humerus: the articular surface, the greater and the lesser tuberosity, and the shaft. Displacement is defined as an at least 1-cm distance and/or a 45° angle between fragments.[22, 23]

Classification

All images were classified independently by two senior shoulder expert trauma surgeons (DDH and NWLS) and by two senior radiologists with primary orthopedic trauma focus (GSRM and LFMB). All images were provided in random order, and the observers were given as much time as needed for accurate assessment. The observers were blinded to clinical information and treatment strategies of the patients, and were not allowed to discuss their observations with other investigators. All observers were familiar with the Neer and Hertel classification. In order to ensure unambiguous application of both fracture classification systems, a clarification of both classification systems was provided with each questionnaire, along with a standard evaluation form.

The images were classified three times, and were randomly provided in different order each time. The first evaluation was used for determining the inter-observer agreement on X-rays, CT-scans, and 3D-reconstructions separately. In order to determine the intra-observer agreement, the images were re-evaluated again after at least two months.

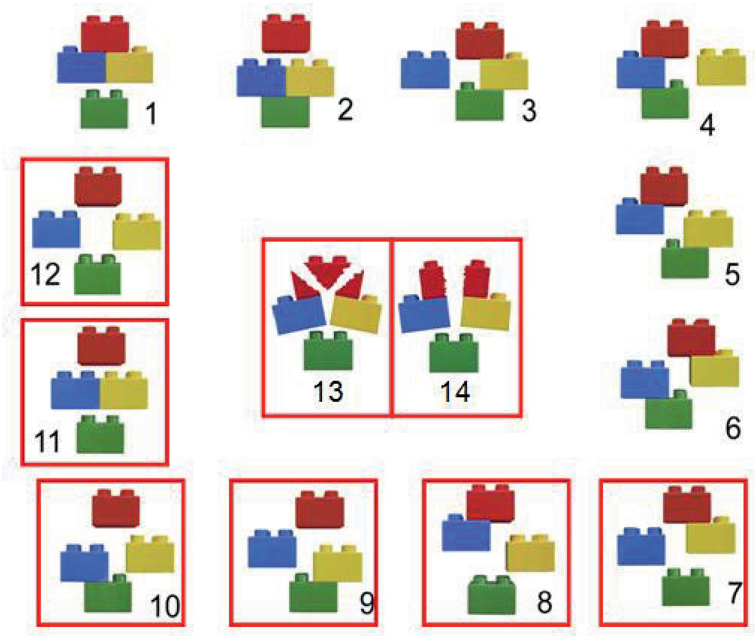


Figure 1. Hertel classification

Combining the fracture planes between the head (red), the greater (blue) and lesser (yellow) tuberosity and the shaft (green) results in 12 possible fracture patterns. Eight fracture patterns were considered as comminuted and were included this study (7, 8, 9, 10, 11, 12, 13 and 14). (Reprinted with permission from Hertel R, Hempfing A, Stiehler M, Leunig M. Predictors of humeral head ischemia after intracapsular fracture of the proximal humerus. J Shoulder Elbow Surg 2004;13:427-33.)[18, 19]

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 16.0 (SPSS, Chicago, Ill., USA). Kappa statistics were calculated using MedCalc version 12.4.0. Normality of continuous data was tested by inspecting frequency histograms (Q-Q plots), and homogeneity of variances was tested using the Levene's test.

Data were analyzed using kappa statistics, as described by Cohen.[24] The kappa coefficient represents the agreement between two sets of observations compared with the likelihood of agreement based on chance alone. The kappa coefficient ranges from 1 (perfect agreement) to <0 (systematic disagreement, or no more agreement than would be expected by chance alone). The kappa values for inter-observer agreement were calculated for each possible pair of observers in the first round before calculating the mean kappa value. The kappa values for intra-observer agreement were calculated for each of the four individual observers before calculation the mean kappa value.[25] Interpretation of the values was carried out according to the guidelines of Landis and Koch which suggest that values <0 represent poor reliability; 0.00-0.20 slight agreement; 0.21-0.40 fair agreement; 0.41-0.60, moderate agreement; 0.61-0.80, substantial agreement; and 0.81-1.00 almost perfect agreement.[26] Kappa values are reported with a 95% confidence interval.

The inter- and intra-observer kappa-values of both classifications and for comparing the radiographic modalities (*i.e.*, X-ray versus CT-scan, X-ray versus 3D-reconsruction, and CT-scan versus 3D-reconstruction) were compared using the Student's t-test. The Levene's test was used for assessing equality of variance. The corresponding p-value of the Student's t-test was used accordingly. A P-value of < 0.05 was considered statistically significant.

Ethical approval

The study was exempted by the local Medical Research Ethics Committee Erasmus MC (No. MEC-2011-151). For this type of study formal consent is not required.

RESULTS

Inter-observer agreement

An overview of the inter-observer agreement between the Hertel and Neer classifications for comminuted proximal humeral fractures on plain radiographs, CT-scans and CT-scans with 3D-reconstructions is shown in Table 1. The inter-observer agreement on plain radiographs was fair for both the Hertel classification (κ=0.39; 95% CI 0.23-0.62) and the Neer classification (κ=0.29; 95% CI 0.09-0.42). The inter-observer agreement on CT-scans was substantial for the Hertel classification (κ=0.63; 95% CI 0.56-0.72) and moderate for the Neer classification (κ=0.51; 95% CI 0.29-0.68). The inter-observer agreement on CT-scans with 3D-reconstructions was moderate for both the Hertel classification (κ=0.60; 95% CI 0.52-0.72) and the Neer classification (κ=0.51; 95% CI 0.39-0.58). Despite the kappa being consistently approximately 0.1 point higher for the Hertel classification on X-ray, CT-scans, and CT-scans with 3D-reconstructions, no statistically significant differences were found between the Hertel and Neer classification for these three modalities.

Inter-observer agreement was lowest for fractures between the head and the lesser tuberosity in radiographs. All four investigators consistently classified the radiographs as Hertel type 7 (n=4; see a typical example in Figure 2a) or Hertel type 12 (n=3; Figure 2b). However, in 18 other patients, disagreement was noted (*i.e.*, at least one investigator scored different from the others; Figure 2c) and were classified as Hertel type 7 or 12. For Neer classification only one fracture was classifies unanimously (Figure 2d). As opposed to the Hertel classification, no consistent disagreement was identified.

Table 1. Inter-observer agreement of the Hertel and Neer classification on X-rays, CT-scans and 3D-reconstructions

Observer	X-ray		CT-scan		3D-reconstruction	
	Hertel	Neer	Hertel	Neer	Hertel	Neer
1 + 2	0.23 (0.00-0.46)	0.31 (0.07-0.56)	0.59 (0.39-0.78)	0.68 (0.54-0.83)	0.53 (0.32-0.75)	0.58 (0.38-0.77)
1 + 3	0.34 (0.11-0.56)	0.39 (0.17-0.61)	0.60 (0.40-0.79)	0.49 (0.31-0.68)	0.52 (0.32-0.72)	0.53 (0.31-0.75)
1 + 4	0.31 (0.07-0.54)	0.38 (0.12-0.65)	0.64 (0.45-0.83)	0.57 (0.32-0.82)	0.71 (0.55-0.86)	0.58 (0.35-0.80)
2 + 3	0.62 (0.46-0.78)	0.09 (-0.13-0.31)	0.56 (0.35-0.77)	0.29 (0.17-0.40)	0.57 (0.40-0.74)	0.52 (0.28-0.75)
2 + 4	0.37 (0.15-0.59)	0.15 (-0.12-0.43)	0.66 (0.47-0.85)	0.52 (0.33-0.72)	0.57 (0.37-0.77)	0.45 (0.22-0.68)
3 + 4	0.46 (0.23-0.70)	0.42 (0.20-0.64)	0.72 (0.57-0.88)	0.49 (0.28-0.69)	0.71 (0.54-0.89)	0.39 (0.16-0.63)
Total	**Fair 0.39 (0.23-0.62)**	**Fair 0.29 (0.09-0.42)**	**Substantial 0.63 (0.56-0.72)**	**Moderate 0.51 (0.29-0.68)**	**Moderate 0.60 (0.52-0.72)**	**Moderate 0.51 (0.39-0.58)**
	P = 0.249		P = 0.067		P = 0.065	

Kappa values, with the 95% confidence interval between brackets, are shown. For the total scores the strength of agreement according to the guidelines of Landis and Koch is also shown.[26]

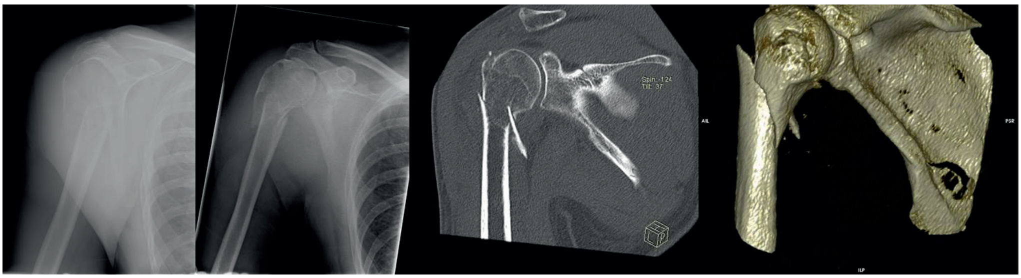
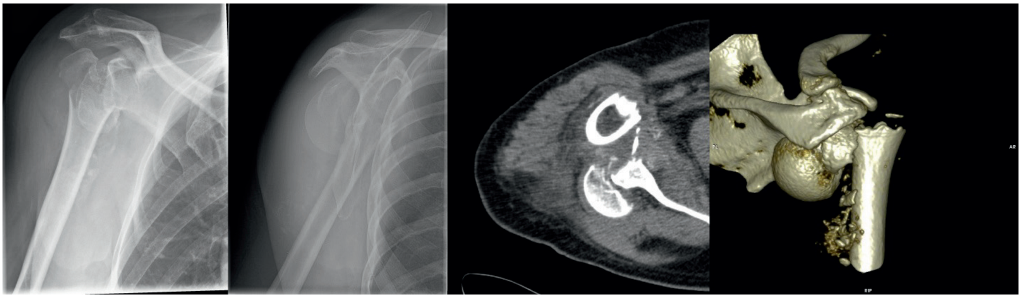
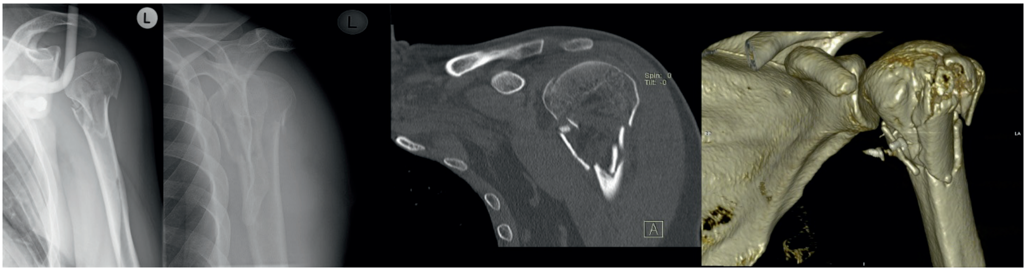


Figure. 2 Radiographs of proximal humeral fractures

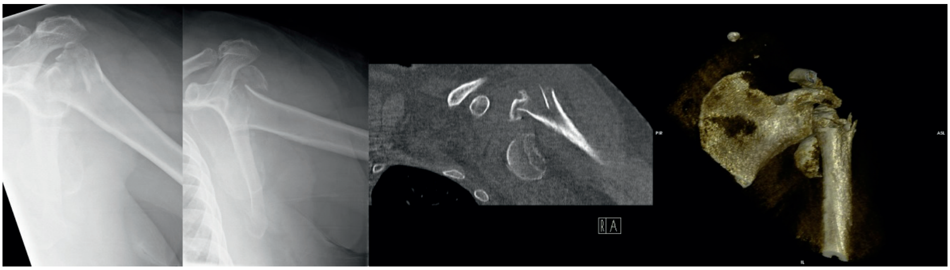
a. Fracture pattern classified by all observers as a Hertel type 7. This fracture was classified as a Neer two-part surgical neck fracture and a two-part greater tuberosity fracture by the observers.



b. Fracture pattern classified by all observers as a Hertel type 12. This fracture was classified as Neer three-part greater tuberosity fracture, three-part anterior fracture dislocation, four-part anterior fracture dislocation and four-part posterior fracture dislocation by the observers



c. Fracture pattern classified as a Hertel type 7 by two observers and Hertel type 12 by the other two observers. This fracture was classified as Neer two-part surgical neck fracture by three and as a Neer two-part greater tuberosity fracture by one observer.



d. Fracture pattern classified by all observers as a Neer three-part anterior fracture dislocation. This fracture was classified as Hertel type 7 by two and Hertel type 12 by the other two observers.

Intra-observer agreement

An overview of the intra-observer agreement comparing the Hertel with the Neer classification is shown in Table 2. On plain radiographs, the intra-observer agreement was fair for the Hertel classification (κ=0.38; 95% CI 0.27-0.59) as well as for the Neer classification (κ=0.40; 95% CI 0.15-0.52). On CT-scans, it was moderate for the Hertel classification (κ=0.50; 95% CI 0.38-0.66) as well as the Neer classification (κ=0.42; 95% CI 0.35-0.52). 3D-reconstructions showed the highest agreement. It was moderate for the Hertel classification (κ=0.55; 95% CI 0.45-0.64) and even substantial for the Neer classification (κ=0.63; 95% CI 0.48-0.79). No statistically significant differences were found. No clear trend towards specific fracture lines causing disagreement was found for either classification.

When comparing the agreement between different radiographic modalities, the agreement between X-rays and either CT-scans or 3D-reconstructions was fair for Hertel and poor for Neer (Table 3). Agreement was moderate when comparing CT-scans with 3D-reconstructions for both classification systems.

Table 2. Intra-observer agreement of the Hertel and Neer classification for X-rays, CT-scans and 3D-reconstructions

Observer	X-ray		CT-scan		3D-reconstruction	
	Hertel	**Neer**	**Hertel**	**Neer**	**Hertel**	**Neer**
1	0.59 (0.42-0.76)	0.52 (0.27-0.77)	0.38 (0.23-0.53)	0.43 (0.29-0.58)	0.55 (0.36-0.75)	0.55 (0.38-0.72)
2	0.27 (0.10-0.43)	0.15 (0.03-0.28)	0.47 (0.31-0.62)	0.39 (0.24-0.54)	0.49 (0.30-0.69)	0.74 (0.59-0.90)
3	0.41 (0.32-0.59)	0.52 (0.37-0.66)	0.66 (0.50-0.82)	0.35 (0.20-0.49)	0.63 (0.45-0.81)	0.55 (0.34-0.76)
4	0.27 (0.10-0.45)	0.41 (0.52-0.57)	0.52 (0.35-0.69)	0.52 (0.37-0.66)	0.52 (0.32-0.71)	0.69 (0.53-0.86)
Total	**Fair 0.38 (0.27-0.59)**	**Fair 0.40 (0.15-0.52)**	**Moderate 0.50 (0.38-0.66)**	**Moderate 0.42 (0.35-0.52)**	**Moderate 0.55 (0.45-0.64)**	**Substantial 0.63 (0.48-0.79)**
	P = 0.902		P = 0.288		P = 0.188	

Kappa values, with the 95% confidence interval between brackets, are shown. For the total scores the strength of agreement according to the guidelines of Landis and Koch is also shown.[26]

Table 3. Intra-observer agreement of the Hertel and Neer classification on X-rays vs. CT-scans, X-rays vs. 3D-reconstructions and CT-scans vs. 3D-reconstructions

Observer	**X-ray vs. CT-scan**		**X-ray vs. 3D-reconstruction**		**CT-scan vs. 3D-reconstruction**	
	Hertel	**Neer**	**Hertel**	**Neer**	**Hertel**	**Neer**
1	0.04 (-0.11-0.19)	0.17 (0.5-0.30)	0.01 (-0.14-0.17)	0.13 (0.02-0.24)	0.35 (0.18-0.51)	0.34 (0.20-0.49)
2	0.15 (-0.03-0.34)	0.01 (-0.10-0.12)	0.11 (-0.07-0.29)	0.10 (-0.01-0.21)	0.39 (0.23-0.56)	0.30 (0.17-0.44)
3	0.28 (0.11-0.45)	0.17 (0.03-0.30)	0.25 (0.08-0.42)	0.11 (0.00-0.22)	0.48 (0.31-0.66)	0.33 (0.19-0.48)
4	0.43 (0.28-0.57)	0.37 (0.22-0.52)	0.45 (0.29-0.61)	0.35 (0.20-0.49)	0.59 (0.44-0.75)	0.64 (0.51-0.78)
Total	**Fair 0.23 (-0.04-0.49)**	**Poor 0.18 (-0.05-0.41)**	**Fair 0.21 (-0.01-0.51)**	**Poor 0.17 (-0.02-0.36)**	**Moderate 0.46 (0.28-0.63)**	**Moderate 0.41 (0.15-0.66)**
	P = 0.692		P = 0.756		P = 0.628	

Kappa values, with the 95% confidence interval between brackets, are shown. For the total scores the strength of agreement according to the guidelines of Landis and Koch is also shown.[26]

DISCUSSION

The results of this study showed that for classification of comminuted proximal humeral fractures both the Neer and the Hertel classification had a fair to substantial inter- and intra-observer agreement. There was no statistically significant difference between the inter-observer agreement for both classification systems, nor when comparing the different radiographic modalities. Overall, the Hertel classification showed a trend towards being a more reliable classification system. The Hertel classification showed a 35, 24 and 18% higher mean kappa value for inter-observer agreement than the Neer classification when applied to plain radiographs, CT-scans, and CT-scans with 3D-reconstructions, respectively. In previous studies, both the inter-observer agreement (kappa 0.27-0.64) as well as the intra-observer agreement (kappa 0.19-0.66) for the Neer classification on plain radiographs were generally higher than the agreement observed in the current study (κ=0.29 and κ=0.40, respectively).[11, 27] This difference could be explained by the fact that we selected only patients with comminuted fractures. Classification of these types of fractures is known to have poorer inter- and intra-observer agreement.[14] One study used 3D-printed models of proximal humeral fractures instead of radiographic images. They demonstrated a higher inter-observer agreement for the Hertel classification compared with the Neer and AO classification (κ=0.44 versus κ=0.33 and κ=0.11, respectively), which is in line with the present study results. [14]

The inter-observer reliability for both the Hertel and the Neer classification was higher when classified on CT-scans (with or without 3D-reconstructions) than when classified on X-rays. The 3D-volume rendering, however, did not improve the inter-observer agreement of the Neer classification. Although this may be due to the fact that the reviewers were more used to assessing fracture patterns on plain CT-scans, it is also in agreement with previous data.[14, 28] This study showed that the same holds true for the Hertel classification. Inter-observer agreement of the Hertel classification was substantial (κ=0.63) when applied to CT-scans alone and fair (κ=0.60) when applied to CT-scans with 3D-reconstructions. The intra-observer reliability for the Neer and Hertel classifications increased from fair on X-ray to moderate on CT. Reliability using 3D-reconstructions improved even further for the Neer classification, but not for the Hertel classification. All observers judged the Hertel classification as the simpler to use system. For the Hertel classification, the observers had difficulties discriminating type 7 from 12, implying that the fracture line separating these types requires specific attention. For the Neer classification, no specific disagreement was found. Most difficulties for the Neer classification were directly related to the measurements required to be able to use this classification appropriately. Especially the reference points for the degrees of dislocation and the measurement of the degrees of angulation proved difficult. This suggests that the Hertel classification is a more straightforward classification, although this was not supported by a significantly improved agreement.

This study had some limitations. The inter- and intra-observer agreement for the two classification systems was not studied when applied to a combination of plain radiographs and CT-scans in the same session. Although this would more closely reflect common practice, most previous studies used the same method. Moreover by this method it was possible to assess both classification systems for the different imaging modalities separately. Nevertheless, it could be an interesting topic for further research. Another limitation is the selection of the radiographic images by a single person. This person however was not an observer. All radiographic images were blinded and randomized for each observer during all of the evaluations. This minimized the chance that images would be memorized and made exchange of data between observers impossible. Also, in order to accurately reflect daily routine, the quality of the radiographic images was not used as an exclusion criterion. The radiographs used by the treating surgeons were considered as of good enough quality, since the treatment strategies were based on them. So no additional quality aspects were added to the inclusion criteria. Although the strength of this study is the number of patients enrolled, the number of observers was relatively low. This may have contributed to not finding statistically significant results when comparing the Hertel and Neer classifications. As a final limitation, both classification systems share the inability to designate risk factors for a disrupted perfusion of the humeral head; an important determinant in the choice of treatment in comminuted fractures of the proximal humerus. These factors include the size of the calcar segment, the part of the metaphysis that remains attached to the head (metaphyseal extension), of less than 8 mm and disruption of the medial hinge of more than 2 mm, which is the pivot point of the head at the level of the posteromedial fracture line. An intra-operative perfusion study has proven that Hertel fracture types 2, 9, 10, 11 and 12 are prone to develop avascular necrosis.[18]

In conclusion, the results of the current study showed a moderate inter-observer agreement for both the Hertel and the Neer classifications for radiographs. When applied to CT-scans, the Hertel classification showed a trend towards a higher inter-observer agreement than the Neer classification, *i.e.*, substantial versus moderate, respectively, but this was not a significant difference. Although inter-observer agreement was highest for Hertel classification on CT-scans, Neer classification had the highest intra-observer agreement on 3D-reconstructions. Data of this study do not confirm superiority of either classification system for the classification of comminuted proximal humeral fractures.

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Chapter 4

Reliability and Reproducibility of the OTA/AO Classification for Humeral Shaft Fractures

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ABSTRACT

Objectives: This study aimed to determine inter-observer reliability and intra-observer reproducibility of the OTA/AO classification for humeral shaft fractures, and to evaluate differences between fracture types, fracture groups, and surgical specializations.
Methods: 30 observers (25 orthopedic trauma surgeons and five general orthopedic surgeons) independently classified 90 humeral shaft fractures according to the OTA/AO classification. Patients of 16 years and older were included. Periprosthetic, recurrent, and pathological fractures were excluded. Radiographs were provided in random order, and observers were blinded to clinical information. To determine intra-observer agreement, radiographs were reviewed again after two months in a different random order. Agreement was assessed using kappa statistics.
Results: Inter-observer agreement for the three fracture types was moderate (κ=0.60; 0.59-0.61). It was substantial for type A (κ=0.77; 0.70-0.84), and moderate for type B (κ= 0.52; 0.46-0.58) and type C fractures (κ=0.46; 0.42-0.50). Inter-observer agreement for the nine fracture groups was moderate (κ=0.48; 95% CI 0.48-0.48). Orthopedic trauma surgeons had better overall agreement for fracture types, and general orthopedic surgeons had better overall agreement for fractures groups. Observers classified 64% of fractures identically in both rounds. Intra-observer agreement was substantial for the three types (κ=0.80; 0.77-0.81) and nine groups (κ=0.80; 0.77-0.82). Intra-observer agreement showed no differences between surgical disciplines.
Conclusions: The OTA/AO classification for humeral shaft fractures has a moderate inter-observer and substantial intra-observer agreement for fracture types and groups.

INTRODUCTION

A fracture classification system should not only provide a reliable and reproducible means of communication between physicians, but also provide for repeated viewings of the same material.[1] Ideally it should have a prognostic value for the outcome of patients, assist in managing fractures, and assist documentation and research.[2] Humeral shaft fractures are most widely classified using the OTA/AO classification system.[1, 3]

Despite its widespread use, the OTA/AO classification has not been validated for humeral shaft fractures, including the complete range of fracture types and groups. The primary aim of this study was therefore to determine the inter-observer reliability and intra-observer reproducibility of the OTA/AO classification for humeral shaft fractures. The secondary aims were to evaluate if reliability and reproducibility differed between the three different fracture types or the nine fracture groups, and to assess if agreement was dependent on surgical specialization or time spent on classifying the radiographs.

METHODS

Classification

In the OTA/AO classification, number 1 stands for the humerus and number 2 for the diaphyseal segment. As shown in Figure 1, three types of fractures are defined and coded with letters: type A consists of simple fractures, type B of wedge-type fractures, and type C of complex fractures. Each of these three types can be further subdivided into groups 1, 2, or 3. Overall, the OTA/AO classification system for humeral shaft fractures has nine groups (12-A1/2/3, 12-B1/2/3, 12-C1/2/3).[2]

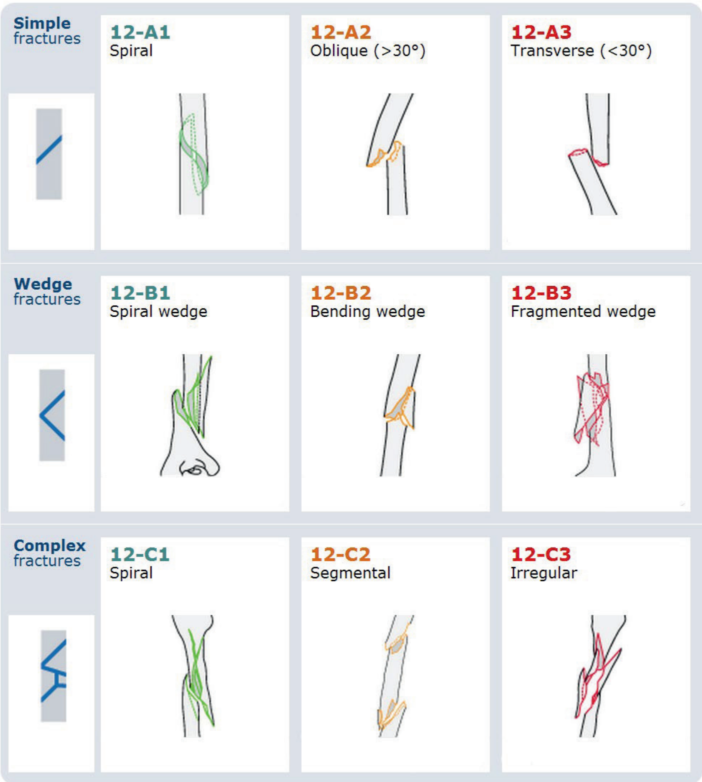

Figure 1. OTA/AO classification for humeral shaft fractures[1, 3]

Study subjects

Patients were selected from the hospital records and from the radiology system PACS (Picture Archiving and Communication System) of three hospitals. Eligible patients had already been identified from hospital databases as part of another study.[4] All patients aged 16 years or older treated for a humeral shaft fracture in one of three hospitals were included in this study. The humeral shaft was defined as the area between the surgical neck and the area immediately above the supracondylar ridge. Radiographs had to include initial (i.e., before treatment) anterior-posterior or lateral images. Patients with periprosthetic, recurrent, or pathological fractures were excluded. Patients with fractures extending outside the predefined shaft area were excluded as well. A total of 90 patients representing the full spectrum of humeral shaft fractures were selected by the clinical investigator (KCM). The investigator was adequately trained, had sufficient experience to select the radiographs of humeral shaft fractures and was not involved as observer. The sample size of 90 patients allowed for all groups to be represented with ten subjects. The first ten subjects per group were included. In order to reflect routine day-to-day practice the quality of the images was not used as an exclusion criterion. The radiographs that were accepted for clinical decision making were also considered adequate for this classification study. All radiographs available (two or three for 85 patients and one for the other five) were used. Radiographs had no identifying information. Following randomization using a web-based list randomizer (www.random.org), they were imported into an open-source Digital Imaging and Communications in Medicine (DICOM) compliant viewer (RadiAnt DICOM Viewer 1.9.14, Medixant, Poznan, Poland). This viewer provided all necessary tools for adequate viewing (e.g., fluid zooming and panning, brightness and contrast adjustments, and angle measurements). The same workstation and DICOM viewer were used for all observations in order to guarantee identical viewing conditions.

Observers

Thirty-seven consultant upper extremity (orthopedic) trauma surgeons experienced in the treatment of humeral fractures were invited to act as observer. All surgeons act as site principal investigator in a multicenter clinical study comparing the operative and non-operative treatment of humeral shaft fractures (HUMMER study).[5] Years of independent practice and whether the OTA/AO classification is used in daily practice were noted for each observer.

Study procedure

Each observer independently classified 90 humeral shaft fractures according to the classification system. All radiographs were provided in random order, and the observers were given as much time as needed for accurate assessment. Observers were blinded to clinical information and were not allowed to discuss their observations with other investigators. All observers were familiar with the OTA/AO classification system used in this study. In order to ensure unambiguous application of the fracture classification system, an overview of the classification system was available to the surgeons during the classification (Figure 1). The amount of time needed to classify all radiographs was recorded.

In order to determine the intra-observer agreement, all radiographs were reviewed a second time at least two months after the first review. On the second occasion, images were provided in a different random order. Inter-observer reliability is the degree of agreement when two or more independent observers classify the same fracture. Intra-observer reproducibility is agreement when one observer classifies the same fracture more than once.

Statistical analysis

Normality of continuous data was judged from frequency histograms and Q-Q plots, homogeneity of variances was tested using the Levene's test. Data were analyzed using Kappa statistics, as described by Cohen.[6] The kappa coefficient represents the agreement between two sets of observations compared with the likelihood of agreement based on chance alone. The kappa coefficient ranges from 1 (perfect agreement) to <0 (systematic disagreement, or no more agreement than would be expected by chance alone). The kappa value for inter-observer agreement was calculated for each possible pair of observers before calculating the mean kappa value.[7] Interpretation of the values were carried out according to the guidelines of Landis and Koch, which suggest that values <0 represent poor reliability; 0.00-0.20 slight agreement; 0.21-0.40 fair agreement; 0.41-0.60 moderate agreement; 0.61-0.80 substantial agreement; and 0.81-1.00 almost perfect agreement.[8] The kappa value for intra-observer agreement were calculated for each of the individual observers before calculation the mean kappa value. The kappa values were classified according to Landis and Koch as described in the previous section.

Kappa values for both inter- and intra-observer agreement were assessed for the nine groups (12-A1/2/3, 12-B1/2/3, 12-C1/2/3), as well as for the three types (A, B and C) in order to judge if kappa values differ between fractures. Statistical significance of differences in the kappa values across these groups and types were tested with a one-way Analysis of Variance

(ANOVA). Statistical significance of differences between orthopedic trauma and general orthopedic surgeons and time spent on the classification of all radiographs were tested with the a Student's t-test. Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 21 or higher (SPSS, Chicago, Ill., USA).

RESULTS

Twenty-five of the observers were orthopedic trauma surgeons and five were general orthopedic surgeons. Of the observers 11 worked ten years or less in an independent practice and 19 had more than ten years of experience in an independent practice.

As shown in Table 1, the inter-observer reliability was moderate for the three fracture types (κ=0.60; 95% CI 0.59-0.61). It was substantial for type A fractures (κ=0.77; 95% CI 0.70-0.84), and moderate for type B (κ= 0.52; 95% CI 0.46-0.58) and type C fractures (κ=0.46; 95% CI 0.42-0.50).

The inter-observer agreement for the nine groups was moderate (κ=0.48; 95% CI 0.48-0.48). It was highest for 12-A3 fractures (κ=0.68; 95% CI 0.64-0.71) and 12-C3 fractures (κ=0.63; 95% CI 0.60-0.66) and lowest for 12-C1 fractures (κ=0.24; 95% CI 0.21-0.27). The overall inter-observer agreement for three fracture types and nine groups both showed statistical significance differences between orthopedic trauma and general orthopedic surgeons. Orthopedic trauma surgeons had better overall agreement for fracture types (κ=0.60; 95% CI 0.61-0.59 and κ=0.58; 95% CI 0.53-0.62, respectively). For overall inter-observer agreement for the nine groups it was the other way around and general orthopedic surgeons had better overall agreement (κ=0.47; 95% CI 0.47-0.48 and κ=0.51; 95% CI 0.50-0.53, respectively).

No differences were found between surgical specialization and agreement of specific fracture types or groups, except for the 12-B1 fracture group. Orthopedic trauma surgeons had a lower inter-observer agreement for that specific group than general orthopedic surgeons (κ=0.33; 95% CI 0.28-0.37 and κ=0.47; 95% CI 0.31-0.62, respectively).

The intra-observer reproducibility was substantial as shown in Table 2 (κ=0.80; 95% CI 0.77-0.81) for the three types, as well as for the nine groups (κ=0.80; 95% CI 0.77-0.82). Observers classified 64% (95% CI 62-67%) of the fractures identically in both rounds. Intra-observer agreement for types, groups or the percentage of identically classified fractures in both rounds did not differ between surgical specializations.

Both the inter- and intra-observer agreement were not significantly associated with the time spent on the classification of all radiographs.

Table 1. Inter-observer reliability of all observers and separate for the two surgical disciplines

	All observers (n=30)	Strength of agreement	Orthopedic trauma surgeons (n=25)	Strength of agreement	General orthopedic surgeons (n=5)	Strength of agreement[B]	P value
Types	0.60 (0.59-0.61)	moderate	0.60 (0.61-0.59)	moderate	0.58 (0.53-0.62)	moderate	0.012
A	0.77 (0.70-0.84)	substantial	0.77 (0.70-0.85)	substantial	0.73 (0.51-0.94)	substantial	0.647
B	0.52 (0.46-0.58)	moderate	0.52 (0.46-0.59)	moderate	0.51 (0.32-0.71)	moderate	0.930
C	0.46 (0.42-0.50)	moderate	0.46 (0.41-0.51)	moderate	0.45 (0.28-0.62)	moderate	0.871
Groups	0.48 (0.48-0.48)	moderate	0.47 (0.47-0.48)	moderate	0.51 (0.50-0.53)	moderate	<0.001
A1	0.61 (0.57-0.65)	substantial	0.61 (0.57-0.65)	moderate	0.63 (0.47-0.79)	substantial	0.700
A2	0.55 (0.51-0.58)	moderate	0.53 (0.49-0.57)	moderate	0.61 (0.46-0.77)	substantial	0.152
A3	0.68 (0.64-0.71)	substantial	0.67 (0.63-0.71)	substantial	0.69 (0.53-0.85)	substantial	0.684
B1	0.35 (0.31-0.39)	fair	0.33 (0.28-0.37)	fair	0.47 (0.31-0.62)	moderate	0.025
B2	0.45 (0.42-0.48)	moderate	0.46 (0.43-0.50)	moderate	0.44 (0.29-0.60)	moderate	0.674
B3	0.27 (0.24-0.30)	fair	0.25 (0.22-0.28)	fair	0.33 (0.18-0.49)	fair	0.106
C1	0.24 (0.21-0.27)	fair	0.24 (0.20-0.28)	fair	0.27 (0.11-0.42)	fair	0.620
C2	0.30 (0.27-0.32)	fair	0.28 (0.26-0.31)	fair	0.34 (0.14-0.53)	fair	0.318
C3	0.63 (0.60-0.66)	substantial	0.63 (0.60-0.67)	substantial	0.61 (0.46-0.77)	substantial	0.709

Data are shown as mean kappa value, with 95% confidence intervals between brackets. Interpretation of the strength of agreement is according to the guidelines of Landis and Koch[8].

Chapter 4

Table 2. Intra-observer reproducibility of all observers and separate for the two surgical disciplines

	All observers (n=30)	Strength of agreement	Orthopedic trauma surgeons (n=25)	Strength of agreement	General orthopedic surgeons (n=5)	Strength of agreement	P-value
Types[A] (ABC)	0.80 (0.77-0.81)	substantial	0.80 (0.76-0.82)	substantial	0.78 (0.74-0.81)	substantial	0.600
Groups[A] (A1-C3)	0.80 (0.77-0.82)	substantial	0.80 (0.77-0.82)	substantial	0.79 (0.75-0.83)	substantial	0.772
% Agreement[B]	64 (62-67)	N.A.	64 (61-67)	N.A.	64 (56-72)	N.A.	0.978

[A] Data are shown as mean kappa value, with 95% confidence intervals between brackets. [B] Data are shown as percentage, with 95% confidence intervals between brackets. Interpretation of the strength of agreement is according to the guidelines of Landis and Koch[8]. N.A., not applicable.

Table 3 shows an overview of the number of dominant classifications of the 90 fractures classified. In addition, it shows the mostly chosen alternative per fracture type and group. When the 12-A fracture type was the dominant classification, 12-B was the mostly chosen alternative (61% of classifications). For type 12-B, the mostly chosen alternative was type 12-C (66%). The type 12-B classification was mostly chosen as alternative (91%) when the type 12-C classification was dominant. For the type 12-A1 (simple spiral fracture), the 12-B1 (spiral wedge fracture) was the mostly chosen alternative. The 12-A2 and 12-A3 groups (oblique and transverse fractures, respectively), were both chosen mostly as alternative when these were the dominant classification. For 12-B1 and 12-C1 groups (spiral wedge and complex spiral fractures, respectively) and for 12-B2 and 12-B3 groups (bending wedge and fragmented wedge fractures, respectively) this was also the case. When the 12-C2 segmental group was dominant, the 12-A3 transverse group was chosen mostly as alternative.
Figure 2 shows an example of a fracture with perfect agreement. This fracture was classified in the 12-A2 group by all observers in both rounds. This was also the only fracture with perfect agreement in the entire study. An example of poor agreement is shown in Figure 3. This fracture was classified in six different groups.

Table 3. Overview of dominant classifications with mostly chosen alternative per fracture type and group

	Dominant classification	Alternative classification		
	Number (%) patients	N of classifications	Dominant classification	Percentage of observers with dominant classification
Types				
A	41 (46%)	2	B	61%
B	33 (37%)	2	C	66%
C	16 (18%)	2	B	91%
Groups				
A1	18 (19%)*	4	B1	46%
A2	11 (12%)	2	A3	71%
A3	12 (13%)	2	A2	94%
B1	17 (18%)*	3	C1	43%
B2	10 (11%)	5	B3	49%
B3	6 (6%)	3	B2	43%
C1	10 (11%)*	3	B1	84%
C2	1 (1%)	1	A3	100%
C3	9 (10%)	4	B3	49%

* One patient is included in A1 and B1 as both were the dominant classifications in this patient. For the same reason, two other patients are included in B1 and C1.

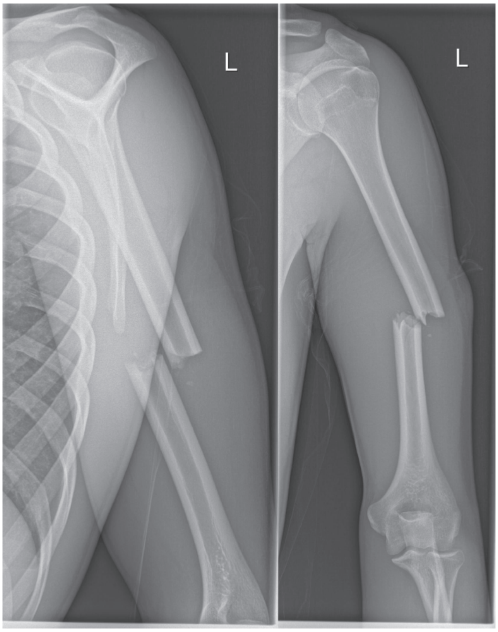

Figure 2. Example of a fracture with perfect agreement

Classified as 12-A3 by all observers in both rounds.

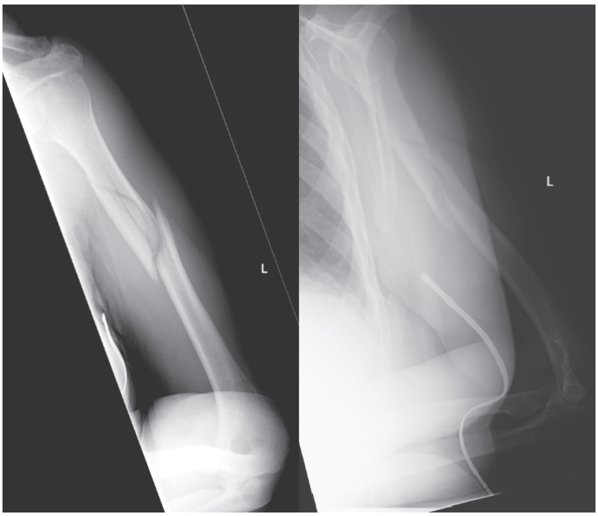

Figure 3. Example of a fracture with poor agreement

Classified into six different groups.

DISCUSSION

The main purpose of the current study was to determine whether the OTA/AO classification is a reliable and reproducible system for the classification of humeral shaft fractures. The inter-observer reliability was moderate and the intra-observer reproducibility was substantial. Although the usability of the OTA/AO classification has previously been questioned, it remains the most widely used classification system in the research of humeral shaft fractures.[9] The validity of the classification has also been studied in various bone segments, but specific results of the classifications used for humeral shaft fractures are scarce.[10-16] Johnstone et al. concluded in 1993 that the classification system for long bone fractures demonstrated a significant inter-observer variation, but no humeral shaft fractures were included in that study.[17] In the same year, Newey et al. concluded that the classification system was only useful for audit options, but again no humeral shaft fractures were included.[18] Meling et al. reported a moderate inter-observer agreement for the OTA/AO classification for long bone fractures(κ= 0.67 (95% CI: 0.62-0.72)).[19] A study comparing the OTA/AO classification for long bone fractures with a newly proposed classification, including 40 humeral shaft fractures classified by six observers, reported a fair inter-observer agreement (κ=0.30) and also a fair intra-observer agreement (κ=0.38) for the OTA/AO classification.[20] That classification system, describing fractures by location (proximal, middle, distal, or in combinations when the fracture is located in multiple zones) and morphology (simple [transverse, oblique or spiral], intermediate and complex), had a good inter-observer (κ=0.66) as well as a moderate intra-observer (κ=0.56) agreement.

As shown in Table 3, observers did not agree on specific fracture patterns. When most observers classified a fracture as a simple spiral fracture (12-A1), the remaining observers classified it as a spiral wedge (12-B1). When most observers classified a fracture as a spiral wedge the remaining observers chose the complex spiral fracture (12-C1). Apparently, the fracture lines discriminating these fracture types were easily missed (or thought to be seen). Also, the angle of the fracture seemed difficult to determine. The angle separating the oblique (12-A2) and transverse (12-A3) fracture groups of 30 degrees seemed to cause observers to disagree. For future classifications, specific attention should be paid to these items.

CONCLUSIONS

The OTA/AO classification system for humeral shaft fractures has a moderate inter-observer agreement for the fracture types and fracture groups. Apart from a substantial agreement for type A fractures the agreement for the other fracture types was moderate. Agreement for specific fracture groups ranged from fair to substantial. The intra-observer agreement was substantial for the fracture types and groups, with 64% fractures classified identically in both rounds. Specific attention should be paid to discriminating A1 from B1, B1 from C1, and A2 from A3 as fracture lines or angles discriminating these two were often misinterpreted.

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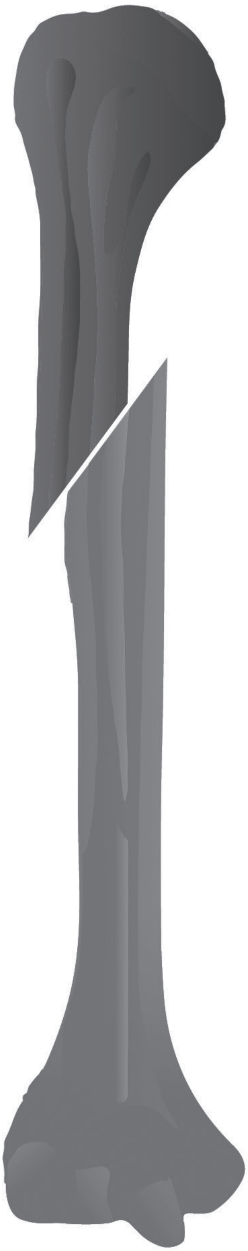

PART IV

Outcome

Chapter 5

Functional outcome and complications after operative and non-operative treatment of humeral shaft fractures: a systematic review and pooled analysis

Submitted

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ABSTRACT

Introduction Humeral shaft fractures can be treated operatively or non-operatively. The optimal management is subject of scientific and clinical debate. The current systematic review and pooled analysis aimed to compare outcome of non-operative and operative treatment of humeral shaft fractures, focusing especially on complications, functional outcome scores, and range of motion.

Materials and Methods Databases of MEDLINE (PubMed), Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) were systematically searched for publications reporting outcome and complications of non-operative treatment with a functional brace or operative treatment by intramedullary nailing (IMN) or plate osteosynthesis. A pooled analysis of the results was performed using MedCalc and MetaXL.

Results A total of 114 studies, describing the results of 8,431 patients, were included. Mean fracture healing time (15 weeks) and consolidation rate (93%) was similar in each group. The prevalence of iatrogenic radial nerve palsies was 1% in patients treated non-operatively, 3% in the IMN and 5% in the plating group. Intraoperative complications and implant failures occurred more frequently in the IMN group than in the plating group. Implant removal rates were comparable for patients treated by IMN and plate osteosynthesis (12% and 7%, respectively). No differences were observed in ASES, Constant-Murley or MEPI scores after IMN or plating osteosynthesis. Shoulder abduction and anteflexion did not differ between the IMN (132°and 120°, respectively) and plate groups (125° and 136° , respectively). A better anteflexion was seen in patients treated using minimally invasive plate osteosynthesis (MIPO) than using an open plating technique (120° and 166° , respectively).

Conclusions This study showed no differences in consolidation time and rates between non-operative treatment, IMN, and plate osteosynthesis. Iatrogenic radial nerve palsies were more common in patients treated with open plating than in patients treated non-operatively. Intraoperative complications and implant failures occurred more frequently in the IMN groups than in the plating group. Implant removal rates were comparable between patients treated by IMN and plate osteosynthesis. A well-designed and powered prospective study and uniform outcome reporting is needed in order to be able to compare the results in the future.

INTRODUCTION

The optimal management of humeral shaft fractures remains the subject of scientific and clinical debate.[1] They can be treated operatively or non-operatively. Historically non-operative treatment was preferred over operative treatment. The most commonly used method for non-operative treatment nowadays is a functional brace.[2] Despite the possibility of early mobilization of the shoulder and elbow joints, impairment of range of motion (ROM) of especially the shoulder joint should be anticipated.[3, 4]

Operative treatment for humeral shaft fractures consists of 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. It preserves the periosteal blood supply and minimizes disruption of fracture biology. The incisions are small and require less soft tissue stripping than plate osteosynthesis.[5] However, shoulder related complaints are frequently reported.[6]

Plate osteosynthesis offers direct visualization and anatomic reduction of the fracture. Plate osteosynthesis requires extensive soft-tissue exposure.[7] A potential disadvantage of this is a possible higher rate of iatrogenic radial nerve palsies. MIPO has the advantage of less soft tissue dissection and avoids the need to expose the radial nerve.[8] The development of these different osteosynthesis techniques and designs has expanded the surgical indications, even when no absolute indication for surgery is present.[9, 10] Since the year 2002 an increase in plate osteosynthesis is observed.[11, 12] Nevertheless, the best treatment of humeral shaft fractures is still unclear. Despite the recommendation by some authors to use IMN in the operative treatment of these fractures, no differences in complications and outcome between IMN and plating have been observed so far.[13-16]

The aim of the current systematic review and pooled analysis was to compare clinical outcome and complications between non-operative and operative treatment of humeral shaft fractures. Outcome included consolidation, complications, functional outcome scores and range of motion.

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).[17] Methods used for the analysis, search strategy, and inclusion criteria were specified in advance.

Search strategy

Databases of MEDLINE (PubMed), Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) were electronically searched for English and non-English articles. Searched items were specified for each individual database in collaboration with an experienced librarian and consisted of terms related to the treatment of humeral shaft fractures (Table 1). Reference lists of review articles and eligible studies were reviewed for additional studies that may have been missed. The last search was run on March 29 2016.

Eligibility criteria

Studies were included if they met the following inclusion criteria: 1) primary treatment of humeral shaft fractures, 2) patients aged 16 or older, 3) primary data reported, 4) clinical outcome reported, 5) outcome of five or more patients reported, 6) functional brace in case of non-operative treatment, and 7) published after the year 2000. No restrictions related to the length of follow-up or languages were defined. All study designs, except case reports, were included in this systematic review. Corresponding author of studies with no available full text version were contacted.

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) alternative operative methods for humeral shaft fractures (*e.g.*, Ender nails, Marchetti nails, Rushs nails, Hackethal nailing, K wires, expandable, flexible or elastic nails).

Table 1. Search strategy

Database	Query	Hits
MEDLINE	(((humer*[tiab] AND (shaft*[tiab] OR diaphys*[tiab])) AND fracture*[tiab]) AND (surger*[tiab] OR surgic*[tiab] OR operation*[tiab] OR operative*[tiab] OR nail*[tiab] OR pins[tiab] OR plate[tiab] OR plates[tiab] OR plated[tiab] OR plating[tiab] OR fix*[tiab] OR screw*[tiab] OR conservative*[tiab] OR brace*[tiab] OR bracing[tiab] OR sling*[tiab] OR plaster*[tiab] OR cast[tiab] OR casting[tiab] OR non operative*[tiab] OR nonoperative*[tiab] OR non-operative*[tiab] OR non surgical*[tiab] OR nonsurgical*[tiab] OR non-surgical*[tiab] OR Sarmiento[tiab] OR splint*[tiab] OR traction[tiab] OR immobili*[tiab])) NOT (pediatric[title] OR paediatric[title] OR child*[title] OR Case report*[title] OR case study[title] OR meta-analysis[title] OR meta analysis[title] OR fibula*[title] OR animal*[tiab] OR arthroplasty[tiab] OR cyst[tiab] OR metast*[title] OR biomechanic* [title] OR benign [tiab])	1051
Embase	(((humer*:ab,ti AND (shaft*:ab,ti OR diaphys*:ab,ti)) AND fracture*:ab,ti) AND (surgery/exp OR ‘orthopedic fixation device’/exp OR ‘fracture fixation’/exp OR surger*:ab,ti OR surgic*:ab,ti OR operation*:ab,ti OR operative*:ab,ti OR nailing:ab,ti OR nails:ab,ti OR pins:ab,ti OR plate*:ab,ti OR plating:ab,ti OR screw*:ab,ti OR fixat*:ab,ti OR brace/de OR ‘plaster cast’/de OR immobilization/de OR conservative*:ab,ti OR brace*:ab,ti OR bracing:ab,ti OR sling*:ab,ti OR plaster*:ab,ti OR cast:ab,ti OR casting:ab,ti OR (non NEXT/1 (operative* OR surgical*)):ab,ti OR nonoperative*:ab,ti OR nonsurgical*:ab,ti OR sarmiento:ab,ti OR splint*:ab,ti OR traction:ab,ti OR immobili*:ab,ti)) NOT (pediatric:ti OR paediatric:ti OR child*:ti OR (case NEXT/1(report* OR stud*)):ab,ti OR meta-analysis:ab,ti OR animal*:ab,ti OR arthroplasty:ti OR cyst:ab,ti OR metast*:ti OR biomechanic*:ti OR ununited:ti)	1280
CENTRAL	(((humer*:ab,ti and (shaft*:ab,ti or diaphys*:ab,ti)) and fracture*:ab,ti) and (surger*:ab,ti or surgic*:ab,ti or operation*:ab,ti or operative*:ab,ti or nailing:ab,ti or nails:ab,ti or pins:ab,ti or plate*:ab,ti or plating:ab,ti or screw*:ab,ti or fixat*:ab,ti or conservative*:ab,ti or brace*:ab,ti or bracing:ab,ti or sling*:ab,ti or plaster*:ab,ti or cast:ab,ti or casting:ab,ti or (non next/1 (operative* or surgical*)):ab,ti or nonoperative*:ab,ti or nonsurgical*:ab,ti or sarmiento:ab,ti or splint*:ab,ti or traction:ab,ti or immobili*:ab,ti)) not (pediatric:ti or paediatric:ti or child*:ti or (case next/1 (report* or stud*)):ab,ti or meta-analysis:ab,ti or animal*:ab,ti or arthroplasty:ti or cyst:ab,ti or metast*:ti or biomechanic*:ti or ununited:ti)	50
Total		2381

Search performed on March 29 2016.

Study selection

Three reviewers (KCM, TVDT and CAWN) performed a first-stage screening and independently screened the titles and abstracts of the studies and selected those meeting the inclusion and none of the exclusion criteria. Of the remaining publications the full text was reviewed. Any disagreement was resolved through consensus.

Data collection and data items

Data were extracted from the reports independently by two reviewers (KCM 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, open plating or MIPO, antegrade or retrograde IMN), fracture classification according to the AO/OTA classification, complications, functional outcome score, including patients-reported outcome measures (PROMs) and range of motion.

The extracted data were compared and disagreements were resolved by discussion between the two reviewers. Consensus was reached on all occasions. For the 22 studies the authors did not have access to the full text, the corresponding authors were contacted and asked to provide a full-text version. Five authors replied and sent the full text version of their publication. Five publications had no contact details available.

Risk of bias assessment

The MINORS (Methodological Index for Non-Randomized Studies) instrument was used to assess methodological quality of the included publications.[18] The MINORS scale yields a maximum score of 16 for non-comparative cohort studies and a maximum of 24 for comparative cohort studies.

Statistical analysis

Data were analyzed using MetaXL software (Version 5.2; Epigear International Pty Ltd, Australia; 2010-2016) and MedCalc (Version 14.10.2; MedCalc Software, Ostend, Belgium). Prevalence of adverse events were transformed using a double arcsine transformation in order to ensure normal distribution.[19] The transformed rates and 95% confidence intervals were transformed back to prevalence estimates. Forest plots were constructed with 95% confidence intervals. Cochrane Chi-squared (χ^2) Q-test was applied in order to test for heterogeneity (significance set at $p < 0.10$), and the I^2 statistic was calculated in order to quantify the degree of between-study heterogeneity. An I^2 statistic greater than 40% was considered to represent significant heterogeneity. A fixed effects model was used for pooling data if the I^2 statistic was smaller than 40%, otherwise a random effects model was used. The Q-value, I^2 value, and pooled estimate are reported with 95% confidence interval.

RESULTS

Study selection

The search strings identified 2,381 publications (Figure 1). Duplicates were eliminated, resulting in 1,515 unique publications. Studies published before the year 2000 were eliminated. The remaining 920 publications were reviewed for inclusion and exclusion criteria. A total of 136 eligible publications were identified. After excluding studies of which, despite contacting the corresponding authors, no full text versions were available, 114 publications were included in this review and meta-analysis.

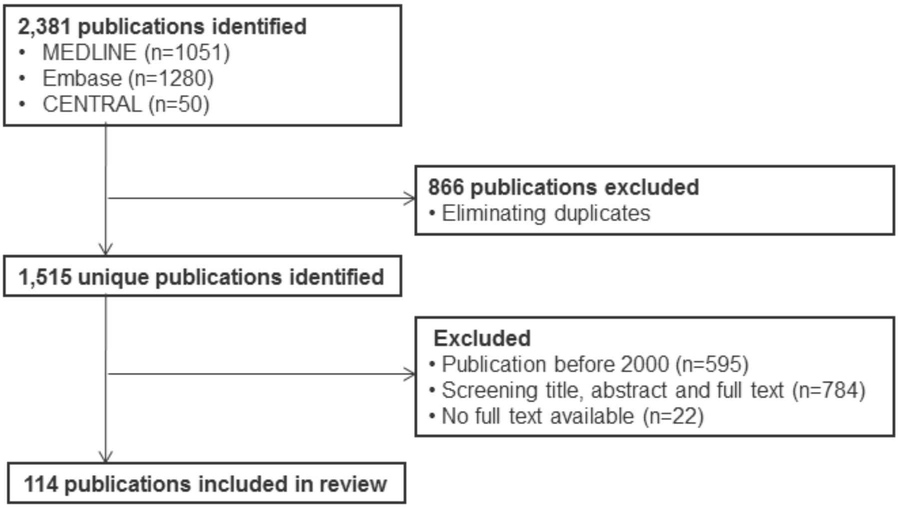

Figure 1. Flow diagram of study selection

Study characteristics

Of the 114 included studies, 10 were randomized controlled trials, 35 prospective cohort studies and 69 retrospective studies. Supplemental Table S1 shows the study characteristics. The included studies describe a total of 8,431 patients. Of these, 2,483 were treated non-operatively with a functional brace, 2,006 were treated by intramedullary nailing and 3,942 by plate osteosynthesis. The mean age of the patients was 45 years (41 for the non-operative group, 48 for the IMN group and 46 for the plate group).

Fracture healing and complications

Overall fracture healing time was 15 weeks (95% CI 14-16). Time to consolidation was 16 weeks (95% CI 14-19) for the non-operative group, 13 weeks (95% CI 11-14) for the IMN group and 16 weeks (95% CI 15-17) for the plate osteosynthesis group (Table 2). The overall consolidation rate was 93% (95% CI 92-94%). For the non-operative groups it was 90% (95% CI 85-94%), for the IMN group 92% (95% CI 90-94%) and for the plating group 95% (95% CI 94-96%) (Supplemental Figure S1).

Nonunion rates were comparable between groups (overall prevalence of 6% (95% CI 5-7)) (Table 3). The prevalence of primary radial nerve palsies (*i.e.* caused during the trauma and not as a complication of treatment) showed no variation between the treatment groups. It varied from 6% (95% CI 5-7%) in the open plating group to 1% (95% CI 0-4%) in the non-operatively treated group. In the IMN group iatrogenic radial nerve palsy had a prevalence of 3% (95% CI 2-4%).

The prevalence of intraoperative complications was 6% (95% CI 3-10%) in patients treated by IMN and 1% (95% CI 1-2%) in patients treated with plate osteosynthesis. Implant failures were more frequent in the IMN group than in the plating group (6% (95% CI 4-9%) and 2% (95% CI 2-3), respectively). Implant removal rates were 12% (95% CI 8-16%) in the IMN and 7% (95% CI 3-12%) in the plating group.

Malunion had an overall prevalence of 3% (95% CI 2-4%). It was higher for the non-operatively treated group (8% (95% CI 0-21%)), than in the IMN (3% (95% CI 1-6%) and plating groups (1% (95% CI 1-2%)).

Overall infection rate was 2% (95% CI 2-3%). Skin problems occurred in 6% (95% CI 3-9%) of the patients treated non-operatively with functional brace (7 studies, N=259, 15 cases, not shown in Table 3). Nail protrusion was seen in 9% (95% CI 6-14%) of patients treated by IMN. Subacromial impingement was seen more in the IMN group compared with the plate osteosynthesis group (15% (95% CI 10-20%) and 2% (95% CI 0-6%), respectively). No differences were seen in rate of shoulder or elbow dysfunction between the three treatment groups.

Table 2. Fracture healing time and rate of consolidation of humeral shaft fracture treatment

	Treatment	Studies N	Population N	Cases N	Heterogeneity Cochran's Q (p-value)	I^2 (%) (95% CI)	Pooled value (95% CI)
Fracture healing time (weeks)	**Non-operative**	3	184	N.A.	22 (0.00)	91 (76-97)	16.1 (13.5-18.7)
	IMN	8	354	N.A.	98 (0.00)	93 (88-96)	12.5 (11.0-14.1)
	Antegrade	5	208	N.A.	39 (0.00)	90 (79-95)	12.6 (10.6-14.7)
	Retrograde	2	68	N.A.	16 (0.00)	94 (79-98)	10.8 (8.2-13.3)
	Plate	19	701	N.A.	302 (0.00)	94 (92-96)	15.8 (14.5-17.1)
	Open	14	610	N.A.	286 (0.00)	95 (94-97)	15.9 (14.4-17.5)
	MIPO	5	91	N.A.	13 (0.01)	68 (19-88)	15.4 (13.6-17.1)
Consolidation rate (%)	**Non-operative**	18	1624	1481	115 (0.00)	85 (78-90)	90 (85-94)
	IMN	47	1921	1780	97 (0.00)	53 (34-66)	92 (90-94)
	Antegrade	29	1089	1026	40 (0.07)	29 (0-55)	92 (90-94)
	Retrograde	7	250	236	8 (0.25)	24 (0-66)	94 (90-97)
	Plate	76	2804	2676	118 (0.00)	36 (16-52)	95 (94-96)
	Open	45	2040	1936	85 (0.00)	48 (27-64)	94 (93-96)
	MIPO	31	764	740	30 (0.49)	0 (0-39)	97 (95-98)

I^2, I^2-statistic for study heterogeneity; 95% CI, 95% confidence interval; IMN, intramedullary Nail; MIPO, minimally invasive plate osteosynthesis; N.A., not applicable.

Table 3. Complication rates of humeral shaft fracture treatment

	Treatment	Studies	Population	Cases	Heterogeneity		Pooled value
		N	N	N	Cochran's Q (p-value)	I^2 (%) (95% CI)	(%) (95% CI)
Nonunion	**Non-operative**	15	1547	134	119 (0.00)	88 (82-92)	11 (6-17)
	IMN	45	1740	110	63 (0.03)	31 (0-52)	7 (6-9)
	Antegrade	30	1097	74	31 (0.35)	7 (0-39)	7 (6-9)
	Retrograde	6	223	10	6 (0.28)	20 (0-65)	5 (2-9)
	Plate	70	2689	108	112 (0.00)	38 (17-54)	4 (3-6)
	Open	43	2022	91	92 (0.00)	55 (36-68)	5 (4-7)
	MIPO	27	667	17	18 (0.87)	0 (0-17)	3 (2-5)
Primary radial nerve palsy	**Non-operative**	17	1438	119	12 (0.72)	0 (0-37)	8 (7-10)
	IMN	29	1243	117	100 (0.00)	72 (60-81)	10 (7-14)
	Antegrade	16	553	73	69 (0.00)	78 (65-86)	12 (7-19)
	Retrograde	5	186	11	6 (0.17)	37 (0-77)	7 (2-12)
	Plate	39	1507	238	161 (0.00)	76 (68-83)	12 (9-16)
	Open	27	1191	218	107 (0.00)	76 (65-83)	15 (10-19)
	MIPO	12	316	20	21 (0.04)	47 (0-73)	6 (3-11)
Iatrogenic radial nerve palsy	**Non-operative**	12	1117	10	35 (0.00)	69 (43-83)	1 (0-4)
	IMN	43	1763	43	51 (0.17)	17 (0-43)	3 (2-4)
	Antegrade	28	1022	14	24 (0.62)	0 (0-35)	2 (1-3)
	Retrograde	6	209	8	3 (0.76)	0 (0-52)	5 (2-8)
	Plate	82	3376	169	151 (0.00)	46 (31-59)	5 (4-6)
	Open	51	2602	145	111 (0.00)	55 (38-67)	6 (5-7)
	MIPO	31	774	24	35 (0.25)	14 (0-44)	3 (2-5)
Infection	**Non-operative**	3	233	2	4 (0.14)	49 (0-85)	1 (0-3)
	IMN	38	1481	18	34 (0.60)	0 (0-32)	1 (1-2)
	Antegrade	27	934	13	29 (0.33)	9 (0-42)	2 (1-3)
	Retrograde	5	220	1	2 (0.65)	0 (0-66)	1 (0-2)
	Plate	63	2886	63	107 (0.00)	42 (21-57)	3 (2-4)
	Open	42	2308	58	92 (0.00)	56 (37-69)	3 (2-5)
	MIPO	21	578	5	12 (0.91)	0 (0-14)	1 (1-2)
Malunion	**Non-operative**	5	225	20	34 (0.00)	88 (75-94)	8 (0-21)
	IMN	16	596	20	42 (0.00)	64 (39-79)	3 (1-6)
	Antegrade	11	353	17	37 (0.00)	73 (51-85)	4 (1-9)
	Retrograde	1	41	0	N.A.	N.A.	0 (0-4)
	Plate	35	1165	12	20 (0.98)	0 (0-0)	1 (1-2)
	Open	20	681	5	8 (0.99)	0 (0-0)	1 (1-2)
	MIPO	15	484	7	11 (0.60)	0 (0-47)	2 (1-3)
Intraoperative complications	**Non-operative**	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
	IMN	27	1133	95	151 (0.00)	83 (76-88)	6 (3-10)
	Antegrade	15	522	27	46 (0.00)	69 (48-82)	5 (2-10)
	Retrograde	5	187	9	12 (0.02)	68 (17-88)	4 (0-11)
	Plate	14	835	5	20 (0.11)	34 (0-65)	1 (0-2)
	Open	8	598	3	13 (0.08)	44 (0-75)	1 (0-4)
	MIPO	6	237	2	6 (0.27)	22 (0-66)	1 (0-3)

Implant failure	**Non-operative**	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
	IMN	20	770	50	25 (0.15)	25 (0-56)	6 (4-9)
	Antegrade	12	404	30	19 (0.06)	43 (0-71)	6 (3-10)
	Retrograde	3	128	8	3 (0.24)	31 (0-93)	6 (2-12)
	Plate	43	1839	31	66 (0.01)	37 (8-56)	2 (2-3)
	Open	29	1480	22	47 (0.01)	41 (9-62)	2 (1-3)
	MIPO	14	359	9	16 (0.28)	16 (0-54)	3 (1-5)
Nail protrusion	**Non-operative**	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
	IMN	16	642	59	40 (0.00)	62 (35-78)	9 (6-14)
	Antegrade	10	380	29	27 (0.00)	66 (34-83)	9 (4-14)
	Retrograde	2	83	4	0 (0.87)	0 (0-0)	6 (1-11)
	Plate	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
	Open	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.
Implant removal	**Non-operative**	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
	IMN	30	1173	153	158 (0.00)	81 (74-87)	12 (8-16)
	Antegrade	20	723	92	91 (0.00)	79 (68-86)	12 (7-18)
	Retrograde	4	179	32	48 (0.00)	94 (87-96)	15 (0-40)
	Plate	36	1316	111	329 (0.00)	90 (87-92)	7 (3-12)
	Open	22	910	42	136 (0.00)	85 (78-89)	5 (1-9)
	MIPO	14	406	69	156 (0.00)	91 (88-94)	11 (2-24)
Subacromial impingement	**Non-operative**	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
	IMN	11	315	45	17 (0.07)	42 (0-72)	15 (10-20)
	Antegrade	9	247	33	14 (0.10)	40 (0-73)	14 (9-20)
	Retrograde	0	0	0	N.A.	N.A.	N.A.
	Plate	5	189	5	5 (0.27)	22 (0-68)	2 (0-6)
	Open	4	115	1	2 (0.54)	0 (0-79)	1 (0-4)
	MIPO	1	74	4	0 (0.00)	0 (0-0)	5 (1-12)
Shoulder dysfunction	**Non-operative**	2	82	5	14 (0.00)	93 (76-98)	8 (0-46)
	IMN	13	497	50	26 (0.01)	55 (16-76)	10 (6-15)
	Antegrade	11	386	46	17 (0.06)	43 (0-71)	12 (7-16)
	Retrograde	1	27	2	N.A.	N.A.	7 (0-21)
	Plate	8	331	24	18 (0.01)	60 (14-82)	5 (2-11)
	Open	6	3278	20	17 (0.00)	71 (32-87)	4 (0-11)
	MIPO	2	53	4	0 (0.64)	0 (0-0)	9 (2-17)
Elbow dysfunction	**Non-operative**	2	25	2	0 (0.56)	0 (0-0)	10 (0-23)
	IMN	9	456	11	13 (0.13)	37 (0-71)	2 (1-5)
	Antegrade	5	160	5	9 (0.06)	56 (0-84)	3 (0-8)
	Retrograde	2	101	3	3 (0.08)	68 (0-93)	2 (0-10)
	Plate	7	292	16	9 (0.18)	33 (0-72)	6 (3-10)
	Open	5	255	13	7 (0.13)	44 (0-79)	5 (2-10)
	MIPO	2	37	3	0 (0.36)	0 (0-0)	9 (1-20)

I^2, I^2-statistic for study heterogeneity; 95% CI, 95% confidence interval; IMN, intramedullary Nail; MIPO, minimally invasive plate osteosynthesis; N.A., not applicable.

Functional outcome scores

Functional outcome scores are shown in Table 4. The American Shoulder and Elbow Surgeons (ASES) score ranges from 0 to100 points, with a higher score representing better outcome.[20] The ASES score of the IMN (92 (95% CI 90-95)) and plating groups (94 (95% CI 91-97)) overlapped. The Constant-Murley score ranges from 0 to 100 points, with a higher score representing better outcome.[21] It was 92 (95% CI 87-97) for the IMN and 93 (95% CI 90-95) for the plating group. The Disabilities of the Arm, Shoulder and Hand (DASH) score ranges from 0 to 100 points, with a lower score representing better outcome.[22] Only the results of three studies describing the DASH score in open plate osteosynthesis were available for analysis. The DASH score in this treatment group was 15 (95% CI 3-27). The Mayo Elbow Performance Index (MEPI) ranges from 5 to 100 points, with a higher score representing better outcome.[23] MEPI scores were comparable after IMN (97 (95% CI 94-100)) and plate osteosynthesis (97 (95% CI 96-98)). The University of California at Los Angeles (UCLA) shoulder score ranges from 0 to 35 points, with a higher score representing better outcome.[24] Only for patients treated with plate osteosynthesis data were available. These showed no difference between open plating and MIPO (33 (95% CI 32-34) and 34 (95% CI 33-35), respectively).

For the non-operatively treated patient no data of functional outcome scores were available for analyses. The Broberg-Morrey, Gill, Hospital for Special Surgery, l'Insalata, Neer Shoulder, Oxford Shoulder, Rommens, Simple Shoulder Test and Short Musculoskeletal Functional Assessment scores, as well as the Hunter and Rodriguez-Merchan criteria did not have enough reported data for analyses.

Range of motion

No differences between the IMN and plate osteosynthesis groups were seen in shoulder abduction and anteflexion (Table 5). Anteflexion was betterafter MIPO than after open plating (166° (95% CI 164-168°) and 120° (95% CI 85-156°), respectively). Data on elbow function were only available for the plating group. These showed no difference in the elbow flexion – extension arc (overall 132° (95% CI 129-135°)) between the open plating and MIPO groups. For the non-operatively treated patient no data were available.

Table 4. Functional outcome scores

Instrument	Treatment	Studies N	Population N	Heterogeneity Cochran's Q (p-value)	Heterogeneity I^2 (%) (95% CI)	Pooled value (points) (95% CI)
ASES score	**Non-operative**	0	N.A.	N.A.	N.A.	N.A.
	IMN	3	74	11 (0.00)	81 (42-94)	92 (90-95)
	Antegrade	3	74	11 (0.00)	81 (42-94)	92 (90-95)
	Retrograde	0	N.A.	N.A.	N.A.	N.A.
	Plate	6	135	93 (0.00)	95 (91-97)	94 (91-97)
	Open	5	113	85 (0.00)	95 (92-97)	94 (91-98)
	MIPO	1	22	N.A.	N.A.	N.A.
Constant-Murley score	**Non-operative**	0	N.A.	N.A.	N.A.	N.A.
	IMN	7	243	1217 (0.00)	100 (99-100)	92 (87-97)
	Antegrade	5	184	24 (0.00)	84 (64-93)	91 (89-93)
	Retrograde	1	23	N.A.	N.A.	N.A.
	Plate	6	160	100 (0.00)	95 (92-97)	93 (90-95)
	Open	5	138	96 (0.00)	96 (93-98)	92 (89-96)
	MIPO	1	22	N.A.	N.A.	N.A.
DASH score	**Non-operative**	1	32	N.A.	N.A.	N.A.
	IMN	1	28	N.A.	N.A.	N.A.
	Antegrade	1	28	N.A.	N.A.	N.A.
	Retrograde	0	N.A.	N.A.	N.A.	N.A.
	Plate	3	132	106 (0.00)	98 (97-99)	15 (3-27)
	Open	3	132	106 (0.00)	98 (97-99)	15 (3-27)
	MIPO	0	N.A.	N.A.	N.A.	N.A.
MEPI	**Non-operative**	0	N.A.	N.A.	N.A.	N.A.
	IMN	4	194	62 (0.00)	97 (93-98)	97 (94-100)
	Antegrade	2	126	25 (0.00)	96 (88-99)	98 (95-100)
	Retrograde	2	68	0.96 (0.33)	0 (0-0)	100 (100-100)
	Plate	14	495	274 (0.00)	95 (93-97)	97 (96-98)
	Open	9	198	258 (0.00)	97 (95-98)	96 (95-97)
	MIPO	5	97	14 (0.01)	71 (26-88)	98 (97-100)

UCLA shoulder score	**Non-operative**	0	N.A.	N.A.	N.A.	N.A.
	IMN	1	19	N.A.	N.A.	N.A.
	Antegrade	1	19	N.A.	N.A.	N.A.
	Retrograde	0	N.A.	N.A.	N.A.	N.A.
	Plate	10	388	138 (0.00)	94 (91-96)	34 (33-34)
	Open	5	275	66 (0.00)	95 (91-98)	33 (32-34)
	MIPO	5	113	40 (0.00)	90 (80-95)	34 (33-35)

I^2, I^2-statistic for study heterogeneity; 95% CI, 95% confidence interval; ASES, American Shoulder and Elbow Surgeons; DASH, Disabilities of the Arm, Shoulder and Hand; MEPI, Mayo Elbow Performance Index; UCLA, University of California at Los Angeles; IMN, intramedullary Nail; MIPO, minimally invasive plate osteosynthesis; N.A., not applicable.

Table 5. Range of motion

		Studies	Population	Heterogeneity		Pooled value
		N	N	Cochran's Q (p-value)	I^2 (%) (95% CI)	(degrees) (95% CI)
Shoulder abduction	**Non-operative**	0	N.A.	N.A.	N.A.	N.A.
	IMN	2	34	307 (0.00)	100 (99-100)	132 (77-189)
	Antegrade	2	34	307 (0.00)	100 (99-100)	132 (77-189)
	Retrograde	0	N.A.	N.A.	N.A.	N.A.
	Plate	4	39	916 (0.00)	100 (100-100)	125 (86-164)
	Open	4	39	916 (0.00)	100 (100-100)	125 (86-164)
	MIPO	0	N.A.	N.A.	N.A.	N.A.
Shoulder anteflexion	**Non-operative**	0	N.A.	N.A.	N.A.	N.A.
	IMN	2	34	183 (0.00)	100 (99-100)	120 (33-207)
	Antegrade	2	34	183 (0.00)	100 (99-100)	120 (33-207)
	Retrograde	0	N.A.	N.A.	N.A.	N.A.
	Plate	9	134	4201 (0.00)	100 (100-100)	136 (112-160)
	Open	6	74	3583 (0.00)	100 (100-100)	120 (85-156)
	MIPO	3	60	1 (0.77)	0 (0-87)	166 (164-168)
Elbow flexion – extension arc	**Non-operative**	0	N.A.	N.A.	N.A.	N.A.
	IMN	0	N.A.	N.A.	N.A.	N.A.
	Antegrade	0	N.A.	N.A.	N.A.	N.A.
	Retrograde	0	N.A.	N.A.	N.A.	N.A.
	Plate	10	497	175 (0.00)	95 (92-96)	132 (129-135)
	Open	5	406	68 (0.00)	94 (89-97)	131 (127-135)
	MIPO	5	91	81 (0.00)	95 (91-97)	132 (125-139)
Elbow flexion	**Non-operative**	0	N.A.	N.A.	N.A.	N.A.
	IMN	0	N.A.	N.A.	N.A.	N.A.
	Antegrade	0	N.A.	N.A.	N.A.	N.A.
	Retrograde	0	N.A.	N.A.	N.A.	N.A.
	Plate	9	152	285 (0.00)	97 (96-98)	127 (122-131)
	Open	8	145	279 (0.00)	97 (96-98)	127 (123-132)
	MIPO	1	N.A.	N.A.	N.A.	N.A.

Elbow extension	**Non-operative**	0	N.A.	N.A.	N.A.	N.A.
	IMN	0	N.A.	N.A.	N.A.	N.A.
	Antegrade	0	N.A.	N.A.	N.A.	N.A.
	Retrograde	0	N.A.	N.A.	N.A.	N.A.
	Plate	8	133	16 (0.02)	57 (5-80)	4 (3-6)
	Open	7	126	15 (0.02)	59 (6-82)	4 (3-5)
	MIPO	1	N.A.	N.A.	N.A.	N.A.

I^2, I^2-statistic for study heterogeneity; 95% CI, 95% confidence interval; IMN, intramedullary Nail; MIPO, minimally invasive plate osteosynthesis; N.A., not applicable.

DISCUSSION AND CONCLUSIONS

The best treatment of humeral shaft fractures is still at debate. In this study complications, functional outcome scores and range of motion were compared . No differences in consolidation time and rates, as well as nonunion rates between non-operative treatment by functional bracing, IMN, and plate osteosynthesis of humeral shaft fractures were shown. A higher prevalence of iatrogenic radial nerve palsies was observed in patients treated by open plating than in patients treated non-operatively. Intraoperative complications and implant failures were more frequently reported in the IMN groups than in the plating group. Implant removal rates were comparable between patients treated by IMN and plate osteosynthesis. No differences were observed in ASES, Constant-Murley or MEPI scores after IMN or plating osteosynthesis treatment. Shoulder abduction and anteflexion did not differ between the IMN and plate groups. Anteflexion was better after MIPO than after open plating.

Each included study had different criteria for treating patients non-operatively or operatively. Despite the possible introduction of bias of treating patients with the more severe fracture types (*e.g.*, displaced, comminuted etc.) operatively, no apparent differences in fracture healing time, consolidation rate, infection, or malunion were found between the three treatment groups. Patients treated by open plating had a higher rate of iatrogenic radial nerve palsies than patients treated with a functional brace. However, patients treated by MIPO did not show a difference in the prevalence of iatrogenic radial nerve palsies compared with the non-operatively and IMN groups. Operative treatment might result in earlier functional recovery because it allows for early mobilization. The functional outcome scores and range of motion of patients treated non-operatively were unfortunately not available and could therefore not be included in the pooled analysis.

Chen et al. concluded that no significant differences in complications, secondary procedures and one-year mortality rates were found, comparing open plating and IMN.[25] Fan *et al.* however, found that the IMN group had a significantly lower mean union time than the locking compression plate. Radial nerve palsy was found to be higher in the plating group than in the IMN group.[26] These results differ from the current study, which found no differences in consolidation time between the three groups and a higher prevalence of iatrogenic radial nerve palsy in the patients treated with plating.

A meta-analysis of RCTs by Wang *et al.* described that both the number of complications and the functional measurements were better in the plating group than in the intramedullary nailing group, suggesting plating is superior than IMN.[27] A meta-analysis by Qiu *et al.* stated that MIPO was the better choice in treatment of humeral shaft fractures.[28] They reported the rate of radial nerve injury to be the highest in the IMN group and the lowest in the plating group. However, the current study showed a higher prevalence of iatrogenic radial nerve palsies in the plating group, but a higher rate of intraoperative complications and implant failures in the IMN group. Another meta-analysis by Hohmann et al. reported MIPO to be the better surgical approach since it has less complications and better clinical outcome than the open plating group and the IMN group.[29] These meta-analyses all have limitations since they only included randomized control trials of six to 17 published studies in total. The current study included all types of study designs, with a total of 114 studies available for analysis. Some limitations are the low methodological quality of the included studies as reflected by the MINORS scores. The studies meeting the inclusion criteria often had a small sample size without an adequate power calculation. 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. The results of this study should be interpreted with care given the large statistical and clinical heterogeneity.

Despite these limitations, one of the strengths of the current study is that 114 studies are included reporting the results of 8,431 patients. Randomized trials or high-quality observational studies comparing non-operative and operative treatment of humeral shaft fractures are scarce. By including all study designs valuable results of patients treated for a humeral shaft fractures could be analyzed.

A well-designed and powered prospective study is needed in order to better guide clinicians in the treatment of humeral shaft fractures. A more uniform reporting of outcome of treatment helps to compare the results of different studies. For instance, in the included studies 16 different functional outcome scores were reported. The use of many different instruments makes it hard to compare results. The authors of the current study propose to use the DASH score as an instrument to measure functional outcome. This is currently the only instrument validated to use in patient with a humeral shaft fracture.

The results of this systematic review and pooled analysis shows small variation in outcome and complications of the non-operative and operative treatment of patients with a humeral shaft fracture.

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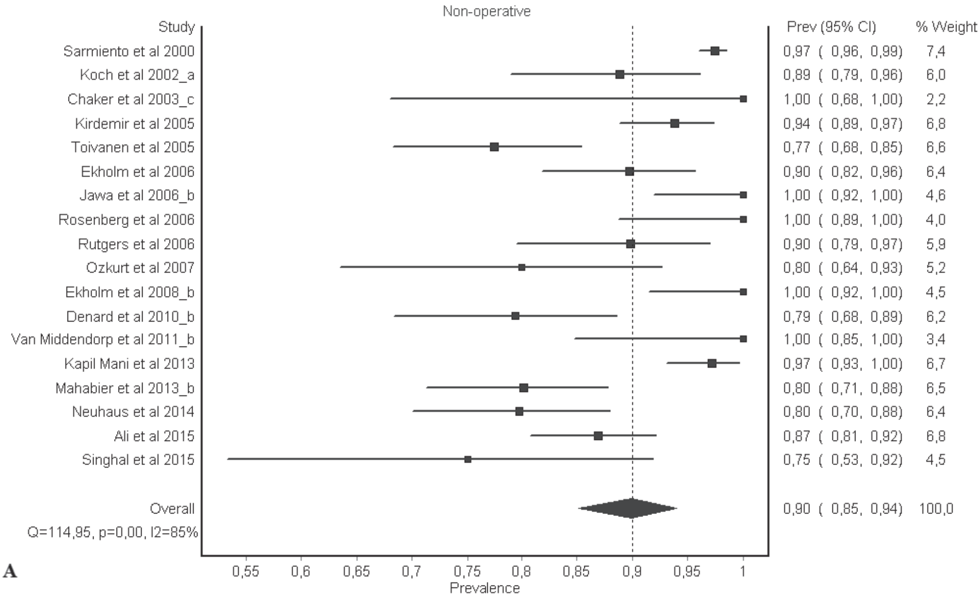
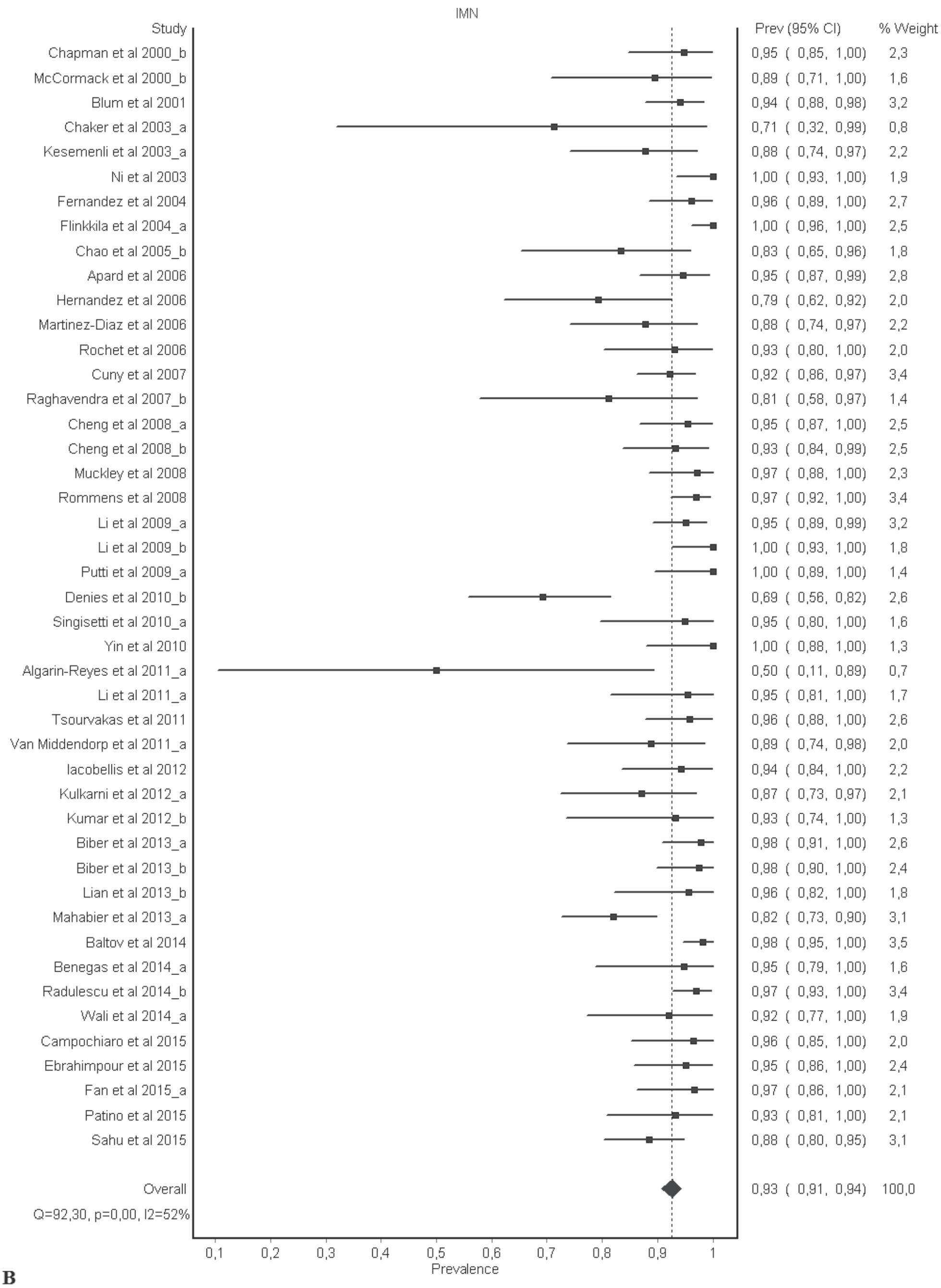
SUPPLEMENTAL FIGURES

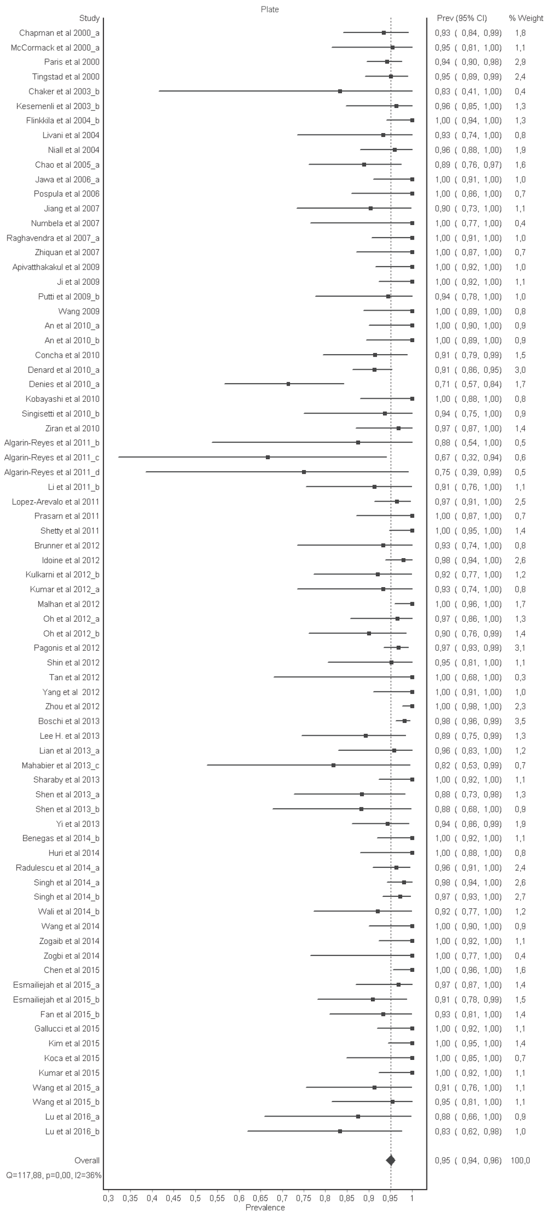
Supplemental Figure S1. Consolidation rate per treatment: non-operative (A), IMN (B) and plate osteosynthesis (C)



A


IMN
Study
Prev (95% CI)
% Weight
Chapman et al 2000_b 0,95 (0,85, 1,00) 2,3
McCormack et al 2000_b 0,89 (0,71, 1,00) 1,6
Blum et al 2001 0,94 (0,88, 0,98) 3,2
Chaker et al 2003_a 0,71 (0,32, 0,99) 0,8
Kesemenli et al 2003_a 0,88 (0,74, 0,97) 2,2
Ni et al 2003 1,00 (0,93, 1,00) 1,9
Fernandez et al 2004 0,96 (0,89, 1,00) 2,7
Flinkkila et al 2004_a 1,00 (0,96, 1,00) 2,5
Chao et al 2005_b 0,83 (0,65, 0,96) 1,8
Apard et al 2006 0,95 (0,87, 0,99) 2,8
Hernandez et al 2006 0,79 (0,62, 0,92) 2,0
Martinez-Diaz et al 2006 0,88 (0,74, 0,97) 2,2
Rochet et al 2006 0,93 (0,80, 1,00) 2,0
Cuny et al 2007 0,92 (0,86, 0,97) 3,4
Raghavendra et al 2007_b 0,81 (0,58, 0,97) 1,4
Cheng et al 2008_a 0,95 (0,87, 1,00) 2,5
Cheng et al 2008_b 0,93 (0,84, 0,99) 2,5
Muckley et al 2008 0,97 (0,88, 1,00) 2,3
Rommens et al 2008 0,97 (0,92, 1,00) 3,4
Li et al 2009_a 0,95 (0,89, 0,99) 3,2
Li et al 2009_b 1,00 (0,93, 1,00) 1,8
Putti et al 2009_a 1,00 (0,89, 1,00) 1,4
Denies et al 2010_b 0,69 (0,56, 0,82) 2,6
Singisetti et al 2010_a 0,95 (0,80, 1,00) 1,6
Yin et al 2010 1,00 (0,88, 1,00) 1,3
Algarin-Reyes et al 2011_a 0,50 (0,11, 0,89) 0,7
Li et al 2011_a 0,95 (0,81, 1,00) 1,7
Tsourvakas et al 2011 0,96 (0,88, 1,00) 2,6
Van Middendorp et al 2011_a 0,89 (0,74, 0,98) 2,0
Iacobellis et al 2012 0,94 (0,84, 1,00) 2,2
Kulkarni et al 2012_a 0,87 (0,73, 0,97) 2,1
Kumar et al 2012_b 0,93 (0,74, 1,00) 1,3
Biber et al 2013_a 0,98 (0,91, 1,00) 2,6
Biber et al 2013_b 0,98 (0,90, 1,00) 2,4
Lian et al 2013_b 0,96 (0,82, 1,00) 1,8
Mahabier et al 2013_a 0,82 (0,73, 0,90) 3,1
Baltov et al 2014 0,98 (0,95, 1,00) 3,5
Benegas et al 2014_a 0,95 (0,79, 1,00) 1,6
Radulescu et al 2014_b 0,97 (0,93, 1,00) 3,4
Wali et al 2014_a 0,92 (0,77, 1,00) 1,9
Campochiaro et al 2015 0,96 (0,85, 1,00) 2,0
Ebrahimpour et al 2015 0,95 (0,86, 1,00) 2,4
Fan et al 2015_a 0,97 (0,86, 1,00) 2,1
Patino et al 2015 0,93 (0,81, 1,00) 2,1
Sahu et al 2015 0,88 (0,80, 0,95) 3,1
Overall 0,93 (0,91, 0,94) 100,0
Q=92,30, p=0,00, I2=52%
0,1 0,2 0,3 0,4 0,5 0,6 0,7 0,8 0,9 1
Prevalence

B



C

IMN, intramedullary nail.

Chapter 5

Supplemental Table S1. Study characteristics

Publication	Study design	MINORS	Treatment per group	N	Males N (%)	Follow-up per group (months)	OTA/AO class (% of total) A	B	C
Benegas et al 2014[1]	RCT	23	IMN antegrade	19	14 (74)	12	47	21	32
			Plate MIPO	21	12 (57)	12	57	33	10
Singh et al 2014[2]	Retrospective	21	Plate open	102	73 (72	12	51	39	10
			Plate open	110	75 (68)	12	50	39	11
Yin et al 2014[3]	Retrospective	21	Plate open	30	16 (53)	16	17	53	30
			Plate open	26	14 (54)	16	23	46	31
Neuhaus et al 2014[4]	Retrospective	13	Non-operative	79	46 (58)	9	100	0	0
Baltov et al 2014[5]	Retrospective	13	IMN antegrade and retrograde	111	71 (64)	42	34	41	25
Lee T. et al 2013[6]	Prospective	12	Plate open	35	26 (74	28	n.r.	n.r.	n.r.
Tyllianakis et al 2013[7]	Retrospective	12	IMN antegrade	64	33 (52)	78	56	34	10
Lian et al 2013[8]	RCT	21	Plate MIPO	24	15 (63)	14	38	38	24
			IMN antegrade and retrograde	23	16 (70)	15	35	52	13
Verdano et al 2013[9]	Retrospective	12	IMN antegrade	48	26 (54)	33	n.r.	n.r.	n.r.
Wang et al 2013[10]	RCT	20	IMN antegrade	22	16 (73)	18	45	41	14
			Plate open	23	16 (70)	18	22	52	26
Yi et al 2013[11]	Prospective	13	Plate open	53	34 (64)	17	74	26	0
Lee H. et al 2013[12]	Retrospective	12	Plate MIPO	28	19 (68)	21	24	59	17
Kapil Mani et al 2013[13]	Prospective	11	Non-operative	108	63 (58)	n.r.	n.r.	n.r.	n.r.
Shen et al 2013[14]	Retrospective	20	Plate MIPO	26	18 (69)	32	19	58	23
			Plate MIPO	17	10 (59)	17	35	30	35
Sharaby et al 2013[15]	Prospective	14	Plate open	22	15 (68)	25	55	36	9
Biber et al 2013[16]	Retrospective	19	IMN antegrade	46	22 (48)	n.r.	n.r.	n.r.	n.r.
			IMN retrograde	41	34 (83)	n.r.	n.r.	n.r.	n.r.
Chen et al 2013[17]	Retrospective	21	Plate open	172	42 (21)	12	n.r.	n.r.	n.r.
			IMN antegrade and retrograde	279	77 (25)	12	n.r.	n.r.	n.r.
Malhan et al 2012[18]	Prospective	12	Plate MIPO	42	28 (67)	25	62	38	0
Kulkarni et al 2012[19]	Prospective	21	IMN antegrade	31	25 (81)	10	52	45	3
			Plate open	25	19 (76)	12	68	32	0
Boschi et al 2013[20]	Retrospective	13	Plate open	280	280 (100)	101	75	25	0
Zhou et al 2012[21]	Retrospective	11	Plate MIPO	74	26 (35)	17	12	61	27
Firat et al 2012[22]	Retrospective	20	Plate open	36	20 (56)	74	78	19	3
			IMN antegrade	30	23 (77)	74	87	13	0
			Non-operative	62	38 (61)	74	85	12	3

Mahabier et al 2013[23]	Retrospective	17	IMN antegrade and retrograde	78	32 (41)	n.r.	n.r.	n.r.	n.r.
			Plate open	11	6 (55)	n.r.	n.r.	n.r.	n.r.
			Non-operative	91	36 (40)	n.r.	n.r.	n.r.	n.r.
Tan et al 2012[24]	Retrospective	10	Plate MIPO	5	5 (100)	6	60	40	0
Shin et al 2012[25]	Prospective	13	Plate MIPO	21	13 (62)	17	52	43	5
Algarin-Reyes et al 2011[26]	Retrospective	20	IMN antegrade	6	2 (33)	3	67	33	0
			Plate open	8	4 (50)	3	25	38	38
			Plate open	9	6 (67)	3	44	34	22
			Plate open	8	7 (88)	3	25	75	0
Pagonis et al 2012[27]	Retrospective	12	Plate open	158	40 (22)	163	61	14	25
Oh et al 2012[28]	Retrospective	19	Plate MIPO	29	16 (55)	18	38	38	24
			Plate open	30	16 (53)	22	50	27	23
Shetty et al 2011[29]	Prospective	15	Plate MIPO	32	19 (59)	31	28	31	41
Yang et al 2012[30]	Prospective	12	Plate open	19	15 (79)	17	47	42	11
Iacobellis et al 2012[31]	Prospective	14	IMN antegrade	35	14 (40)	24	40	31	29
Grass et al 2011[32]	Retrospective	12	IMN antegrade	24	18 (47)	25	n.r.	n.r.	n.r.
Brunner et al 2012[33]	Retrospective	11	Plate MIPO	15	7 (47)	27	33	47	20
Tsourvakas et al 2011[34]	Prospective	13	IMN antegrade	48	36 (69)	18	42	31	27
Idoine et al 2012[35]	Retrospective	12	Plate open	96	55 (57)	58	n.r.	n.r.	n.r.
Lopez-Arevalo et al 2011[36]	Retrospective	11	Plate MIPO	86	60 (70)	n.r.	51	40	9
Li et al 2011[37]	RCT	23	IMN antegrade	22	16 (73)	12	45	41	14
			Plate open	23	16 (70)	12	22	52	26
Denies et al 2010[38]	Retrospective	18	Plate open	42	25 (60)	n.r.	55	35	10
			IMN antegrade and retrograde	49	21 (43)	n.r.	65	29	6
Kirin et al 2011[39]	Retrospective	9	Plate open	420	340 (81)	n.r.	n.r.	n.r.	n.r.
Prasarn et al 2011[40]	Retrospective	11	Plate open	13	7 (47)	30	40	33	27
Denard et al 2010[41]	Retrospective	19	Plate open	150	82 (55)	8	n.r.	n.r.	n.r.
			Non-operative	63	34 (54)	7	n.r.	n.r.	n.r.
Ziran et al 2010[42]	Retrospective	12	Plate MIPO	32	n.r.	16	n.r.	n.r.	n.r.
Kobayashi et al 2010[43]	Prospective	14	Plate MIPO	14	11 (79)	14	36	64	0
Apivatthakakul et al 2009[44]	Retrospective	11	Plate MIPO	20	16 (70)	14	20	25	55
Concha et al 2010[45]	Prospective	12	Plate MIPO	35	26 (74)	12	20	29	51
Wang 2009[46]	Retrospective	10	Plate MIPO	15	11 (73)	10	40	53	7
Putti et al 2009[47]	RCT	20	IMN antegrade	16	n.r.	24	n.r.	n.r.	n.r.
			Plate open	18	n.r.	24	n.r.	n.r.	n.r.
Singisetti et al 2010[48]	Prospective	19	IMN antegrade	20	n.r.	12	n.r.	n.r.	n.r.
			Plate open	16	n.r.	12	n.r.	n.r.	n.r.
Li et al 2009[49]	Retrospective	17	IMN antegrade	82	59 (72)	n.r.	60	10	30
			IMN retrograde	23	19 (83)	n.r.	65	0	35

An et al 2010[50]	Retrospective	17	Plate MIPO	17	12 (71)	26	n.r.	n.r.	n.r.
			Plate open	16	9 (56)	33	n.r.	n.r.	n.r.
Ekholm et al 2008[51]	Retrospective	9	Non-operative	20	5 (25)	n.r.	n.r.	n.r.	n.r.
Cheng et al 2008[52]	RCT	23	IMN antegrade	44	26 (59)	19	64	29	7
			IMN retrograde	45	28 (62)	20	80	15	5
Rommens et al 2008[53]	Retrospective	12	IMN antegrade and retrograde	99	36 (36)	28	43	41	16
Ji et al 2009[54]	Retrospective	12	Plate MIPO	22	n.r.	17	n.r.	n.r.	n.r.
Muckley et al 2008[55]	Prospective	14	IMN antegrade and retrograde	36	21 (58)	22	36	58	6
Numbela et al 2007[56]	Prospective	11	Plate MIPO	7	n.r.	12	0	72	28
Cuny et al 2007[57]	Retrospective	12	IMN antegrade	104	62 (42)	32	55	30	15
Zhiquan et al 2007[58]	Prospective	13	Plate MIPO	13	9 (69)	13	8	77	15
Raghavendra et al 2007[59]	Prospective	20	Plate open	18	17 (94)	n.r.	89	11	0
			IMN antegrade	16	15 (83)	n.r.	61	39	0
Ozkurt et al 2007[60]	Prospective	11	Non-operative	30	19 (63)	20	n.r.	n.r.	n.r.
Jiang et al 2007[61]	Prospective	13	Plate MIPO	21	14 (67)	29	0	0	100
Rochet et al 2006[62]	Retrospective	12	IMN antegrade	29	18 (62)	36	n.r.	n.r.	n.r.
Rutgers et al 2006[63]	Retrospective	12	Non-operative	49	25 (51)	14	n.r.	n.r.	n.r.
Ekholm et al 2006[64]	Retrospective	12	Non-operative	78	33 (42)	26	50	33	17
Jawa et al 2006[65]	Retrospective	19	Plate open	19	11 (58)	21	n.r.	n.r.	n.r.
			Non-operative	21	9 (43)	21	n.r.	n.r.	n.r.
Pospula et al 2006[66]	Retrospective	10	Plate MIPO	12	11 (92)	n.r.	n.r.	n.r.	n.r.
Rosenberg et al 2006[67]	Prospective	12	Non-operative	15	10 (67)	30	60	27	13
Apard et al 2006[68]	Prospective	13	IMN retrograde	56	30 (52)	10	57	24	19
Chao et al 2005[69]	Retrospective	18	Plate open	36	20 (56)	92	n.r.	n.r.	n.r.
			IMN antegrade	24	15 (63)	20	n.r.	n.r.	n.r.
Toivanen et al 2005[70]	Retrospective	11	Non-operative	93	38 (41)	n.r.	89	11	0
Flinkkila et al 2004[71]	Retrospective	18	IMN antegrade	44	24 (55)	66	68	27	5
			Plate open	29	18 (62)	74	66	34	0
Livani et al 2004[72]	Prospective	13	Plate MIPO	15	11 (73)	24	33	47	20
Niall et al 2004[73]	Retrospective	10	Plate open	49	30 (61)	n.r.	61	37	2
Fernandez et al 2004[74]	Prospective	12	IMN retrograde	51	31 (61)	15	69	29	2
Ni et al 2003[75]	Retrospective	13	IMN antegrade and retrograde	26	19 (73)	16	84	12	4
Chaker et al 2003[76]	Retrospective	18	IMN retrograde	7	7 (39)	38	n.r.	n.r.	n.r.
			Plate open	6	6 (33)	38	n.r.	n.r.	n.r.
			Non-operative	5	5 (28)	38	n.r.	n.r.	n.r.

Kesemenli et al 2003[77]	Prospective	18	IMN antegrade	33	24 (73)	42	n.r.	n.r.	n.r.
			Plate open	27	19 (70)	42	n.r.	n.r.	n.r.
Koch et al 2002[78]	Retrospective	9	Non-operative	54	35 (65)	n.r.	59	26	15
			Non-operative	13	n.r.	n.r.	67	25	8
Blum et al 2001[79]	Prospective	12	IMN antegrade and retrograde	84	46 (55)	12	53	36	11
Tingstad et al 2000[80]	Retrospective	9	Plate open	82	44 (54)	n.r.	n.r.	n.r.	n.r.
Paris et al 2000[81]	Retrospective	10	Plate open	138	95 (61)	n.r.	n.r.	n.r.	n.r.
McCormack et al 2000[82]	RCT	21	Plate open	22	15 (65)	14	35	48	17
			IMN antegrade and retrograde	19	13 (62)	14	48	38	14
Chapman et al 2000[83]	RCT	19	Plate open	46	25 (54)	12	n.r.	n.r.	n.r.
			IMN antegrade	38	26 (68)	15	n.r.	n.r.	n.r.
Sarmiento et al 2000[84]	Prospective	11	Non-operative	620	391 (63)	n.r.	n.r.	n.r.	n.r.
Kumar et al 2012[85]	Prospective	17	Plate open	15	10 (67)	n.r.	93	7	0
			IMN antegrade	15	8 (53)	n.r.	67	33	0
Yin et al 2010[86]	Retrospective	12	IMN antegrade and retrograde	14	14 (77)	11	n.r.	n.r.	n.r.
Hernandez et al 2006[87]	Retrospective	11	IMN antegrade	29	21 (60)	5	63	37	0
Martinez-Diaz et al 2006[88]	Retrospective	11	IMN antegrade	33	7 (21)	15	79	15	6
Kirdemir et al 2005[89]	Retrospective	13	Non-operative	129	85 (66)	13	n.r.	n.r.	n.r.
Van Middendorp et al 2011[90]	Prospective	22	IMN retrograde	27	19 (58)	12	70	30	0
			Non-operative	11	5 (36)	12	79	21	0
Lu et al 2016[91]	Retrospective	18	Plate open	16	10 (67)	12	50	31	19
			Plate open	18	12 (63)	12	56	22	22
Lee et al 2016[92]	Retrospective	21	Plate MIPO	24	15 (63)	25	n.r.	n.r.	n.r.
			Plate open	28	18 (64)	26	n.r.	n.r.	n.r.
Shields et al 2015[93]	Retrospective	12	Non-operative	32	n.r.	47	63	34	3
Singhal et al 2015[94]	Retrospective	12	Non-operative	20	10 (50)	3	70	15	15
Koca et al 2015[95]	Retrospective	11	Plate open	11	7 (64)	14	0	100	0
Esmailiejah et al 2015[96]	Prospective	20	Plate MIPO	32	24 (75)	n.r.	31	28	41
			Plate open	33	8 (25)	n.r.	36	31	33
Wang et al 2015[97]	Prospective	20	Plate open	23	16 (70)	n.r.	22	52	26
			Plate MIPO	22	14 (64)	n.r.	23	36	41
Gallucci et al 2015[98]	Retrospective	13	Plate MIPO	21	13 (62)	22	0	95	5
Fan et al 2015[99]	RCT	19	IMN antegrade	30	18 (60)	n.r.	37	46	17
			Plate open	30	19 (63)	n.r.	40	50	10
Ebrahimpour et al 2015[100]	Prospective	14	IMN antegrade	41	34 (83)	12	n.r.	n.r.	n.r.
Kim et al 2015[101]	Retrospective	12	Plate open	31	31 (100)	16	74	19	7
Sahu et al 2015[102]	Prospective	12	IMN antegrade	78	65 (83)	n.r.	n.r.	n.r.	n.r.

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Campochiaro et al 2015[103]	Retrospective	12	IMN antegrade	28	9 (32)	19	0	89	11
Patino et al 2015[104]	Retrospective	12	IMN antegrade	30	20 (67)	36	73	24	3
Radulescu et al 2014[105]	Prospective	17	Plate open	82	n.r.	n.r.	n.r.	n.r.	n.r.
			IMN antegrade	102	n.r.	n.r.	n.r.	n.r.	n.r.
Zogbi et al 2014[106]	Retrospective	12	Plate MIPO	7	5 (71)	30	n.r.	n.r.	n.r.
Wang et al 2014[107]	Retrospective	11	Plate MIPO	17	11 (65)	17	6	88	6
Wali et al 2014[108]	RCT	17	IMN antegrade	25	21 (84)	n.r.	64	24	12
			Plate open	25	20 (80)	n.r.	68	24	8
Kumar et al 2015[109]	Prospective	12	Plate open	22	n.r.	15	32	59	9
Huri et al 2014[110]	Retrospective	11	Plate open	14	8 (62)	18	50	36	14
Chen et al 2015[111]	Retrospective	12	Plate open	39	15 (35)	37	14	28	58
Ali et al 2015[112]	Retrospective	10	Non-operative	138	71 (46)	n.r.	n.r.	n.r.	n.r.
Zogaib et al 2014[113]	Retrospective	13	Plate MIPO	22	15 (56)	52	n.r.	n.r.	n.r.
Aydin et al 2013[114]	Retrospective	11	Non-operative	5	5 (100)	n.r.	n.r.	n.r.	n.r.

RCT, randomized controlled trial; IMN, intramedullary nail; MIPO, minimally invasive plate osteosynthesis; n.r., not reported.

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Chapter 6

Reliability, validity, responsiveness, and minimal important change of the Disabilities of the Arm, Shoulder and Hand and Constant-Murley scores in patients with a humeral shaft fracture

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ABSTRACT

Background: The Disabilities of the Arm, Shoulder and Hand (DASH) and Constant-Murley scores are commonly used instruments. The DASH is patient reported, and the Constant-Murley combines a clinician reported and a patient-reported part. For patients with a humeral shaft fracture, their validity, reliability, responsiveness, and Minimal Important Change (MIC) have not been published. This study evaluated the measurement properties of these instruments in patients who sustained a humeral shaft fracture.

Methods: The DASH and Constant-Murley instruments were completed five times until one year after trauma. Pain score, Short Form 36, and EuroQol-5D were completed for comparison. Internal consistency was determined by the Cronbach α. Construct and longitudinal validity were evaluated by assessing hypotheses about expected Spearman rank correlations in scores and change scores, respectively, between patient-reported outcome measures (sub)scales. The Smallest Detectable Change (SDC) was calculated. The MIC was determined using an anchor-based approach. The presence of floor and ceiling effects was determined.

Results: A total of 140 patients were included. Internal consistency was sufficient for DASH (Cronbach $\alpha = 0.96$), but was insufficient for Constant-Murley ($\alpha = 0.61$). Construct and longitudinal validity were sufficient for both patient-reported outcome measures (>75% of correlations hypothesized correctly). The MIC and SDC were 6.7 (95% confidence interval 5.0-15.8) and 19.0 (standard error of measurement, 6.9), respectively, for DASH and 6.1 (95% confidence interval, -6.8 to 17.4) and 17.7 (standard error of measurement, 6.4), respectively, for Constant-Murley.

Conclusions: The DASH and Constant-Murley are valid instruments for evaluating outcome in patients with a humeral shaft fracture. Reliability was only shown for the DASH, making this the preferred instrument. The observed MIC and SDC values provide a basis for sample size calculations for future research.

INTRODUCTION

Patient-reported outcome measures (PROMs) are becoming increasingly important instruments to evaluate clinical outcome and functional recovery from the patient's perspective.[1] An advantage of generic quality of life PROMs, such as like the Short Form 36 (SF-36) and EuroQoL-5D (EQ-5D), is that they allow comparison across populations with different medical conditions. Region-specific instruments give insight in disabilities, pain, and problems caused by a specific disease or condition. Some instruments combine a patient-reported part with a clinician-reported part. Effects of treatment can be monitored over time with all three types of instruments, and they can be used to compare different treatment strategies. Instruments should only be used if proven reliable and valid.

The Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire is a region-specific PROM developed in 1996 by a collaborative effort of researchers of the American Academy of Orthopedic Surgeons, and the Institute for Work and Health.[2] It was designed to describe disability experienced by patients with any musculoskeletal condition of the upper extremity and to monitor change in symptoms and upper limb function over time.[3] The DASH outcome measure has been validated in more than 15 languages in patients with a number of upper extremity musculoskeletal disorders, including rheumatoid arthritis and shoulder impingement syndrome.[2, 4] Normative data have been established for the American and Norwegian populations.[2, 5] The Dutch version of the DASH (DASH-DLV) has also been validated in patients with a range of upper extremity disorders.[6]

The Constant-Murley score was developed in 1987 and is currently one of the most-used scales for shoulder (dys)function.[7] The Constant-Murley score evaluates shoulder function by including clinician-assessed physical examination findings and patient-reported assessments. It has been validated for different shoulder pathologies[8, 9] but is also widely used for reporting outcome of patients with a humeral shaft fracture.[10-15]

Although the DASH and Constant-Murley scores have been validated for a number of upper extremity disorders, including shoulder disorders, the measurement properties in the specific population of patients with a humeral shaft fracture are unknown. Also, the Minimal Important Change (MIC) for patients with this injury has not been published before. Knowing this value is important because it may be used as an input parameter for calculating sample sizes for future clinical studies.

The aim of this study was therefore to evaluate the measurement properties of the DASH and Constant-Murley scores in patients who sustained a humeral shaft fracture by comparing them with those of general health-related quality of life instruments subscales (*i.e.*, SF-36 and EuroQoL-5D) and pain measured with a visual analog scale (VAS).

MATERIALS AND METHODS

Data of the first 140 consecutive patients included in a multicenter, prospective cohort study comparing operative and nonoperative treatment of adults with a humeral shaft fracture were used. This study is registered at the Netherlands Trial Register (NTR3617). The study protocol for this trial has been published elsewhere.[16] The medical research ethics committees of all hospitals approved this study, and all patients provided signed informed consent.

Study population

Patients aged 18 years or older presenting with a humeral shaft fracture (AO type 12-A or 12-B) to the Emergency Department of one of 32 participating hospitals in the Netherlands were included. Exclusion criteria were pathological, recurrent, or open fractures, concomitant injuries affecting treatment and rehabilitation of the affected arm, treatment with an external fixator, neurovascular injuries requiring immediate surgery (excluding radial nerve palsy), additional traumatic injuries of the affected arm that influenced upper extremity function, impaired upper extremity function before to the injury, retained hardware around the affected humerus, rheumatoid arthritis, any bone disorder possibly impairing bone healing (excluding osteoporosis), problems of ensuring follow-up (*e.g.*, no fixed address or cognitive impairment), or insufficient comprehension of the Dutch language.

Questionnaires and follow-up measurement

Patients were asked to complete the DASH Dutch language version questionnaire (DASH-DVL),[6] the Constant-Murley score [7], the VAS for the level of pain, EQ-5D,[17] and SF-36[18] at two and six weeks and at three, six, and 12 months after initiation of treatment.

The DASH questionnaire was developed to describe disability experienced by patients with any musculoskeletal condition of the upper extremity and to monitor change in symptoms and upper limb function over time.[4] The DASH questionnaire consists of 30 items, scored 1-5. The DASH score is calculated using the formula: ([sum of all item/number of questions answered] - 1) x 25. The overall score ranges from 0 to 100 points. High scores represent higher disability. Patients needed to have completed at least 27 of 30 of the disability/symptom items of the DASH questionnaire to enable calculation of a total DASH score.[19] The DASH questionnaire has two optional four-item modules enabling measurement of symptoms and upper extremity dysfunction in athletes, performing artists, and other workers whose jobs require more advanced physical activity. These optional modules were not used because they did not apply to the current study population.

The Constant-Murley score evaluates shoulder function by including clinician-assessed physical examination findings and patient-reported assessments.[8] The right and left shoulder are evaluated independently by two clinician-reported items assessing range of motion (ROM) and power and two patient-reported items for pain and activities of daily life (ADL). These are summarized in four dimensions (Constant-Murley pain, ADL, ROM, and power) to create a Constant-Murley total score of 0 to 100 points (15 for pain, 20 for ADL, 40 for ROM, and 25 for power), with a higher score representing a better function. The power subscale was set to zero in patients who were unable to reach 90° abduction or who reported pain during the power measurement. Scores were not normalized to age. Detailed calculations of the Constant-Murley (sub)scales are published elsewhere.[7]

The VAS is used to measure a variety of continuum outcomes. In this study, it was used to measure level of pain. Patients were asked to rate level of pain at each follow-up evaluation by putting a mark on a horizontal line, 100 mm in length, with word descriptors at each end (‘no pain’ at 0 mm and ‘worst pain imaginable’ at 100 mm).[20]

The SF-36 is a validated health survey with 36 questions that represent eight health domains that are combined into a Physical Component Summary (PCS) and a Mental Component Summary (MCS). The score ranges from 0 to 100, with higher scores representing higher quality of life. The scores are converted and compared with the norms for the general population of the United States. The SF-36 is the most widely PROM for assessing general health.[18, 21] A validated Dutch version was used.[22]

The EQ-5D is a standardized instrument for measuring health outcome. It consists of two parts: the EQ-5D utility score (US), and the EQ Visual Analog Scale (EQ-VAS). The EQ-5D US ranges from 0 to 1 and the EQ-VAS ranges from 0 to 100. For both scores, a higher score represents a higher quality of life.[23] A validated Dutch version was used.[17]

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 21 or higher software (IBM Corp., Armonk, NY, USA). Receiver operating characteristic (ROC) and Youden index were analysed using MedCalc 14.10.2 software (MedCalc Software, Ostend, Belgium). As the raw data for individual items were analyzed, missing data were not imputed.

The measurement properties of the DASH and Constant-Murley scores were determined by comparing them with those of the general health-related quality of life instruments subscales on the SF-36 and EQ-5D and pain measured with a VAS.

Reliability was determined by evaluating internal consistency. The data at six months were used because the largest heterogeneity (ranging from substantial limitation to full recovery) in scores were expected at that time. At an earlier moment, most patients were expected to have substantial functional disability, and at a later time a ceiling effect was expected owing to a large proportion of full recovery. Internal consistency is defined as the extent to which items in a (sub)scale are intercorrelated, thus measuring the same concept.[24] The correlation between items on a (sub)scale was evaluated by calculating the Cronbach α for every (sub)scale. Internal consistency was considered sufficient if the value for Cronbach α was between 0.70 and 0.95, provided that the scale is unidimensional. This analysis requires a sample size of 10 per item in the instrument, with a minimum of 100 patients.[24]

Construct validity represents the extent to which scores on a specific questionnaire relate to other measures in a way that is in agreement with prior theoretically derived hypotheses concerning the concepts that are being measured.[24] The six-months data were used. Continuous data were tested for normality using the Shapiro-Wilk test and by inspecting the quantile-quantile plots. Because the continuous variables were not normally distributed, Spearman rank correlations of the DASH with the (sub)scales of the Constant-Murley score, EQ-5D, and SF-36 scores were calculated to assess DASH construct validity. Correlation coefficients above 0.6, between 0.6 and 0.3, and less than 0.3 were considered high, moderate, and low, respectively.[25] A high correlation between the DASH score and Constant-Murley total and subscale scores with all other (sub)scales or items measuring physical health and functioning (*i.e.*, SF-36 Physical Functioning [PF], SF-36 PCS, EQ-5D ADL, and EQ-5D US) was anticipated. In addition, a moderate-to-low correlation was expected between the SF-36 MCS and the (sub)scales of all other PROMs. A moderate correlation of VAS pain with all other (sub)scales was expected. Finally, we hypothesized that the other individual pain measures (*i.e.*, the Constant-Murley pain subscale, the SF-36 Bodily Pain [BP] subscale, and the EQ-5D pain item) would correlate highly with one another. Construct validity was considered sufficient if at least 75% of the results were in accordance with predefined hypotheses in a (sub)sample of at least 50 patients.[24]

Responsiveness refers to the ability of a questionnaire to detect clinically important changes over time.[24] This was evaluated by assessing longitudinal validity, which refers to the extent to which change in one measurement instrument relates to corresponding change in a reference measure.[26] In addition, the effect size (ES) and standardized response mean (SRM) were determined as measures of the magnitude of change over time.

Longitudinal validity was evaluated by testing predefined hypotheses about expected correlations between DASH and Constant-Murley change scores and the change scores of the EQ-5D and SF-36 (sub)scales. Change scores were calculated as the difference in score from the first to the last follow-up of all instruments that were completed (*i.e.*, six weeks to 12 months). Normality was tested according to the Shapiro-Wilk test and by inspecting the quantile-quantile plots. Correlation coefficients above 0.6, between 0.6 and 0.3, and less than 0.3 were considered high, moderate, and low, respectively.[26] Apart from the Constant-Murley total score, SF-36 BP, and SF-36 PCS, none of the continuous variables showed a normal distribution. Therefore, nonparametric Spearman rank correlations were calculated for all variables of interest. A moderate-to-high correlation between the change scores of the DASH score, the Constant-Murley total score, and the change scores of all other (sub)scales or items measuring physical health and functioning (*i.e.*, SF-36 PF, SF-36 PCS, EQ-5D ADL, and EQ US) was anticipated. A moderate-to-high correlation between the individual pain measures (*i.e.*, Constant-Murley pain subscale, SF-36 BP subscale, and EQ-5D pain item) was expected. Longitudinal validity was considered sufficient if at least 75% of the results were in accordance with predefined hypotheses in a (sub)sample of at least 50 patients.[24]

The ES was calculated by dividing the mean change in score between two time points (*i.e.*, score at 12 months minus the score at six weeks) divided by the standard deviation of the first measurement.[27] The SRM was calculated by dividing the mean change in score between two time points (*i.e.*, score at 12 months minus the score at six weeks) divided by the standard deviation of this change.[27] These effect estimates were interpreted according to Cohen: a value of 0.2 to 0.4 is considered a small, 0.5 to 0.7 a moderate, and ≥ 0.8 a large effect.[25] A large ES was expected a priori because patients were expected to have substantial functional limitations at six weeks, whereas large improvement was expected at 12 months for most patients.

Floor and ceiling effects are present if more than 15% of the study population rates the lowest (floor effect) or highest (ceiling effect) possible score on any PROM (sub)scale.[28] This might limit content validity and responsiveness. In the presence of floor and ceiling effects, items might be missing from the upper or lower ends of the scale, reducing content validity. Likewise, patients with the highest or lowest scores cannot be distinguished from one another, indicating limited reliability.[24] Data of all follow-up moments were evaluated separately.

The MIC represents the smallest measurable change in an outcome score that is perceived significant by patients. This was calculated using an anchor-based method. Patients were asked to complete an 'anchor question' or 'transition item' at six weeks and at three, six, and 12 months evaluating their perception of change in the general condition of the affected upper limb. The question was: "How is your affected upper arm at this point, in comparison to the previous follow-up moment?" The item scored from 1 "much better" through 2 "a little better", 3 "more or less the same (no change)", 4 "a little worse" and 5 "much worse". The anchor or transition item was considered sufficient if a Spearman rank correlation (r) exceeding 0.29 between the anchor and the change score of the PROM could be demonstrated.[29] The change score (score at last follow-up minus the score at completion of the transition item) of patients who selected "a little better" on the transition item was considered the MIC.

The MIC was calculated for the total scores by plotting the ROC curve of the change in score for patients who scored "a little better" on the transition item compared with patients who scored "more or less the same (no change)." The area under the ROC curve is provided as a measure of discriminatory power. The optimal ROC cutoff point calculated with the Youden index reflected the value of the MIC. The Youden index is shown with its 95% confidence interval (CI) after bootstrapping (1,000 replicates and 900 random-number seeds).

The smallest intrapersonal change in score that represents (with $P < .05$) a "real" difference above measurement error is defined by the Smallest Detectable Change (SDC) of a measurement instrument.[1] This was based on the change scores of patients who answered "more or less the same/no change" on the transition item; patients were assumed to be stable in the interim period. For the individual patient, the SDC was derived from the standard error of measurement (SEM) according to the following formula: $SDC = 1.96 \times \sqrt{2} \times SEM$. SEM was calculated as $SD_{change} / \sqrt{2}$. Ideally, for evaluative purposes, the SDC should be smaller than the MIC[24]

RESULTS

Study population

This study population comprised 140 patients who sustained a humeral shaft fracture; of these, 19 patients were lost to follow-up (four after two weeks follow-up, five after six weeks, six after three months, and four after six months). In addition, seven patients missed one follow-up visit (five missed two weeks, one six weeks, and one six months). The median age was 58 years (25th percentile-75th percentile, 41-68) and 63 patients (45.0%) were male. The right arm was affected in 65 patients (46.4%), and the dominant arm was affected in 64 patients (45.7%).

The changes over time in DASH, Constant-Murley total and subscales, and VAS pain of patients with a humeral shaft fracture are shown in Fig. 1. All scores showed a decrease in symptoms, disability,y or pain over time, except for the Constant-Murley pain subscale, which displayed a similar score at all follow-up assessments. The change in SF-36 PCS, SF-36 MCS, EQ-5D US, and EQ-5D VAS scores over time is shown in Fig 2. The PROM (sub)scales scores measuring physical health and general health (SF-36 PCS and EQ-5D US) increased over time, but the mental health-related quality of life and the perception of health-related quality of life state (SF-36 MCS and EQ-5D VAS) were stable over time.

Reliability

The Cronbach α value of DASH score (α = 0.96) was sufficient, indicating high correlation among the 30 items (Table 1). Cronbach α values of the Constant-Murley ROM subscale (α=0.88) also indicated sufficient internal consistency. Internal consistency of the Constant-Murley total score (α = 0.61) and the Constant-Murley ADL subscale (α = 0.60) was insufficient. No Cronbach α was determined for the Constant-Murley pain and power subscales, because internal consistency does not apply to a single-item domain.

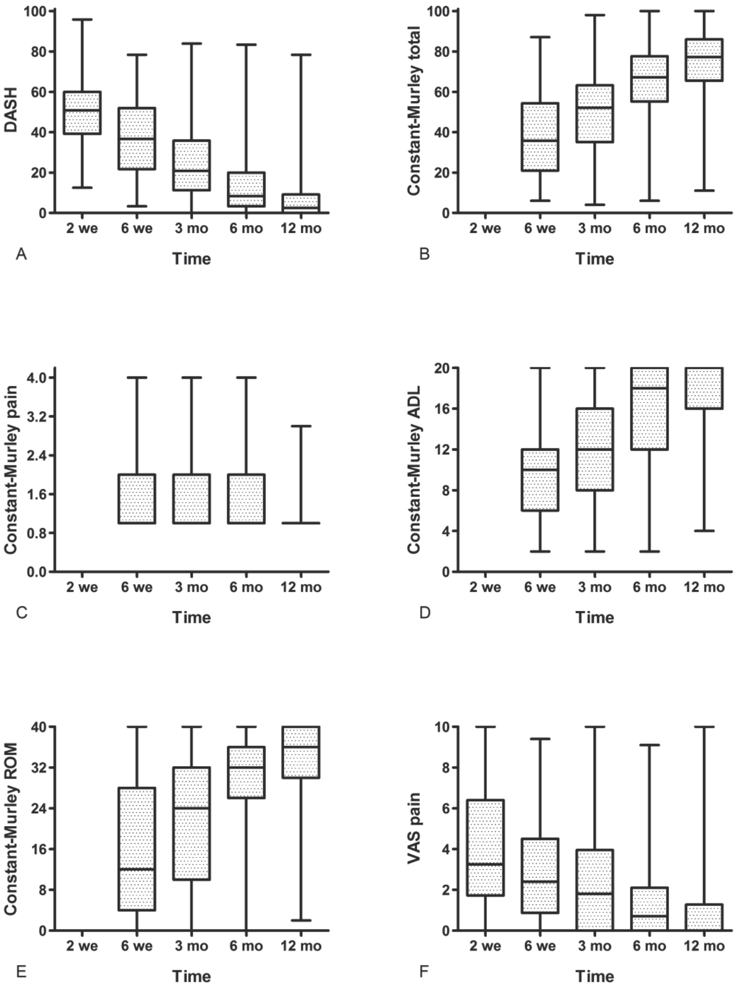

Figure 1. (A) Disabilities of the Arm, Shoulder and Hand (DASH), (**B**) Constant-Murley total, (**C**) Constant-Murley pain, (**D**) Constant-Murley Activities of Daily Life (ADL), (**E**) Constant-Murley Range of Motion (ROM), and(**F**) visual analog scale(VAS) pain scores at each follow-up visit in patients with a humeral shaft fracture. The horizontal line in the middle of each box indicates the median, the top and bottom borders of the box mark the 75th and 25th percentiles, respectively, and the whiskers mark the 90th and 10th percentiles.

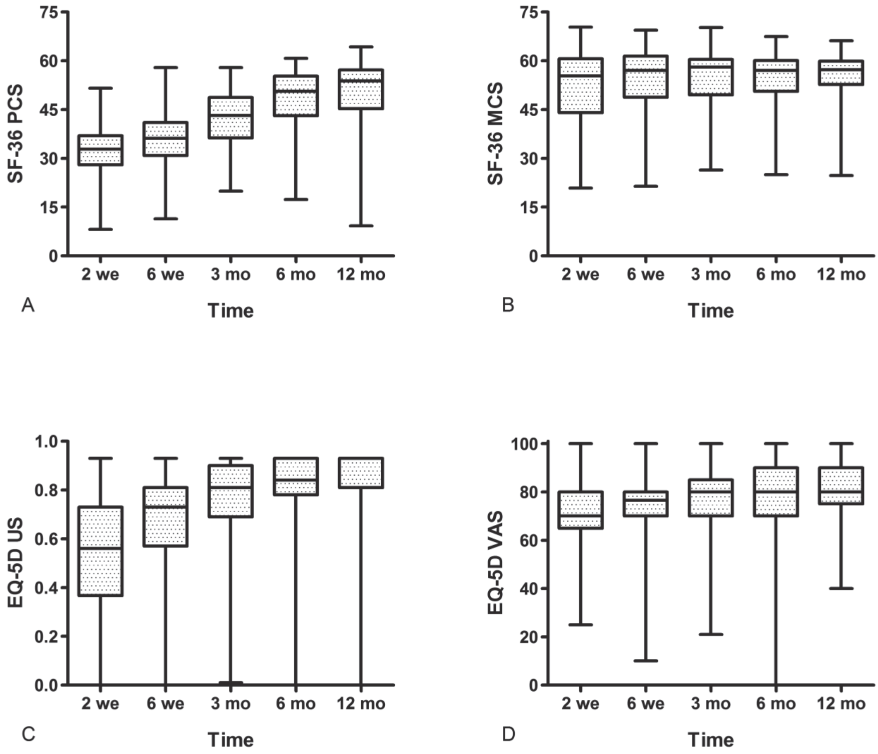

Figure 2. (**A**) Short Form 36 (SF-36) Physical Component Summary (PCS), (**B**) SF-36 Mental Component Summary MCS, (**C**) EuroQoL-5D (EQ-5D) Utility Score (US), and (**D**) EQ-5D visual analog scale (VAS) scores at each follow-up visit in patients with a humeral shaft fracture. The horizontal line in the middle of each box indicates the median, the top and bottom borders of the box mark the 75th and 25th percentiles, respectively, and the whiskers mark the 90th and 10th percentiles.

Table 1. Internal consistency of the instruments in patients with a humeral shaft fracture*

Instrument	No.	No. of items	Cronbach α
DASH (all items)	115	30	0.96
Constant-Murley (all items)	115	10	0.61†
ADL	122	4	0.60
ROM	122	4	0.88
Pain	122	1	N.D. ‡
Power	115	1	N.D. ‡

ADL, activities of daily life; DASH, Disabilities of the Arm, Shoulder and Hand; N.D., not determined; ROM, range of motion.

* Data are shown for the six months' follow-up. The maximum number of patients was 125.

† Value should be interpreted carefully because the total scale is not unidimensional.

‡ The Constant-Murley pain and power subscales consist of single items. Internal consistency does not apply to a single-item domain.

Construct validity

Construct validity is presented in Table 2. The calculated Spearman rank correlations confirmed 12 of 14 prior hypothesized correlations (85.7%) between the DASH and (sub)scales of the other PROMs, indicating sufficient construct validity. The construct validity was sufficient for the Constant-Murley total score, and Constant-Murley power (11 of 14 [78.6%]) was also sufficient. However, construct validity for the other subscales was not sufficient. A high correlation of the DASH score and the Constant-Murley total score was found with the subscales of other PROMs focusing on physical health and functioning (*i.e.*, SF-36 PCS, SF-36 PF, and EQ-5D US). The DASH showed a moderate correlation with the SF-36 MCS, whereas the Constant-Murley total and subscale scores showed low correlations with SF-36 MCS. The moderate correlation between the Constant-Murley pain subscale and the VAS pain score was hypothesized correctly, but the moderate correlation with the other individual pain measures (*i.e.*, SF-36 BP subscale and EQ-5D pain item) contradicted the predefined hypotheses. The moderate correlation between the Constant-Murley ROM subscale and EQ-5D ADL scores was also not expected.

Table 2. Construct validity of the instruments in patients with a humeral shaft fracture*

Variable	DASH	Constant-Murley				
		Total	Pain	ADL	ROM	Power
DASH	1	-0.78 [114]	0.52 [121]	-0.71 [121]	-0.60 [121]	-0.57 [114]
Constant-Murley (total score)	-0.78 [114]	1	-0.52 [115]	0.72 [115]	0.89 [115]	0.82 [115]
Pain	0.52 [121]	-0.52 [115]	1	-0.45 [122]	-0.31 [122]	-0.24 [115]
ADL	-0.71 [121]	0.72 [115]	-0.45 [122]	1	**0.48 [122]**	0.45 [115]
ROM	-0.60 [121]	0.89 [115]	-0.31 [122]	**0.48 [122]**	1	**0.69 [115]**
Power	-0.57 [114]	0.82 [115]	-0.24 [115]	0.45 [115]	0.69 [115]	1
VAS Pain	0.72 [123]	-0.53 [115]	0.57 [122]	-0.48 [122]	-0.34 [122]	**-0.40 [115]**
SF-36 PCS	-0.79 [121]	0.65 [112]	-0.38 [119]	**0.55 [119]**	**0.50 [119]**	0.54 [112]
SF-36 MCS	-0.31 [121]	0.14 [112]	-0.14 [119]	0.11 [119]	0.03 [119]	0.09 [112]
PF	-0.73 [123]	0.65 [114]	**-0.27 [121]**	**0.46 [121]**	**0.53 [121]**	0.59 [114]
BP	-0.65 [123]	**0.46 [114]**	**-0.55 [121]**	0.40 [121]	**0.27 [121]**	0.38 [114]
EQ-5D US	-0.67 [123]	0.60 [114]	-0.33 [121]	**0.43 [121]**	0.42 [121]	0.55 [114]
ADL	-0.60 [123]	**0.53 [114]**	-0.30 [121]	**0.55 [121]**	**0.38 [121]**	0.35 [114]
Pain	**-0.57 [123]**	0.44 [114]	**-0.40 [121]**	0.35 [121]	**0.24 [121]**	**0.38 [114]**
VAS	**-0.53 [123]**	**0.48 [114]**	**-0.24 [121]**	**0.31 [121]**	0.37 [121]	0.45 [114]

ADL, activities of daily life; BP, bodily pain; DASH, Disabilities of the Arm, Shoulder and Hand; EQ-5D, EuroQoL-5D; MCS, Mental Component Summary; PCS, Physical Component Summary; PF, Physical Functioning; ROM, range of motion; SF-36, Short Form-36; VAS, Visual Analog Scale; US, utility score.

* Data are shown for the six months' follow-up. The maximum number of patients was 125. Construct validity is shown as Spearman rank correlation coefficients (r) with brackets showing the number of patients included in the correlation: r > 0.6 high correlation, r = 0.3 to 0.6 moderate correlation, and r < 0.3 low correlation. Bold correlations were not hypothesized correctly.

Responsiveness

Longitudinal validity is presented in Table 3. The DASH score demonstrated sufficient longitudinal validity, with 11 of 14 change score correlations (78.6%) hypothesized correctly. As anticipated, a high correlation was found between the change scores of the DASH, the Constant-Murley total, and Constant-Murley ADL subscale scores. The moderate correlation between the DASH and the SF-36 PCS and SF-36 PF was not expected. The low correlation between the DASH and the Constant-Murley power subscale was also not expected.

The longitudinal validity of the Constant-Murley total score was sufficient. Of the 14 hypotheses, (85.7%) 12 were correct. The high correlation with the DASH and Constant-Murley ADL and ROM subscales was as expected. The moderate correlation with the SF-36 PCS and PF was not expected. The individual Constant-Murley subscales of pain, ADL, ROM, and power showed insufficient longitudinal validity, with 57.1%, 71.4%, 64.3% and 64.3% correct hypotheses, respectively.

The SRM and the ES of the DASH and Constant-Murley instruments are reported in Table 4. The magnitude of change over time was large for the DASH and Constant-Murley total and ADL, ROM, and power subscales (SRM and ES >1.3). The magnitude of change for the Constant-Murley pain subscale was medium (SRM -0.58 and ES -0.64).

Table 3. Longitudinal validity of the instruments in patients with a humeral shaft fracture*

	DASH	Constant-Murley				
		Total	Pain	ADL	ROM	Power
DASH	1	-0.60 [104]	0.45 [114]	-0.64 [114]	-0.54 [114]	**-0.14 [104]**
Constant-Murley (total score)	-0.60 [104]	1	-0.43 [105]	0.76 [105]	0.90 [105]	0.53 [105]
Pain	0.45 [114]	-0.43 [105]	1	**-0.26 [116]**	**-0.29 [115]**	-0.12 [105]
ADL	-0.64 [114]	0.76 [105]	**-0.26 [116]**	1	0.70 [115]	0.23 [105]
ROM	-0.54 [114]	0.90 [105]	**-0.29 [115]**	0.70 [115]	1	**0.29 [105]**
Power	**-0.14 [104]**	0.53 [105]	-0.12 [105]	0.23 [105]	**0.29 [105]**	1
VAS Pain	0.55 [118]	-0.46 [105]	**0.45 [116]**	-0.46 [116]	-0.33 [115]	-0.18 [105]
SF-36 PCS	**-0.56 [116]**	**0.54 [102]**	-0.40 [112]	**0.52 [112]**	**0.48 [112]**	**0.24 [102]**
SF-36 MCS	-0.20 [116]	0.02 [102]	0.01 [112]	0.01 [112]	0.02 [112]	-0.07 [102]
PF	**-0.57 [117]**	**0.34 [103]**	**-0.16 [113]**	**0.34 [113]**	**0.40 [113]**	**0.07 [103]**
BP	-0.47 [118]	0.40 [104]	**-0.36 [115]**	0.42 [115]	0.37 [114]	0.12 [104]
EQ-5D US	-0.55 [118]	0.51 [104]	-0.25 [115]	0.40 [115]	0.46 [114]	0.09 [104]
ADL	-0.50 [118]	0.44 [104]	-0.19 [115]	**0.41 [115]**	0.34 [114]	**0.21 [104]**
Pain	-0.41 [118]	0.35 [104]	**-0.43 [115]**	0.34 [115]	**0.26 [114]**	0.18 [104]
VAS	-0.18 [118]	0.25 [104]	-0.23 [115]	0.18 [115]	0.15 [114]	0.15 [104]

ADL, activities of daily life; BP, bodily pain; DASH, Disabilities of the Arm, Shoulder and Hand; EQ-5D, EuroQoL-5D; MCS, Mental Component Summary; PCS, Physical Component Summary; PF, Physical Functioning; ROM, range of motion; SF-36, Short Form-36; VAS, Visual Analog Scale; US, utility score.

* Responsiveness is shown as Spearman rank correlation coefficients (r) of change in scores between six weeks and 12 months with the number of patients included in the correlation between brackets. The maximum number of patients was 121. Values of $r > 0.6$ indicate high correlation, $r = 0.3$ to 0.6 indicate moderate correlation, and $r < 0.3$ indicate low correlation. The bold correlations were not hypothesized correctly.

Table 4. Responsiveness: standardized response mean and effect size of the instruments in patients with a humeral shaft fracture*

Instrument	No.	Mean change	SD_{change}	SRM	$SD_{6\ weeks}$	ES
DASH	118	-27.8	17.1	-1.63	18.0	-1.55
Constant-Murley	105	34.2	21.4	1.60	20.0	1.71
Pain	116	-0.5	0.9	-0.58	0.8	-0.64
ADL	116	8.6	4.8	1.78	4.3	2.01
ROM	115	17.7	13.0	1.36	13.1	1.35
Power	105	6.9	6.3	1.10	4.0	1.75

ADL, activities of daily life; DASH, Disabilities of the Arm, Shoulder and Hand; ES, effect size; ROM, range of motion; SD, standard deviation of mean change; SRM, standardized response mean.

* Change scores were calculated from six weeks to 12 months. The maximum number of patients was 121.

Floor and ceiling effects

Floor effects were not present in the DASH and Constant-Murley total and ADL and ROM subscale scores at any of the follow-up assessments (Fig. 3, A). However, floor effects were present in the Constant-Murley pain subscale at all follow-up assessments.

A ceiling effect was seen for the DASH score at 12 months of follow-up, with 31.1% of patients reporting no disability at that assessment (Fig. 3, B). For the Constant-Murley ADL and ROM subscale scores, ceiling effects were demonstrated at six and 12 months.

MIC and SDC

Anchor-based MIC and distribution-based SDC values are given in Table V. Thirty percent of transition items were reported as "a little better" and 14.4% as "more or less the same (no change)." The transition item displayed a sufficient correlation (*i.e.*, r > 0.3) with the change scores of the DASH, Constant-Murley total scores, as well as with the Constant-Murley ADL and ROM subscales. Insufficient Spearman rank correlations with the transition item was found for the change scores of the Constant-Murley pain subscale (r = 0.21) and power subscale (r = -0.18); therefore the MIC for the pain and power subscale could not be determined. The MIC value was 6.7 (95% CI, 5.0-15.8) for the DASH score and 6.1 (95% CI -6.8 to 17.4) for the Constant-Murley score. The MIC was smaller than the SDC for all total and subscale scores. The SDC was 19.0 (SEM, 6.9) for the DASH score and 17.7 (SEM 6.4) for the Constant-Murley score.

Chapter 6

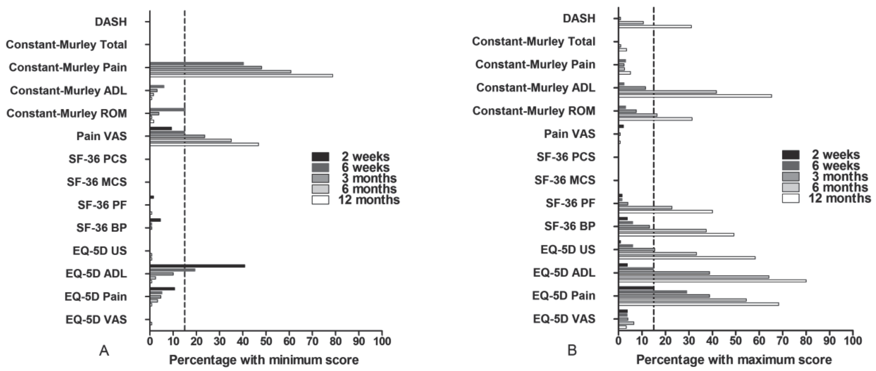

Figure 3. (A) Floor and(B) ceiling effects of the instruments at each follow-up visit in patients with a humeral shaft fracture. ADL, activities of daily life; BP, bodily pain; DASH, Disabilities of the Arm, Shoulder and Hand; EQ-5D, EuroQoL-5D; ROM, range of motion; SF-36, Short Form-36; MCS, Mental Component Summary; PCS, Physical Component Summary; PF, Physical Functioning; US, utility score; VAS, visual analog scale.

Table 5 Minimal Important Change and Smallest Detectable Change values of the instruments in patients with a humeral shaft fracture

Instrument	Scoring range	Anchor-based approach*					Distribution-based approach*			
		No.	AUC	MIC	Sensitivity (%)	Specificity (%)	No.	SD_{change}	SEM	SDC
DASH	0-100	150	0.66 (0.58-0.73)	6.7 (5.0-15.8)	45.3	80.8	73	9.7	6.9	19.0
Constant-Murley (total score)	0-100	105	0.59 (0.50-0.68)	6.1 (-6.8 to 17.4)	58.1	61.8	55	9.0	6.4	17.7
Pain	0-15	120	0.52 (0.44-0.59)	N.D.	N.D.	N.D.	59	0.6	0.4	1.2
ADL	0-20	120	0.59 (0.51-0.67)	N.D.	N.D.	N.D.	58	2.4	1.7	4.7
ROM	0-40	120	0.62 (0.54-0.70)	N.D.	N.D.	N.D.	58	5.1	3.6	9.9
Power	0-25	105	0.57 (0.48-0.66)	N.D.	N.D.	N.D.	55	4.1	2.9	8.0

ADL, activities of daily life; AUC, area under the curve; DASH, Disabilities of the Arm, Shoulder, and Hand; MIC, minimal important change; N.D., not determined; ROM, range of motion; SD, standard deviation of mean change; SDC, smallest detectable change; SEM, standard error of measurement.

* Anchor-based and distribution-based methods for MIC and SDC values, respectively. For the MIC, the area under the receiver operating characteristic curve and MIC are shown with 95% confidence intervals between brackets.

DISCUSSION

Results of the current study show that the DASH and Constant-Murley are valid instruments to describe symptoms and disability experienced by patients who sustained a humeral shaft fracture over time. The DASH was also found to be reliable.

The DASH instrument and the Constant-Murley ROM subscale demonstrated sufficient internal consistency in this population, as reflected by Cronbach α values of at least 0.70. The observed value for the DASH was consistent with previously published values, which range from 0.91 to 0.98.[30, 31] The Cronbach α, however, exceeded 0.95, suggesting that some of the items of the DASH questionnaire might be redundant for adequate construct measurement in this research setting. The internal consistency of the Constant-Murley total score of 0.61 was within the range of 0.60 to 0.75 described previously.[8] The value should be interpreted carefully because the total instrument is multidimensional. The insufficient internal consistency of the Constant-Murley ADL subscale was a novel finding. However, because the Cronbach α is dependent on the number of items in a (sub)scale, the inferior result might be related to the small number of items (three items) in the Constant-Murley ADL subscale.[24]

Construct validity of the DASH score was sufficient, with 85.7% of the predicted correlations confirmed. More specifically, the DASH displayed high correlations with the Constant-Murley total score, the Constant-Murley ADL and ROM subscales, and subscales of other PROMs focusing on physical health and functioning. The unexpected low correlation between the DASH and the Constant-Murley power subscale may suggest that not all activities asked in the DASH are affected by differences in power of the shoulder. The high correlation between the DASH and the EQ-5D has been published in patients with a proximal humeral fracture and was of comparable strength.[3] To the contrary, the correlations between the DASH and the SF-36 MCS found in this study was much lower than previously described.[32] The unexpected moderate correlation between the DASH and the SF-36 PCS and PF may be because patients more often than expected had functional limitations caused by conditions not affecting the upper extremity; these affect the SF-36 but not the DASH. Interestingly, only a moderate correlation was found between the DASH and the EQ-5D VAS. This suggests that sustaining a humeral shaft fracture does not necessarily affect a patient's general health perception. Cederlund *et al.* reported a similar finding in patients who received treatment for major hand surgery. The patients in their study had the same median general health perception as scored by the EQ-5D VAS at three and six months after initiation of treatment.[33]

According to Cohen's[25] interpretation, the SRM values of the DASH (-1.63), the Constant-Murley total score (1.60) and its (sub)scale scores suggested good to excellent ability to detect clinical change over time.[25] Other studies reported SRM values for the DASH in different contexts, with values ranging from -0.48 to -1.64.[34, 35] No published SRM values for the Constant-Murley score were found.

In this study, the DASH and Constant-Murley scores displayed sufficient longitudinal validity as reflected by 78.6% and 85.7% of correctly hypothesized correlations, respectively. Correlations in change scores of the DASH with the SF-36 PCS and SF-36 MCS were comparable to a previous study.[36]

The DASH score displayed a ceiling effect at 12 months' follow-up. Treatment of humeral shaft fractures is aimed at full recovery, and achieving this will cause a ceiling effect because patients who have a full recovery report no disabilities on PROMs. In this study, population full recovery of a substantial portion of the patients was expected one year after the start of treatment, and so a ceiling effect was expected. But because of the ceiling effect, differences in the group of patients who reported no disabilities at 12 months' follow-up cannot be distinguished, making it not suitable to, for example, use this time point to compare differences of different treatment strategies.

The anchor-based MIC for the DASH was 6.7 (95% CI, 5.0-15.8), which is a little lower than found in previous studies. Previously published MIC values range from seven in patients who sustained ulnar nerve decompression to 15 in patients with shoulder impingement syndrome.[33, 37] Because MIC values are known to be patient and context dependent, it is likely that the differences in study populations explain the differences in reported MIC values.[24] MICfor the Constant-Murley score has not been reported previously.[8] The SDC as found for this instrument in the current study, 17.7 points, is in line with 17 to 23 points reported previously for shoulder impingement, supraspinatus tears, and massive rotator cuff tears.[38] For monitoring changes in individual patients (*e.g.* in clinical practice), the MIC should be larger than the SDC. This is necessary to make a distinction between "real' change and change induced by measurement error. In research, however, the MIC is used differently (*e.g.*, to determine percentages of responders)', and the measurement error is much smaller. For all PROM (sub)scales in this study, the anchor-based MIC was smaller than the SDC. This suggests that the observed MIC values in this study fall into the range that could be due to chance.

This study has some limitations. Because there was too much time between two subsequent follow-up moments, performing an adequate test-retest analysis was not possible. Therefore, calculation of the SEM was done with the corresponding change scores of patients who answered “no change” on the transition item. This may have resulted in incorrect SEM, because the Spearman rank correlations between the transition item and change scores of the Constant-Murley pain subscale was insufficient. For the other items, however, the correlation was sufficient, so this did not apply to those items. Similarly, this may have hindered correct anchor-based MIC and SDC calculations. As a second limitation, the calculations were done using the non-normalized Constant-Murley scores because the sample size did not allow stratification by age.

CONCLUSIONS

This study confirms, for the first time, that the DASH and Constant-Murley scores are valid for evaluating outcome over time in patients who sustained a humeral shaft fracture. Reliability was confirmed only for the DASH, making this the most suitable instrument. Ceiling effects were noted at one-year follow-up, likely owing to increasing numbers of patients with full recovery. For the DASH, the MIC was 6.7 (95% CI, 5.0-15.8) and the SDC was 19.0 (SEM, 6.9). For the Constant-Murley score, the MIC was 6.1 (95% CI, -6.8 to 17.4) and the SDC was 17.7 (SEM, 6.4). The MIC and SDC values enable adequate sample size calculations for future research.

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Ethical approval

This study was exempted by the Erasmus MC Medical Research Ethics Committee (No. MEC-2015-217).

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Chapter 7

Humeral shaft fractures: Retrospective results of non-operative and operative treatment of 186 patients

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ABSTRACT

Background: Humeral shaft fractures account for 1-3% of all fractures and 20 % of the fractures involving the humerus. The aim of the current study was to compare the outcome after operative and non-operative treatment of humeral shaft fractures**,** by comparing the the time to radiological union and the rates of delayed union and complications.

Methods: All patients aged 16 years or over treated for a humeral shaft fracture during a five-year period were included in this retrospective analysis; periprosthetic and pathological fractures were excluded. Radiographs and medical charts were retrieved and reviewed in order to collect data on fracture classification, time to radiographic consolidation and the occurrence of adverse events.

Results: A total of 186 patients were included; 91 were treated non-operatively and 95 treated operatively. Mean age was 58.7 ± 1.5 years and 57.0% were female. In 83.3% of the patients only the humerus was affected. A fall from standing height was the most common cause of the fracture (72.0%). Consolidation time varied from a median of 11 to 28 weeks. The rate of radial nerve palsy in both groups was similar; 8.8% versus 9.5%. In 5.3% of the operatively treated patients the palsy resulted from the operation. Likewise, delayed union rates were similar in both groups; 18.7% following non-operative treatment versus 18.9% following surgery.

Conclusion: The data indicated that consolidation time and complication rates were similar after operative and non-operative treatment. A prospective randomized clinical trial comparing non-operative with operative treatment is needed in order to examine other aspects of outcome, meaning shoulder and elbow function, post-operative infection rates, trauma related quality of life and patient satisfaction.

INTRODUCTION

Fractures of the shaft of the humerus account for 1-3% of all fractures[1] and approximately 20% of all fractures involving the humerus.[2] The incidence is 14.5 per 100,000 per year, gradually increasing from the fifth decade and reaching its peak of 60 per 100,000 per year in the ninth decade. Also a minor peak is seen in the third decade.[1, 3]

Both operative and non-operative treatment is used in the management of humeral shaft fractures. Traditionally, the treatment has generally been non-operative, nowadays using the Sarmiento brace as functional bracing therapy.[4] Operative approaches include intramedullary nailing, plate osteosynthesis and an external fixation.[5]

Both non-operative and operative treatment strategies have their pros and cons. Although functional treatment is believed to be associated with a very low rate of delayed union and excellent functional results,[6] in certain groups of patients functional bracing does not provide sufficient immobilization. For instance, non-operative treatment in overweight patients result in a high rate of delayed union.[7]

There is substantial controversy on the best approach of humeral shaft fractures. Kocht et al. for example stated that though newer intramedullary techniques are probably less invasive and technically less complicated, the Sarmiento brace remains the gold standard and first treatment of choice.[8] Schratz et al. on the contrary favors intramedullary nailing.[9] Schittko et al. claimed that the operative therapy should be considered as the gold standard because of the development of new intramedullary and rotation stable implants in addition to the classical osteosynthesis using a plate.[5]

So the best treatment is still at debate and the type of treatment highly depends on the physician's personal view. The current literature lacks an answer to the question whether operative or non-operative treatment results in different clinical outcomes The aim of the current study was to compare the outcome after operative versus non-operative treatment of humeral shaft fractures, by comparing the time to radiological union and the rates of delayed union and complications.

PATIENTS AND METHODS

All patients aged sixteen years or over treated for a humeral shaft fracture in the Erasmus MC (Rotterdam, the Netherlands) between January 2002 and December 2006, the Albert Schweitzer Hospital (Dordrecht, the Netherlands) between January 2003 and December 2007, and the Maasstad Hospital (Rotterdam, the Netherlands) between January 2004 and December 2008 were included in this retrospective analysis. Periprosthetic and pathological fractures were excluded.

The patients were identified from the radiology program PACS (Picture Archiving and Communication System). Reports of all radiographs of the upper arm, including the shoulder and elbow, were searched using 'Humerus' AND 'Fracture' as search terms. Eligible patients with humeral shaft fractures were further identified by reading all radiology reports and reviewing all radiographs. Humeral shaft fractures were defined as the area between the surgical neck and the area immediately above the supracondylar ridge. All fractures were classified using the AO-system[10] by reviewing the radiographs (K.C.M.).

Information about the affected side, the consolidation period, and presence of a delayed union were collected from the radiographs, radiology reports and the patient's hospital records. Radiological consolidation was defined as cortical bridging of at least three out of four cortices and was expressed in weeks from the day of the fracture. Delayed union was defined as a failure to heal at twenty-four weeks post fracture with no progress toward healing seen on the most recent radiographs.[11]

The medical charts of all patients were reviewed and the following items were retrieved: age, gender, trauma mechanism, other injuries besides the humeral shaft fracture, type of treatment and radial nerve palsy. The type of treatment was non-operative or operative. The decision between the two was made by the attending physician at each hospital and was based upon the surgeon's best judgment, knowledge and expertise.

The trauma mechanism was classified as a simple fall, meaning a fall from persons height, high-energetic (e.g., a traffic-related accident) or 'other'. Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 16.0 for Windows. Outcome after operative and non-operative treatment was compared. Results of categorical variables (gender, AO-types and subtypes, delayed-union, radial nerve palsy, injuries, and trauma mechanism) were analyzed using Chi-square test. Results of numerical variables (age and consolidation time) were analyzed using the Mann-Whitney U-test. All tests were two sided. P-values < 0.05 were considered statistically significant.

RESULTS

In total 186 patients were included in this study. Table 1 shows the demographic data of this cohort for the patients in this study. Ninety one patients had been treated non-operatively. The majority was female (60.4%) and the mean age was 58.7 ± 1.5 years. The operatively treated group consists of 95 patients, 53.7% was female, with a median age of 61.1 years. No statistically significant difference could be found with respect to this data between the groups.

In the non-operatively treated group the left humerus was affected in 51.6% of patients, which was not statistically different from the operative group (62.2%). In 83.3% of the patients the humeral shaft injury was a solitary injury, and in 72% of patients the fracture resulted after a simple fall. No statistical difference was found between both groups. In the operative group 82.1% of the patients were treated using intramedullary nailing, 11.6% using plate osteosynthesis, 5.3% using external fixation and in 1 (1.1%) patient only Cerclage wires were used.

Figure 1 shows a detailed overview of fractures by AO subgroups. This shows type A humeral shaft fractures were found most frequently (50.0% of the patients) and type C was least common (8.1% of the patients). In the non-operatively treated group the A1 spiral fracture was the most common subtype (28.6%) and in the operatively treated group the A3 transverse fracture (26.3%).

Table 2 shows the time it took to achieve radiological consolidation in weeks from the day of the fracture per AO type and subtype. In the non-operatively treated group the time to achieve radiological consolidation ranged from a median of 11 weeks in the AO type A2 subgroup to 15 weeks in the B2 and A3 subgroups. In the operative group, time to consolidation ranged from a median of 12 weeks (A2 subtype) to 28 weeks (B3 subtype), which did not differ statistically from the non-operative group.

Overall, 17 of the patients (9.1%) developed radial nerve palsy (Table 3). No statistically significant difference was found between the two groups. In the non-operatively treated group this originated from the trauma or fractures itself in eight patients. In the operatively treated group, radial nerve palsy originated from the trauma or fracture in 13 patients. In 4 patients it occurred after surgery.

Delayed union occurred in 18.8% of the patients, *i.e.*, in 18 patients treated non-operatively and in 18 patients treated operatively ($p>0.05$; 14 treated with intramedullary nailing, two with plate osteosynthesis, one with an external fixator and one with cerclage wires).

Table 1. Characteristics of the study population by type of treatment

	Overall (N=186)	Non-operative (N=91)	Operative (N=95)	P-value
Female[1]	106 (57.0)	55 (60.4)	51 (53.7)	0.377+
Age[2] **(year)**	60.8 (44.2-76.5)	60.6 (45.7-77.7)	61.1 (39.7-74.7)	0.424++
Left side affected[1]	106 (57.0)	47 (51.6)	59 (62.1)	0.183+
Concomitant injuries:				0.092+
Monotrauma[1]	155 (83.3)	79 (86.8)	76 (80.0)	
Polytrauma[1]	29 (15.6)	10 (11.0)	19 (20.0)	
Unkown[1]	2 (1.1)	2 (2.2)	0 (0.0)	
Trauma mechanism:				0.147+
Simple fall[1]	134 (72.0)	69 (75.8)	65 (68.4)	
High energy[1]	32 (17.2)	10 (11.0)	22 (23.2)	
Other[1]	13 (7.0)	8 (8.8)	5 (5.3)	
Unknown[1]	7 (3.8)	4 (4.4)	3 (3.2)	

+ Pearson Chi-square test, ++Mann-Whitney U-test

Data are shown as [1] number of patients with the percentages given within brackets, or as [2] median with the first and third quartile given within brackets

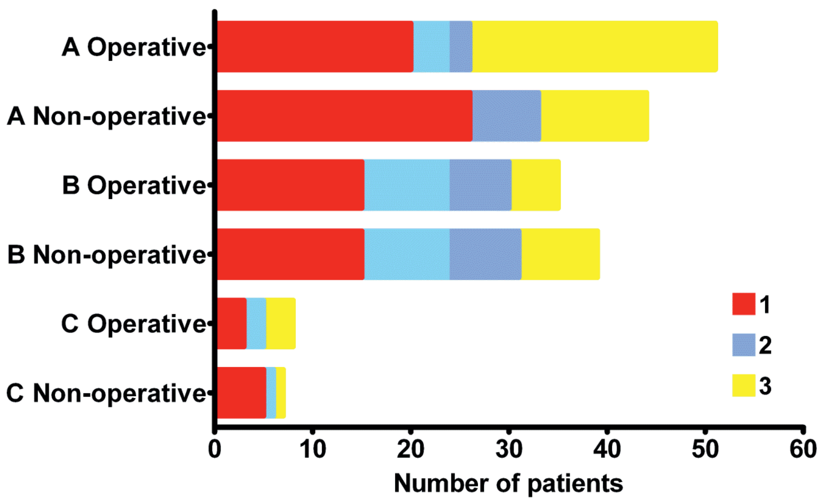

Figure 1. Distribution of the humeral shaft fractures into AO types and subtypes by type of treatment

Table 2. Consolidation time in weeks from day of humeral shaft fracture per AO type and subtypes by type of treatment

	Overall	Non-operative	Operative	P-value
A all	14 (11-18)	13 (8-18)	14 (11-19)	0.169
A1	14 (10-18)	13 (9-18)	16 (11-18)	0.381
A2	11 (8-13)	11 (6-13)	12 (10-20)	0.221
A3	15 (12-22)	15 (11-22)	14 (12-23)	0.890
B all	15 (12-22)	14 (11-21)	17 (13-23)	0.166
B1	16 (12-21)	14 (9-18)	18 (14-23)	0.065
B2	15 (12-21)	15 (14-26)	14 (11-20)	0.173
B3	22 (12-31)	12 (9-22)	28 (23-34)	0.034
C all	22 (16-24)	No data	22 (16-24)	N.A.
C1	20 (16-24)	No data	20 (16-24)	N.A.
C2	No data	No data	No data	N.A.
C3	22 (22-22)	No data	22 (22-22)	N.A.

Data are shown as median with the first and third quartile given within brackets. P-values were calculated with the Mann-Whitney U-test.

N.A., not applicable.

Table 3. Origin of radial nerve palsy and delayed union in patients with humeral shaft fractures by type of treatment

	Overall	Non-operative	Operative	P-value
Radial nerve palsy				
Trauma/fracture	13 (7.0)	8 (8.8)	5 (5.3)	
Surgery	4 (2.2)	N.A.	4 (4.2)	
Total	17 (9.1)	8 (8.8)	9 (9.5)	0.053
Delayed union	35 (18.8)	18 (18.7)	18 (18.9)	0.580

Patient numbers are displayed, with the percentages given within brackets. P-values were calculated with the Pearson Chi-square test.

N.A., not applicable.

DISCUSSION

The aim of the current retrospective study was to compare the outcome after operative versus non-operative treatment of humeral shaft fractures, by comparing the the time to radiological union and the rates of delayed union and complications. In this series of 186 patients, no statistically significant differences were found in the time to radiological consolidation between the two groups, nor in the rates of delayed union or occurrence of radial nerve palsy.

The demographic data of the current study are to a large extent in agreement with published epidemiologic studies on humeral shaft fractures.[1, 3] In the most recent epidemiologic study the average age of patients with a humeral shaft fracture was 62.7 years,[1] the average age of the patients in our study was 58.7 years..

Data from previous studies showed delayed union rates of 2-23%[12, 13] after non-operative treatment versus 15-30%[14] for operatively treated patients. Data of the current study (18.7% versus 18.9%, respectively) are consistent with the literature data. Increased delayed union rates as suggested previously[15] could not be confirmed in the current study.

Due to the high variability in fracture subtypes, our study lacked adequate statistical power to show statistically significant difference in time to radiographic healing between both groups. For the B3 type fractures, a trend was seen, suggesting that the time to radiographic healing was shorter in the non-operative group (median 12 weeks) than in the operative group (median 28 weeks).

In the current study 9.1% of the patients had radial nerve palsy. Rates between 2 and 17% are described of in the literature[16], but a review by Shao et. al reported an average rate of 11.8%.[17] Even though primary radial nerve palsy is considered by many an absolute indication for surgery[5] the data of our study do not support this, as radial nerve palsies occurred equally frequent in both groups. In the operatively treated group less radial nerve palsies were seen as a result of the fracture or the trauma (8.8 vs 5.3%). Spontaneous recovery is seen in 70.7% of the patients treated conservatively for the palsy, and after including surgical management the overall recovery rate is 88.1% as reported by Shao et al.

The retrospective nature and the lack of randomization was a limitation of our study. The decision between operative and non-operative treatment was made by the attending surgeon, based upon his preferences and previous experience. Given the low and similar rates of delayed union in both groups, it is tempting to speculate that the surgeons were quite good at identifying which fractures should be operated. Whether or not this is true should be studied in more detail.

Data on other essential aspects of outcome were unavailable. Possible residual deformity of the arm or impaired function could be a disadvantage of non-operative treatment compared with operative treatment. Rotational or axial malalignment up to 20–25 degrees and shortening less than 2 cm are regarded as acceptable following non-operative treatment.[13, 18, 19] Surgery could improve the alignment of the fracture site; but is unclear at this moment if improved alignment also results in better functional outcome. As a disadvantage of surgery shoulder impairment is often mentioned, though impaired shoulder function may also occur following non-operative treatment.[20] Moreover, infections after surgery, the time and ability to full resumption of activities of daily living, and patient satisfaction with the outcome are all important factors that should be taken into consideration in the treatment of humeral shaft fractures.

CONCLUSIONS

In conclusion, the current study revealed similar time to consolidation and rates of delayed union and radial nerve palsy after non-operative and operative treatment of humeral shaft fractures. A randomized clinical trial comparing non-operative with operative treatment is needed in order to examine all aspects of outcome, taking into account consolidation time, delayed union and radial nerve palsy rates as well as the shoulder and elbow function, pain, post-operative infection rates, numbers of patients returning to their previous work and residual deformity.

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Chapter 8

HUMeral Shaft Fractures: MEasuring Recovery after Operative versus Non-operative Treatment (HUMMER): a multicenter comparative observational study

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ABSTRACT

Background: Fractures of the humeral shaft are associated with a profound temporary (and in the elderly sometimes even permanent) impairment of independence and quality of life. These fractures can be treated operatively or non-operatively, but the optimal tailored treatment is an unresolved problem. As no high-quality comparative randomized or observational studies are available, a recent Cochrane review concluded there is no evidence of sufficient scientific quality available to inform the decision to operate or not. Since randomized controlled trials for this injury have shown feasibility issues, this study is designed to provide the best achievable evidence to answer this unresolved problem. The primary aim of this study is to evaluate functional recovery after operative versus non-operative treatment in adult patients who sustained a humeral shaft fracture. Secondary aims include the effect of treatment on pain, complications, generic health-related quality of life, time to resumption of activities of daily living and work, and cost-effectiveness. The main hypothesis is that operative treatment will result in faster recovery.

Methods/Design: The design of the study will be a multicenter prospective observational study of 400 patients who have sustained a humeral shaft fracture, AO type 12A or 12B. Treatment decision (*i.e.*, operative or non-operative) will be left to the discretion of the treating surgeon. Critical elements of treatment will be registered and outcome will be monitored at regular intervals over the subsequent 12 months. The primary outcome measure is the Disabilities of the Arm, Shoulder, and Hand score. Secondary outcome measures are the Constant score, pain level at both sides, range of motion of the elbow and shoulder joint at both sides, radiographic healing, rate of complications and (secondary) interventions, health-related quality of life (Short-Form 36 and EuroQol-5D), time to resumption of ADL/work, and cost-effectiveness. Data will be analyzed using univariate and multivariable analyses (including mixed effects regression analysis). The cost-effectiveness analysis will be performed from a societal perspective.

Discussion: Successful completion of this trial will provide evidence on the effectiveness of operative versus non-operative treatment of patients with a humeral shaft fracture.

Trial Registration: The trial is registered at the Netherlands Trial Register (NTR3617).

BACKGROUND

Humeral shaft fractures are associated with a profound temporary (in elderly sometimes even permanent) impairment of independence and quality of life. Fractures of the humeral shaft account for 1-3% of all fractures.[1] The cumulative incidence shows a peak in the working population (14.5/100,000 person years) as well as in the elderly (60/100,000).[1-3]

Humeral shaft fractures can be treated operatively or non-operatively. Operative treatment is mostly performed by intramedullary nailing, plate osteosynthesis, or external fixation. Non-operative immobilization is mostly done with a functional (Sarmiento) brace.[4] Operative and non-operative treatment strategies both have their pros and cons. Operative fracture fixation allows for early mobilization, which may lead to earlier functional recovery and reduced pain. However, surgical complications and fixation failure may occur.[5] Non-operative treatment may be associated with more pain (as the fracture is not stabilized) and discomfort (due to pain and immobilization) in the first weeks and may be associated with a higher malunion risk due to the lack of fracture re-alignment.[6, 7] Longer immobilization may delay functional recovery.

Complications of operative and non-operative treatment overlap and data are lacking to determine treatment relatedness. Non-union occurs in 15-30% after operative treatment[5] versus 2-23% after non-operative treatment (for which most patients require secondary surgical treatment)[6, 7]. The most feared disabling complication is radial nerve palsy, occurring in 2-17% of all patients.[8-10] A systematic review (n=4,517 patients) reported an average radial nerve palsy of 11.8%. Although 70% recover spontaneously, the palsy was permanent in 12% of cases accounting for a substantial impairment and costs.[9]

Regaining function is extremely important from a patient and societal perspective. From the few retrospective and prospective case series published, each using other outcomes, better functional outcome is expected after operative treatment.[8, 11-17]

The best type of treatment is still debated. Surgeons state that their experience, patient characteristics and expected physical demands in daily living guides treatment decision. In the elderly patients, some surgeons might prefer immobilization while others may primarily operate as they fear inferior functional outcome after non-operative treatment. In younger patients, some surgeons directly perform a surgical intervention while others primarily choose non-operative immobilization, followed by surgical intervention if needed. However, our retrospective study showed an approximately 50% operation rate irrespective of fracture subclass with no obvious differences in patient or fracture characteristics across classes.[18]

Since randomized or high-quality comparative observational studies are lacking, a recent Cochrane review concluded there is no evidence of sufficient scientific quality available to inform the decision to operate or not.[19] High-quality clinical studies are thus urgently needed to resolve this clinically relevant problem. RCTs for this injury have shown feasibility issues; one RCT continued as an observational study due to severe recruitment problems.[20] The HUMMER study is designed to provide the best achievable evidence to answer this unresolved problem using an observational trial design.

The primary objective of this study is to examine the effect of operative versus non-operative treatment on the DASH (Disabilities of the Arm, Shoulder, and Hand) score, reflecting functional outcome and pain of the upper extremity, in adult patients who sustained a humeral shaft fracture. Secondary aims are to examine the effect of operative versus non-operative treatment on functional outcome, the level of pain, range of motion of the shoulder and elbow joint, the rate of secondary interventions and complications, the time to resumption of work and activities of daily living, health-related quality of life, costs, and cost-effectiveness in these patients.

METHODS/DESIGN

Study design

The HUMMER trial will follow a multicenter, prospective observational trial design. Approximately 30 hospitals in The Netherlands will participate.

The decision to provide operative or non-operative treatment will be left to the discretion of the attending physician. We chose an observational design because a randomized controlled trial (RCT) would currently not be feasible. Many surgeons prefer not to participate in trials that involve randomization[21] and we know from experience that patients easily refuse to be randomized between operative and non-operative treatment. Inclusion problems were the main reason for failure of a previous RCT with the same research question as this study.[20] Well-designed and adequately reported observational studies are good alternatives to RCTs.[22, 23] Preference of observational studies over RCTs in orthopedic trauma has been acknowledged.[24, 25] They lead to similar outcomes without the limitations of randomization which may in practice decrease the validity of the outcomes.[26, 27] These designs are increasingly used and accepted in surgical studies.[28] In order to answer our research question, we will make adjustments in the statistical analysis by using the propensity matching score method.[29-32]

The trial is registered at the Netherlands Trial Register (NTR3617).

Recruitment and consent

Eligible persons presenting to the ED with a humeral shaft fracture will be informed about the trial at the ED. After an explanation of the study, they will receive information and a consent form from the attending physician, the clinical investigator, or a research assistant. Patients meeting all inclusion criteria and none of the exclusion criteria will be included while they are still at the ED or at the time of their first outpatient visit.

As with many surgical trials, patients and surgeons cannot be blinded for treatment. In order to reduce bias, a research physician or research assistant will perform the follow-up measurements using a standardized protocol. Radiographs can also not be blinded for treatment; however, evaluating radiographs in duplicate by two trauma surgeons independently will improve reliability of fracture healing assessment. In case of disagreement they will discuss the results until they reach consensus. Finally, the analysis will be performed by a statistician without knowledge of treatment.

Study population

All persons aged 18 years or older presenting to the ED with a humeral shaft fracture (AO type 12A or 12B) are eligible for inclusion.[33] The AO type 12C fractures will be excluded due to their low occurrence rate. Humeral shaft fractures are defined as fractures located in the area between the surgical neck and the area immediately above the supracondylar ridge.

Patients meeting the following inclusion criteria are eligible for enrolment:

1. Adult men or women aged 18 years or older (with no upper age limit)
2. A fracture of the humeral shaft, AO class 12A or 12B (confirmed on X-ray)
3. Operation within 14 days after presentation to the ED (if this is the treatment of choice)
4. Provision of informed consent by patient

If any of the following criteria applies, patients will be excluded:

1. Patients with concomitant injuries affecting treatment and rehabilitation of the affected arm
2. Patients with a humeral fracture treated with an external fixator
3. Patients with a pathological, recurrent or open humeral shaft fracture
4. Patients with neurovascular injuries requiring immediate surgery (excl. radial nerve palsy)
5. Additional traumatic injuries of the affected arm that influence upper extremity function
6. Patients with an impaired upper extremity function (*i.e.*, stiff or painful arm or neurological disorder of the upper limb) prior to the injury
7. Retained hardware around the affected humerus
8. Patients with rheumatoid arthritis
9. Bone disorder which may impair bone healing (excluding osteoporosis)
10. Patients incapable of ensuring follow-up (*e.g.*, no fixed address or cognitive impairment)
11. Insufficient comprehension of the Dutch language to understand the rehabilitation program and other treatment information, as judged by the treating physician of researcher. Exclusion of a patient because of enrolment in another ongoing drug or surgical intervention trial will be left to the discretion of the attending surgeon on a case-by-case basis.

Intervention

The decision on treatment will be left to the discretion of the attending surgeon. The choice will be between operative and non-operative treatment. Also, the rehabilitation after treatment will not be standardized, but will be provided as in real life. Although this may create some heterogeneity across groups, it will improve the generalizability of the study results.

If a surgeon decides to operate the patient, the choice between plate osteosynthesis or intramedullary nailing will be left to the treating surgeon. No restrictions will be applied to the approach for reduction and fixation of the fracture, *e.g.*, open or closed, antegrade or retrograde. The type and brand of the materials as well as the use of cerclage wires and other elements of the surgery will be left to the surgeon, local availability and expertise. Critical elements of the operative treatment will be recorded (*e.g.*, type of implant, identification of the radial nerve, surgical approach, operative delay, duration of surgery) and the effect on outcome will be assessed.

In order to maximize generalizability, the type of non-operative treatment will also be left to the attending surgeon. Usually it consists of a splint, plaster, collar and cuff or hanging cast for 1-2 weeks, followed by a Sarmiento brace for 4-6 weeks. Critical elements of this treatment will be recorded and the effect on outcome will be assessed.

Due to a lack of evidence favoring a particular approach, the physical therapy and rehabilitation program will be recorded but not standardized. This will improve generalization of the study results.

Outcome measures

The Disabilities of the Arm, Shoulder and Hand (DASH) outcome measure will serve as primary outcome measure. The DASH is a validated 30-item, self-report questionnaire designed to help describe the disability experienced by people with upper-limb disorders and also to monitor changes in symptoms and function over time.[34, 35] It is scored in two components: the disability/symptom section (30 items, scored 1-5) and two optional Work and high performance Sport/Music modules (each 4 items, scored 1-5). The DASH disability/symptom score is a summation of the responses to 30 questions on a scale of 1 to 5, with an overall score ranging from 0 (no disability) to 100 (severe disability). At least 27 of the 30 items must be completed for a score to be calculated. The DASH optional modules aim to measure symptoms and function in athletes, performing artists and other workers whose jobs require a high degree of physical performance. These optional models are scored separately and each contains four items, scored 1-5. All items must be completed for a score to be calculated.

The secondary outcome measures are:

- Constant score
- Pain level at both sides (VAS)
- Range of Motion of the shoulder and elbow joint at both sides
- Rate of complications
- Rate of secondary interventions
- Time to resumption of work and other activities of daily living
- Health-related quality of life: SF-36 and EQ-5D
- Radiographic healing
- Cost of health care use and production loss
- Cost-effectiveness

The Constant score reflects both function and pain.[36] This scoring system consists of four variables that are used for assessing shoulder function. The right and left shoulder are assessed separately. The subjective variables are pain (15 points), activities of daily living (ADL; *i.e.*, sleep, work, recreation / sport; 10 points), and arm positioning (10 points), which give a total of 35 points. The objective variables are range of motion (ROM; 40 points) and strength (25 points), which give a total of 65 points. ROM includes forward flexion (10 points), lateral elevation (10 points), external rotation related to the head (10 points) and internal rotation related to the spine column (10 points). ROM will be measured with a goniometer. Strength of abduction will be measured using a calibrated spring balance.

Pain level will be determined using a 10-point Visual Analog Scale (VAS), in which 0 implies no pain and 10 implies the worst possible pain.

The range of motion (ROM) of the shoulder (*i.e.*, abduction and forward flexion) and the elbow joint (*i.e.*, flexion and extension) will be measured using a goniometer. Both sides will be assessed separately, and the loss of ROM will be calculated.

Complications will be recorded from medical charts. Complications may include: 1) surgical site infection; 2) wound dehiscence; 3) skin problems (*e.g.*, skin at risk, skin necrosis); 4) dystrophia; 5) radial nerve palsy; 6) malunion; 7) implant failure (screw breakout); 8) cuff pathology; 9) secondary fracture dislocation; or 10) non-union. Non-union is defined as a failure to heal at twenty-six weeks post fracture with no progress towards healing seen on the most recent radiographs.[37]

Secondary intervention within one year of initial treatment to promote fracture healing, relieve pain, treat infection, or improve function will be recorded from medical charts. Interventions will be categorized as: 1) osteosynthesis with or without bone grafting; 2) implant exchange with or without bone grafting; 3) implant removal; 4) incision and drainage for superficial surgical site infection; or 5) incision and drainage for deep surgical site infection. The indication and admission duration for all intervention will also be recorded.

Presence of radiographic healing will be determined using X-rays. Fracture consolidation is defined when one of the three criteria listed is present; 1) bridging of fracture by callus/bone trabeculae or osseous bone; 2) obliteration of fracture line/cortical continuity; or 3) bridging of fracture at three out of four cortices.

The time to resumption of work and activities of daily living will be recorded using a custom-made questionnaire.

The Short-Form 36 (SF-36) is a validated multi-purpose, health survey with 36 questions, representing eight health domains that are combined into a physical and a mental component scale.[38] The Physical Component Summary (PCS) combines the health domains physical functioning (PF; 10 items), role limitations due to physical health (RP; 4 items), bodily pain (BP; 2 items), and general health perceptions (GH; 5 items). The Mental Component Summary (MCS) combines the health domains vitality, energy, or fatigue (VT; 4 items), social functioning (SF; 2 items), role limitations due to emotional problems (RE; 3 items), and general mental health (MH; 5 items). Scores ranging from 0 to 100 points are derived for each domain, with lower scores indicating poorer function. These scores will be converted to a norm-based score and compared with the norms for the general population of the United States (1998), in which each scale was scored to have the same average (50 points) and the same standard deviation (10 points).

The EuroQol-5D is a validated questionnaire for measuring health-related quality of life.[39, 40] Its use is recommended for assessing quality of life in trauma patients, especially for economic assessments.[41, 42] The EQ-5D descriptive system consists of five dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Scores are converted to a utility score ranging from zero to one, with lower scores indicating poorer quality of life. The EQ VAS records the respondents self-rated health status on a vertical (0-100) visual analog scale.

The cost-effectiveness analysis will be performed from a societal perspective and will include costs for health care and production losses. Patients will be asked to complete a custom-made questionnaire that contains detailed information on both items. Health care costs will include general practice care, medical specialist care, nursing care, physical therapy, hospitalization, medication, home care, and other costs directly associated with diagnosis, treatment, and rehabilitation.

In addition to the outcome variables mentioned above, the following data will be collected:
a) Intrinsic variables (baseline data): age, gender, American Society of Anesthesiologists' ASA classification, tobacco consumption, alcohol consumption, comorbidities (including osteoporosis), dominant side, and medication use.
b) Injury related variables: affected side, mechanism of injury, fracture classification according to the AO classification system, additional injuries, and admission duration.
c) Intervention-related variables: time between injury and start of treatment, days of collar and cuff, sling or plaster, time between injury and start of physical therapy, and number of physical therapy sessions.

Study procedures [Table 1]
Clinical evaluation will occur 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. These visits are standard of care for the targeted patient group. At each follow-up visit, the research coordinator or research assistant will ascertain patient status (*i.e.*, adverse events/complications, secondary interventions, etcetera, and will verify information within medical records).

At each follow-up visit, the range of motion of the shoulder and elbow will be measured using a goniometer by a physician or research assistant. In addition, patients will be asked to complete the questionnaires relating to disability (DASH score including optional modules), pain (VAS), health-related quality of life (SF-36, EQ-5D), health care consumption and production loss. From six weeks onwards, the research coordinator or research assistant will determine the Constant score.

At each clinical follow-up visit, anterior-posterior and lateral radiographs are generally routinely obtained. All images available from three months onwards will be analyzed. Apart for the 6-month follow-up, during which X-rays are needed for assessing signs of nonunion, local radiographical protocols will apply. For this reason, the follow-up at six month should not be done earlier. In case no radiographic healing is seen at six months, an X-ray at 12 months is also required. At the last visit, the surgeon or researcher will also document any secondary intervention that is planned for the patient.

Table 1. Schedule of events

Radiographs & Events	**Screening**	**Enrolment**	**Baseline**	**Post surgery**	**2 weeks (7-21 d)**	**6 weeks (4-8 we)**	**3 months (11-15 we)**	**6 months (6-7 mo)**	**12 months 12-14 mo)**
X-Ray	X						X[1]	X[1]	X[1]
Screening	X								
Informed Consent		X							
Baseline Data			X						
Surgical Report Form				X					
DASH					X	X	X	X	X
Pain (VAS)					X	X	X	X	X
SF-36					X	X	X	X	X
EQ-5D					X	X	X	X	X
Clinic FU					X	X	X	X	X
Range of Motion					X	X	X	X	X
Secondary Interventions					X	X	X	X	X
Complications					X	X	X	X	X
Health Care Consumption					X	X	X	X	X
ADL / Work Resumption					X	X	X	X	X
Physical Therapy					X	X	X	X	X
Constant Score						X	X	X	X
Early Withdrawal					*	*	*	*	*

[1] X-rays will be taken according to local protocol; all X-rays after three months will be analyzed. The six-month X-ray is needed for assessing fracture healing. If no signs of healing are seen at six months, the 12-month X-ray is also required.

* Only at time of withdrawal

Chapter 8

Sample size calculation

Calculation of the required sample size for the primary analysis is based on the assumption that the mean DASH in the non-operative group will be 16, with a Standard Deviation (SD) of 16.[8] We expect less disability (*i.e.*, lower DASH score) at three months in the operative group; the expected DASH score in the operative group will be 10 (SD 10).[8] A two-sided test with an α level of 0.05 and a β level of 0.2 requires 78 patients in every group. In order to account for loss
of patients due to mortality (10%) and loss-to-FU (10% anticipated based upon previous studies by the research team), a sample size of 95 patients per group is needed.

Results of a retrospective study assessing clinical outcome of humeral shaft fractures, showed that 45-55% of all AO-subclasses were treated operatively.[18] In order to assess whether functional outcome scores differ between the fracture subtypes, a minimum of 2x20 patients per fracture subtype is sufficient. In order to achieve that, we need to include until at least 200 patients in both the operative groups and the non-operative group.

For the secondary analysis, some patients may be lost during the propensity score matching. Although we do not have a-priori data to determine how many patients will be lost, the 400 targeted patients will be more than sufficient.

Statistical analysis

Data will be analyzed using the Statistical Package for the Social Sciences (SPSS) version 21 or higher (SPSS, Chicago, Ill., USA) and will be reported following the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines. Normality of continuous data will be assessed by inspecting the frequency distributions (histograms), and homogeneity of variances will be tested using the Levene's test.

Descriptive analysis will be performed to report baseline characteristics (intrinsic variables and injury-related variables) and outcome measures for both treatment groups.
For continuous data mean and SD (parametric data) or medians and percentiles (non-parametric data) will be calculated and reported. For categorical data, numbers and frequencies will be calculated and reported for both treatment groups.

Univariate analysis will be performed in order to test the difference in the primary and secondary outcome measures between the operative and the non-operative group. Continuous data such as the DASH score at the different time points (primary outcome) will be tested using a Student's T-test (parametric data) or a Mann Whitney U-test (non-parametric data).

Chi-square analysis will be used for statistical testing of categorical data such as the nonunion rate. A p-value <0.05 will be taken as threshold of statistical significance.

For the primary analysis, a mixed linear regression model will be developed in order to model the relation between different covariates and the DASH score over time. Intrinsic and fracture-related variables that display a p-value <0.5 in univariate analyses will be added as covariate. Similar models will be developed for the Constant, SF-36, and EQ-5D score. Subgroup analysis (*e.g.*, elderly versus <65 years) will be performed.

For the secondary analysis we will develop a propensity score model as published before.[43, 44] Characteristics including fracture type, age, gender, mechanism of injury, dominance, and activity levels will be included in this model; the resulting propensity score represents the chance of being operated. Next, the logit of the propensity score will be used in order to match each patient receiving operative treatment with one or more patients receiving non-operative treatment. The effect of operative treatment will be analyzed with linear or ordinal logistic mixed effects regression analysis taking the matched-pairs design into account. In the matched cohort, comparisons will be performed using a McNemar test (for categorical data), and a paired sample t test (parametric, continuous data) or a Wilcoxon signed rank test.

The economic evaluation will be performed from a societal perspective. Costs will be measured in accordance with Dutch guidelines for economic evaluations, using standard cost prices as published by Oostenbrink where possible[45]; effects will be discounted at a rate of 1.5% and costs at 4% per year [44]. The incremental cost-effectiveness ratio (ICER) of operative versus non-operative treatment will be expressed in a cost-utility ratio (*i.e.*, cost per QALY) using the EQ-5D utility score as effect measure. Uncertainty around this ratio will be presented using confidence ellipses on the cost-effectiveness plane and acceptability curves.

Ethical considerations

The study will be conducted according to the principles of the Declaration of Helsinki (59th World Medical Association General Assembly, Seoul, October 2008). This study has been given a waiver of consent by the medical research ethics committee (MREC); in Dutch: Medisch Ethische Toetsings Commissie (METC). Following review of the protocol, the MREC concluded that this study is not subject to the Medical Research Involving Human Subjects Act (WMO). They concluded that the study is a medical/scientific research, but no patients are subjected to procedures or are required to follow rules of behavior. Consequently, the statutory obligation to provide insurance for subjects participating in medical research (article 7, subsection 6 of the WMO and Medical Research (Human Subjects) Compulsory Insurance Decree of 23 June 2003) was also waived. The MREC Erasmus MC (Rotterdam, The Netherlands) acts as central ethics committee for this trial (reference number MEC-2012-296). Approval has been obtained from the local hospital boards in all participating centers.

DISCUSSION

The HUMMER trial will study outcome after operative versus non-operative treatment of humeral shaft fractures. Operative treatment is expected to result in earlier recovery than non-operative treatment. Earlier functional recovery will result in a better quality of life of patients, earlier work and ADL resumption, a higher level of independency, and less health care needs. Although costs for initial treatment will be higher in the operative group (due to surgery), we hypothesize that costs will be saved by less health care needs during the recovery process and less productivity loss. Despite higher initial costs, we expect that primary surgery will be more cost-effective. To the best of our knowledge, this is the first high-quality multicenter prospective observational study that will look at patient, medical and societal perspective in patients with a humeral shaft fracture.

Thirty hospitals in the Netherlands will participate. Inclusion of patients has started October 01, 2012 and the expectation is to include 10 patients per month. With a follow-up of one year the presentation of data will be expected in the beginning of 2016.

Abbreviations

ADL, Activities of Daily Living; AO, Arbeitsgemeinschaft für Osteosynthesefragen (German for "Association for the Study of Internal Fixation"); ASA, American Society of Anesthesiologists; BP, Bodily Pain; DASH, Disabilities of the Arm, Shoulder and Hand score; ED, Emergency Department; EQ-5D, EuroQol-5D; GH, General Health perception; HR-QoL, Health-related Quality of Life; MCS, Mental Component Summary; MH, general Mental Health; MREC, Medical Research Ethics Committee; NTR, Netherlands Trial Registry (in Dutch: Nederlands Trial Register); PCS, Physical Component Summary; PF, physical functioning; QALY, Quality-Adjusted Life Years; QoL, Quality of Life; RCT, Randomized Controlled Trial; RE, Role limitations due to Emotional problems; ROM, Range Of Motion; RP, role limitations due to physical health; SD, Standard Deviation; SF, Social Functioning; SF-36, Short Form-36; SPSS, Statistical Package for the Social Sciences; STROBE, STrengthening the Reporting of OBservational studies in Epidemiology guidelines; VAS, Visual Analog Scale; VT, vitality, energy, or fatigue.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

KCM, DDH, and EMMVL developed the trial and drafted the manuscript. DDH will act as trial principal investigator. SP assisted in the design of the health care consumption questionnaire and will perform the health economic analyses. KCM and EMMVL will perform statistical analysis of the trial data. KCM, EMMVL, HWB, PKB, MWGAB, MMMB, JDH, ARD, BJD, MGE, JCG, RH, MJH, AJHK, KAK, PAL, SAGM, RO, MP, RWP, BJP, WHR, GRR, AKFT, JBS, NMRS, EJTTH, MVDE, FHWMVDH, FMVDL, PVDZ, JPVD, HPWVJ, EJMMV, JPAMV, MW, PW, WPZ, SP, MHJV and DDH will participate in patient inclusion and assessment. All authors have read and approved the final manuscript.

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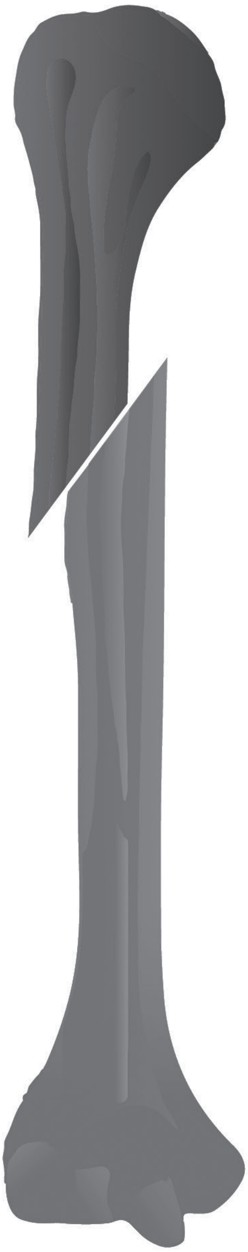

PART V

General discussion, future perspectives and summary

Chapter 9

General discussion and future perspectives

GENERAL DISCUSSION

In this chapter the results of the studies described in this thesis are put into perspective and are discussed. This chapter also elaborates on how the study results fit in the already existing knowledge on the topic. Finally, implications of the current study findings are outlined and suggestions for future research are made.

Epidemiology

The increase in humeral fractures over time in general (**Chapter 2**) may be attributable to population aging, with increasing numbers of elderly (women) being at risk for fractures due to osteoporosis.[1] The incidence rate of proximal fractures increased mostly in women, similar to studies from Finland and Austria.[2-4] The even faster increase in clinical admissions since 2002 may also be attributable to introduction of new implant systems and the improvement of existing ones.[5, 6] Since 1993 the length of hospital stay (LOS) decreased from nine to five days per case. Previous data (13.8 days in 1989 and 9.3 days in 2013) seem to support this trend.[7, 8] Elderly women with a proximal humeral fracture contributed most significantly to the cumulative LOS. As costs for hospital stay are only a part of the total medical costs, reduced LOS did not cause a reduction in these total costs. Falling was the dominant trauma mechanism for all three types of humeral fractures.[9-12] This supports the relevance of fall prevention strategies as a measure to reduce the number of fractures.[13]

Classification

For proximal humeral fractures the Hertel classification showed a trend towards being a more reliable classification system than the Neer classification (**Chapter 3)**. In previous studies, both the inter-observer agreement as well as the intra-observer agreement for the Neer classification on plain radiographs were generally higher than the agreement observed in this study.[14, 15] This difference could be explained by the fact that we selected only patients with comminuted fractures. Classification of these types of fractures is known to have poorer inter- and intra-observer agreement.[16] The inter-observer reliability for both the Hertel and the Neer classification was higher when fractures were classified on CT-scans (with or without 3D-reconstructions) than when classified on X-rays. The 3D-volume rendering, however, did not improve the inter-observer agreement of the Neer classification. Observers judged the Hertel classification as the simpler to use system. For the Hertel classification, the observers had difficulties discriminating type 7 from 12, implying that the fracture line between the head and the lesser tuberosity requires specific attention. For the Neer classification, no specific disagreement was found. Most difficulties for the Neer classification were directly related to the measurements required to be able to use this classification appropriately.[17, 18] Especially the reference points for the degrees of dislocation and the measurement of the degrees of angulation proved difficult. This suggests that the Hertel classification is a more straightforward classification, although this was not supported by a statistically significantly improved agreement.

For the AO/OTA classification of humeral shaft fractures (**Chapter 4**) the inter-observer reliability was moderate and the intra-observer reproducibility was substantial. The validity of the classification has also been studied in various other bone segments, but specific studies focusing on humeral shaft fractures are scarce.[16, 19-24] Previous studies concluded that the classification system for long bone fractures demonstrated a significant inter-observer variation, but no humeral shaft fractures were included.[25, 26] Observers did not agree on specific fracture patterns. When most observers classified a fracture as a simple spiral fracture (12-A1), the remaining observers classified it as a spiral wedge (12-B1). When most observers classified a fracture as a spiral wedge the remaining observers chose the complex spiral fracture (12-C1). Apparently, the fracture lines discriminating these fracture types were easily missed or thought to be seen. Also, the angle of the fracture seemed difficult to determine. The angle of 30 degrees separating the oblique (12-A2) and transverse (12-A3) fracture groups seemed to cause observers to disagree. For future classification systems, specific attention should be paid to these items.

Outcome

The best treatment of humeral shaft fractures is still at debate. In our systematic review and pooled analysis (**Chapter 5)** no differences in fracture healing time, consolidation rate, as well as nonunion rate between non-operative treatment by functional bracing, intramedullary nailing (IMN), and plate osteosynthesis of humeral shaft fractures were shown. A meta-analysis of randomized controlled trials described that both the number of complications and the functional measurements were better in the plating group than in the intramedullary nailing group.[27] Another meta-analysis showed minimally invasive plate osteosynthesis (MIPO) was the better choice in treatment of humeral shaft fractures and reported the rate of radial nerve injury to be the highest in the IMN group and the lowest in the plating group.[28] However, the current study showed a higher prevalence of iatrogenic radial nerve palsies in the plating group, but a higher rate of intraoperative complications and implant failures in the IMN group, this differs from 2 other systematic reviews. Chen *et al.* concluded that no significant differences in complications, secondary procedures and one-year mortality rates were found, comparing literature on open plating and IMN.[29] Fan *et al.* however, found that the IMN group had a significantly lower mean union time than the locking compression plate and radial nerve palsy was found to be higher in the plating group than in the IMN group.[30] These are different results compared with this study, which found no differences in fracture healing time between the three groups and a higher prevalence of iatrogenic radial nerve palsy in the patients treated with plating.

Each included study in our systematic review and pooled analysis had different criteria for treating patients non-operatively or operatively. Despite the possible introduction of bias of treating patients with the more severe fracture types (*e.g.*, displaced, comminuted etc.) operatively, no apparent differences in fracture healing time, consolidation rate, infection, or malunion were found between the three treatment groups. Patients treated by open plating had a higher rate of iatrogenic radial nerve palsy than patients treated with a functional brace. However, patients treated by MIPO did not show a difference in the prevalence of iatrogenic radial nerve palsies compared with the non-operative and IMN groups. Operative treatment might lead to earlier functional recovery because it allows for early mobilization. The functional outcome scores and range of motion of patients treated non-operatively were unfortunately not available and could therefore not be included in the pooled analyses.

The main limitation is the low methodological quality of the included studies as reflected by the MINORS scores. The studies meeting the inclusion criteria often had a small sample size without an adequate power calculation. Moreover, different outcome parameters and methods of reporting the results were used, hampering the pooling of data. Results were frequently reported without a standard deviation and thus could not be included in the pooled analyses either. The results of this chapter should be interpreted with care given the large statistical and clinical heterogeneity.

The Disabilities of the Arm, Shoulder and Hand (DASH) score and the Constant-Murley ROM subscale (**Chapter 6)** demonstrated sufficient internal consistency in patients with a humeral shaft fracture. The observed value for the DASH was consistent with previously published values.[31, 32] The Cronbach α, however, exceeded 0.95, suggesting that some of the items of the DASH questionnaire might be redundant for adequate construct measurement in this research setting. The internal consistency of the Constant-Murley total score was within the range with previously published data.[33] The value should be interpreted carefully because the total instrument is multidimensional. Construct validity of the DASH score was sufficient, with 85.7% of the predicted correlations confirmed. The unexpected low correlation between the DASH and the Constant-Murley power subscale may suggest that not all activities asked in the DASH are affected by differences in power of the shoulder. The high correlation between the DASH and the EQ-5D has been published before in patients with a proximal humeral fracture and was of comparable strength.[34] Interestingly, only a moderate correlation was found between the DASH and the EQ-5D VAS. This suggests that sustaining a humeral shaft fracture does not necessarily affect a patient's general health perception. This is in line with previously published results.[35] The DASH score displayed a ceiling effect at 12 months' follow-up. Treatment of humeral shaft fractures is aimed at full recovery, and achieving this will cause a ceiling effect because patients who have a full recovery report no disabilities on PROMs. In our study, full recovery of a substantial portion of the patients was expected one year after the start of treatment, and so a ceiling effect was expected. But because of the ceiling effect, differences in the group of patients who reported no disabilities at 12 months' follow-up cannot be distinguished, making it not suitable to, for example, use this time point to compare differences of different treatment strategies. The anchor-based minimal important change (MIC) for the DASH was a little lower than found in previous studies.[35, 36] Because MIC values are known to be patient and context dependent, it is likely that the differences in study populations explain the differences in reported MIC values.[37] MIC for the Constant-Murley score has not been reported previously.[33] The smallest detectable change (SDC) as found for this instrument in the current study is in line with those reported previously for shoulder impingement, supraspinatus tears, and massive rotator cuff tears.[38] For monitoring changes in individual patients (*e.g.*,in clinical practice), the MIC should be larger than the SDC. In research, however, the MIC is used differently (*e.g.*, to determine percentages of responders)', and the measurement error is much smaller. For all PROM (sub)scales in this study, the anchor-based MIC was smaller than the SDC. This suggests that the observed MIC values in this study fall into the range that could be due to chance.

In our retrospective study comparing the outcome after operative versus non-operative treatment of humeral shaft fractures (**Chapter 7**), no statistically significant differences were found in the time to radiological consolidation between the two groups, nor in the rates of delayed union or occurrence of radial nerve palsy. Delayed and nonunion rates are consistent with the previously reported data.[39, 40] Due to the high variability in fracture subtypes, our study lacked adequate statistical power to show statistically significant difference in time to radiographic healing between both groups. For the B3 type fractures, a trend was seen, suggesting that the time to radiographic healing was shorter in the non-operative group (median 12 weeks) than in the operative group (median 28 weeks). In the current study 9.1% of the patients had radial nerve palsy. Rates between 2 and 17% are described in literature.[41] In a pooled review by Shao *et al.* the average rate was 11.8%.[42] The retrospective design was a limitation of this study. The decision between operative and non-operative treatment was made by the attending surgeon, based upon his preferences and previous experience. Given the low and similar rates of delayed union in both groups, it is tempting to speculate that the surgeons were quite good at identifying which fractures should be operated. Data on other aspects of outcome (*e.g.,* pain, functional outcome, malunion, return to previous work, resumption of activities of daily living, etc.) were unavailable and should be studied more closely.

FUTURE PERSPECTIVES

This thesis answered some questions regarding the epidemiology, diagnostics and treatment of humeral fractures, with emphasis on humeral shaft fractures, but raised so many new ones. The main question still remains: what is the best treatment of humeral shaft fractures, operative or non-operative? In **Chapter 8** we begin answering this question with the start of the HUMMER study.[43] In this study we set out to evaluate functional recovery after operative versus non-operative treatment in adult patients who sustained a humeral shaft fracture. Secondary aims include the effect of treatment on pain, complications, generic health-related quality of life, time to resumption of activities of daily living and work, and cost-effectiveness. The main hypothesis is that operative treatment will result in faster recovery. To measure functional recovery the DASH score is used. In this thesis we validated the measurement properties of this instrument to evaluate outcome in patients who sustained a humeral shaft fracture. At this moment this is the only instrument with sufficient internal consistency and construct validity, as well as a known MIC and SDC and should thus be used in research of patients with humeral shaft fractures.

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Chapter 10

Summary and conclusions

SUMMARY AND CONCLUSIONS

Chapter 1 is an introduction of this thesis. It elucidates the epidemiological aspects of humerus fractures and gives insight into the treatment and outcome of humeral shaft fractures.

Chapter 2 examines the long-term population-based trends in the incidence rate of patients with a humeral fracture admitted to a hospital in the Netherlands from 1986 to 2012 and gives a detailed overview of the associated costs for health care and lost productivity. Between 1986 and 2012 112,910 patients were admitted for a humeral fracture. The incidence rate increased from 17.8 per 100,000 person years in 1986 to 40.0 per 100,000 person years in 2012. Incidence rates of proximal fractures increased most, especially in elderly women. Surgery rates decreased in patients aged 70 years or older. The mean LOS decreased from nine days in 1997 to five days in 2012. The cumulative LOS of all patients in 2012 was 28,880 days of which 73% were caused by women and 81% were caused by patients aged 50 years or older. Cumulative medical costs in 2012 were M€55.4, of which M€43.4 was spent on women. Costs increased with age. Costs for hospital care contributed most to the overall costs per case until 70 years of age. From 70 years onwards, the main cost determinants were hospital care, rehabilitation/nursing care, and home care. Cumulative costs due to lost productivity were M€23.5 in 2012. Costs per case increased with age in all anatomic regions.

Conclusions

- The crude number of patients admitted for a humeral fracture increased 124% in 27 years, and was associated with age and gender.
- Proximal fractures in elderly women accounted most significantly for this increase and most of the costs.
- The main cost determinants were hospital care and productivity loss

Chapter 3 compares the inter-observer reliability and intra-observer reproducibility of the Hertel with the Neer classification for comminuted proximal humeral fractures. Inter-observer agreement on plain X-rays was fair for both Hertel (κ=0.39; 95% CI 0.23-0.62) and Neer (κ=0.29; 0.09-0.42). Inter-observer agreement on CT-scans was substantial (κ=0.63; 0.56-0.72) for Hertel and moderate for Neer (κ=0.51; 0.29-0.68). Inter-observer agreement on 3D-reconstructions was moderate for both Hertel (κ=0.60; 0.53-0.72) and Neer (κ=0.51; 0.39-0.58) classifications. Intra-observer agreement on plain X-rays was fair for both Hertel (κ=0.38; 0.27–0.59) and Neer (κ=0.40; 0.15-0.52). Intra-observer agreement on CT-scans was moderate for both Hertel (κ=0.50; 0.38-0.66) and Neer (κ=0.42; 0.35-0.52). Intra-observer agreement on 3D-reconstructions was moderate for Hertel (κ=0.55; 0.45-0.64) and substantial for Neer (κ=0.63; 0.48-0.79).

Conclusions

- The Hertel and Neer classifications showed a fair to substantial inter- and intra-observer agreement on the three diagnostic modalities used. Although inter-observer agreement was highest for Hertel classification on CT-scans, Neer classification had the highest intra-observer agreement on 3D-reconstructions.
- Data of this study do not confirm superiority of either classification system for the classification of comminuted proximal humeral fractures.

Chapter 4 describes the inter-observer reliability and intra-observer reproducibility of the OTA/AO classification for humeral shaft fractures. Inter-observer agreement for the three fracture types was moderate (κ=0.60; 0.59-0.61). It was substantial for type A (κ=0.77; 0.70-0.84), and moderate for type B (κ= 0.52; 0.46-0.58) and type C fractures (κ=0.46; 0.42-0.50). Inter-observer agreement for the nine fracture groups was moderate (κ=0.48; 95% CI 0.48-0.48). Orthopedic trauma surgeons had better overall agreement for fracture types, and general orthopedic surgeons had better overall agreement for fractures groups. Observers classified 64% of fractures identically in both rounds. Intra-observer agreement was substantial for the three types (κ=0.80; 0.77-0.81) and nine groups (κ=0.80; 0.77-0.82). Intra-observer agreement showed no differences between surgical disciplines.

Conclusions

- The OTA/AO classification for humeral shaft fractures has a moderate inter-observer and substantial intra-observer agreement for fracture types and groups.

Chapter 5 examines the validity, reliability, responsiveness, and Minimal Important Change (MIC) of the Disabilities of the Arm, Shoulder and Hand (DASH) and Constant-Murley scores for patients with a humeral shaft fracture. A total of 140 patients were included. Internal consistency was sufficient for DASH (Cronbach α = 0.96), but was insufficient for Constant-Murley (α = 0.61). Construct and longitudinal validity were sufficient for both patient-reported outcome measures (>75% of correlations hypothesized correctly). The MIC and SDC were 6.7 (95% CI 5.0-15.8) and 19.0 (standard error of measurement (SEM), 6.9), respectively, for DASH and 6.1 (95% CI -6.8 to 17.4) and 17.7 (SEM, 6.4), respectively, for Constant-Murley.

Conclusions

- The DASH and Constant-Murley scores are valid instruments for evaluating outcome in patients with a humeral shaft fracture.
- Reliability was only shown for the DASH, making this the preferred instrument.
- The observed MIC and SDC values provide a basis for sample size calculations for future research.

In **Chapter 6** outcome after operative versus non-operative treatment of humeral shaft fractures was retrospectively examined. A total of 186 patients were included; 91 were treated non-operatively and 95 treated operatively. Mean age was 58.7 ± 1.5 years and 57.0% were female. In 83.3% of the patients only the humerus was affected. A fall from standing height was the most common cause of the fracture (72.0%). Consolidation time varied from a median of 11 to 28 weeks. The rate of radial nerve palsy in both groups was similar; 8.8% versus 9.5%. In 5.3% of the operatively treated patients the palsy resulted from the operation. Likewise, delayed union rates were similar in both groups: 18.7% following non-operative treatment versus 18.9% following surgery.

Conclusions

- Consolidation time and complication rates after operative and non-operative treatment were similar.
- A prospective comparative clinical study comparing non-operative with operative treatment is needed in order to examine other aspects of outcome, meaning shoulder and elbow function, post-operative infection rates, trauma related quality of life and patient satisfaction.

Chapter 7 describes a systematic literature review and pooled analysis comparing clinical outcome and complications between non-operative and operative treatment of humeral shaft fractures. A total of 114 studies, describing the results of 8,431 patients, were included. Mean consolidation time (15 weeks (95% confidence interval (95% CI) 14-16)) and consolidation rate (93%; 95% CI 92-94%) was similar in each group. The prevalence of iatrogenic radial nerve palsies was 1% (95% CI 0-4%) in patients treated non-operatively, 3% (95% CI 2-4%) in the intramedullary nailing (IMN) and 5% (95% 4-6%) in the plating group. Intraoperative complications and implant failures occurred more frequently in the IMN group than in the plating group. Implant removal rates were comparable for patients treated by IMN and plate osteosynthesis (12% (95% CI 8-16%) and 7% (95% CI 3-12%), respectively). No differences were observed in ASES, Constant-Murley or MEPI scores after IMN or plating osteosynthesis. Shoulder abduction and anteflexion did not differ between the IMN (132 degrees (95% CI 77-189) and 120 degrees (95% CI 33-207), respectively) and plate groups (125 degrees (95% CI 86-164) and 136 degrees (112-160), respectively). A better anteflexion was seen in patients treated with minimally invasive plate osteosynthesis (MIPO) than using an open plating technique (120 degrees (95% CI 85-156) and 166 degrees (164-168), respectively).

Conclusions

- The systematic review and pooled analysis showed no differences in consolidation time and rates between non-operative treatment, IMN and plate osteosynthesis.
- No differences were observed in functional outcome score after operative treatment.
- A well-designed and powered prospective study is needed in order to better guide clinicians in the treatment of humeral shaft fractures. A more uniform reporting of outcome of treatment helps to compare the results of different studies.

Chapter 8 describes the protocol of a multicenter prospective study (HUMMER study) to examine the effect of operative versus non-operative treatment of humeral shaft fractures on the DASH score, on functional outcome, the level of pain, range of motion of the shoulder and elbow joint, the rate of secondary interventions and complications, the time to resumption of work and activities of daily living, health-related quality of life, costs, and cost-effectiveness.

Conclusions

- Successful completion of this study will provide evidence on the effectiveness of operative versus non-operative treatment of patients with a humeral shaft fracture.

Finally, the general discussion and future perspectives are discussed in **Chapter 9**.

Chapter 11

Nederlandse samenvatting en conclusies

Nederlandse samenvatting en conclusies

Hoofdstuk 1 is de introductie van dit proefschrift. Het licht de epidemiologische aspecten van humerusfracturen toe en geeft inzicht in de behandeling van humerusschachtfracturen en de resultaten hiervan.

Hoofdstuk 2 onderzoekt de populatie gebaseerde trends op de lange termijn in de incidentie van patiënten met een humerusfractuur die in de periode 1986-2012 in een ziekenhuis in Nederland zijn opgenomen en geeft een gedetailleerd overzicht van de bijbehorende kosten voor de gezondheidszorg en verloren productiviteit. Tussen 1986 en 2012 werden 112.910 patiënten opgenomen wegens een humerusfractuur. De incidentie steeg van 17,8 per 100.000 persoonsjaren in 1986 tot 40,0 per 100.000 persoonsjaren in 2012. De incidentie van proximale fracturen nam het meest toe, vooral bij oudere vrouwen. Het percentage operatief behandelde patiënten daalden bij patiënten van 70 jaar of ouder. De gemiddelde opnameduur nam af van negen dagen in 1997 tot vijf dagen in 2012. De cumulatieve opnameduur van alle patiënten in 2012 bedroeg 28.880 dagen, waarvan 73% werd veroorzaakt door vrouwen en 81% werd veroorzaakt door patiënten van 50 jaar of ouder. De cumulatieve medische kosten in 2012 bedroegen M€55,4, waarvan M€43,4 werd uitgegeven aan vrouwen. De kosten namen toe met de leeftijd. Kosten voor ziekenhuiszorg droegen het meest bij aan de totale kosten per casus tot 70 jaar. Vanaf 70 jaar waren de belangrijkste kostenbepalende factoren de ziekenhuiszorg, de revalidatie- en verpleegkundige zorg en de thuiszorg. De cumulatieve kosten als gevolg van verloren productiviteit waren M€23,5 in 2012. De kosten per patiënt namen toe met de leeftijd in alle anatomische regio's.

Conclusies

- Het totaal aantal patiënten dat werd opgenomen wegens een humerusfractuur nam in 27 jaar toe met 124% en is geassocieerd met leeftijd en geslacht.
- Proximale fracturen bij oudere vrouwen hebben het meeste bijgedragen aan deze toename en zorgden voor de meeste kosten.
- De belangrijkste kostenbepalende factoren waren ziekenhuiszorg en productiviteitsverlies.

Hoofdstuk 3 vergelijkt de interbeoordelaar betrouwbaarheid en intrabeoordelaar reproduceerbaarheid van de Hertel en de Neer classificaties voor communitieve proximale humerusfracturen. Interbeoordelaar overeenstemming van röntgenfoto's was matig voor zowel de Hertel (κ=0,39; 95% CI 0,23-0,62) als de Neer classificatie (κ=0,29; 0,09-0,42). Interbeoordelaar overeenstemming van CT-scans was goed (κ=0,63; 0,56-0,72) voor de Hertel en redelijk voor de Neer classificatie (κ=0,51; 0,29-0,68). Interbeoordelaar overeenstemming van 3D-reconstructies was redelijk voor zowel de Hertel (κ=0,60; 0,53-0,72) als de Neer classificatie (κ=0,51; 0,39-0,58). Intrabeoordelaar overeenstemming van röntgenfoto's was matig voor zowel de Hertel (κ=0,38; 0,27-0,59) als de Neer classificatie (κ=0,40; 0,15-0,52). Intrabeoordelaar overeenstemming van CT-scans was redelijk voor zowel de Hertel (κ=0,50; 0,38-0,66) als de Neer classificatie (κ=0,42; 0,35-0,52). Intrabeoordelaar overeenstemming van 3D-reconstructies was redelijk voor de Hertel (κ=0,55; 0,45-0,64) en goed voor de Neer classificatie (κ=0,63; 0,48-0,79).

Conclusies

- De Hertel- en Neer-classificaties laten een een matig tot goede inter- en intrabeoordelaar overeenstemming zien van de drie onderzochte diagnostische modaliteiten. Hoewel de interbeoordelaar overeenstemming het hoogst was voor de Hertel classificatie op CT-scans, had de Neer-classificatie de hoogste intrabeoordelaar overeenkomst op 3D-reconstructies.
- Uit de resultaten van deze studie blijkt niet dat een van beide classificatiesystemen superieur is voor de classificatie van communitieve proximale humerusfracturen.

Hoofdstuk 4 beschrijft de interbeoordelaar betrouwbaarheid en intrabeoordelaar reproduceerbaarheid van de OTA/AO classificatie voor humerusschachtfracturen. Interbeoordelaar overeenstemming van de drie fractuurtypes was redelijk (κ=0,60; 0,59-0,61). Het was goed voor type A (κ=0,77; 0,70-0,84) en redelijk voor type B (κ=0,52; 0,46-0,58) en type C fracturen (κ=0,46; 0,42-0,50). Interbeoordelaar overeenstemming van de negen fractuurgroepen was redelijk (κ=0,48; 95% CI 0,48-0,48). Traumachirurgen hadden een betere overeenstemming van de fractuurtypes en orthopedisch chirurgen hadden een betere overeenstemming van de fracturengroepen. Beoordelaars classificeerden 64% van de fracturen identiek in beide rondes. Intrabeoordelaar overeenstemming was goed voor zowel de drie typen (κ=0,80; 0,77-0,81) als de negen groepen (κ= 0,80; 0,77-0,82). Intrabeoordelaar overeenstemming toonde geen verschillen tussen de chirurgische disciplines.

Conclusie

- De OTA/AO-classificatie voor humerusschachtfracturen heeft een redelijke interbeoordelaar en goede intrabeoordelaar overeenkomst voor fractuurtypen en fractuurgroepen.

Hoofdstuk 5 onderzoekt de validiteit, betrouwbaarheid, responsiviteit en minimale belangrijke verandering van de *Disabilities of the Arm, Shoulder and Hand* (DASH) en de Constant-Murley scores voor patiënten met een humerusschachtfractuur. In totaal werden 140 patiënten geïncludeerd. De interne consistentie was voldoende voor de DASH score (Cronbach α=0,96), maar was onvoldoende voor de Constant-Murley score (α=0,61). De construct- en longitudinale validiteit waren voldoende voor beide instrumenten (> 75% van de voorspelde correlaties bleken correct). De minimale belangrijke verandering en kleinste detecteerbare verandering waren respectievelijk 6,7 (95% CI 5,0-15,8) en 19,0 (standaard meetfout (SEM), 6,9) voor de DASH en 6,1 (95% CI -6,8 tot 17,4) en 17,7 (SEM, 6,4) respectievelijk voor de Constant-Murley score.

Conclusies

- De DASH- en Constant-Murley-scores zijn valide instrumenten voor het evalueren van de uitkomst bij patiënten met een humerusschachtfractuur.
- Betrouwbaarheid werd alleen getoond voor de DASH score, waardoor dit het voorkeursinstrument is.
- De waargenomen minimale belangrijke verandering en kleinste detecteerbare verandering bieden een basis voor steekproefgrootte berekeningen voor toekomstig onderzoek.

In **Hoofdstuk 6** werd de uitkomst van operatieve versus niet-operatieve behandeling van humerusschachtfracturen retrospectief onderzocht. In totaal werden 186 patiënten geïncludeerd; 91 werden niet-operatief en 95 werden operatief behandeld. De gemiddelde leeftijd was 58,7 ± 1,5 jaar en 57,0% was vrouw. Bij 83,3% van de patiënten was alleen sprake van een humerusschachtfractuur. Een val van persoon hoogte was de meest voorkomende oorzaak van de fractuur (72,0%). Consolidatietijd varieerde van een mediaan van 11 tot 28 weken. De aanwezigheid van nervus radialis uitval was in beide groepen vergelijkbaar; 8,8% versus 9,5%. Bij 5,3% van de operatief behandelde patiënten was het radialis uitval het gevolg van de operatie. Het optreden van vertraagde fractuurgenezing was vergelijkbaar in beide groepen: 18,7% na niet-operatieve versus 18,9% na operatieve behandeling.

Conclusies

- Consolidatietijd en complicaties na operatieve versus niet-operatieve behandeling waren vergelijkbaar.
- Er is een prospectief vergelijkende klinische studie nodig, waarbij de niet-operatieve met de operatieve behandeling wordt vergeleken om andere aspecten van de uitkomst te onderzoeken, zoals schouder- en elleboogfunctie, post-operatieve infecties, traumagerelateerde kwaliteit van leven en tevredenheid van de patiënt.

Hoofdstuk 7 beschrijft een systematisch literatuuroverzicht en gepoolde analyse, waarin klinische uitkomsten en complicaties van niet-operatieve en operatieve behandeling van humerusschachtfracturen worden vergeleken. De resultaten van in totaal 114 studies, die 8.431 patiënten beschrijven, werden geïncludeerd. De gemiddelde consolidatietijd (15 weken (95% betrouwbaarheidsinterval (95% CI) 14-16)) en consolidatiepercentage (93%, 95% BI 92-94%) was vergelijkbaar in elke groep. De prevalentie van iatrogene radiale uitval was 1% (95% CI 0-4%) bij niet-operatieve patiënten, 3% (95% CI 2-4%) in de intramedullaire pen (IP) en 5% (95% 4-6%) in de plaat-groep. Intra-operatieve complicaties en implantaat falen kwamen vaker voor in de IP-groep dan in de plaat-groep. Het percentages van het verwijderen van het osteosynthesemateriaal was vergelijkbaar voor patiënten behandeld met een IP en plaatosteosynthese (respectievelijk 12% (95% CI 8-16%) en 7% (95% CI 3-12%)). Er werden geen verschillen waargenomen in ASES, Constant-Murley of MEPI scores na IP of plaatosteosynthese. Schouderabductie en -anteflexie verschilden niet tussen de IP (respectievelijk 132 graden (95% CI 77-189) en 120 graden (95% CI 33-207) en plaatgroepen (125 graden (95% CI 86-164) en 136 graden (112-160), respectievelijk). Een betere anteflexie werd gezien bij patiënten die werden behandeld met minimaal invasieve plaatosteosynthese (MIPO), in vergelijkingen met patiënten die werden behandeld met open plaatosteosynthese (respectievelijk 120 graden (95% CI 85-156) en 166 graden (164-168)).

Conclusies

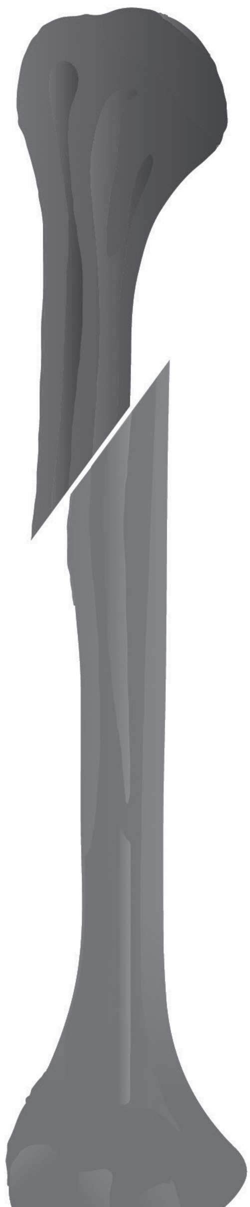
- Het systematische review en de gepoolde analyse toonden geen verschillen in consolidatietijd en -percentage tussen niet-operatieve behandeling, IP en plaatosteosynthese.
- Er werden geen verschillen waargenomen in functionele uitkomstscores na operatieve behandeling.
- Een goed ontworpen prospectief onderzoek is nodig om artsen beter te begeleiden bij de behandeling van humerusschachtfracturen. Een meer uniforme rapportage van de uitkomst van de behandeling helpt om de resultaten van verschillende onderzoeken te vergelijken.

Hoofdstuk 8 beschrijft het protocol van een prospectieve studie met meerdere deelnemende centra (de HUMMER-studie) waarin de operatieve versus niet-operatieve behandeling van humerusschachtfracturen wordt onderzocht op de DASH-score, op functionele uitkomst, pijn, bewegingen van de schouder en de ellebooggewrichten, het aantal secundaire interventies en complicaties, de tijd tot hervatting van het werk en activiteiten in het dagelijks leven, alsook gezondheidsgerelateerde kwaliteit van leven, kosten en kosteneffectiviteit.

Conclusies

- Het afronden van deze studie zal bewijs leveren over de effectiviteit van operatieve versus niet-operatieve behandeling van patiënten met een humerusschachtfractuur.

Ten slotte worden de algemene discussie en toekomstperspectieven besproken in **hoofdstuk 9**.



Appendices

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Mahabier KC, Van Lieshout EMM, Van der Torre T, Notenboom CAW, Jawahier PA, Den Hartog D, Verhofstad MHJ
Submitted

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PHD PORTFOLIO SUMMARY

Summary of PhD training and teaching activities

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Co-promotors:	dr. D. Den Hartog and dr. E.M.M. Van Lieshout

1. PhD training

	Year	**Workload (ECTS)**
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- Biomedical English Writing and Communication	2015	2.0
- Research Integrity	2014	0.3
- BROK - Basiscursus Regelgeving en Organisatie van Klinische trials (GCP course)	2012	2.0
- Traumadagen	2012-2017	4.0
- Chirurgendagen	2012-2017	4.0
Research skills		
- Biostatistical Methods I	2014	2.0
- Methodologie van Patiëntgebonden Onderzoek en Subsidieaanvragen	2012	0.3
Presentations on conferences		
- Chirurgendagen 2015	2015	1.0
- European Congress of Trauma & Emergency Surgery (ECTES) 2015	2015	1.0
- Assistentensymposium Traumachirurgie 2015	2015	1.0
- Wetenschapsdag Heelkunde 2014	2014	1.0
- Najaarsdag NVvH 2014	2014	1.0
- Traumadagen 2014	2014	1.0
- Gevorderden Symposium Traumachirurgie 2013	2013	2.0
- ZWOT 2012	2012	1.0

Seminars and workshops	2013	1.0
- NFU Platform Klinisch Onderzoek De onderzoeker aan zet		

2. Teaching activities

	Year	Workload (ECTS)
Supervising practicals and excursions		
- Examination of Basic Life Support of medical students	2011 - 2016	1.0
Supervising Master's theses		
- Jelle Bousema		2.0
- Tim van der Torre		2.0
- Marije Notenboom		2.0
- Boyd van der Schaaf		2.0
- Joyce van Veldhuizen		2.0
- Nina Theyskens		2.0

ABOUT THE AUTHOR

Kiran Chander Mahabier was born on December 18th, 1984 in Heerlen, the Netherlands. After graduating high school at DevelsteinCollege in Zwijndrecht in 2003, he started medical school at the Erasmus University Rotterdam. During this time the groundwork for this thesis was laid with a study comparing the operative and non-operative treatment of humeral shaft fractures. In January 2011 he obtained his medical degree and started working at the Department of Surgery at the Maasstad Hospital in Rotterdam as a resident not in training. In July 2012 he had the opportunity to return to the Erasmus MC at the Trauma Research Unit, Department of Surgery and continue the research of humeral fractures, which led to this thesis. In October 2016 Kiran started the training to become an orthopedic surgeon at the St. Antonius Hospital (dr. D. Boerma and dr. M. Van Dijk), Onze Lieve Vrouwe Gasthuis (drs. D.F.P. Van Deurzen), and UMC Utrecht (dr. J.J. Verlaan). He is married to Eva and proud father of two beautiful sons (Julius and Tobias).