HUMERAL FRACTURES

Epidemiology, treatment and reoperations in the Swedish Fracture Register

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There is a crack
in everything.
That’s how the
light gets in.

– LEONARD COHEN

ABSTRACT

Fractures are common, but the knowledge on outcomes, treatment methods or the actual number of fractures treated each year has been sparse. With the introduction of the Swedish Fracture Register (SFR) in 2011, prospective registration and analysis of detailed population-based fracture data was made possible for the first time.

Aim: The overall aim of this thesis was to analyse the quality of data in the SFR and to determine whether, and to which extent, the SFR can be used in epidemiological research. Particularly, the incidence of humeral fractures and the mortality associated with proximal humeral fractures were analysed, and changes in treatment practice for proximal humeral fractures in recent years were evaluated.

Methods: All the papers in this thesis were based on fracture registrations in the SFR. Comparisons with other data sources were made; fracture registrations in the National Patient Register (NPR) were used to examine data quality, and information from Statistics Sweden were used to calculate fracture incidence and to compare mortality rates between fracture patients and the general population.

Result: In this thesis, Study I demonstrates that 88% of humeral fractures were registered in the SFR, and that all registrations were valid fracture registrations. The SFR therefore constitutes a complete, accurate and efficient source of information, well suited to epidemiological research. In contrast, data from the NPR contain a large proportion of non-valid fracture registrations and need to be improved in order to function as a solid basis for epidemiological research. Studies II-IV in this thesis demonstrate that the incidence of humeral fractures, regardless of fractured segment, increases significantly after the age of 50 years and is predominantly related to low-energy falls. This indicates the important influence of age-related risk factors, such as osteoporosis. Moreover, a proximal humeral fracture is associated with a substantially increased mortality, especially within the first weeks following the fracture. Male gender and low-energy trauma mechanisms were two independent risk factors for death following a humeral fracture. Finally, there was no significant change in the overall proportion of patients treated surgically between 2011 and 2017. However, considerable changes within the different surgical treatment modalities were observed. The use of plate fixation decreased significantly, while the use of intramedullary nails and reversed shoulder arthroplasty increased. Unfortunately, these changes in treatment practice did not affect the reoperation rate, which continued to be high throughout the study period.

Conclusion: The SFR is a reliable tool for population-based observational research. Data from the SFR demonstrate that proximal humeral fractures predominately affect frail people. A surprisingly high reoperation rate calls for awareness of the importance of choosing the right treatment to the right patient.

SAMMANFATTNING PÅ SVENSKA

Trots att frakturer är vanligt förekommande i befolkningen har det länge saknats tillförlitliga uppgifter om hur många frakturer som inträffar per år, hur de behandlas och hur utfallet har blivit. Länge har detaljerade, populationsbaserade data efterfrågats som kan ge svar på frågor som dessa. I och med introduktionen av det Svenska Frakturregistret (SFR) finns det nu för första gången ett register som kontinuerligt samlar detaljerad information om alla frakturer oavsett behandling. Registret innehåller även information om reoperationer och patientrapporterade utfallsmått.

De ingående studierna i denna avhandling syftar till att utvärdera tillförlitligheten av data i SFR samt att öka kunskapen kring överarmsfrakturer. Specifikt undersöks epidemiologi, mortalitet, och om de senaste årens ändrade sätt att behandla överarmsfrakturer har inneburit en minskad risk för reoperationer.

Ett nytt register behöver utvärderas avseende registreringarnas korrekthet och tillförlitlighet innan innehållet kan analyseras och tolkas på bred front. Värdet av ett register är avhängigt datakvalitén, och utan tillförlitliga data blir resultatet av analyser missvisande. Med tanke på att data i SFR oftast samlas in under pressade tidsförhållanden på akutmottagningar runt om i landet är det viktigt att undersöka hur stor andel av frakturerna som registreras i registret, och hur korrekta dessa registreringar är. I första delarbetet jämförs registreringar av akuta överarmsfrakturer i SFR och Nationella Patientregistret (NPR). Studien fann att de allra flesta överarmsfrakturerna var registrerade i SFR (88%) och att samtliga registreringar motsvarade en verklig akut överarmsfraktur (100%). Vad gäller NPR var i stort sett alla överarmsfrakturer (97%) registrerade, men det förekom ett stort antal ”falska” registreringar av akuta överarmsfrakturer (registreringar som i själva verket motsvarade något annat än en akut överarmsfraktur). Endast 70% av överarmsfraktur-registreringarna i NPR motsvarade en akut överarmsfraktur. Som slutsats kan man konstatera att det inte är tillförlitligt att använda sig av NPR-data för att undersöka överarmsfraktur-epidemiologi.

Nästa studie i avhandlingen undersöker förekomsten av överarmsfrakturer i befolkningen och redovisar epidemiologiska data med hjälp av SFR från konsekutivt behandlade patienter på Sahlgrenska Universitetssjukhuset under tre års tid. Ungefär 105 personer per 100,000 invånare drabbas årligen av en överarmsfraktur och en majoritet av dessa personer är kvinnor (kvinnor:män 2,4:1). Förekomsten av överarmsfrakturer ökar markant efter 50 års ålder, oavsett vilken del av överarmen som drabbas, och en stor majoritet (79%) av frakturerna orsakas av ett enkelt fall från stående. Sammantaget talar resultatet för att åldersrelaterade riskfaktorer såsom osteoporos har stor betydelse för uppkomsten av överarmsfrakturer.

Den tredje studien undersöker om det föreligger en ökad risk för död hos patienter som drabbas av en fraktur på övre (proximala) delen av överarmen. Vi vet sedan länge att höft- och kotfrakturer är associerade med en ökad dödlighet, men det har varit mer osäkert om detsamma gäller för proximala överarmsfrakturer. Med hjälp av data från hela SFR och länkning med Skatteverket kunde alla dödsfall identifieras hos frakturpatienterna. Vidare kunde ålders- och könsmatchade kontroller till frakturpatienterna identifieras via Statistiska centralbyrån. Vid jämförelse kunde vi visa att patienter med en proximal överarmsfraktur löper en fem gånger ökad risk för död 30 dagar efter frakturen jämfört med normalpopulationen. Dödligheten hos frakturpatienterna avtog med tiden men var fortsatt dubblerad ett år efter frakturen. Hög ålder, manligt kön, annan samtidig fraktur och icke-kirurgisk behandling var alla oberoende faktorer associerade med en ökad dödlighet.

Det har rapporterats om att sättet att behandla proximala överarmsfrakturer har ändrats de senaste åren trots avsaknad av vedertagna behandlingsrekommendationer. Risken för att behöva genomgå ytterligare operationer är olika stor beroende på vilken behandlingsmetod som initialt används, men någon signifikant skillnad i funktionellt utfall med de olika behandlingsmetoderna har inte kunnat påvisas. I det fjärde arbetet studerades val av behandling av proximala överarmsfrakturer under en sjuårsperiod vid Sahlgrenska Universitetssjukhuset, och om val av behandlingsmetod påverkade risken för reoperation. Vi såg att andelen patienter som behandlades operativt var oförändrad över tid, men de kirurgiska behandlingsmetoderna ändrades drastiskt. Andelen som behandlades med vinkelstabil platta halverades samtidigt som andelen som behandlades med märgspik eller omvänd axelprotes ökade markant. Ändringarna i behandlingspraxis påverkade dock inte risken för reoperation. Under studieperioden utgjordes en fjärdedel av alla operationer för proximala överarmsfrakturer av en reoperation.

Sammanfattningsvis visar avhandlingen att SFR är en tillförlitlig källa och en viktig tillgång i populationsbaserad observationell forskning. Proximala överarmsfrakturer drabbar sköra personer och det finns anledning att revidera synen på dessa frakturer för att optimera behandlingen och omhändertagandet.

LIST OF PAPERS

The thesis is based on the following papers, referred to in the text by their Roman numerals.

I. Carl Bergdahl, Filip Nilsson, David Wennergren, Carl Ekholm, Michael Möller.
Completeness in the Swedish Fracture Register and the Swedish National Patient Register: an assessment of humeral fracture registrations.
Clinical Epidemiology 2021;13:325-333.

II. Carl Bergdahl, Carl Ekholm, David Wennergren, Filip Nilsson, Michael Möller.
Epidemiology and pathoanatomical pattern of 2,011 humeral fractures: data from the Swedish Fracture Register.
BMC Musculoskeletal Disorders 2016;17:159 DOI 10.1186/s12891-016-1009-8

III. Carl Bergdahl, David Wennergren, Jan Ekelund, Michael Möller.
Mortality after a proximal humeral fracture – data on 18,452 patients from the Swedish Fracture Register.
Bone Joint Journal 2020;102-B(11):1484-1490.

IV. Carl Bergdahl, David Wennergren, Eleonora Swensson-Backelin, Jan Ekelund, Michael Möller.
No change in reoperation rates despite shifting treatment trends: results of a population-based study of 4,070 proximal humeral fractures.
Acta Orthopaedica 2021;30:1-7 DOI 10.1080/17453674.2021.1941629

CONTENTS

ABBREVIATIONS

AO	Arbeitsgemeinschaft für Osteosynthesefragen
AVN	Avascular necrosis
EQ-5D	EuroQual 5 Dimensions
ICD-10	International classification of diseases tenth revision
HA	Hemiarthroplasty
NBHW	National Board of Health and Welfare
NPR	National Patient Register
NQR	National quality register
ORIF	Open reduction internal fixation
OTA	Orthopaedic Trauma Association
PHF	Proximal humeral fracture
PIN	Personal identity number
PROM	Patient reported outcome measure
RCT	Randomised controlled trial
RSA	Reverse shoulder arthroplasty
SFR	Swedish Fracture Register
SMFA	Short Musculoskeletal Function Assessment
SMR	Standardised mortality ratio

BRIEF DEFINITIONS

Accuracy	The degree to which a measurement/variable conforms to the correct value, i.e. how correct a measurement is. In this thesis the accuracy of registration refers to the proportion of cases in the register that truly have the recorded condition.
Completeness	The proportion of all cases in a population that is included in a measurement, survey or a register database.
Incidence	The occurrence of new cases of a given medical condition in a population in a specified time period.
Mortality	Number of deaths in a particular population in a certain period of time.
Crude mortality	Mortality from all causes.
Standardised mortality ratio	The ratio quantifying the increase, or decrease, in mortality of a study cohort with respect to the general population.
Arthroplasty	A surgical procedure in which the articulating surface of a skeletal joint is replaced with an artificial joint implant.
ORIF	Open reduction internal fixation refers to a surgical treatment of a fracture where the fragments are exposed, re-aligned and fixated with an implant. In this thesis ORIF includes all types of internal implant such as plates, intramedullary nails and combination methods.
Reoperation	An unplanned surgical procedure related to the initial treatment. In this thesis reoperation refers to all unplanned secondary surgeries, regardless of the primary treatment.
Reoperation rate	The proportion of patients treated with a given treatment modality later subjected to a reoperation.

01

INTRODUCTION

Every year in Sweden, approximately 140,000 persons sustain fractures and the incidence of fractures has been projected to increase.[1-3] In addition to affecting the everyday life of many people, these fractures consume larges economic and social resources.[4] Despite this, surprisingly little is known about the actual number of fractures, who they affect and what the outcome is following treatment. Accordingly, conducting research on patients that have sustained a fracture is difficult. The acute nature of fractures, the fact that there is great heterogeneity between fractures in the same location and that patients of all ages and backgrounds are affected contribute to the difficulty involved in fracture research. Historically, the development of new surgical techniques and the introduction of new implants, supported by the results of small case series, have influenced the way fractures are treated.[5-7] Unfortunately, the implications of study results for everyday clinical practice can be difficult to predict. Outside the strict setting of clinicals trials, the positive results of these case series have often been difficult to reproduce.[7-9] Today, few evidence-based guidelines exist to help direct clinicians in treatment decisions for different fractures.[10]

Fractures of the humerus are one of the most common fractures and it is projected that one in every six women will sustain a fracture of this kind during her lifetime.[11,12] In spite of this, the treatment of humeral fractures, especially proximal, is controversial and one of the most debated of all fracture treatments.[10,13,14] There are no definitive data on who will benefit from surgical treatment or which method of surgical treatment is preferred for which patient. Randomised controlled trials (RCTs) have not shown any advantages of surgical treatment, but high rates of complications have instead been reported following surgery.[15-18] However, surgeons have continued to explore new modes of treatment, since specific subgroups of patients are believed to benefit from surgical intervention.[16,19-21]

With an ageing population and the continuous development of surgical techniques and implants, updated data on the epidemiology, mortality and complications of modern treatment are essential. As a result, there has been a widely recognised need for population-based register data in order to promote better outcomes and develop evidence-based trauma orthopaedics.[18] When the Swedish Fracture Register (SFR) started in 2011, there was finally a national register that prospectively collects detailed data on fractures of all types, regardless of location and type of treatment.

This thesis aims to examine whether data from the SFR are reliable and to use these data to bridge gaps of knowledge related to humeral fractures, perhaps the most debated fracture of all.

1.1 ANATOMY

The humerus is a long bone in the upper arm, connecting the scapula with the two bones of the lower arm, the radius and the ulna. It is the third largest long bone in the body and the largest bone in the upper extremities. The humerus is usually divided into three segments, the proximal, shaft and distal segments. The distinction between these segments will be further explained in the section on the classification of fractures. The proximal humerus connects the arm with the scapula via the glenohumeral joint and consists of a rounded head with the articular surface, two short processes (the greater and lesser tuberosities) and a narrow neck (Figure 1). In fact, there are two necks of the proximal humerus. The anatomic neck comprises the transition between the articular surface and the tuberosities, while the narrow neck below the tuberosities is referred to as the surgical neck. The surgical neck is so called due to its tendency to fracture, thereby often becoming the focus of surgeons. Distal to the proximal part of the humerus is the shaft, which is cylindrical in its upper part and becomes more triangularly shaped distally. The distal segment of the humerus articulates with the two bones of the forearm. The trochlea and the capitellum comprise the articular surface of the distal humerus and projecting on either side are the lateral and medial epicondyles. The epicondyles are the points of origin for the stabilising ligaments of the elbow and the common extensor and flexor muscles of the forearm.

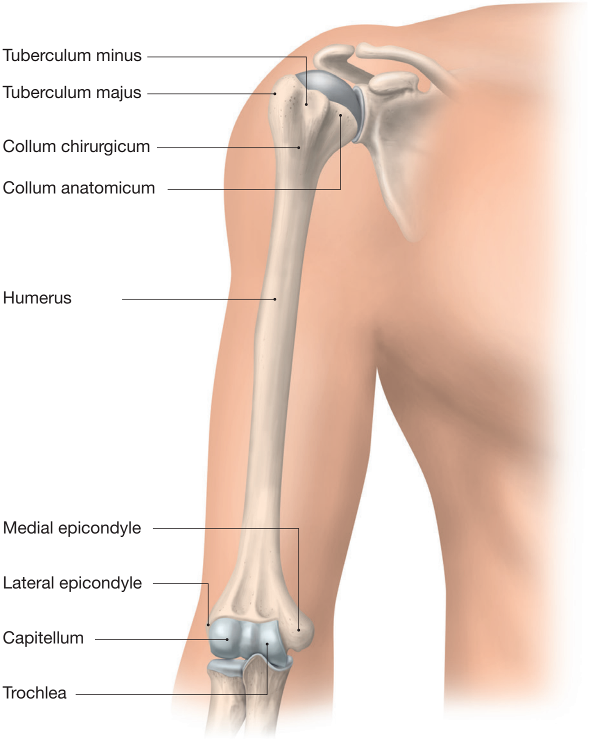

FIGURE 1.
The humerus.

The proximal end and the shaft of the humerus are well covered by soft tissues. The large muscle of the deltoid attaches laterally to the shaft at the deltoid tuberosity and covers the upper part of the humerus. The muscles functioning across the elbow joint originate from and cover the remaining parts of the shaft. By contrast, the distal end of the humerus is more exposed. Only skin and a thin layer of subcutaneous fat cover the epicondyles, making the distal humerus theoretically more prone to open fractures.

The neurovascular bundle of the arm, the axillary artery and the plexus brachialis, runs medially and in close proximity to the proximal humerus (Figure 2). These neurovascular structures are especially at risk in anterior fracture dislocations or when the distal segment of a fracture through the surgical neck is pulled medially by the dislocating forces of the pectoralis muscle.

The blood supply to the proximal humerus is comprised of two main vessels that arise from the axillary artery in the transition between the proximal and shaft segments of the humerus. These two vessels, the anterior and posterior humeral circumflex arteries, wind around the surgical neck and ascend to the head of the humerus, thus placing them at risk in the event of a displaced surgical neck fracture.

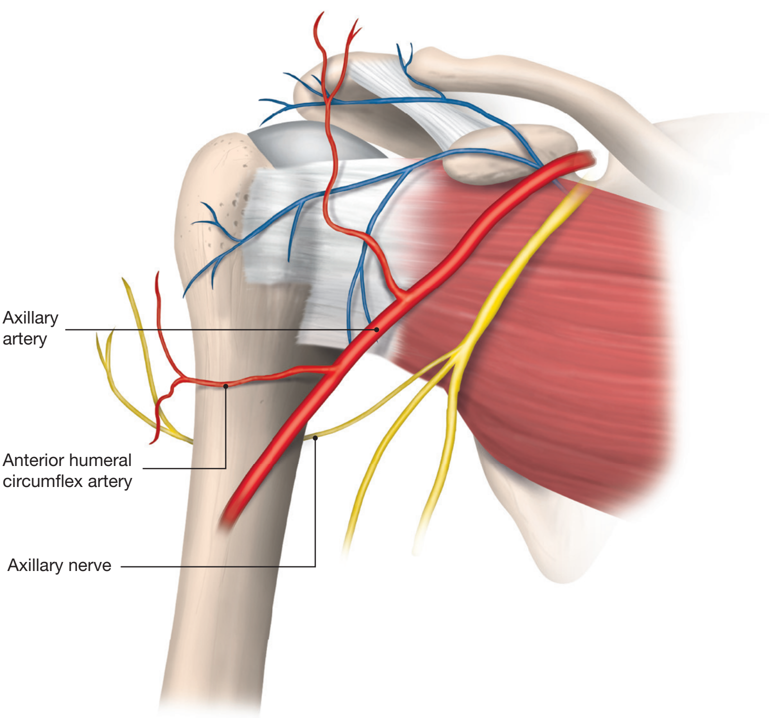

FIGURE 2. The neurovascular bundle of the arm.

The proximal surface of the humerus articulates with the small and shallow glenoid fossa of the scapula, forming the shoulder joint. The shoulder joint has often been described as a golf ball (humeral head) sitting on a golf tee (glenoid fossa) and it is the most mobile joint in the body. The muscles and tendons of the rotator cuff embrace the humeral head and are of significant importance for shoulder function. These four muscles originate from the scapula and insert to the tuberosities of the proximal humerus, functioning as primary stabilisers of the joint, as well as being vital to shoulder movement. The supraspinatus, infraspinatus and teres minor tendons attach to the greater tuberosity and aid in the abduction and external rotation of the arm, while the subscapularis attaches to the lesser tuberosity and aids in the internal rotation of the arm. During shoulder abduction and flexion, all four muscles of the rotator cuff interact to compress the humeral head into the shallow cavity of the glenoid in order to allow the forces of the large deltoid muscle to elevate the arm. Without a functioning rotator cuff, for instance following a tendon tear or a fracture, the humeral head will partially disconnect from the glenoid fossa whenever the upward-pulling forces of the deltoid muscle act on the humerus. This leads to an impaction between the humeral head and the acromion (i.e. impingement) which manifests as pain and reduced function of the arm. It is therefore of the utmost importance to restore the integrity and function of the rotator cuff in order to maintain a functional shoulder following shoulder trauma.[21-23] The integrity of the rotator cuff generally deteriorates with increasing age and this has been attributed to the poor outcome associated with displaced fractures of the proximal humerus in the elderly.[24-26]

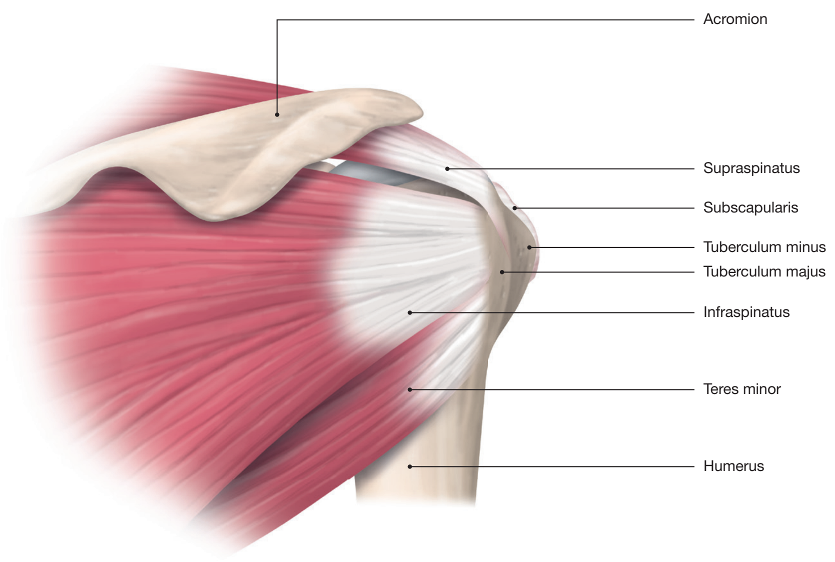

FIGURE 3. The shoulder and the rotator cuff, dorsal view.

1.2 CLASSIFICATION OF FRACTURES

The classification of fractures is essential in fracture management. Understanding the morphology of fractures and clustering them into different groups provides a framework for communicating effectively on clinical cases. Fracture classification is therefore a prerequisite for data collection in national quality registers and for clinical research. It allows comparisons between different groups of fractures or among similar groups treated differently. An ideal fracture classification system should be sensitive enough to identify different fracture patterns but simple enough to be reliable and reproducible.[27] Moreover, it should preferably reflect the severity of the bony lesion, thereby predicting outcome and function as a tool in clinical decision-making.[28]

There are numerous classification systems for fractures of the different segments of the humerus, as well as several classification systems for the same humeral segment.[29-31] This could perhaps indicate that the perfect classification system is yet to be presented. However, the AO/OTA classification system is comprehensive, widely recognised and covers most parts of the body (Figures 4, 5 and 6). It is therefore regarded as the best available option for classifying fractures in the SFR. Consequently, the AO/OTA classification system was used in the studies in this thesis.

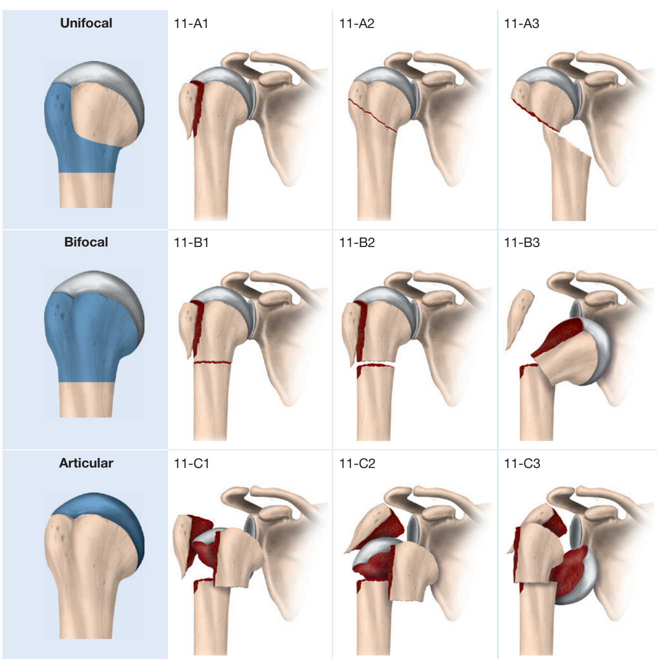

FIGURE 4. The AO/OTA classification of proximal humeral fractures

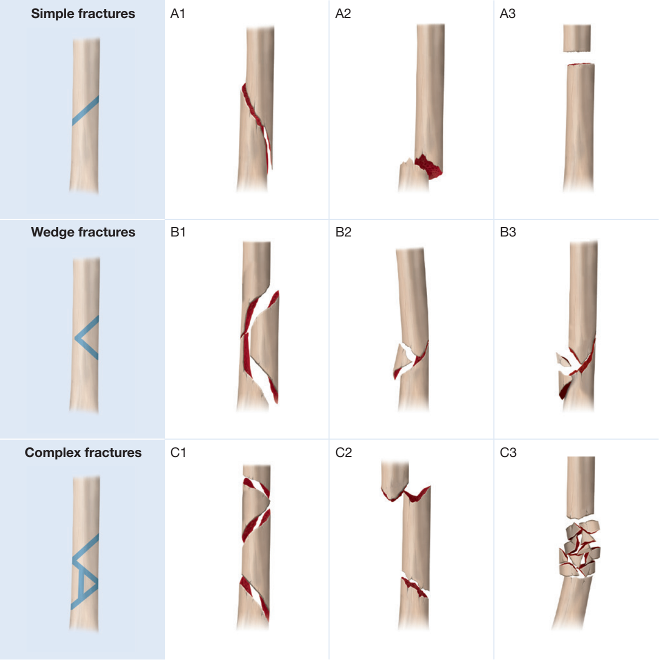

FIGURE 5. The AO/OTA classification of humeral shaft fractures

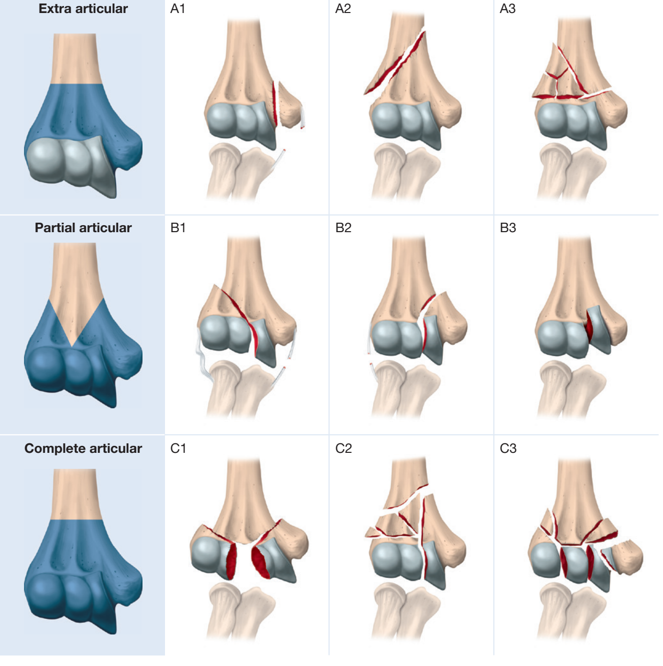

FIGURE 6. The AO/OTA classification of distal humeral fractures

The most widely used classification system today for diaphyseal and distal humeral fractures is the AO/OTA classification system.[30,32-34] This system will be described later. However, for proximal humeral fractures, the classification system developed and named by Charles Neer is perhaps even better known and more commonly used than the AO/OTA system.[35] The Neer system is based on Codman's findings in 1934 that fractures of the proximal humerus most frequently occur between four different anatomical segments; the greater tuberosity, lesser tuberosity, articular surface and humeral shaft.[35,36] Charles Neer developed this observation into a classification system, taking the displacement effects of the musculotendinous forces on the fracture segments and the blood supply to the humeral head into account. As a result, the classification system is based upon displacement rather than the actual number of fracture lines. To be counted as a separate segment, a displacement greater than 10 mm and/or an angulation of ≥ 45 degrees must be present. Consequently, if a fractured part is less displaced, it is not regarded as a separate segment. These displacement criteria were not based on observations but were arbitrarily established on the request of the editor when the original article was published in 1970.[35,37] Neer revised the system in 1975 and 2002, so that it now includes one- to four-part fractures, with additional categories for articular fractures or dislocations, describing a total of 16 fracture categories (Figure 7).

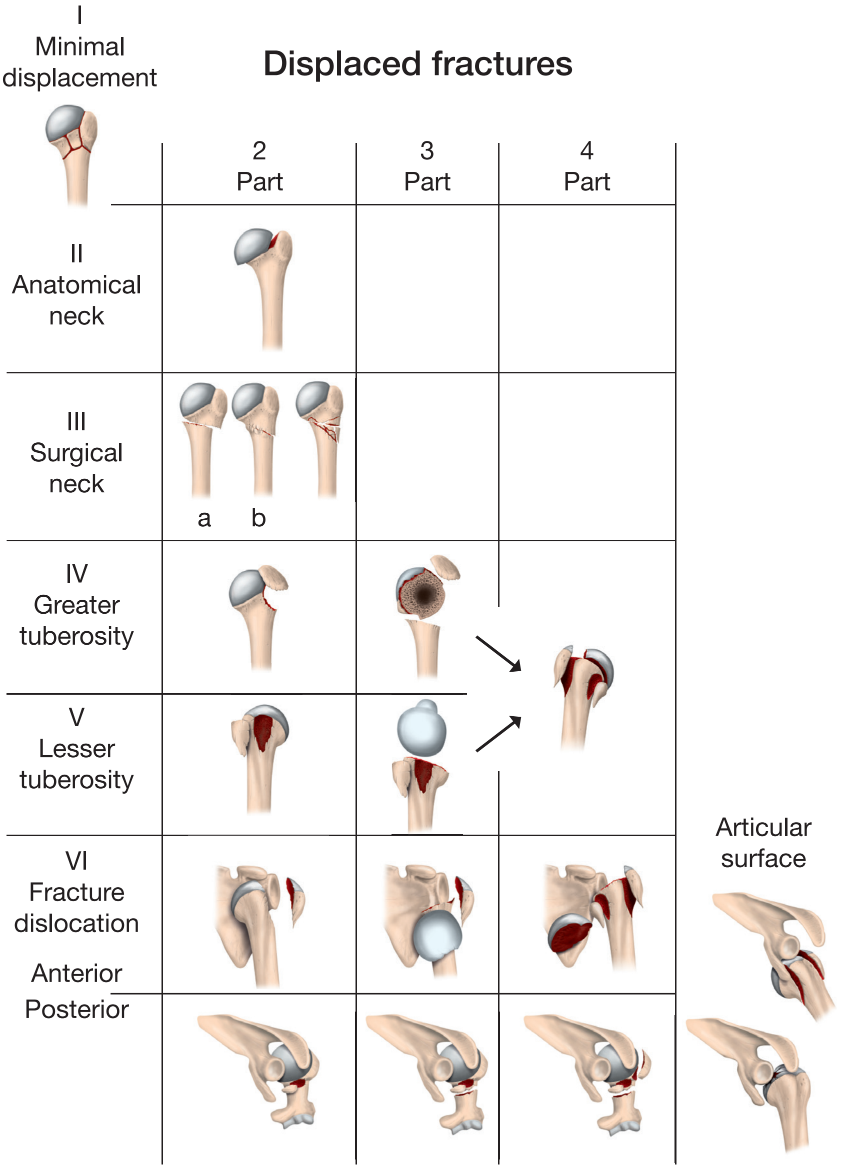

FIGURE 7. The Neer classification of proximal humeral fractures.

1.2.1 AO/OTA classification

The AO/OTA classification of fractures is the result of a collaboration between the Arbeitsgemeinschaft für Osteosynthesefragen (AO) and the Orthopaedic Trauma Association (OTA) in 1996.[38] Their work was in turn based on the original Müller classification of long bones and it was later revised and updated in 2007 and 2018.[30,39,40] The stated purpose of the AO/OTA classification is to be a comprehensive classification, designed to have a similar structure for all the bones in the body, thereby creating a uniform terminology for fracture classifications that encompasses the entire skeleton and facilitates the development and use of trauma databases. The AO/OTA classification is based on a five-positional alphanumeric code, which focuses on the progressive severity of the fracture. All the positions within the code have a similar meaning for different fractures in the body. The first position represents the bone in question (1 for humerus) and the second represents the affected segment of the bone (1=proximal, 2=diaphyseal, 3=distal). The third position is a letter, which has a similar meaning for end-segment fractures (metaphyseal/articular segments) and for diaphyseal fractures respectively. For end-segment fractures, A represents an extra-articular fracture, B a partial articular fracture and C a complete articular fracture. For diaphyseal fractures, A represents simple fractures, B fractures with an intermediate fragment (wedge) and C fractures with intermediate fragments without bony contact between the main fragments (complex). The final two positions (group and subgroup) demonstrate specific features of the bone and segment in question and consist of the numbers 1, 2 or 3. This generates three types (3rd position codes), nine groups (4th position codes) and a total of 27 sub-groups (5th position codes) for each segment of a bone. Typically, the severity of the fracture increases with higher classification numbers.

The localisation of the different segments (proximal, shaft, distal) within a long bone is defined by the rule of squares, the so-called "Müller square".[40] This means that the end segment of a long bone is defined as a square where the sides are as long as the width of the broadest part of the segment in question (Figure 8). The border between the shaft and the end segment is defined by the proximal or distal sides of the square. The centre of the fracture determines the segment into which it should be classified and a fracture is always end-segmental if intra-articular. The rule of squares may appear simplistic, but most other classification systems lack a definition of the fractures that are actually included in the classification of interest.

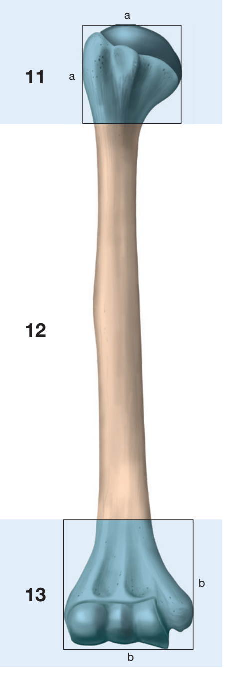

FIGURE 8. The definition between the different segments of the humerus according to the rule of squares, i.e. the "Müller square", in the AO/OTA classification system. The proximal and distal segments are defined as the part within a square whose sides are as long as the broadest part of the bone in that segment.

For the classification of proximal humeral fractures in the SFR, a modified version of the AO/OTA classification system was adopted. This version maintains the original principles of the AO/OTA system with regard to definitions and the basic coding system, but the description of the classification is parallel with Neer's terminology. This resulted in a classification system with three main types (type A; extra-articular, unifocal, two-part fractures, type B; extra-articular, bifocal, three-part fractures, type C; articular or four-part fractures) and 12 sub-groups (Figure 19 in the Method section). Interestingly, the latest revision of the AO/OTA classification in 2018 introduced changes in proximal humerus classification, which are almost identical to the modified version of the AO/OTA system developed for and used in the SFR.[39] To facilitate the clinicians' comprehension of the terminology and to simplify the classification system, the AO/OTA classification from 2018 also integrated the four-part Neer classification into the fracture descriptions of the AO/OTA system and the sub-groups were reduced from 27 to 13. A recently published study demonstrated substantially higher reliability for the revised AO/OTA system compared with the version from 2007.[41] The SFR has not implemented the newer version of the AO/OTA classification system but still uses the version from 2007, including the modified version for the proximal humerus.

1.3 EPIDEMIOLOGY

Epidemiology is defined as the study of the distribution and causes of health-related events or diseases in a specified population. This is important in order to understand the disparity between the common and the rare, thereby making it possible to distribute healthcare resources in the best possible manner and to plan and evaluate preventive measures. Humeral fractures can affect people of all ages and can be caused by various types of trauma mechanism. Since humeral fractures affecting children are a totally different entity compared with fractures in a mature skeleton, patients aged < 16 years are not included in the studies of this thesis. The spectrum of humeral fracture injuries ranges from non-displaced fractures suitable for treatment with a sling, brace or a cast, to severely displaced fractures with associated soft tissue injuries requiring acute, surgical interventions. As we live in an evolving society, with constant changes in the demography of the population, it is important to have access to updated epidemiological data.

Historically, there has been no easy way to evaluate the epidemiology of fractures. Nationwide administrative data, such as national hospital discharge registers, most often only include inpatients, or surgically treated fractures.[1,42-44] In addition to not always including all fractures in a population, this type of data also lacks detailed information on patient level, such as the fracture morphology and the cause of the fracture. Moreover, the completeness of nationwide registers is often unknown. Another way to obtain data used in past epidemiological evaluations includes retrospective reviews of radiographs, medical charts or operating theatre logs.[45-48] However, the retrospective design of these studies can lead to heterogeneity and deficiencies in the data set. Overall, few epidemiological studies present their methods for achieving high levels of completeness.

Humeral fractures have been reported to comprise approximately 7-8% of all adult fractures in the western world and fractures of the proximal humerus are the third most common fracture in elderly patients.[49,50] Only fractures of the hip and distal radius are more common. However, a changing incidence of fractures in many locations has been reported. An increasing incidence is mainly attributed to the increasing number of fragility fractures in the growing elderly population.[2,3,12] Kannus et al. reported on data from the Finnish National Hospital Discharge Register and found a rapidly increasing incidence of patients with proximal humeral fractures admitted to hospitals from 1970 until the end of the 1990s, followed by stabilised incidence rates until 2007.[43]

At the start of work on this thesis, the four most recently published studies on the epidemiology of humeral fractures were based on data collected during, or before, the 1990s. One study considered proximal fractures, two studies were related to diaphyseal fractures, while another considered distal fractures.[32-34,51] No recent study which includes fractures affecting all segments of the humerus was found. Court-Brown et al. and Robinson et al. demonstrated that proximal and distal humeral fractures have a similar age distribution pattern, with a low incidence in younger adults but a rapid increase with age.[33,51] Early in life, the incidence is higher in men than in women, probably as a result of the higher rate of high-energy trauma in younger men. Later in life, the majority are caused by low-energy falls and the incidence is higher in women, most likely as a result of their more fragile skeleton. As a result, osteoporosis has been mentioned as a significant risk factor for these fractures.[47,49] Humeral shaft fractures show a slightly different age and gender pattern, with generally younger patients being affected and proportionally more males than in the other two segments of the humerus.[32,34] This indicates that osteoporosis is not as important as a risk factor for humeral shaft fracturs as it is for proximal and distal humeral fractures.

1.4 REGISTERS

Sweden has a long tradition of register-based clinical research and observational register-based studies are able to address clinical issues that cannot easily be resolved by prospective randomised, controlled trials (RCTs).[52,53] Register-based studies assess real life and the results of clinical practice. They provide an ability to monitor trends in treatment and to evaluate the result of treatment algorithms used in everyday clinical practice. Due to non-randomisation, register-based research has limited potential to compare different treatment modalities, but it is able to evaluate the effect of high-quality evidence from RCTs outside the strict setting of these clinical trials. Register-based research is also able to detect crucial differences, while the patient groups in RCTs are too small to be able to detect these differences.[52,54] Sweden has a unique opportunity to run registers, due to the Swedish personal identity number (PIN), which allows data to be linked from a register to a specific individual.[55] Patients can be registered and monitored over time, even when they are treated by different healthcare providers. Moreover, different registers can be merged due to the common use of PINs.

Sweden has a long history of population registration dating back several hundred years to the parish registers. Today, several population-based registers containing personal data are maintained. The ongoing Swedish registers can be divided into national public authority registers, which are registers that have been collected as part of the authorities' activities, and national quality registers (NQR), which are run by the profession. The national public authority registers are administrative registers available at Statistics Sweden or the National Board of Health and Welfare (NBHW) and they include population and socioeconomic data, as well as data on health care and social services.[1,56]

1.4.1 National Patient Register (NPR)

The National Patient Register is one of several population-based databases administered by the Swedish Board of Health and Welfare and it is probably the best known.[42] The NPR started in 1964 and has had nationwide coverage of in-patient admissions in Sweden since 1987 and out-patient specialist visits since 2001. Primary care is not included in the NPR. The NPR is an administrative system and no active registration process is needed. Instead, healthcare providers continuously submit data from medical records and administrative systems, which are automatically extracted and recorded in the NPR. Information in the NPR includes the age and gender of the patient, their personal identification number (PIN), admission and discharge dates and the name of the hospital/out-patient clinic, as well as main and side-diagnoses according to the assigned ICD-10 codes (International Statistical Classification of Diseases and Related Health Problems – 10th revision) in the medical records.[57] In the event of surgical treatment, the KVÅ (Klassifikation av vårdåtgärder, Classification of health measures) coding system is used.[58] However, information in terms of the laterality of the injured body part or the time of injury is lacking in the NPR.

It is mandatory for all healthcare providers in Sweden to submit data to the NPR (regulated by law; SFS 1998:543 6§) and data from the NPR have been widely used in epidemiological research and as a reference for the completeness calculations of other registers (such as national quality registers) or surveys.[42,53,59] However, the data in the NPR are based on diagnostic codes (ICD-10) extracted from medical records and several limitations to this methodology have been highlighted.[42,60-63] Firstly, a medical condition could be interpreted by the treating physician as something else (i.e. diagnostic error), or a medical condition could be given a faulty ICD-10 code in the medical records (i.e. coding error), which results in diagnostic coding errors. Secondly, the same medical event could be recorded multiple times. Fracture recordings are typically prone to this type of error, since neither the time of injury nor laterality is recorded in the NPR. As a result, repeat admissions due to causes related to an old fracture are recorded as separate new fractures if the patient is assigned an acute fracture code on readmission.

Few previous studies have examined the completeness or the accuracy of registrations in the NPR. The existing studies have demonstrated varying results in terms of the correct number of recorded patients. A considerable proportion of both over- and underdiagnoses have been reported for different clinical conditions.[62,64-66] No previous study has examined the completeness and accuracy of fracture registrations in the Swedish NPR.

1.4.2 National quality registers (NQRs)

The first NQRs were initialised more than 50 years ago, with the introduction of the Swedish Knee and Hip Arthroplasty Registers.[67,68] All NQRs have been started by individuals within the medical profession and have therefore developed according to the professional need for a register. The NQR contains individualised data relating to the patient and the medical condition, medical interventions and outcomes after treatment. Today, more than 100 NQRs are in use in Sweden and over the years they have been used for continuous learning, clinical quality improvement, adherence to guidelines and research.[53] All NQRs are still managed by representatives of the profession, with funding from the Swedish Association of Local Authorities and Regions (SALAR) and the government in co-operation.

There has long been a need for more detailed population-based fracture data in order to develop evidence-based trauma orthopaedics and promote better outcomes. The former national collection of data (i.e. the NPR) was regarded as inadequate, since the classification of fractures according to ICD-10 codes is highly unspecific. A variety of different fracture types, with varying degrees of severity, are bundled into one anatomic location when ICD-10 codes are used. Moreover, the NPR contains no tools for assessing outcome following treatment. Other orthopaedic NQRs, such as the Swedish Knee and Hip Arthroplasty Registers, have proven important and have had a major impact on the evaluation and development of orthopaedic care not only in Sweden but also globally.[69] However, despite previous efforts, there has been no NQR that prospectively collects data on fractures of all types, regardless of location and type of treatment, prior to the initialisation of the SFR.[70-74]

1.4.3 The Swedish Fracture Register (SFR)

The SFR was created by orthopedic surgeons at Sahlgrenska University Hospital and, following years of preparation, the SFR was started on 1 January 2011.[74] Only tibial and humeral fractures were registered during the initial period and the registration was restricted to Sahlgrenska University Hospital. The register expanded rapidly following its introduction and, by October 2012, fractures of all long bones, foot, pelvis, shoulder and hand were included in the register. Fractures of the spine and paediatric fractures were added in 2015. As a result, the SFR contains information on all "orthopaedic fractures", i.e. all fractures except the skull and the ribs, from 2015 onwards.[75]

The aim of the SFR is to obtain full national coverage and all departments at Swedish hospitals treating orthopaedic trauma have been offered the chance to participate. However, participation is voluntary. In spite of this, the register has continuously expanded since its start and, in 2021, it reached 100% coverage of departments treating fractures in Sweden.[76] To date, more than 600,000 fractures have been registered. In

2019, the first orthopaedic large-scale, register-based randomised trials (R-RCTs) were started, using the SFR as the inclusion instrument.[77,78]

Data collection in the SFR is conducted prospectively and is not compulsory. Unlike other orthopaedically oriented NQRs, data entry is performed by the treating orthopaedic surgeon at the affiliated departments.[74] The SFR is fully web based and the registration process is preferably conducted in conjunction with the patient seeking medical attention for the injury. As a result, the physician on call at the accident and emergency department most frequently enters the data in the SFR. Detailed data on the injury, the fracture and the treatment (regardless of whether it is surgical or non-surgical) are collected in the SFR. The data collection process will be further explained in the method section.

Data from the SFR have to be reliable if research of high quality is to be accomplished. However, the registration process, which is most frequently performed under considerable time constraints by junior residents with no formal training in the registration process, raises questions in terms of how many of the available fractures that are actually registered in the SFR and how correct and accurate the registrations are. The involved departments are encouraged to ensure that the data are as complete and accurate as possible. At Sahlgrenska, the medical records are searched every week for ICD codes related to fractures and the results are matched for entries in the SFR. Fractures that have not been registered in the SFR are assigned to orthopaedic surgeons in the department to register secondarily. However, the actual completeness of registrations in the SFR has not been thoroughly scrutinised.

1.4.4. Validation of data in NQRs

The usefulness of a register relies on the quality of the reported data. Two fundamental concerns should govern the evaluation of registry data: the completeness and the accuracy of the registered data. The completeness of data is defined as the proportion of all cases in the target population that appear in the register database and the accuracy of registrations could be defined in this context as the proportion of cases in the register that actually have the recorded variable/disease/medical condition.

To evaluate completeness, the registrations in the register must be compared with all cases in the target population. However, the total number of cases in the target population is unknown and must therefore be estimated and ascertained. Several methods have been used to ascertain the reference with which to compare the recordings in the register. The two most commonly used methods to construct a reference population are either sending out questionnaires to the target population or making a direct comparison of data with another register believed to contain a larger proportion of all cases.[79-81] This method of comparing the number of cases found in the register with those ascertained in independent reference material is called *independent case ascertainment*. This is the most widely acknowledged method for evaluating completeness.[82]

The value of *independent case ascertainment* is greatly enhanced if cases found in the reference material can be linked to cases found in the register.[82] The cross-linking of patients enables a further evaluation of the reasons for the missing registration by conducting a medical records review. This would contribute to the further detection of missed registrations, as well as the detection of systematic registration errors or case-selection bias in the register (if one type of patient is overrepresented). A medical record review is also the recommended method for assessing the accuracy of register data.[42,65,82] By scrutinising the medical records for patients found in the registers, the validity of the recorded data can be evaluated. For this reason, cross-linked *independent case ascertainment* with a medical records review is a valid method for assessing the completeness and accuracy of registrations in a register.

The method of cross-linking patients between registers and a further medical records review is a time-consuming procedure that requires the handling of PINs. The handling of PINs always requires a separate ethical permit.[53,55,83] For this reason, cross-linkage and a medical record review is not a suitable method for routine assessments of completeness in a NQR. As described previously, the use of an existing register as a reference is an easily conducted assessment process. Today, almost half of the NQRs in Sweden use data from the NPR as a reference regularly to assess completeness, thus assuming that the NPR actually contains all cases.[53,84] This is a simple method that could be used for routine completeness calculations. However, if the reference used to evaluate the completeness is imperfect, the evaluation will be misleading. Since the NPR is known to contain non-valid data, such as doublet registrations, the quality of data needs to be investigated and improved. One way previously used to enhance the data quality in the reference material was to construct administrative selection algorithms. If these selection algorithms were able to exclude systematic errors of registration in a data set, the data quality would be enhanced. This might enable data to be used as a valid reference in routine completeness calculations, even if the data are not perfect in their original form. The construction of these selection algorithms has been created for registrations of stroke and myocardial infarction in the NPR, enabling modified NPR data to be used as a reference in completeness calculations in their respective NQR (i.e. Riksstroke and Swedeheart).[85,86] The creation of a selection algorithm of this kind, which would enhance the accuracy and completeness of NPR data regarding fracture patients, would potentially provide a cost- and time-effective way of regularly assessing completeness in the SFR by using modified NPR data as a reference. However, the creation of an algorithm of this kind requires a thorough examination of the reference material (i.e. the NPR).

1.5 TREATMENT

The segment of the humerus that will be discussed in terms of treatment, complications and mortality is the proximal segment, as only proximal humeral fractures (PHFs) are included in the studies investigating these issues in this thesis.

1.5.1 Treatment changes over time

The first recorded treatments of humeral fractures date back as far as 1600 BC, when

three cases of humeral fractures were described.[87] Reduction by traction followed by bandaging with linen was recommended, but the final result is unknown.
Treatment by closed reduction followed by bandaging was recommended by the ancient Greeks and Romans and this remained remarkably unchanged until the late nineteenth century, when the introduction of anaesthesia and radiology enabled surgeons to plan and perform surgery in a modern way.[88] The first known surgical procedure for a PHF was the resection of the humeral head, whereas internal fixation was not considered until the early 20th century.[89] Several implants, including screws, wires and sutures, were used in the first decades of the 20th century, but the surgeries were accompanied by high rates of complication. Infections, avascular necrosis (AVN) and malunion were common, thereby reducing the enthusiasm for internal fixation and a general return to non-surgical treatment was seen.

In the 1950s and 1960s, several events led to a new increase in surgical treatment for proximal humeral fractures. Firstly, antibiotics became available in the early 1950s and intramedullary nailing was developed during that period.[90,91] Secondly, in the 1960s, the AO group in Switzerland defined their principles of exact open reduction and stable internal fixation.[92] To realise these principles and allow for early mobilisation, plates and screws were introduced. However, the early good results relating to the use of these techniques were difficult to reproduce.[93] Multiple complications were reported due to the inappropriate handling of soft tissues and the tendency for the implants to loosen in osteoporotic bone. As a result, non-surgical treatment regained popularity once again.

Charles Neer popularised the use of hemiarthroplasty (HA) for fractures of the proximal humerus in his classic work from 1970.[7] However, despite several improvements in the prosthetic design and surgical techniques, the results in terms of functional outcome were difficult to reproduce and they are still unpredictable and somewhat disappointing.[8,9]

During the last two decades, the introduction of new implants has once again influenced the way proximal humeral fractures are treated. During the early years of the 21st century, anatomic locking plates were developed. These plates were shown to be mechanically superior to ordinary plates.[94] The prospect of better preserving reduction, especially in osteoporotic bone, led to a tremendous increase in popularity and an overall increase in the surgical management of PHFs.[5,95] For instance, in Sweden, the number of surgically treated patients with a PHF more than doubled between 2001 and 2010 (Figure 9).[1,59] The overall increase in surgical management was especially evident among patients aged > 60 years and open reduction and fixation with a plate became the most popular surgical treatment modality. However, the number of patients treated with other surgical methods, such as arthroplasty, also increased during this period.[5] Unfortunately, the rate of implant failure was still high in certain groups of patients and for certain types of fracture.[5,17,96] Consequently, the widened indications for surgery that followed the introduction of these implants were accompanied by an overall increase in complication rates.[5] Concurrently with the emerging reports of high complication rates following ORIF and HAs, reversed shoulder arthroplasty (RSA) was introduced as a treatment choice for complex PHFs (the treatment modalities will be further explained in the next paragraph). RSAs were reported to have lower complication rates and more predictable results compared with treatment with HAs or plates in patients with complex PHFs.[97-99] Consequently, the incidence of plate fixation following a PHF started to decline slowly in Sweden following a peak in 2011 and the use of RSAs has increased substantially since then.[1,59,100] Similar trends in treatment, with a reduction in the use of plates and HAs, whereas RSAs have increased, have been seen all over the western world.[6]

In addition to changing indications for the treatment of PHFs, multiple modifications of surgical techniques and implant developments have also been introduced during the last decade. The use of calcar screws and/or the addition of a medial support, valgus positioning of the head, tension-band suturing of the rotator cuff, meticulous restoration of the tuberosities in HAs and RSAs and the development of new generations of intramedullary nails have all been shown to reduce complications and improve outcome in small case series.[21,101-103] However, the effects of these modifications have not been comprehensively evaluated in large-scale cohort studies.

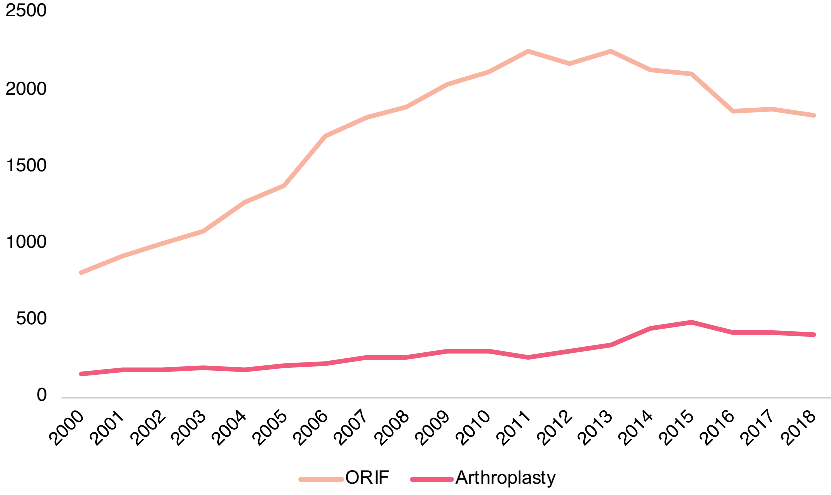

FIGURE 9. Number of surgical procedures for acute PHFs in Sweden in 2000-2018. Data from the NPR and the Swedish Shoulder Arthroplasty Register. ORIF = Open reduction internal fixation.

1.5.2 Treatment modalities

The range of treatment options for patients with PHFs consists of non-surgical therapy, open reduction and plate fixation, intramedullary nailing, fixation with a combination of screws and/or sutures and primary arthroplasty (HA or RSA).

Non-surgical treatment

Treatment with a short period of immobilisation (1-4 weeks) in a sling, followed by early physiotherapy, is recommended for non-displaced fractures or for patients with low physical demands and severe comorbidities, where the risks of surgery outweigh the potential benefits. Non-surgical treatment has advantages, such as a minimal risk of infection and surgical complications and good to excellent outcomes have been reported following non-displaced fractures.[104-108] However, the functional result is correlated to the complexity and the degree of displacement of the fracture. Poorer clinical results have been reported following more complex and displaced fractures and secondary displacement of the fracture fragments have been observed in a quarter of non-surgically treated PHFs.[104,107,109,110] Consequently, most non-surgically treated fractures are subjected to an early clinical and radiographic follow-up approximately 10 days after fracture. Approximately 5% of fractures primarily treated non-surgically are then (< 4 weeks post injury) converted to surgical treatment.[111]

FIGURE 10. a) Non-surgical treatment of a PHF with a sling. **b)** Plain radiograph of a two-part PHF deemed appropriate for non-surgical treatment.

Plate

Plate fixation can be used for displaced two- to four-part fractures involving the surgical neck. This method has the potential to restore the anatomy in an excellent manner since fracture fixation is achieved by open reduction through a deltopectoral or a lateral delta-split approach. Pre-contoured, anatomical plates with locking screws are used and displaced tubercles are reduced and secured to the plate with additional sutures (Figure 11). As previously stated, locking plates have been shown to be accompanied by high risks of complication. Screw cut-out, i.e. screws penetrating the articular surface, is the most commonly reported complication.[13] The cut-out can be either primary, due to intra-operatively misplaced screws, or due to secondary displacement of the fracture fragments. Secondary displacement is most commonly seen in complex fractures or fractures initially displaced in varus and in older patients with osteoporotic bone.[96,112-116]

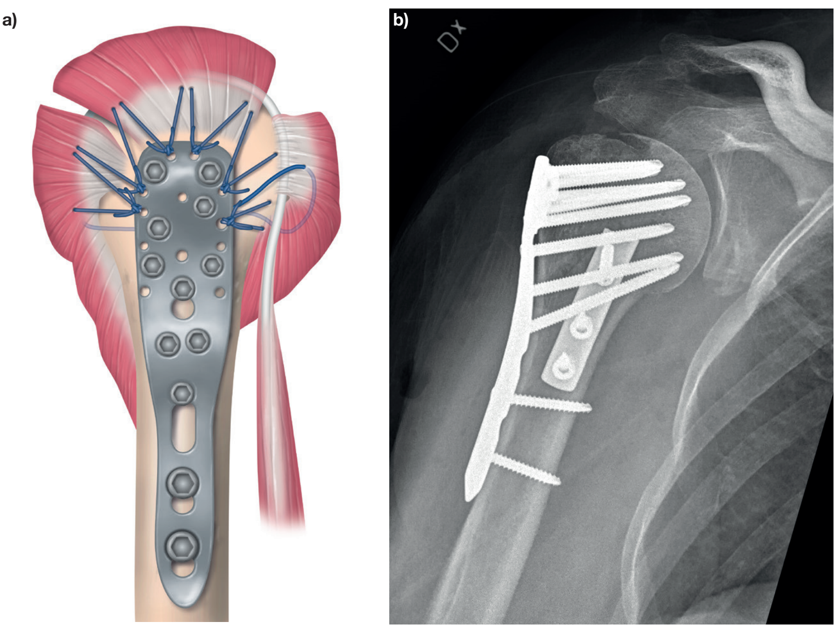

FIGURE 11. a) Lateral view of an anatomical plate for PHFs, with additional sutures securing the tubercles. **b)** Post-operative radiograph of a four-part PHF fixated with an anatomical plate and an additional mini plate for medial support.

Intramedullary nail

The indications for osteosynthesis with an intramedullary locking nail (IM nail) are predominantly two-part fractures involving the surgical neck or three-part fractures with only minor displacement of the tuberosity in older patients (Figure 12).[117] Osteosynthesis with an IM nail is most often performed as a percutaneous method and an exact, anatomic reduction is therefore difficult to achieve. Compared with open reduction and plate fixation, osteosynthesis with an IM nail has been shown to have significantly shorter surgery time and less blood loss.[118] Due to better biomechanical properties, potentially withstanding dislocating forces in osteoporotic bone, there is less secondary displacement of the head fragment in nail osteosynthesis.[117,119] An IM nail could therefore potentially be better suited than plate osteosynthesis for initially varus displaced fractures. Common complications include screw cut-out/ secondary displacement and iatrogenic rotator cuff lesions due to the introduction of the nail through the supraspinatus muscle/tendon.[118,120] The overall complication rate compared with plate fixation is similar for three- and four-part fractures but lower for two-part fractures.[117,118,120]

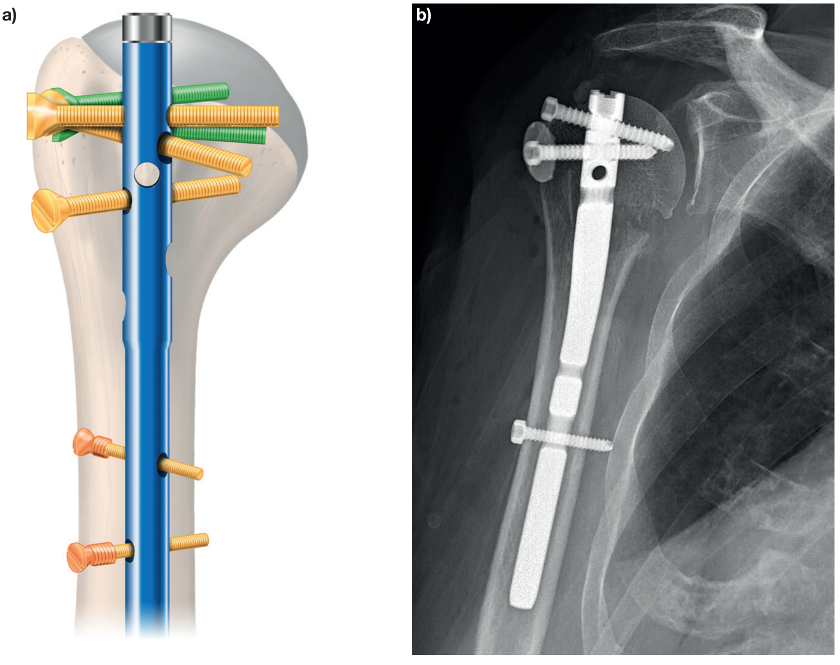

FIGURE 12. a) Schematic image of an intramedullary nail. **b)** Post-operative radiograph of a three-part PHF fixated with an intramedullary nail.

Combination methods

Combination methods refer to fracture fixation with screws, cerclage wires, suture anchors, mini-plates or a combination thereof (Figure 13). They are typically used for isolated tuberosity fractures, where the fixation of the surgical neck is not necessary. The aim of treatment is to restore the integrity of the rotator cuff. A displacement of the tuberosity of > 5 mm is the most generally accepted indication for surgery, but the accepted displacement is dependent on age and the physical activity level of the patient.[22] A displacement of > 10 mm in older patients with osteoporotic bone and only > 3 mm in young, active patients has been suggested as an indication for surgery. Common complications include the loss of reduction/secondary displacement and rotator cuff dysfunction, resulting in pain and stiffness.[22]

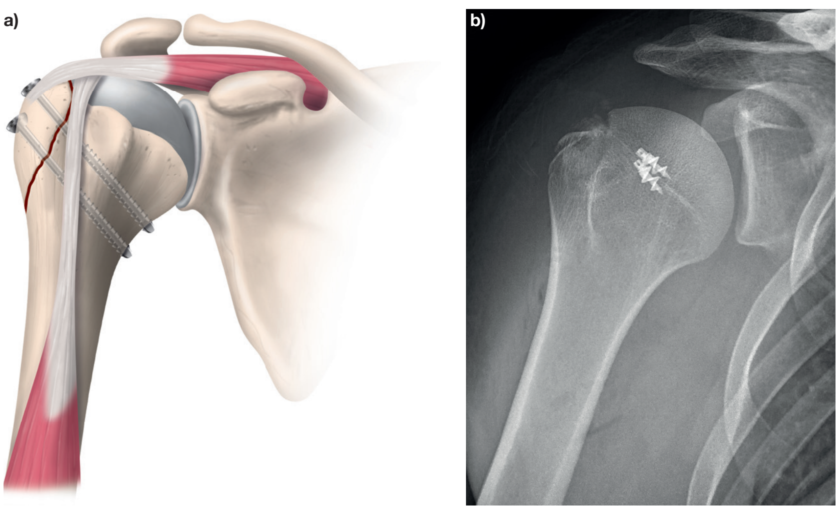

FIGURE 13. Examples of combination methods. **a)** Schematic image of an isolated greater tuberosity fracture fixated with screws. **b)** Post-operative radiograph of a multifragmentary greater tuberosity fracture fixated with suture anchors.

Arthroplasty

Primary arthroplasty may solve complex fracture situations, where adequate reduction and fixation cannot be achieved. The indication for primary arthroplasty is not entirely clear, but it is mainly considered for complex fractures in osteoporotic bone. These fractures run a high risk of complications following osteosynthesis and usually result in poor function and dissatisfaction following non-surgical treatment.[110,121] The fracture can be treated with either a hemiarthroplasty (HA) or a reverse shoulder arthroplasty (RSA).

Hemiarthroplasty (HA)

An HA substitutes the humeral joint surface, but it is dependent on a functioning rotator cuff for a good outcome.[9,21] The tubercles therefore need to be anatomically reconstructed perioperatively (Figure 14). The fixation and reconstruction of the tubercles, and thereby the rotator cuff tendons, are performed with sutures anchoring them to the prosthesis and autologous bone transplantation to augment them into an anatomic position. The pre-injury quality of the rotator cuff and the subsequent anatomic reconstruction, and healing, of the tubercles play a decisive part in the functional result.[8,9,21,112] In most cases, HA results in good pain relief, but the functional result is unpredictable.[9,21,121] The most common complication following an HA relates to the anchorage and healing of the tuberosities and tuberosity absorption, non-union or poor preinjury quality of the rotator cuff can result in rotator cuff dysfunction and subsequent poor function.[9,21]

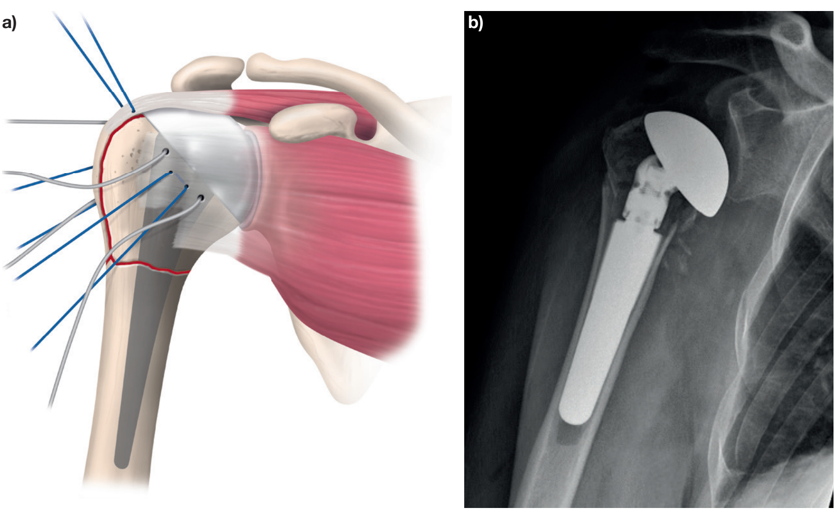

FIGURE 14. a) Schematic image of a hemiarthroplasty (HA) where the tubercles are anatomically reconstructed and attached to the prosthesis with sutures. **b)** Post-operative radiograph of a three part PHF treated with an HA and anatomical reconstruction of the tubercles.

Reversed shoulder arthroplasty (RSA)

An RSA alters the normal anatomy of the shoulder by replacing the concave surface of the glenoid with a convex component and vice versa on the humerus (Figure 15). It is therefore not as dependent on a functioning rotator cuff as HA. In spite of this, the tubercles are attached perioperatively to the prosthesis via sutures, although an anatomic positioning is not mandatory. The importance of healed tuberosities in patients with RSA have long been unclear, but recent data have demonstrated better functional results and less instability with healed tuberosities.[99,122,123] The most frequent reasons for reoperations in patients with RSA-treated PHFs are loosening of the glenoid component and instability of the implants.[124] Acromial insufficiency fractures represent another typical complication, with subsequent instability, pain and poor function due to the loss of function of the deltoid muscle.[125,126]

RSA also offers a salvage procedure for failed first-line treatment, since the reverse prosthesis is able to compensate for tuberosity dysfunction. A reoperation with RSA can therefore be useful after complications like malunion, non-union or failed osteosynthesis or HA.[124,127] However, although patients improve substantially following salvage RSA after failed osteosynthesis, the functional result is poorer than that for PHFs primarily treated with RSA.[128,129]

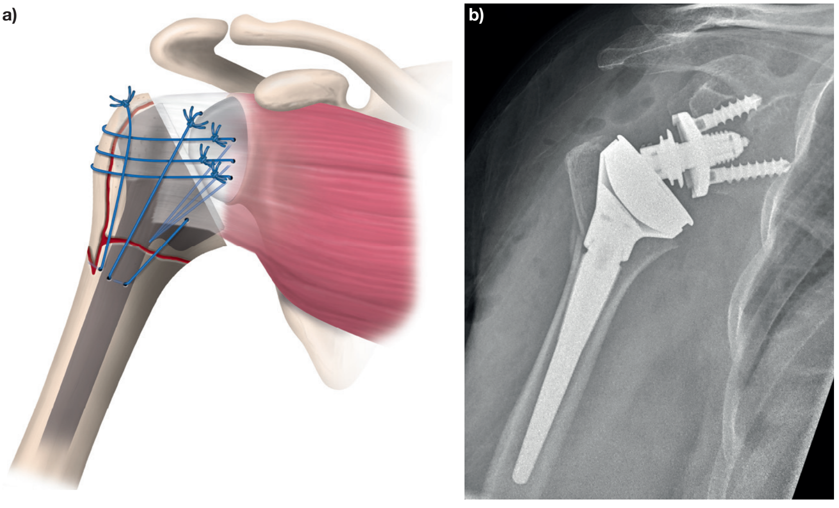

FIGURE 15. a) Schematic image of a reversed shoulder arthroplasty (RSA). The tubercles are attached to the prosthesis with sutures, but the supraspinatus tendon is often removed peri operatively. **b)** Post-operative radiograph of a four part PHF, treated with an RSA.

1.5.3 Choice of treatment

The choice of treatment for proximal humeral fractures depends on a variety of underlying fracture- and patient-related factors, e.g. age, functional demands, comorbidity, the bone mineral density (osteoporosis), displacement of the fracture, number of fragments and the experience of the surgeon.[130] Currently, there are no clear guidelines to direct the treatment of proximal humeral fractures.

There is general consensus that non-displaced or minimally displaced proximal humeral fractures, which constitute approximately 50-80% of all fractures, can be treated non-surgically with acceptable functional outcomes.[35,47,51,104,105,107] Moreover, the indication for surgery is almost absolute in fracture dislocations, head-splitting fractures and fractures without bony contact between the head and the shaft fragment. These complex fractures are almost always excluded from randomised trials comparing surgery with non-surgery, due to ethical reasons.

The main controversy in terms of the treatment of proximal humeral fractures pertains to displaced fractures. In young patients with these fractures, surgical treatment is not controversial, due to higher functional demands and better bone quality.[113] However, the treatment of displaced fractures in elderly patients is extremely controversial.

Randomised studies have not been able to demonstrate any significant difference in terms of function or patient-reported symptoms between various surgical treatment options, apart from recently published data indicating some advantages in patients treated with RSA compared with HA or plates (Table 1).[20,97,118,119,131,132] Nor have studies comparing the surgical and the non-surgical treatment of proximal humeral fractures in the elderly reported any clear differences.[15-18,121,133,134] Neither function nor patient-reported symptoms have been shown to improve with surgery. In addition, most of these studies report high rates of complications and reoperations among the surgically treated patients. Consequently, the latest Chochrane review concludes that, for patients with a displaced PHF, surgical treatment does not result in a better outcome than non-surgical.[13] Regardless of the primary treatment, surgical or non-surgical, these displaced fractures result in a functional impairment of the shoulder and have a major negative influence on the quality of life of patients, especially the elderly population.[17,121]

TABLE 1: An overview of results in randomised controlled trials comparing treatment modalities, still at use, for the treatment of proximal humeral fractures.

Methods	Study	Patients (N; mean age)	Fracture type	Outcome (PROM and ROM)	Method with most reoperations
N-S vs Plate	Olerud 2011b*	60; 74 years	3 part	No difference in PROM or ROM	Plate
	Fjalestad 2012*	50; 72 years	3-4 part	No difference in PROM or ROM	Plate
	Launonen 2019*	88; 72 years	2 part	No difference in PROM or ROM	Plate
N-S vs Op	Rangan 2015	250; 66 years	2-4 part	No difference in PROM	No difference
N-S vs HA	Olerud 2011a*	55; 77 years	4 part	Less pain HA. No difference in disease specific PROM or ROM.	HA
	Boons 2012*	50; 78 years	4 part	No difference in PROM or ROM	HA
N-S vs RSA	Lopiz 2019**	59; 84 years	3-4 part	Less pain RSA. No difference in PROM or ROM.	No difference
Plate vs IM Nail	Zhu 2012	51; 53 years	2 part	No difference in PROM or ROM	Plate
	Plath 2019*	55; 76 years	2-4 part	No difference in PROM or ROM	No difference
Plate vs HA	Cai 2012*	32; 72 years	4 part	Less pain HA. No difference in ROM	No difference
Plate vs RSA	Fraser 2020*	124; 75 years	3-4 part	RSA better PROM and ROM	Plate
RSA vs HA	Sebastia-Forcada 2014*	61; 74 years	3-4 part	RSA better PROM and ROM	HA
	Jonson 2020*	84; 80 years	3-4 part	RSA better PROM and ROM	No difference

* Studies only including patients > 55 years old.
** Studies only including patients > 80 years old.
PROM = Patient reported outcome measure, ROM = Range of motion, N-S = Non-surgical treatment, Op = Plate/HA, IM Nail = Intramedullary nail, HA = Hemiarthroplasty, RSA = Reverse shoulder arthroplasty

The result from the RCTs of non-superior outcome in surgically versus non-surgically treated patients might give the impression that surgery has no place in the treatment of PHFs. However, it is important to consider the limitations of RCTs. Firstly, patients with clear surgical indications, such as young patients and all patients with fractures where surgery is deemed beneficial, are not included in RCTs. Secondly, most RCTs have included fractures according to Neer's displacement criteria. However, as described previously, these displacement criteria were arbitrarily established by Neer and were never intended to be used as an indication for surgery.[35,37] Consequently, these studies include patients with fractures that do not benefit from surgical intervention and, in the same way, patients with fractures most likely to benefit from surgery are excluded. This obviously hampers the result and is therefore important to consider when these studies are interpreted. Within the profession, there is general consensus that surgical intervention still has a role to play in the treatment of PHF. As a result, surgeons continue to explore options to improve outcome. However, without solid functional and patient-reported evidence to support one treatment over another, the risk of complications and reoperations must be considered when evaluating changes in treatment indications.

1.6 OUTCOME MEASUREMENTS FOLLOWING FRACTURE TREATMENT

The functional level of the affected limb instantly deteriorates following a fracture. Regardless of treatment, few patients return to their preinjury level of function.[135,136] The overall aim of treatment is to enable the patient to regain as much function as possible without exposing him or her to major risks. The treatment objective varies between patients and is dependent on the preinjury activity level and patient expectations. Some patients are satisfied with a stable, non-painful limb, while others are willing to undergo high-risk treatments in order to have a chance of a better functional outcome.

There are several ways to evaluate outcome following fracture treatment. Different measurements have been used; they include radiological healing, functional level of impairment and cost related to treatment and/or loss of function. However, the two most common ways are to evaluate the patient's own perception of symptoms and function, most commonly by using patient-reported outcome measures (PROM), or the evaluation of complications related to the fracture and the treatment.[13] The SFR uses both PROMs and complications (i.e. reoperations) as outcome measurements.

1.6.1 Patient-reported outcome measures (PROM)

Patient-reported outcome measures (PROMs) are questionnaires that aim to capture a person's perception of their own health and they have gained enormous popularity in recent years. These questionnaires focus on various aspects of health, such as symptoms, daily function and quality of life. PROMs are usually measured on two or more occasions to enable comparisons to be made over time. There are numerous different PROMs, focusing on different aspects of health. Generic PROMs measure general aspects of health and are thereby suitable for use across most patient populations, for most health conditions and for health-economic analyses. Disease-specific PROMs include questions that relate directly to specific health conditions, their treatments and impact on outcome. It is considered good practice to combine one generic PROM with a disease-specific PROM. In the SFR, the two PROMs EQ5-D (generic) and Short Musculoskeletal Function Assessment (SMFA) (disease specific) are used.[137,138] The SMFA aims to capture function in the upper and lower extremities and general health with the emphasis on the musculoskeletal system. The PROMs in the SFR are measured on two occasions.

Firstly, using the recall technique, registering function the week prior to the fracture, and secondly after one year. This makes comparisons possible between the one-year result and the preinjury status.

1.6.2 Complications

A complication following treatment is defined as an unanticipated problem that occurs following, and as a result of, a treatment or an illness. A complication can be either general, affecting the whole patient, or local, affecting the organ or limb in question. In orthopaedic fracture management in general and for the treatment of PHFs in particular, there is no consensus on how to define and grade post-treatment complications.[139,140] Different terms are used to describe complications and there is no system, equivalent to the Clavien-Dindo system widely used in general surgery, to grade the seriousness of a complication.[141] This lack of consensus hampers comparisons of outcome data between different centres and therapies, as well as over time.

Complications related to the treatment or healing of the fracture differ in severity. Some are transient or treatable without additional surgery, while others require additional surgery, i.e. a reoperation. Since complications related to the treatment of PHFs are seldom life threatening, the indication for a reoperation is almost never absolute.[19] The indication for re-do surgery is therefore dependent on the severity of the complication, the patient's symptoms and the risks associated with and the expected benefits of additional surgery. Many complications do not require a reoperation, but a reoperation is almost always a sign of a complication.[19,142] A reoperation is therefore a widespread and commonly used end-point in register studies of orthopaedics and it was used in this thesis to evaluate changes in treatment practice.

There is a well-known challenge of reporting bias in revision surgery, which is highlighted by the vast degree of different reoperation rates reported from different data sources. Register-based research generally reports reoperation rates that are substantially lower than those reported from case series or RCTs. Studies emanating from the Nordic shoulder arthroplasty registers have reported revision rates of 3-4% following HA and 2% following RSA for PHFs, while the equivalent numbers found in RCTs or case series are substantially higher (reoperation rates of 8-20% and 5-10% following HA and RSA for PHFs respectively).[97,100,142-145] Even though reoperation and revision are not always the same, there is still a significant difference between these different sources of data. This highlights the well-known underreporting of reoperation/revision data in register-based studies and supports the need for the validation and completion of reoperation data.[71,146]

1.6.3 Reoperations following proximal humeral fractures

The most important reasons for unplanned surgery following a proximal humeral fracture are non-union, malunion, deep infection, stiffness, avascular necrosis (AVN), screw cut-out and other implant-related failures (Figures 16 and 17).[99,101,145] The rate of unplanned surgery/reoperations varies greatly in different case series or RCTs, but it is reported to be 14-45% for osteosynthesis with plates or IM nails and HAs.[17,44,96,115,117,119,133,145,147] The varying results could be explained by a large variation in the fracture types and patients included in these studies. The reoperation rate of approximately 5-9% following fracture surgery with RSA is substantially lower than that following osteosynthesis and HA.[97,99,145] However, the treatment modality associated with the lowest rates of unplanned surgery is non-surgical treatment (0-5% rate of unplanned, secondary surgery).[17,105,133,136]

It has been suggested that the high rate of complications and reoperations following surgery for PHFs is one of the explanations for the poor overall result in surgically treated PHF patients, since patient-reported outcome is generally poorer in patients with complications than in those without complications.[19,148]

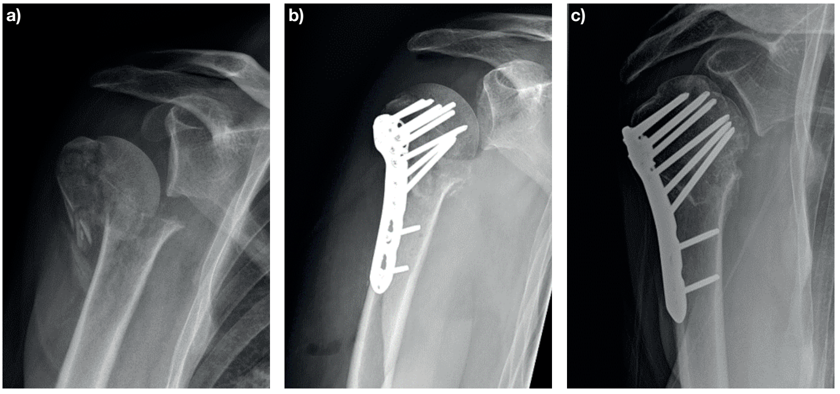

FIGURE 16. Radiographic example of avascular necrosis. **a)** Pre-operative radiograph. **b)** Post-operative radiograph following fixation with an anatomical plate. **c)** Six months post-operative. Interruption of the blood supply have led to subchondral collapse of the humeral head. Patient presented with pain, poor range of motion and mechanical symptoms, and is pending reoperation with extraction of the plate and replacement with a reverse shoulder arthroplasty.

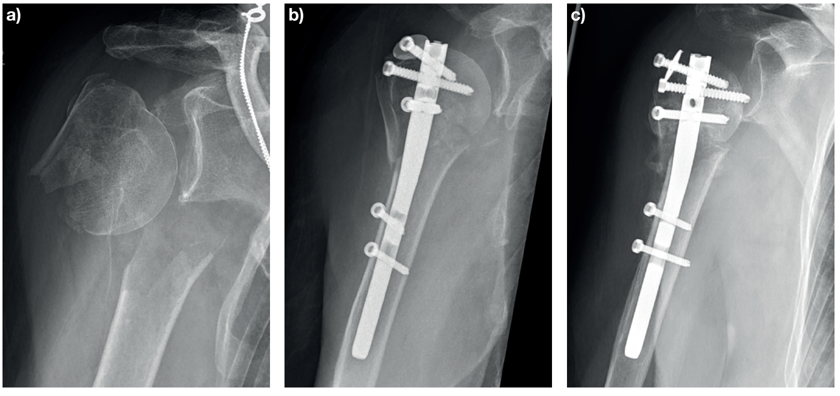

FIGURE 17. Radiographic example of secondary fracture dislocation with screw cut-out. **a)** Pre-operative radiograph. **b)** Post-operative radiograph following fracture fixation with an intramedullary nail. **c)** Radiograph six weeks post-operative showing secondary displacement of the humeral head fragment with screws penetrating the glenohumeral joint. The patient was reoperated with removal of the proximal screws and the fracture healed.

Few studies report on reoperations after PHF treatment in consecutive patients outside the strict setting of clinical trials. These types of observational study are important since the implication of the result from RCTs on clinical practice can be difficult to predict and evaluate. Moreover, RCTs generally include few patients which makes it difficult to draw adequate conclusions regarding reoperations.[14] The few observational studies that exist are either small in terms of cohort size or based on national data samples or hospital discharge registers. Katthagen et al. reported a reoperation rate of 23% in 423 retrospectively reviewed patients, while Sprouss et al. reported an overall reoperation rate of 11% in 192 consecutive patients one year after fracture[147,148] Petrigliano et al. only included surgically treated patients and reported a reoperation rate of 5.4% within 90 days following non-arthroplasty fixation, with data from 1994-2005, in their report based on data from hospital discharge registers in the US[44] As previously mentioned, considerable underreporting of reoperations in registers is common, in both the NQRs and national discharge registers. Taken together, there is a need for updated population-based and validated data on reoperation rates following modern PHF treatment.

1.7 MORTALITY

It could be argued that mortality is the ultimate complication and fractures have been shown to be associated with excess mortality compared with that in the general population.[149-152] This is especially recognised following hip and osteoporotic vertebral fractures, with crude mortality rates reported to be as high as 20-26% following a hip fracture one year after fracture.[153-155] The knowledge on crude survival following other types of fracture is, however, limited.

The reasons behind the excess mortality following hip and other osteoporotic fractures are multifactorial. Firstly, these fractures typically occur in persons who already have severe comorbidities and an increased risk of death.[156,157] Secondly, the severity of the trauma, as well as the treatment and the subsequent immobilisation following different fractures, is most probably important. However, only a small fraction of patients die as a direct result of the fracture. A recent Spanish study of specific causes of death in hip fracture patients reported that pneumonia, cardiovascular events and dementia were the most common causes of death. Only 3.2% died of causes that could be directly related to the fracture or its treatment.[158]

Frailty is a concept that has attracted a great deal of attention in the past few years. A frail person is characterised as an older person with a higher than average risk of negative health outcomes, not entirely explained by the traditionally recognised markers of poor health, such as advanced age, medical comorbidities, bone mineral density or cognitive function. Instead, frailty is often defined by low physical activity and declining physiological systems.[156,157,159] Persons categorised as frail have been shown to have a markedly increased risk of recurrent falls, hip fractures, non-spinal fractures and death after confounders have been controlled for.[157,160,161] In fact, the WHO has stated that the concept of frailty is better suited to stratifying and predicting the risk of subsequent fractures and/or mortality than simply the occurrence of comorbidities.[162] Moreover, frailty has been shown to be reversible.[160] If measures such as dietary counselling, the review and optimisation of the patients' medication and physiotherapy, with the emphasis on muscle strengthening and balance improvement, are taken, the negative spiral of declining mental and physical health that leads to falls, fractures and ultimately death can be broken.

It is important to understand that patients with varying degrees of frailty sustain different types of fracture. The person who sustains a wrist fracture after a fall is probably more physically robust than the person in the same age group who sustains a hip fracture following a similar fall, since a physically robust person has the ability to stretch out their hands when falling, whereas a frailer person falls directly onto their hip.[163] This is supported by findings of equal or even better survival in patients with fractures of the wrist than that of age-matched peers in the general population, whereas patients with hip fractures have a marked excess mortality.[163-166]

To the best of our knowledge, the association between frailty and risk of sustaining proximal humeral fractures has not been examined. However, proximal humeral fractures have been shown to be associated with several factors indicating poor general health[163,167] Despite this, mortality after a proximal humeral fracture has not been studied in any real detail. There are some reports that suggest that proximal humeral fractures are associated with increased mortality during the first year after fracture, especially for male patients and for patients with surgically treated fractures.[168-170] However, these reports are based on either small cohorts or selected cases.

1.8 RATIONALE OF THIS THESIS

Several studies have validated the data in the SFR, but none has examined the completeness or the accuracy of fracture registrations. Moreover, the completeness and validity of fracture registrations in the NPR is also unknown. A detailed knowledge and understanding of the NPR data is of the utmost importance before reliable completeness calculations can be performed using NPR data as a reference.

Previous studies of the epidemiology of humeral fracturs are based on data collected during or before the 1990s. With an increasingly urban and ageing population, updated epidemiological data on humeral fractures are needed.

In order to assess whether patients sustaining fractures of the proximal humerus are subject to a greater-than-average risk of death for their age, data on mortality following a PHF is warranted. To the best of our knowledge, there is no previous study reporting on early and mid-term survival, including all patients and treatments in a large cohort of consecutively registered patients with a PHF.

Since no major patient-perceived differences have been demonstrated between different ways of treating PHFs, the reoperation rate is important. A reoperation is costly, both for society in financial terms and in terms of suffering for the patient. The development of treatment strategies should therefore strive towards reducing the rate of reoperations. With new surgical implants and evolving treatment options, there is a need for updated data on the actual treatment and reoperation rates in a large, consecutive series of patients with a proximal humeral fracture, including all treatment modalities. Moreover, the completeness of the reported reoperations must be validated and accounted for. To the best of our knowledge, there are as yet no such studies.

02

AIMS

The overall aim of this thesis is to examine the quality of the data in the SFR, and to explore humeral fractures in detail using data from the SFR in terms of epidemiology, mortality, treatment changes and risk of reoperations. The objectives of each study are as follows.

- → To evaluate the completeness and accuracy of humeral fracture registrations in the SFR and the NPR in terms of fractures treated at Sahlgrenska University Hospital. Moreover, the study aimed to identify systematic registration errors in the registers in order to suggest ways of increasing future validity. **(Study I)**

- → To analyse the incidence of fractures in all segments of the humerus and to describe the demography and fracture characteristics in a cohort of consecutive patients with a humeral fracture. **(Study II)**

- → To quantify the early and mid-term mortality following a PHF compared with the general population and to study risk factors associated with mortality. **(Study III)**

- → To investigate trends in treatment methods for PHFs over seven years at a large Swedish orthopaedic trauma unit and to explore the rate of and risk factors for reoperations after primary treatment. Moreover, the completeness of the registration of reoperations in the SFR was analysed. **(Study IV)**

03

METHODS AND MATERIAL

This thesis is based on data from the SFR. As a result, various aspects of data collection in the SFR are described. The methodological aspects of the respective studies are then reported.

3.1 THE SWEDISH FRACTURE REGISTER

Inclusion and exclusion criteria

Registration in the SFR is based on personal identity numbers (PIN) and a real-time connection to the Swedish Tax Agency population register facilitates the registration. The patient therefore requires a permanent Swedish PIN in order to be registered in the SFR. The fracture must be diagnosed on radiographs (i.e. plain radiographs, computed tomography (CT), magnetic resonance imaging (MRI) or any other radiological examination) and fractures sustained abroad are not included.[74] Registration is non-compulsory and all patients have the right to decline registration.

Registration process

As previously described, data entry is performed by the physician following contact with the patient. It is therefore most frequently the physician on call who enters the data in the SFR. The data entry is web based and, following verification of the patient's PIN, via links with the Swedish Tax Agency population register, a personal patient file is created in the SFR. Once a file has been created, new injury occasions can be added if the patient sustains new fractures later in life.

Data related to the injury occasion, the classification of the fracture and the treatment are entered on three subsequent panels. The date of the injury, the mechanism of the injury and the whereabouts of the patient when the injury occurred are entered in the first panel (Figure 18). Non-traumatic mechanisms for fractures (i.e. stress, pathological or spontaneous fractures) are distinguished from fractures caused by trauma.

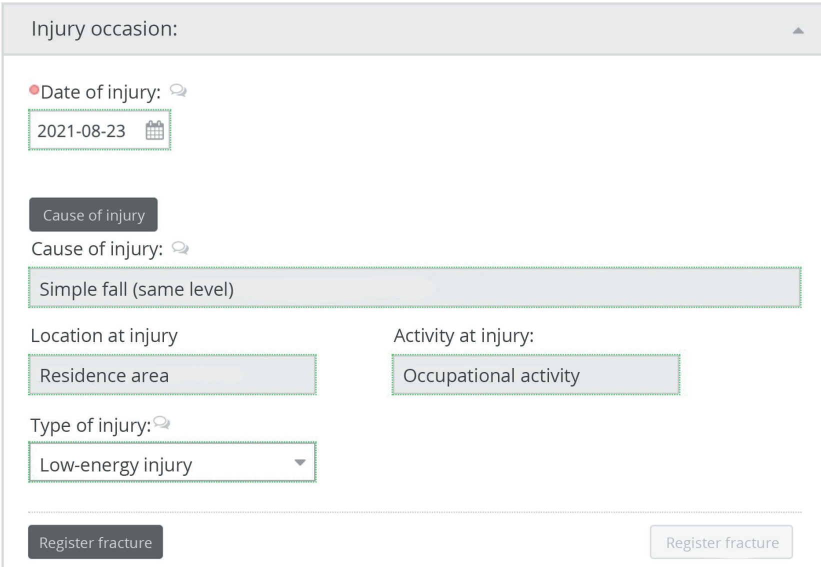

FIGURE 18: Registration of the injury occasion.

In the second panel, the fracture is classified according to the AO/OTA classification, as previously described (Figure 19 a-c). The classification is based on the available radiological information and an AO/OTA-classification manual. Schematic images of the different fracture groups and written explanations accompanying the images are shown to assist with the on-line classification process in the SFR. Additional information entered in the register includes the injured side, whether the fracture is open (then classified according to Gustillo-Anderson), implant related or periprosthetic (then classified in accordance with the Unified Classification System.[171,172] In the event of multiple fractures, additional panels are added for each fracture.

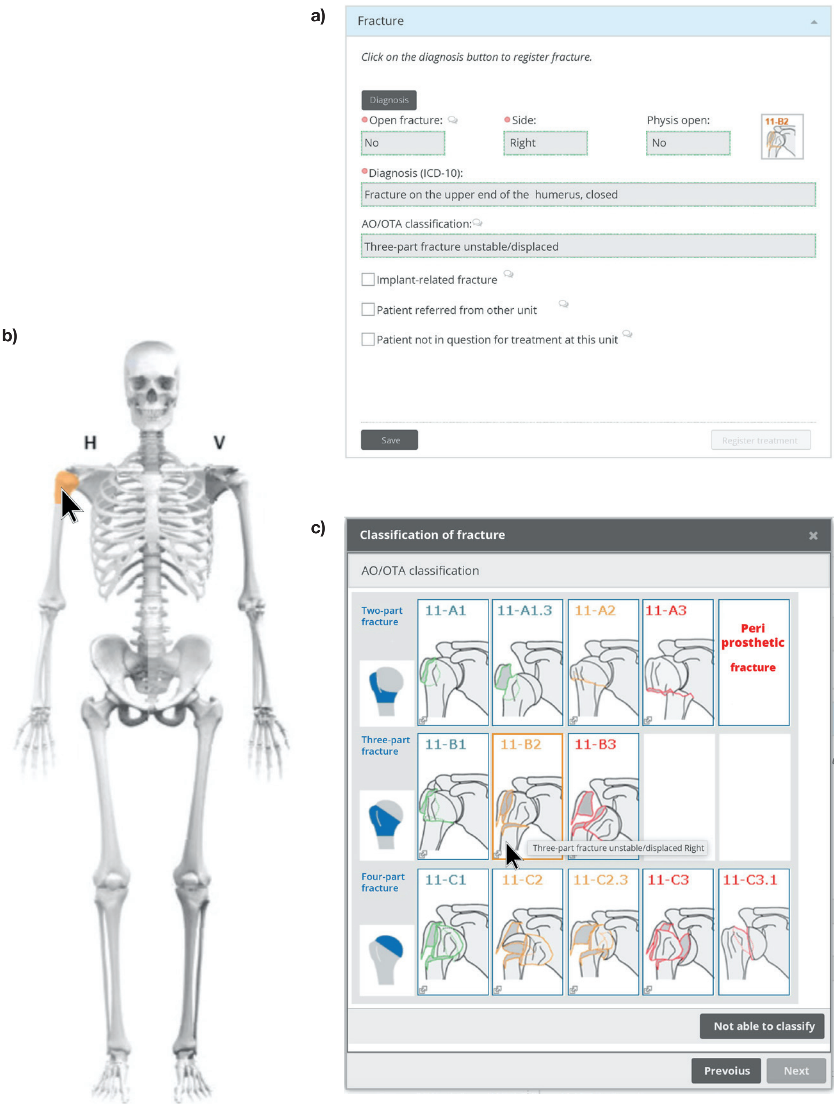

FIGURE 19: Registration and classification of fracture. **a)** The panel in the SFR for fracture registration. **b)** Selecting fracture location and side of the body. **c)** Schematic images and written explanations for the classification of the fracture

The treatment is entered in the final panel once it has been performed (Figure 20). As a result, surgical treatment is entered postoperatively and the surgeon is also able to change the fracture classification at this stage if required. The date, treatment modality, the surgical method and type of implant, as well as the experience level of the treating surgeon, are entered. If subsequent procedures are performed, a new treatment panel linked to the fracture is opened. This allows for secondary procedures, such as altered treatment or reoperations, to be connected to the fracture, regardless of the time that has passed or whether the subsequent procedures are performed by another caregiver. In the event of a reoperation/late surgery, the indication for which of these was performed is registered.

FIGURE 20: Registration of treatment.

PROMs

The PROM registration process is conducted by the patient and the result from the PROM questionnaires, both the pre-injury assessment and the one-year follow-up, are connected to the injury occasion in an additional panel. The PROM-registration process is initiated by an invitation letter with a personal code sent to the patient by the secretaries at the orthopaedic departments participating in the SFR. Since February 2019, the process of collecting PROM data is fully electronic and conducted on line.

Mortality

Since 2015, the Swedish Tax Agency population register, which has information on the vital status of all Swedish citizens, has continuously reported mortality to the SFR, which means that all deaths are immediately registered in the SFR. Deaths that occurred prior to 2015 have been registered retroactively and the SFR therefore contains information on the date of death, if it has occurred, for all registered patients.

3.2 STUDY I

Study population

Data on all individuals aged 16 years or older, with an acute humeral fracture (diagnostic code ICD 10 S42.2-4), treated at Sahlgrenska University Hospital between 1 January 2011 and 31 December 2012, were extracted from the NPR and the SFR and included in the current study.

Methods

Registrations in the SFR were compared with registrations in the NPR in order to assess the validity of humeral fracture registrations in terms of the completeness and accuracy of registrations (Figure 21). An approximated "true" number of humeral fractures was established by cross-linking individuals between the two registers using Swedish personal identification numbers (PIN) and further medical record reviews. A matching registration, defined as a fracture registered in both registers, was regarded as a valid fracture registration. A fracture recorded in only one register was regarded as a non-matching registration. For patients with non-matching registrations, the medical records were reviewed and reasons for the missing registration were searched for. All matching registrations and all unique fractures registered in either register and verified by the medical records constituted the "true" number of humeral fractures subsequently used to assess the completeness and accuracy of registrations in both the SFR and the NPR.

Moreover, non-matching registrations were analysed in detail and systematic errors of registration were identified. An algorithm was then created in order to enhance the validity of the NPR data by excluding as many registration errors (i.e. erroneous registrations) as possible, without excluding valid registrations of humeral fractures, thereby creating a valid reference from modified NPR data, with which routine completeness calculations of the SFR could be performed.

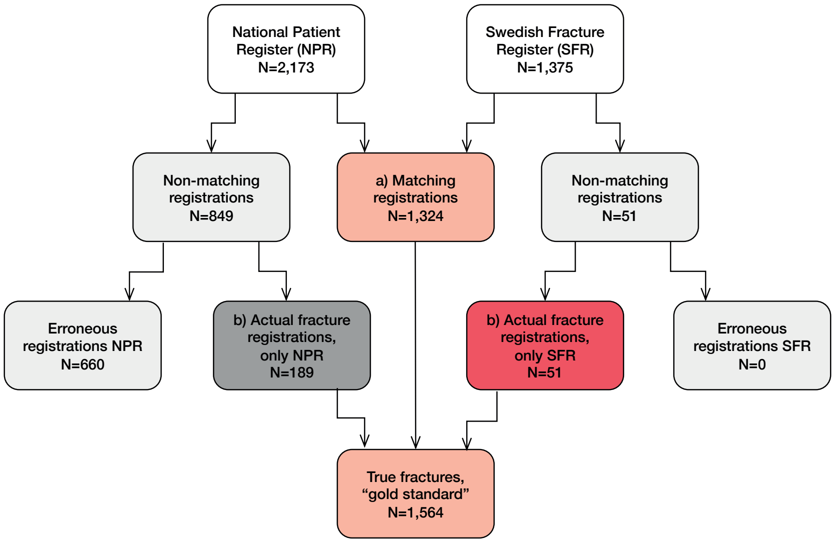

FIGURE 21: Flow chart of Study I and the assessment of the "true" number of acute humeral fractures at Sahlgrenska University Hospital in 2011-2012. The "true" number of fractures was defined by (a) all the fractures registered in both registers and (b) all the unique fractures registered in either register and verified by the medical records. Published with permission from Dove Medical Press; *Clinical Epidemiology 2021;13:325-333. Doi:10.2147/CLEP.S307762*

Study definitions

An actual humeral fracture registration was defined as a first-time visit for an acute humeral fracture subsequently treated at Sahlgrenska during the study period of 2011-2012.

Erroneous registration was defined as all registrations of an acute humeral fracture (S42.2-4) that were not an actual humeral fracture registration (i.e. re-admissions of a fracture already registered or sustained prior to the study period and non-humeral fracture registrations that were erroneously assigned a humeral fracture code).

Completeness was defined as the proportion of the "true" number of cases, as described above, that were registered in the respective register (Figure 22). The National Board of Health and Welfare uses another formula for routine completeness calculations, visualised in Figure 23.

$$\frac{\textbf{Number of “true” fractures registered in the register}}{\textbf{Total number of “true” humeral fractures}} = \textbf{Completeness in Study I}$$

FIGURE 22. Formula for completeness calculation in Study I.

Number of fractures registered in the register (i.e. SFR) / **Matched registration + only SFR + only NPR**	=	**Completeness in routine completeness calculations**

FIGURE 23. Formula for routine completeness calculation used by the National Board of Health and Welfare.

Accuracy of registration was defined as the likelihood of a registration of an acute humeral fracture code in each register being an actual fracture registration (Figure 24).

Number of "true" fractures registered in the register / **Total number of fracture registrations in the register**	=	**Positive predictive value**

FIGURE 24. Formula for accuracy of registrations, i.e. positive predictive value.

Statistical analysis

Completeness was calculated as previously described and assessed descriptively as percentages. Accuracy of registration was quantified by the positive predictive values (PPV) of the different registers (Figure 24). PPV was calculated with 95% confidence intervals (CI), according to normal approximation.

3.3 STUDY II

Study population

All adult patients (≥16 years) registered in the SFR at Sahlgrenska University Hospital with any humeral fracture during the three-year time period between 1 January 2011 and 31 December 2013 were included in the study. Since Sahlgrenska University Hospital is the sole provider of trauma orthopaedics in a defined catchment area, only patients registered there were included in this study.

Methods

Information in relation to the patient, the fracture and the mechanism of injury was retrieved from the SFR. Treatment was not assessed in this study. Population data from Statistics Sweden were used to define the population at risk for age- and gender-specific incidence calculations.[56] Statistics Sweden is an independent, administrative agency under the Swedish Ministry of Financial Affairs that gathers, processes and publishes statistical information about populations and social conditions in Sweden. Public authorities and private companies are obliged to provide information to Statistics

Sweden and data are offered to the public free of charge. However, these data are not on an individual level. The population at risk in the current study was approximately 632,000 inhabitants (1,895,952 person-years) 16 years of age or older.

Study definitions

Mechanism of injury was defined as the reason for the fracture. There are numerous reasons for the fracture in the SFR and, in order to apprehend the diversity of registered reasons for the injury, the mechanism of injury was divided into six categories; simple fall, fall from a height, unspecified fall, traffic related, miscellaneous injuries and pathological fractures. A simple fall was defined as a fall from standing height, a fall from height as one from a higher level, such as from furniture or down a stair. An unspecified fall was a fall that was not classified further when registered in the SFR, meaning that it could be either a simple fall or a fall from height. Miscellaneous injuries included all fractures with a mechanism of injury that did not match the other categories, such as fractures sustained in fights, from falling objects or sports related. There are no established categories in trauma orthopaedics in terms of the mechanism of injury and the categories in this study were established, based to some extent on the categories used by Robinson et al. in 2003.[33]

Fracture classification was in accordance with the AO/OTA classification, as has previously been described. The fractures were divided into segments, i.e. proximal, diaphyseal and distal, and further subdivided into types and groups, creating a total of nine groups per fracture segment. The three subtypes (A1.3, C2.3 and C3.1) available for proximal fractures in the SFR were included in their respective group (A1, C2 and C3 respectively) to be able to compare the results.

Statistical analysis

Age- and gender-specific incidence rates were calculated as numbers of fractures per 100,000 inhabitants and year. The study only contains descriptive statistics and no statistical comparisons between groups were therefore made.

3.4 STUDY III

Study population

The entire SFR was used in this study and all patients (≥ 16 years) with a proximal humeral fracture (PHF) registered in the SFR from 1 January 2011 to 31 December 2017 were included. The minimum follow-up time on mortality was one year (range 1-7 years).

Only one PHF per patient was included in the study and, if a patient sustained two or more PHFs on different occasions during the study period, only the first fracture was included. In the event of bilateral PHFs, surgically treated fractures and/or fractures with a more severe AO classification were included.

Methods

Information related to patients and fractures was retrieved from the SFR. There was no need for other data sources in terms of the mortality among fracture patients, as the vital status (living or dead) of patients is present in the SFR. Data from Statistics Sweden were used for comparisons between the fracture patients and the general population with regard to 30-day, 90-day and one-year mortality. Statistics Sweden provides updated information on the mortality in the general population, divided into age, gender, location of the inhabitants and year of death.[56] Data regarding the general population were extracted for the study period (2011-2017) and each individual included in the study was matched with the corresponding risk of death, based on gender and age, as found in the general population. The gender and age composition of all the control groups therefore matched the patient groups in the study.

Study definitions

Treatment for each patient was at the discretion of the treating orthopaedic surgeon. The treatment was classified as either surgical or non-surgical. Since treatment can be altered for a proximal humeral fracture at an early first follow-up visit, the treatment given at 30 days after the fracture date was used in the study. As a result, primarily non-surgically treated patients who subsequently underwent early surgery (within 30 days) were classified as surgically treated.

Surgical treatment was defined as any procedure in which the skin was breached. Closed reduction was not regarded as a surgical intervention. The surgical treatment was further subdivided into three groups based on the surgical method; *open reduction and internal fixation (ORIF),* including all types of internal implant such as plates, intramedullary nails and combination methods (defined in **Study IV**), *arthroplasties,* including all types of shoulder arthroplasty, and *other operations,* including excision arthroplasties and undefined interventions.

Concomitant fractures and *fractures sustained within the first year after the PHF* (the index fracture) were obtained from the SFR. Since the SFR started registering all extremity fractures in October 2012, this was set as the starting date for these analyses. Proximal humeral fractures registered prior to that date were therefore excluded in the incidence analysis of concomitant fractures and later fractures.

Time to mortality was defined as the time from fracture to death. Patients who died within 30 days of fracture were included in the 90-day calculations and, similarly, patients who died between 30 and 90 days were included in the one-year calculations.

Standardised Mortality Ratios (SMR) were defined as the observed rate of death in the study population divided by the corresponding rate of death in an age- and gender-matched control group of the general population.

Statistical analysis

Demographic data, such as age, gender, mechanism of injury, fracture classification and treatment, were presented descriptively. SMRs were calculated to compare the observed overall mortality among study subjects with the expected overall mortality in the general population in Sweden (matched for age, gender and year of follow-up) at 30 days, 90 days and one year respectively. Comparisons between the mortality in study subjects and the general population were performed using the chi-square test. Significance was set at $P \leq 0.05$. To illustrate the cumulative survival of the study subjects, a Kaplan-Meier survival analysis was undertaken. A Cox proportional hazard regression model was used to identify factors associated with mortality. SPSS statistics, version 25.0 (IBM, Armonk, NY, USA), was used for all statistical analyses.

3.5 STUDY IV

Study population

Patients (≥16 years) registered in the SFR with a PHF at Sahlgrenska University Hospital in 2011-2017 were included in the study. All the patients were followed until 31 Dec 2019, rendering a follow-up time of two to nine years (mean time 4.5 years). Only patients primarily treated at SUH and eligible for follow-up at SUH were included in the study.

Methods

The surgery planning systems and medical records were reviewed for all patients to study the well-known problem of underreporting reoperations and to evaluate the completeness of reoperation registration in the SFR. Consequently, treatments and reoperations not primarily registered in the SFR were included in the study material. The SFR provides the physician with seven different choices with regard to the indication for a reoperation/late surgery. However, some specific reasons for a reoperation related to proximal humeral fractures, such as avascular necrosis, cannot be selected. As a result, all reoperations in this material were thoroughly reviewed and the indications were grouped according to what is described later. Moreover, all arthroplasties were controlled, since the register made no distinction between different types of total shoulder arthroplasty (i.e. anatomic or reversed) prior to 2015.

Study definitions

Treatment was defined, in accordance with **Study III**, as the treatment given at 30 days after the fracture date. There was no recognised treatment algorithm at Sahlgrenska University Hospital for PHFs during the study period, but the treatment of choice and the applied surgical technique were at the discretion of the treating surgeon.

Surgical treatment was divided into five groups: locking plate (LP), intramedullary nail (IMN), hemiarthroplasty (HA), reverse shoulder arthroplasty (RSA) and a combination of methods (combination). The combination method consisted of fixation with screws, cerclage wires, suture anchors, mini-plates or a combination thereof.

Reoperation was defined as an unexpected additional operation after the primary treatment. Moreover, late surgery (≥ 30 days) following initial non-surgical treatment was referred to as a 'reoperation' in this study, since it is an indication of treatment failure.

The indication for a reoperation was grouped into six categories: non-union, malunion, avascular necrosis (AVN) with collapse (Cruess grade 4 or 5), infection, implant failure and reoperation due to patient demands.[173] The "implant failure" group included secondary dislocations with screw penetration, the perioperative misplacement of implants, instability and tuberosity absorption/displacement/malfunction. Reoperation based on patient demands included operations not deemed compulsory, such as the removal of implants without screw penetration and/or the release of adhesions. Implant removal is not routinely performed at Sahlgrenska University Hospital and all reoperations were performed for symptomatic failures in agreement with the patient.

Major reoperation was defined as a reoperation deemed compulsory and *minor reoperation* including reoperation on patient demand. This was established in accordance with the definition made by Olerud et al.[17]

Statistical analysis

Demographics such as age, gender, fracture classification, treatment and reoperations are presented as descriptive data. Changes in patient demographics and treatment between the beginning (2011-2012) and the end (2016-2017) of the study period were analysed using the chi-square test and Student's t-test for categorical and continuous variables respectively. Statistical significance was set at $P \leq 0.05$. Kaplan-Meier survival analysis was undertaken to illustrate the cumulative survival rate (i.e. time to reoperation) for the different treatment modalities. Date of death was used as a censor and reoperation as an event in the analyses, while the end of follow-up was 31 December 2019. Risk factors for reoperations were analysed with a Cox proportional hazards regression model. SPSS statistics version 25.0 (IBM, Armonk, NY, USA) was used for all statistical analyses

3.6 ETHICS

The Swedish Fracture Register is approved by the Swedish Data Inspection Board and operates in accordance with Swedish legislation, i.e. the Swedish Personal Data Act and the Swedish Patient Data Act. All patients are informed that a registration will take place and that they have the right to decline. According to Swedish legislation, NQRs do not require signed consent from the individual registered patient, which is fundamental to the operation of NQRs.

The studies in this thesis were approved by the Central Ethical Review Board, Gothenburg; entry number 1018-13 (Study I), entry number 712-14 (Study II), entry number 1042-17 (Studies III and IV) and entry number T1137-18 (Study IV).

04

RESULTS

4.1 STUDY

Study population

In the NPR, 2,197 acute humeral fractures were reported in 1,876 patients at Sahlgrenska University Hospital during the study period. Following the exclusion of 24 patients without a Swedish PIN, 2,173 registrations were eligible for analysis. During the same period, 1,375 patients with 1,375 registered acute humeral fractures were present in the SFR (Figure 21 in the Method section). Via cross-matching by PINs, 1,375 registrations matched in both registers and were regarded as true, actual humeral fractures. For 900 registrations, 51 in the SFR and 849 in the NPR, the registration was absent in the other register (non-matching registrations). Following a medical charts review, all the 51 non-matching registrations in the SFR were actual humeral fractures missing in the NPR. In the NPR, 189 of the 849 non-matching registrations were actual fractures missing in the SFR. The estimated number of true humeral fractures treated at Sahlgrenska during the study period was therefore 1,564.

Completeness and accuracy of registration

When the estimated number of true acute fractures was used as a reference, the completeness in the NPR was 97% and the positive predictive value (PPV) was 70% (95% CI:68-72). The corresponding numbers for the SFR were a completeness of 88% and a PPV of 100% (95% CI:100-100). However, if all the registrations (n=2,173) in the NPR had been used as a reference, the SFR would have had an apparent completeness of 62% (Study I, Tables 2 and 3).

All the 1,375 registrations in the SFR were actual acute fractures treated at Sahlgrenska University Hospital during the time period for data extraction, while almost a third (n=660/2,173; 30%) of the registrations in the NPR were not (i.e. erroneous registrations) (Study I, Table 1). Re-admissions constituted the vast majority of the erroneous registrations (n=552/660; 84%) in the NPR, while registrations of non-humeral fractures were more uncommon (n=108/660; 16%). Most re-admissions following fractures treated at Sahlgrenska were registered within two years of the initial fracture (n=503/519; 97%). No patient sustained simultaneous bilateral fractures and no patient presented with more than one fracture in the same humeral segment during the study period.

Adjustment algorithm

In order to improve the case selection in the NPR data, the information on the erroneous registrations in the NPR was used to construct a search algorithm. This adjustment algorithm was constructed accordingly: all registrations of individuals with an acute humeral fracture code (S42.2-4) that had been registered with the same fracture code within the two previous years were excluded. When the adjustment algorithm was applied to NPR data, the accuracy for actual acute humeral fractures in the NPR improved from a PPV of 70% (95% CI: 68-72) pre adjustment algorithm to 92% (95% CI: 90-93) post algorithm. In addition, no actual humeral fractures were excluded using the algorithm.

The completeness for humeral fractures in the SFR for different counties in 2016-2018 was calculated (with the method used by the NBHW; Figure 23 in the Method section) as being between 75-90% when NPR data extracted via this adjustment algorithm were used as reference data (Study I**,** Figure 2).

4.2 STUDY II

Study population

Using the SFR, 2,011 humeral fractures in 1,986 patients were identified at Sahlgrenska University Hospital for the given study period. There was no patient with bilateral fractures, but 25 patients sustained two separate humeral fractures during the study period.

Age and gender

Women were generally older than men (mean age 70 years; range 17-103, and 59 years; range 16-96 respectively) at the time of fracture and they were more commonly affected (female/male ratio 2.4:1). The majority of fractures occurred in patients over 50 years of age (83%) and women were in the majority in this age group (77 %) (Table 2 and Study I, Table 1). However, most of the fractures sustained by patients aged 50 years or younger were sustained by men (59%).

Fractures of the proximal humerus were much more common (n=1,582/2,011; 79%) than fractures of the shaft (n=262/2,011; 13%) or distal humerus (n=167/2,011; 8%). Patients with a fracture of the proximal or distal humerus were generally older and a larger percentage of the patients were female compared with patients with a fracture of the humeral shaft (mean age 68 years; range 16-103 and 65 years; range 16-100 and 73% and 72% female for proximal and distal fractures respectively and mean age 59 years; range 16-98 and 54% female for shaft fractures) (Study II, Tables 1 and 3).

TABLE 2. The distribution of fractures in patients over or under the age of 50 years, according to gender and trauma mechanism.

Fracture location	Age (years)	Gender		Trauma mechanism		
		Female		Simple/unspecified fall*		Total
		n	%	n	%	n
Proximal	≤ 50	98	45	109	50	216
	> 50	1,062	78	1,107	81	1,366
Shaft	≤ 50	20	24	21	26	83
	> 50	121	68	118	66	179
Distal	≤ 50	18	51	10	29	35
	> 50	102	77	114	86	132
Total	≤ 50	136	41	140	42	334
	> 50	1,285	77	1,329	79	1,677

*Six patients are missing in relation to trauma mechanism, two patients ≤ 50 years and four patients > 50 years.

Incidence

The overall incidence of humeral fractures was 105 per 100,000 per year (Study II, Figure 3). The segment with the highest incidence rate was the proximal humerus (83 per 100,000/year), whereas shaft and distal fractures demonstrated lower incidence rates (13 and 8 per 100,000/year respectively). From the fifth decade and onwards, a distinct increase in overall incidence was observed for all segments of the humerus and the increasing incidence with age was greater among women than men. A bimodal incidence curve was observed for shaft fractures, with an additional minor peak in younger men, whereas proximal and distal fractures showcased a unimodal incidence curve, as described previously.

Fracture characteristics

Type C fractures were uncommon (four-part 11%) in the proximal humerus, with the majority of fractures being either type A (two-part 45%) or type B (three-part 44%) (Paper II, Table 2). The three most common fracture groups seen in proximal humeral fractures were the B1 (non-displaced/stable three-part fracture 29%), A2 (two-part surgical neck fracture 18%) and A1 (greater tuberosity 16%). Among the humeral shaft fractures, the A fractures were the most common (simple 58%), followed by type B (wedge 26%). Type C fractures (complex) were seen in approximately one in six fractures (16%). Type C fractures (complete intra-articular) were relatively more common in the distal segment of the humerus, comprising every third (34%) fracture. However, in this segment, type A fractures (extra-articular 40%) were also the most common fracture type.

The A1 fractures of the proximal and distal humerus occurred predominantly in younger patients, while C fractures of the shaft and highly complex fractures (C3) of the distal humerus almost exclusively affected patients over the age of 50 years.

Mechanism of injury

A simple fall was the most common mechanism of injury for all humeral fractures (56%) and for each segment separately (59%, 41% and 56% for proximal, shaft and distal fractures respectively) (Study II, Table 3). In patients over the age of 50 years, a simple or an unspecified fall was by far the most common mechanism of injury (79 %) for all segments of the humerus and the majority of these patients were women (77%; Table 2). In patients less than 50 years old, most fractures were caused by more high-energy mechanisms of trauma (traffic-related injuries, miscellaneous injuries and falls from height; 58%) and the majority of these patients were men (59%).
Only 1.2% of all fractures were open injuries and the majority of these (56%) were complex distal humeral fractures (AO/OTA group C3). Pathological fractures predominately affected the humeral shaft segment (70%), comprising 7% of all shaft fractures. Moreover, 17 pathological fractures occurred in men and 10 in women, which corresponds to 3% of all male fractures and 0.7% of all female fractures.

Seasonal variation

The incidence of proximal humeral fractures and shaft fractures increased during the winter months of December to February (Study II, Figure 4). In addition, shaft fractures also peaked in the summer months (May-September), whereas no seasonal variation was observed for distal humeral fractures.

4.3 STUDY III

Study population

The selection of the study cohort is shown in Figure 25 and the final study population comprised 18,452 patients with a proximal humeral fracture (PHF). The mean age of the patients was 69 years (range 16-107; Study III, Table I). Women were generally older at fracture than men (71 years; range 16-104, vs 62 years; range 16-107 respectively) and the majority of patients were female (74%). Type A fractures were most common, followed by type B and type C fractures (51%, 36% and 12% respectively). The vast majority of patients sustained their fracture due to a low-energy trauma mechanism (90%) and most fractures were treated non-surgically (80%). Of the patients treated surgically, almost three-quarters (74%) were treated with ORIF, while every fourth (25%) surgically treated patient underwent an arthroplasty. Concomitant fractures were present in 1,530 patients (9%) with a PHF. Most patients with a concomitant fracture only sustained one other fracture, but a few patients sustained multiple fractures. The three most common sites of concomitant fractures were the hip (24%), distal radius (20%) and humerus (12%). Of the 212 concomitant humeral fractures, 72 (34%) were contralateral fractures of the proximal humerus (Study III, Tables II and III).

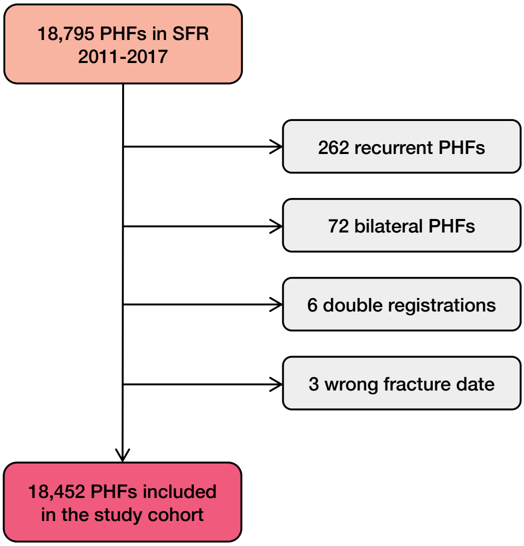

FIGURE 25. Flow chart showing exclusions and final study population in Study III.

Overall mortality

Patients with a PHF displayed significantly higher mortality rates than the corresponding rates in the general population (Study III, Table IV). The overall mortality for patients with a PHF was 1.7% (n=310) within 30 days, 3.3% (n=615) within 90 days and 7.9% (n=1,445) within one year after the fracture. Compared with the general population, the mortality was five times as high among fracture patients (SMR 5.2) during the first 30 days and twice as high at one year post fracture.

The analyses of mortality across age groups demonstrated an increasing risk of death with increasing age. However, the highest risk of death compared with the general population (i.e. SMR) was seen among the middle aged (Study III, Figure 2 and Table V). The relative risk of death then declined with advancing age. Male patients ran a higher risk of death than female patients, except for the very old patients (≥ 100 years), and male patients also demonstrated higher SMRs than women, except for patients over the age of 95 years.

Subgroup analysis

When comparing subgroups of patients with a PHF with age- and gender-matched controls in the general population, all subgroups had higher mortality rates within 30 days of fracture, except for those treated with an arthroplasty (SMR 0.8). The highest relative risk of death was seen in male patients and patients with a concomitant fracture (SMR 7.0 and 7.5 respectively). The elevated mortality seen in all patients with a PHF declined with time from fracture, although it was still elevated for all subgroups one year post fracture (Study III, Table IV).

Factors associated with mortality

Several factors were independently associated with increased mortality (Study III, Table VI). Increasing age, male gender and low-energy trauma mechanism ran the highest risk of death, but also type A fractures, concomitant fractures and non-surgical treatment involved an elevated mortality. Of the different treatment modalities, arthroplasty was associated with the lowest risk of death.

4.4 STUDY IV

Study population

A total of 4,009 patients with 4,092 consecutively registered PHFs at SUH were retrieved from the SFR. Following the exclusion of 22 patients (seven fractures primarily treated elsewhere, 13 set for follow-up at another department and two treated with excision arthroplasty), the final study population comprised 3,987 patients with 4,070 PHFs (Figure 25). Most patients were female (72%) and the mean age at the time of fracture was 68 years (range 16-104) (Study IV, Table 1). According to the AO/OTA-classification system, almost half the fractures were of type A (49%), whereas type C fractures (11%) were least common. Throughout the seven-year study period, there were no statistically significant differences in terms of patient demographics and fracture characteristics.

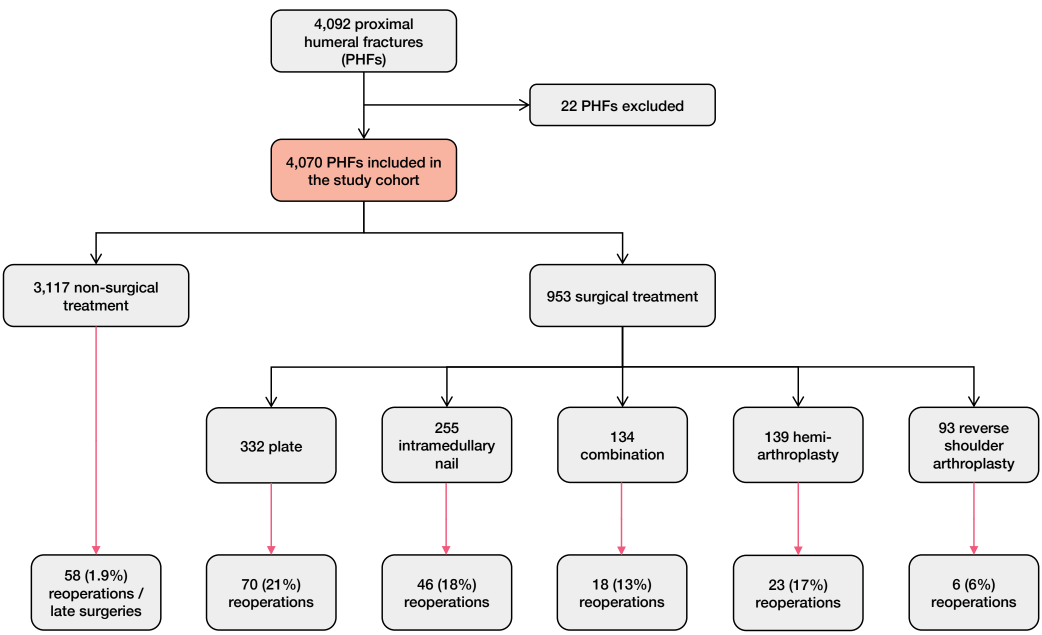

FIGURE 26. Flow chart of Study IV.

Validation

The result of the validation of procedure registrations in the SFR is shown in Table 3. Since treatments that were altered from non-surgery to surgery at an early first follow-up were regarded as surgical in Study IV, the completeness for primary procedures was 97%, while 62% of the reoperations were registered. As previously mentioned, all the initially missing registrations were included in the study material.

TABLE 3. Completeness of registration regarding surgical procedures for proximal humeral fractures at Sahlgrenska University Hospital 2011-2017

	Missed registrations	Total number of procedures	Completeness
Primary procedure	4	766	99.5%
Early change to surgical treatment*	22	187	88.2%
Reoperation**	114	302	62.3%
Total	140	1255	88.9%

*Initial non-surgical treatment changed to surgical ≤ 30 days.
**Includes late, unplanned surgical intervention (> 30 days) in initially non-surgically treated fractures.

Treatment

The majority of PHFs were treated non-surgically (n=3,117; 77%) and of these only 5% were type C (four-part) compared with 31% of the surgically treated fractures (Study IV, Table 1). Of the surgically treated patients (n=953), fixation with a locking plate was the most common treatment modality (35%), followed by fixation with an IM nail (27%). The patients treated with IM nails were generally older (mean age 71 years; range 19-103) than patients treated with a plate (mean age 60; range 16-99) and the fractures were typically two-part fractures (Type A 64%), whereas the most common fracture type treated with a plate was a three-part fracture (Type B 51%). Most fractures treated with a combination method (n=134) were of type A (81%), of which 101 fractures were isolated tuberosity fractures (AO/OTA 11-A1). The group of patients treated with arthroplasty (HA or RSA) had the highest proportion of complex fractures and the highest mean age of all patients treated with the different treatment modalities (AO/OTA type C fractures in 76% and 66%; mean age 70 years; range 35-92 and 75 years; range 51-96 respectively). No fracture was treated with any method requiring the mandatory removal of the fixation device.

Change in treatment practice

When examining changes in treatment practice throughout the seven-year study period, no statistically significant changes in the proportion of non-surgically and surgically treated fractures were observed (24% in 2011-2012 vs. 21% in 2016-2017;

P=0.06). However, among the surgically treated fractures, the proportion treated with a plate almost halved (47% in 2011-2012 vs. 26% in 2016-2017; *P*<0.001), while the proportion treated with an IM nail and RSA increased substantially (22% in 2011-2012 vs. 30% in 2016-2017; *P*=0.03 and 2.0% in 2011-2012 vs. 19% in 2016-2017; *P*<0.001 respectively) (Figure 26 and Study IV, Figure 1). Despite these changes in treatment protocols, the reoperation frequency remained constant during the seven-year study period and no changes were found between the beginning of the study and the end (Table 4)

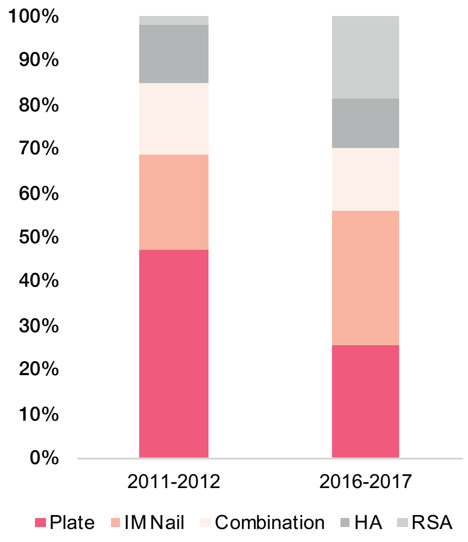

FIGURE 27. Surgically treated proximal humeral fractures (PHFs), presented by treatment modality as the proportion (%) of the total number of surgically treated PHFs in the beginning of the study period (2011-2012) and the end (2016-2017). IM nail= intramedullary nail, HA= hemiarthroplasty, RSA= reverse shoulder arthroplasty.

TABLE 4. Reoperation frequency, in the beginning of the study period (2011-2012) and the end (2016-2017), presented as the proportion of treated proximal humeral fractures (PHFs) later undergoing unplanned surgical intervention.

	All reoperations (%)			Major reoperations (%)		
	2011-2012	2016-2017	P-value*	2011-2012	2016-2017	P-value*
All PHFs	5.5	5.1	0.7	3.8	4.2	0.7
Surgically treated PHFs	18	16	0.6	13	13	0.9

*Chi-square test

Reoperation rate

The overall reoperation rate for all fractures was 5.4% during the study period and non-surgical treatment was the treatment modality associated with the lowest rate of secondary surgery (1.9%; Study IV, Table 2). For the surgically treated fractures, the rate of reoperation was 17%. Most reoperations occurred within two years of the initial treatment and the most common reason for a first reoperation was implant failure (35%), followed by a reoperation due to patient demands (25%; Study IV, Figure 2 and Table 2). Plate fixation was the treatment modality associated with the highest rate of reoperation (all-cause reoperations 21% and major reoperations 15%), but treatment with an IM nail or HA demonstrated almost equally high numbers (reoperations due to all causes 18% and 17% and major reoperations 13% and 14% respectively). RSA had the lowest reoperation rate (all-cause reoperations 6.5% and major reoperations 5.4%) among the surgical treatment modalities.

The 221 patients who underwent a reoperation had a total of 302 unplanned surgical interventions. This comprised almost every fourth surgical intervention (24%) for a PHF during the study period.

Factors associated with a reoperation

Factors associated with an increased risk of reoperation were increased fracture complexity and younger age (Paper IV, Table 4). Increasing fracture complexity was an independent predictor of major reoperations (hazard ratio (HR) 1.6 in AO/OTA type B and HR 5.7 in type C compared with type A), while younger age (age < 75 years) correlated with an increased risk of a reoperation when all causes of a reoperation were included (i.e. including patient-requested reoperations). Neither gender nor injury mechanism (high- /low-energy trauma) was associated with an increased risk of reoperation.

05

DISCUSSION

5.1 VALIDITY OF REGISTERS

The importance of valid data in register-based research cannot be emphasised strongly enough. Observational register-based studies are important complements to the high-quality evidence provided by RCTs, but accurate data are essential if this type of research is to be meaningful. The recently started SFR has the potential to become an important tool for the continuous monitoring of epidemiology, treatment patterns, adherence to treatment guidelines and outcome in everyday clinical practice. To date, several validation studies have been conducted on SFR data.[174-177] However, no study has examined the completeness or the accuracy of fracture registrations, two corner-stones in terms of the validity of a register.

5.1.1 Completeness and accuracy of registrations

In **Study I**, the completeness in the SFR for humeral fractures at SUH was assessed to be 88%. This was surprisingly high, considering the inherent difficulties associated with a fracture register like the SFR. Since registration in the SFR is non-compulsory, made by the surgeon on call and most often performed in an acute setting under considerable time pressure, a lower rate of completeness could have been expected.

To the best of our knowledge, there is no other NQR that collects data on all fractures regardless of treatment modality with which to compare the completeness rates of the SFR. Both the well-established orthopaedic hip and knee arthroplasty registers (completeness rate 98% and 97% respectively, for primary procedures), as well as the diagnosis-specific hip-fracture registers in the Nordic countries (completeness rate 80% and 72% in the Swedish Rikshöft and the Norwegian Hip Fracture register respectively, have different register set-ups; the registration process is completed by employed personnel and the patients are treated surgically as inpatients.[70,79,178,179] Inpatient care and surgical treatment are factors known to have a positive influence on the rate of registration.[42] Since the majority of patients with a humeral fracture are treated as outpatients and/or non-surgically, these fractures could be expected to have lower completeness than fractures predominantly requiring inpatient care and/or surgical treatment (e.g. hip fractures). The register most similar to the SFR is probably the Danish Fracture Database (DNFD).[180] Like the SFR, data entry in the DNFD is made by the treating surgeon and all fracture locations are registered. However, only surgically treated fractures are included. The reported completeness of 88% for primary fracture surgery in the DNFD is identical to the completeness rate in **Study I** of all humeral fractures in the SFR.[71] Together with the finding in **Study I** that all registrations were valid fractures, this indicates that it is possible to obtain both high completeness and valid registrations with the registration methodology used in the SFR.

As was described in an earlier section, the NPR is known to contain non-valid data and no previous study has thoroughly examined the completeness in the Swedish NPR regarding fractures. There are however, reports from the NPRs of the other Nordic countries. These administrative databases are similar to the Swedish NPR with regard to structure, data collection and the verification of inhabitants using PINs, which enables comparisons with the Swedish system. Studies from Norway and Finland have reported completeness rates of between 89 and 100% for hip fractures in their respective NPR, but we are not aware of any study reporting completeness data on other fractures apart from the hip.[60,181,182] In spite of this, the finding in **Study I** of a completeness rate of 97% for humeral fractures in the Swedish NPR supports their findings and it could therefore be concluded that almost all fractures are included in the NPRs.

The main challenge when using fracture data from the NPR appears to be related to an overestimation of fractures. Due to readmissions and diagnostic coding errors, unselected NPR data overestimated the true number of acute fractures by 39% in **Study I**. Similar findings have previously been reported for hip fractures and other incident medical events. Lofthus et al. reported a 19% overestimation of hip fracture incidence in the Norwegian NPR, while two Swedish studies reported an overestimation of hip contusions and stroke of 35% and 30% respectively in the Swedish NPR.[42,60,62] The findings in **Study I** of as many as one in every four registrations of acute humeral fractures in the NPR constituted by a readmission for a previous fracture support the assumption that the main reason for this overestimation of the number of incident events is repeat admissions. Since time of injury is lacking in the NPR, readmissions due to causes related to an old event will be recorded as separate new events if the patient is assigned an acute ICD code on readmission. With an additional 5% of registrations in **Study I** being pure diagnostic coding errors, only 70% of the recordings in the NPR were actual acute humeral fractures. This underscores the need for correct case selection if data from NPR are to be used for epidemiological research or as reference data in completeness calculations.

Algorithms designed to enhance case selection in administrative databases have previously been developed. The incidence of stroke and myocardial infarction has been monitored in Sweden using algorithms of this kind for NPR data and a recently published study assessed an algorithm for identifying incident fractures in the US Medicare database.[66,86,183] The algorithm used by Wright et al. to identify incident fractures in the Medicare population is similar to the algorithm developed in Study I. However, they have a 90-day fracture-free spectrum, as opposed to the two-year free spectrum in Study I, before a new registration for a fracture in the same location is regarded as an actual new acute fracture. They reported a PPV of 95% (95% CI 89-99) when their algorithm was applied compared with the PPV of 92% in Study I.[183]

However, if their algorithm was applied to the material in Study I, a large percentage of the confirmed readmissions would still have been accounted for as new fractures, thereby still greatly overestimating the true number of acute fractures. Since contralateral fractures and new fractures (same humeral location, i.e. S42.2-4) sustained within two years of the first fracture appear to be uncommon for the humerus (Studies II-IV), the adjustment algorithm designed in Study I appears to be better suited to NPR data on humeral fractures than the algorithm used by Wright et al.

The developed adjustment algorithm is easy to use and, with a PPV of 92% and without excluding actual acute fracture registrations, refined NPR data of this kind could be valuable in ensuring regular completeness calculations of SFR data. As no substantial differences have been demonstrated in the reporting of diagnoses between different caregivers obliged to report to the NPR, there is reason to believe that the adjustment algorithm constructed in this study is suitable for NPR data in all parts of Sweden.[1,42] When adjusted NPR data were used as a reference, departments included in the SFR from 2015 and onwards had an estimated completeness of between 75-90% for humeral fractures. These numbers further support the conclusion that it is possible to obtain high completeness for fracture registration using voluntary methods. In fact, the true completeness of the SFR might be even higher, since the reference data on adjusted NPR registrations still overestimate the number of acute humeral fractures in **Study I**. However, the adjustment algorithm needs further validation for different hospitals and counties in Sweden.

5.1.2 Completeness for primary procedures and reoperations

The two main outcome variables used by the SFR are PROMs and reoperations. The response rate for the PROMs is known, while the completeness of reoperations is more difficult to account for.[76] In order to validate the rate of reoperations in the SFR, a retrospective review of surgery planning systems and medical charts for all the patients included in **Study IV** was conducted. The results found during this process warranted the need for this arduous and time-consuming way of ensuring high completeness. Although there was an almost complete registration of primary procedures (99%) in the SFR, the much lower completeness for reoperations (62%) highlights the need to validate the data if trustworthy numbers in terms of reoperations in the SFR are to be presented.

Wennergren et al. reported almost identical numbers in their study of tibial fractures in the SFR (completeness rate 99% for primary procedures and 63% for reoperations), while the DNFB reported better completeness rates (77%) regarding reoperations following fractures, compared with the findings in **Study IV**.[71,146] However, these numbers are significantly lower than the reported completeness rate of 91% for revisions in the Swedish Hip Arthroplasty Register (SHPR).[178] One reason might be that the SHPR constantly validates its revisions by making comparisons with official health databases. This is, however, far more challenging for a fracture register due to the vast number of possible treatment options that exist for re-do surgery following fractures. As a result, no automated search function has so far been developed in terms of the identification of reoperations in the SFR. Until this happens, we recommend that a retrospective validation and completion of data is performed prior to evaluating reoperations with data from the SPR.

5.1.3 Strengths, limitations and methodological considerations

Study I was designed as a single-centre prevalence study using data from two independent registers, the NPR and the SFR. The method of *independent case ascertainment*, with cross-linking and a further medical record review to enhance the quality of the selected method, was used (ref). As previously described, this method is extremely suitable for evaluating the completeness and accuracy of registrations.[82] However, it requires the data sources that are compared to be independent of each other. While the NPR uses several sources for case notification (including data from public and private caregivers), the SFR is an independent source that is not used for case notification by the NPR. As a result, data can be compared between these registers in order to assess ascertained cases and additional cases not primarily registered in the respective register.

The method of case ascertainment used in this study assumes that registered entries found in both the NPR and the SFR are valid fracture registrations. Even though this is most probably the case, we cannot be fully confident that it is. The fact that the case ascertainment is complete does not rule out the risk of both registers containing incorrect information. For this reason, a more precise way of assessing the accuracy of registrations would have been to evaluate the medical records of all the patients found in the study. However, this was not done, since the probability of both registers containing incorrect information was regarded as low.

Another way of increasing the probability of matching registrations being valid cases is to cross-match more than two registers. This has previously been done in relation to completeness evaluations of myocardial infarctions and stroke.[66,86] For those two diagnoses, the Cause of Death Register (CDR) and the Swedish Prescribed Drug Register (SPDR) were combined in addition to the NPR and the respective NQR.[184,185] The combination of multiple sources of information improved the validity of case ascertainment. Moreover, multiple registers could potentially detect fractures not registered in either the SFR or the NPR, fractures that were not detected using the methodology used in **Study I**. However, few administrative databases record events related to fractures. Neither the CDR nor the SPDR would be valid, as few fractures are registered as the cause of death and most prescribed drugs related to fractures (foremost pain killers) are highly unspecific for fractures. One possibility would have been to link sick leave registered at the Swedish Social Security Agency to this material. Although not everyone sustaining a fracture is registered with that agency, it would probably have increased the likelihood of correct registrations and might also have found fractures not recorded in the NPR or the SFR. However, the effect of methodology of this kind on the result in **Study I** is probably marginal and it was therefore not used.

When assessing the validity of a test or a register, terms often used are sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). In order to evaluate these terms, the true positive registration, false positive registration, true negative and false negative registrations must be known (Figure 26). The design of the current study provides information on the true positives (TP; i.e. registered actual humeral fractures), the false negatives (FN; i.e. actual humeral fractures not included in each register) and the false positives (FP; i.e. erroneous registrations in the registers) in both the NPR and the SFR. However, there is no knowledge of the true negatives (TN; i.e. patients without a fracture correctly not registered in the register). Completeness is calculated as the number of valid cases identified in the register divided by the total number of valid cases in the study population (i.e. true positive + false negative), which more or less equals the definition of sensitivity. As a result, the study design in the current paper allowed for calculations of sensitivity and PPV but not specificity and NPV.

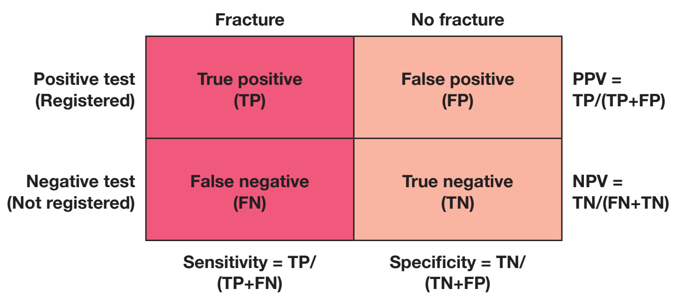

FIGURE 28. The relationship between sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) in a test, or in this case a register.

Study I assessed the completeness of only one location of fractures in a single hospital. This raises questions regarding the generalisability of the study results. At the onset of this study, only humeral and tibial fractures were registered in the SFR and SUH was the only department in the SFR, thereby limiting the potential for other study designs. However, the question with regard to generalisability still remains. An alternative study design would have involved extracting data from a random sample of registered fractures in one of the registers. A medical chart review of the selected cases would validate the registrations in the registers. The result would then be based on estimations rather than on actual numbers and different fracture locations in multiple different hospitals could thereby be included, which would have generated high external validity. This has previously been done on multiple occasions for other medical conditions and it is an excellent method for evaluating the accuracy of registrations.[186-188] However, since the random sample of fractures emanates from one of the registers, fractures missing in that particular register will not be included in the analyses. This would compromise the estimation of completeness, since the "true" number of valid fractures would be unknown. This makes a study method of this kind less useful for completeness evaluations and it is therefore not warranted for the scope of this investigation.

5.2 EPIDEMIOLOGY

In orthopaedics, surgeons usually quantify and classify different traumas in order to focus efforts and resources on the specific areas of need. Instead of trusting one's perception of prevalence, epidemiology is used to obtain a perspective and objectively monitor changes in incidence. With a projected ageing population in the western world, together with rampant costs for healthcare in general, updated and reliable epidemiological data are much requested in order to be able to plan for resource allocation and preventive measures.[4] In order for an epidemiological study to present trustworthy numbers, all fractures occurring in a defined population during a specific time period must be included. **Study I** concluded that the vast majority of fractures were included in the SFR and that the data were of high validity. As a result, with detailed and prospectively collected data of high validity, the SFR offers unique opportunities for epidemiological studies of fractures in Gothenburg.

5.2.1 Epidemiology of humeral fractures

Study II shows that all three segments of the humerus had a rapidly increasing fracture incidence with increasing age, starting from 50 years and upwards. This applied to both genders, although the increasing incidence rate was not as steep for men as for women. For proximal and shaft fractures, a decrease in incidence was even noted for the oldest males. One possible explanation might be a natural selection bias, since life expectancy is shorter in men than in women. Men still alive at those high ages might be generally healthier and less frail and thereby not as prone to falls and subsequent fractures.[189]

Proximal and distal humeral fractures displayed a similar unimodal incidence curve, with fractures almost exclusively affecting patients from 50 years and upwards. Shaft fractures had a bimodal incidence curve with an additional minor incidence peak in younger patients, most notably affecting males between 16 and 30 years of age. However, the majority of fractures were sustained in patients > 50 years of age; this even applied to shaft fractures.

The unimodal incidence curve observed for proximal and distal humeral fractures and the bimodal incidence curve observed for shaft fractures are in agreement with findings reported by Brown et al., Horak et al. and Launonen et al. relating to proximal fractures, Robinson et al. on distal humeral fractures and Tytherleigh-Strong et al. and Ekholm et al. on shaft fractures respectively.[32-34,47,51,190] However, when comparing age-specific incidence rates from **Study II** with the older data in those studies from

Scotland, Sweden and Finland, there is a sharper increase in incidence with age for all segments of the humerus in the more recent cohort from Gothenburg.

Previous epidemiological studies of fractures have focused on either one segment in one bone, for example, only the proximal humerus, or on all fracture locations in the body. CM Brown et al. presented results for all fractures in the body based on data from Edinburgh in 2000.[49] In their study, fractures of the proximal humeral segment were the seventh most common fracture site, while fractures of the shaft and distal humerus were more uncommon (17th and 22nd most common fracture sites respectively). A similar study was conducted by Bergh et al. on SFR data from Gothenburg between 2015 and 2018.[191] They found that PHFs were the fourth most common fracture site, while shaft and distal fractures were the 15th and 21st most common fracture sites respectively. The relationship between the different segments of the humerus in terms of the number of fractures in both these studies was in accordance with the findings in **Study II**. We found that fractures of the proximal segment were six times more common than fractures of the shaft segment (n=1,582/262) and nine times more common than in the distal segment (n=1,582/167). The corresponding numbers in the above-mentioned studies were five to seven times for proximal and shaft fractures and nine to 11 times for proximal and distal fractures.[49,191]

With regard to gender and trauma mechanism, a clear dividing line at 50 years was observed for all segments of the humerus. Fracture patients under 50 years of age were predominantly males (59%) and high-energy related mechanisms of injury (traffic injury, falls from height, miscellaneous) were the most common reason (58%) for the humeral fracture. In patients over 50 years of age, the vast majority were women (77%) and a simple or unspecified fall was by far the most common reason (79%) for fracture. These findings in terms of age, gender and trauma mechanisms are in general agreement with previous epidemiological reports related to each specific segment of the humerus.[32,33,51]

The World Health Organisation (WHO) has described fragility fractures, or osteoporosis-related fractures, as fractures that result from mechanical forces that would not normally lead to a fracture (i.e. a fall from standing).[162] Proximal humeral fractures have long been regarded as osteoporotic in nature, predominantly affecting women and becoming increasingly common with older age.[46-48] In contrast, fractures of the shaft and distal segment of the humerus have historically been considered non-osteoporotic, as the majority of patients were less than 40 years of age and the majority of fractures were caused by high-energy trauma in older studies.[46,48] However, the distribution of fractures in the population has been shown to change with time. Court-Brown et al. reported considerable changes in the individuals that sustained fractures in 2000, compared with the classic study by Buhr and Cook from the 1950s.[46,49] A distal humeral fracture was one of several fractures regarded as non-osteoporotic in the 1950s, but it has been reported to have experienced an apparent shift towards older patients, with predominantly women being affected, in 2000. This indicates the increasing influence of osteoporosis for these fractures, which was suggested to depend on both an ageing population and older people being more active than in previous generations.[49] The findings in **Study II** support the results from the year 2000. The unimodal incidence curves and the crude numbers of older patients predominantly sustaining proximal and distal humeral fractures (86% and 79% of proximal and distal fractures respectively affecting patients over 50 years of age) following a simple or unspecified fall (81% for proximal and 79% for distal humeral fractures in patients over 50 years of age) confirm that these fractures are predominantly osteoporosis related. However, the equivalent numbers for shaft fractures in **Study II** (68% in patients over 50 years of age, 66% of those due to a simple or an unspecified fall) suggest that, nowadays, even fractures of the humeral shaft are osteoporotic to a large extent. There is still the cohort of young patients with high-energy fractures, but the majority of shaft fractures nowadays affect older patients and are influenced by osteoporosis. This finding has subsequently been supported by a study from Scotland.[192] We claim this is important and relatively new knowledge which needs to be taken into consideration when planning future treatment methods for these fractures. Treatment methods not compromised by weak osteoporotic bone need to be evaluated and evidence-based guidelines to select the appropriate fractures for surgical treatment need to be established.

The distribution of humeral fractures according to the AO/OTA classification regarding shaft and distal fractures in **Study II** was in general agreement with previously published data.[32-34,192] The findings in the study cohorts in **Studies II-IV** in terms of the AO/OTA classification of PHFs (51-45% type A, 44-36% type B and 12-11% type C fractures) demonstrated a larger proportion of B and C fractures compared with the studies by Brown et al. (66% A, 27% B and 6% C) and Launonen et al. (62% A, 19% B and 13% C), although the latter only presented their results according to the Neer classification.[51,190] One possible explanation of the differences might be the different displacement criteria in the Neer and the AO/OTA classifications. This has previously been described and it makes it theoretically easier to classify a fracture as a three- or four-part fracture in the AO/OTA system compared with the Neer system.[30,35,37] Moreover, the fact that there was a larger proportion of older patients in the study cohorts in **Studies II-IV** might also explain the difference, since **Study II** found that A fractures were slightly more common in younger patients, whereas B and C fractures become increasingly common with older age. This tendency towards complex fractures more commonly affecting older people, while simpler fractures affect young patients to a greater extent, has previously been shown and also applies to shaft and distal fractures.[33,51,190] This could possibly be explained by the changing bone quality that comes with increasing age. For healthy bone to shatter into a C fracture, a large amount of energy could be expected. **Studies II-IV** reveal that few humeral fractures are caused by high-energy trauma, which could explain why complex fractures in healthy bone are fairly uncommon in Swedish population-based cohorts. On the other hand, osteoporotic bone might break into multiple parts, even following the low energy produced by a simple fall. As a result, if the trend towards increasingly older people sustaining humeral fractures continues, a higher incidence of complex fractures could be expected in the future.

Since the difficulty involved in obtaining a stable, well-functioning osteosynthesis in complex osteoporotic fractures is well known, this will entail a major challenge for health care. It is therefore important that preventive measures are taken, in order to prevent fractures from occurring in the elderly community.

In **Study II,** there was a seasonal variation in the frequency of PHFs and shaft fractures. Both these fractures demonstrated a high occurrence during the winter months. This is in agreement with findings from Scotland and Finland, where the weather conditions are similar to those in Gothenburg, with often icy, slippery roads during the winter.[51,190] The fact that the weather conditions affect the incidence of fractures was further supported in a study of tibial fractures from Gothenburg. Wennergren et al. demonstrated both an incidence peak during the winter and also the highest percentage of fractures sustained due to simple falls occurring at this time of the year.[193] These findings support the assumption that the seasonal peak in fracture incidence observed during the winter is due to an increase in simple falls because of slippery conditions. In fact, most fragility fractures, including hip fractures, display a similar seasonal variation.[194] However, the difference between incidence in the summer and winter is greatest among healthier individuals, since they are more ambulatory than frailer patients and therefore not deterred from going out during cold weather.[169,194]

5.2.2 Incidence

The reported incidence rates in **Study II** are based on prospectively collected data and include all fractures, regardless of the treatment or hospitalisation of the patient. This is an important strength when evaluating epidemiology. The only other studies of humeral fractures, prior to the onset of this thesis, with a similar methodology, are the much cited papers originating from Edinburgh, Scotland. These Scottish studies report incidence rates that are slightly lower than the rates found in **Study II** (Scottish studies vs **Study II** respectively; all humerus 81.7 vs 104.7/100 000, PHF 63.0 vs 83.0/100 000, shaft 12.9 vs 13.4/100 000 and distal 5.7 vs 8.3 /100 000).[33,34,49,51] However, the studies from Edinburgh are all based on data collected during, or before, the 1990s.

Comparing incidence rates with those in other studies is more problematic, due to differences in study designs and data collection. For example, studies based on data from national discharge registers tend to report higher rates of incidence than the single-centre studies from Edinburgh or the results in **Study II**. Bell et al. reported incidence rates for PHFs of 248/100,000 inhabitants, based on nationwide data from emergency department visits in the US, while Sumrein et al. reported an incidence rate for PHFs of 122/100,000 in Sweden in 2012, based on data from the NPR.[5,59] These numbers are substantially higher than the incidence rate for PHFs of 83/100,000 presented in **Study II**.

Study I demonstrates that administrative discharge data tend to overestimate the true number of fractures and similarly single-centre studies might potentially miss certain fractures and therefore underestimate the true incidence. This could explain the diverging incidence rates emanating from different data sources. To the best of our knowledge, no previous study has presented its rate of completeness and few studies account for their methods of data collection. This makes it difficult to evaluate the completeness of data in most epidemiological studies.

Since the first reports of incidence rates emerged in the 1950s, an increasing incidence has been reported for humeral fractures. The initial reports only examined PHFs and Begner et al. found an increasing overall incidence, driven by a progressive increase among older patients, when examining the incidence of PHFs between 1950 and 1980 in Malmö.[45] Kannus et al. reported data from the Finnish National Hospital Discharge Register and found a rapidly increasing incidence of patients with proximal humeral fractures admitted to hospitals from 1970 until the end of the 1990s.[43,195] However, the incidence rates then appeared to stabilise. Sumrein et al. also reported findings of an increasing incidence in PHFs between 2001 and 2011 in Sweden.[59] When comparing the incidence rates in **Study II** with more recently published data from Gothenburg, the incidence rates in the latter study by Bergh et al. are higher for all segments of the humerus (**Study II** vs Bergh et al.; PHF 83 vs 101/100,000, Shaft 13 vs 15/100,000 and distal 8.3 vs 11/100,000).[191] These findings are further supported by Brown et al. who relatively recently published incidence rates for all fractures at a single centre ten years apart (comparing 2000 with 2010) and found increasing incidence rates with advancing time for all humeral segments.[3] These various reports suggest that there is an ongoing trend towards increasing incidence for humeral fractures, which can be mainly attributed to an increase in the numbers of fragility fractures in a growing elderly population. This underlines the need for precautionary measures to be taken, in order to prevent fractures from occurring. It also highlights the importance of both having a valid instrument for evaluating changes in fracture incidence and being able to evaluate the effect of preventive measures. The findings in **Study I** suggest that the SFR could be one such instrument.

5.2.3 Strengths, limitations and methodological considerations

In order to demonstrate the true epidemiology of a fracture, a study has to include all the fractures occurring in a defined population during a specific time period. In **Study II**, only patients treated at Sahlgrenska University Hospital were eligible for inclusion via the SFR. In reality, there are most probably patients not seeking medical attention at all for a fracture, or who are handled by other caregivers in the area and therefore not included in this study. These fractures are probably not severe, as fractures requiring surgical treatment or fractures severely affecting the patient are almost exclusively referred to and handled by the public hospital. This indicates a potential selection bias in the SFR and therefore also in **Study II**. However, the actual number of these fractures not included in the SFR is probably low, considering the organisation of health care in Gothenburg at the time of the study and the low probability of patients not seeking medical attention following a humeral fracture. The effect of these missing fractures on the study results is therefore probably limited.

The opportunity to estimate incidence rates is based on the assumption of a well-defined catchment area. In theory, this applies to the current study, as Sahlgrenska University Hospital is the sole provider of orthopaedic trauma care in Gothenburg.

However, since patients are mobile and free to choose which hospital to visit in the event of trauma, a strict geographical definition of the population at risk is difficult to achieve. Some patients might seek medical attention across the border from their assigned hospital and thereby affect the result of incidence calculations. The effect of this patient mobility is difficult to fully assess and this might have influenced the results in **Study II.**

The quality and usefulness of the data in a register such as the SFR are dependent on the accuracy of the classification of fractures. Current classification systems of the proximal humerus, including both the Neer and AO/OTA systems, have been criticised for limited reliability and reproducibility.[41,196-198] This has been suggested to be due to an inability adequately to interpret the images of the fracture, most probably due to inadequate surgeon experience and poor imaging techniques.[37] Moreover, attempts to improve the reliability and reproducibility of the classification systems have not been uniformly successful. The addition of complementary radiographs, such as two-dimensional (2D) computed tomography (CT) or three-dimensional (3D) CT, has yielded inconsistent results. Some researchers claim a slight improvement when additional radiographs are added, especially for inexperienced physicians, and for complex fractures when 3D CT is used.[196,199] Others have not been able to demonstrate any positive effects of additional, modern radiographs.[200-202] Attempts to increase reliability by reducing the number of fracture categories in the classification systems have demonstrated only a modest improvement, or none at all.[196,200] The inadequate experience of the physician who classifies the fracture is another potential concern. This applies in particular to the classification process in the SFR, since the classification is often made by junior residents in an acute setting. However, clinical experience has not been shown to be of significant importance for the reliability of classification.[200,201] This is supported by several findings that fractures in the SFR, including humeral fractures, are classified with the same accuracy as has previously been reported from studies with expert panels.[175-177,203,204]

5.3 MORTALITY

Patients sustaining fractures run an increased risk of death compared with the general population.[149,151,152] The elevated mortality following a hip fracture is well recognised, but the mortality in patients with fractures in other locations is not equally well studied.

5.3.1 Mortality in patients with a proximal humeral fracture

In **Study III**, we found that patients who sustain a PHF run a markedly increased risk of death compared with their age- and gender-matched peers in the general population. This is especially evident within the first 30 days post fracture, with a more than fivefold increase in the risk of death for fracture patients, while the increased risk of death is still doubled one year post fracture.

The overall increase in mortality in the cohort of patients with PHFs obviously does not apply to all individual patients. Even though far from every patient who sustains a PHF has a shorter than average life expectancy, in **Study III** we found several factors independently associated with excess mortality. They include male gender, concomitant fractures and low-energy trauma mechanisms. Male gender is a known factor associated with excess mortality following osteoporosis-related fractures.[149,151,163,205,206] Men sustaining fragility fractures have more comorbidities and poorer general health than women sustaining these fractures and the presence of osteoporosis has been shown to be an independent predictor of mortality in men.[207-209] As a result, a proportion of the male patients who sustain these fractures are included in a particularly frail part of the population. Similar reasoning might apply to the observed increase in mortality in patients with low-energy trauma mechanisms and concomitant fractures. Patients with poor general health are more prone to falls than their healthier age- and gender-matched peers in the general population and less well equipped to cope with a fall if it occurs.[156,157,161] If low bone mineral density accompanies the increased tendency towards falling, these patients run a high risk of sustaining one or several fractures following minor traumas. Consequently, pre-fracture comorbidities impact both the risk of sustaining a fracture and subsequently the survival. Even if the trauma contributes to the enhanced risk of death, it is more likely that the fracture is merely an indicator of frailty.

A further indicator of the importance of underlying pre-injury factors is the previous finding that patients requiring admission following a PHF have both excessive comorbidities and a markedly elevated mortality risk, compared with patients that are treated as outpatients.[210,211] Unfortunately, this was not possible to investigate in **Study III**, since the SFR lacks data on whether inpatient care was required.

One possible selection bias explains why patients treated with an arthroplasty had the lowest mortality risk, whereas patients treated non-surgically ran the highest risk of mortality. Obviously, there are more risks accompanying advanced surgical treatment than non-invasive treatment with a sling. However, since the general health of the patient is taken into consideration when deciding upon treatment, frail patients not deemed to benefit from advanced surgery are more likely to receive non-surgical management.[10] This survivor treatment selection bias has previously been reported and supports the hypothesis that, from a general health perspective, appropriate case selection is accomplished when treatment is chosen for PHF patients.[10,169,210,211]

The high mortality in patients with hip fractures has attracted a great deal of attention, contrary to the attention paid to mortality in patients with other fractures. Crude mortality rates of 20-26% have been reported one year after a hip fracture and equally high mortality rates have recently been reported in patients with diaphyseal and distal femoral fractures.[154,155,212,213] These mortality rates are substantially higher than the crude one-year mortality rate of 7.8% in patients with a PHF found in **Study III,** which is in agreement with previous studies reporting mortality following a PHF.[169,206,211] However, patients sustaining hip or other femoral fractures are generally older than patients who sustain a PHF (mean age 83 years for femoral-fracture patients in the study by Wolf et al., compared with 69 years for PHF patients in **Study III**).[213]

When age is considered, the mortality rates are more similar. Schnell et al. reported mortality rates of 2.1% in patients aged 60-69 years one year after a hip fracture, 14% in patients aged 70-79 years, 23% in patients aged 80-89 years and 28% in patients aged more than 90 years.[155] The corresponding mortality rates for the same age groups at one year post-PHF in **Study III** were only slightly lower (3.2%, 5.2%, 15% and 34% respectively). In a study by Ravindrarajah et al., primary care patients, who were over 80 years of age, had a one-year mortality rate of 31% following hip fractures, compared with the mortality rate of 20% in PHF patients over 80 years of age in **Study III**.[214] In terms of the mortality in patients with fractures in other parts of the body, Ravindrarajah et al. also reported mortality rates for the same patient cohort following pelvic and wrist fractures (26% and 13% respectively). Other authors have reported one-year mortality rates in patients with vertebral fractures that are in accordance with age-matched results for PHF patients in **Study III.**[149,151,153] So, although a direct comparison between study populations entails uncertainty due to differences in study methodologies, the mortality for patients following a PHF appears to be lower than in patients with a femoral fracture, similar to the mortality rate in patients with pelvic and vertebral fractures and higher than in patients sustaining wrist fractures. The difference in underlying patient factors between different patient cohorts and the impact of the fracture and the treatment itself require further exploration. However, it is clear that patients with fractures other than hip fractures also run a substantially elevated risk of dying compared with the general population.

The high mortality following hip fractures has led to the development of special orthogeriatric care-taking programmes for hip fracture patients, which are now in use in many areas in the western world.[155,215,216] Apart from rapid medical and orthopaedic care, these orthogeriatric programmes aim to evaluate and improve the general health of the patient. Measures almost identical with the ones used to reverse frailty, including dietary counselling and muscle strengthening, have proven effective.[160,217] Compared with previous standardised care, patients taking part in these orthogeriatric programmes have a reduced time to recovery, with a subsequent reduced length of hospital stay, as well as a greater chance of returning to an independent way of living. Moreover, these patients have a lasting reduced risk of falls and subsequent new fractures. Even short- and medium-term mortality have been shown to decrease substantially.[155,160,215-217] These programmes have therefore been shown to be highly effective, both for the patient and for society.

It is known that patients with a PHF generally have more comorbidities than their age-matched peers in the general population.[163,167,214] Together with the findings in **Study III** of high mortality in PHF patients, this indicates that many of these patients are vulnerable and are included in a frail part of the population. Since frailty is reversible to some degree and with the proven efficacy of the hip fracture programmes, many patients sustaining a PHF would most probably benefit from special care-taking programmes aimed at reversing frailty. If these vulnerable patients can be identified in time, these measures could lead to a lower fracture incidence and ultimately increase the quality of life and survival for this population at risk.

5.3.2 Strengths, limitations and methodological considerations

One obvious strength of the methodology used in **Study III** (as well as in **Studies II and IV**) is the large number of patients. To date, the results in **Study III** are based on the largest cohort of patients examining mortality following a PHF and includes all patients regardless of hospitalisation or treatment.

All patients with a proximal humeral fracture were included in **Study III**. This includes patients with pathological fractures. These patients run a greater risk of death than their age and gender matched peers in the general population, thereby increasing the overall mortality rate in the study population. However, the exclusion of pathological fractures from the study cohort would have biased the result and underestimated the standardised mortality ratio (SMR). Since the aim of **Study III** was to investigate overall mortality in patients with a PHF, these patients were therefore included in the study. However, due to the findings in **Study II** of a low incidence of pathological fractures in the proximal humerus, the effect on the result of including pathological fractures is probably negligible.

The SFR did not have full coverage in Sweden during the study period, but the control group was based on data from the entire country. This potential difference between the study group and the control group could have been minimised, since Statistics Sweden provides mortality information based on the location of the inhabitants. If the data for the control group had been selected solely on the regions attached to the SFR, this potential bias could have been minimised. Unfortunately, this was not done and the effect on the result of this selection bias is unclear.

Study III does not contain data on comorbidities and the physical and mental status of the patient, since this type of information is lacking in the SFR. This could be regarded as a major weakness, both in **Study III** specifically and in the SFR in general. However, the number of variables registered in the SFR needs to be limited, due to the sheer number of fractures. Compared with the Cancer Register, which is a well-functioning NQR collecting data on cancer in Sweden, with far larger resources than the SFR, there are more than seven times more fractures each year in Sweden than the two most common forms of cancer (n=140,000 fractures versus 19,000 breast and prostate cancers).[1,218] Since data are entered in the SFR by physicians without any additional time being reserved for the process, the registration of these fractures yields a vast overall administrative burden which is carried by the profession. The registration process therefore needs to be fast and simple. The administrative burden that comes from entering data increases with the number of variables and too many variables might lead to "registration fatigue". This negatively affects the willingness to register and thereby the completeness. As a result, no data on comorbidities are collected in the SFR. However, the Swedish PIN system enables the linking of different data sources. Linking the SFR with other NQRs or administrative databases might have added valuable information, such as comorbidities or non-surgical complications, to the study population in **Study III.** However, this was not the main focus of this study and it was therefore not done.

A common way to evaluate an observational cohort study is to extract a control group of age- and gender-matched peers from the general population and follow them during the same time period as the study cohort. This method is often used in prospective case-control studies and it enables comorbidities to be controlled for. However, as no information on comorbidities was available for the study population in **Study III**, the advantages of a method of this kind is limited. The method used in this investigation provides solid mortality numbers, since they are based on the entire population in Sweden and enable mortality to be evaluated retrospectively.

5.4 TREATMENT AND OUTCOME

For many fracture locations, there is general agreement on the fundamentals of how these fractures should be treated. However, few orthopaedic areas are surrounded by as much controversy and uncertainty as the treatment of PHFs. It is still largely unclear which patients will benefit from surgical treatment and, in the event of surgery, which surgical treatment modality is best for the patient. Clear treatment algorithms have been shown to improve outcome in fracture treatment in terms of other fracture locations, but no such acknowledged algorithms exist for PHFs.[219,220] Two centres in Switzerland have fairly recently published locally developed treatment algorithms and reported lower reoperation rates following the implementation of these algorithms.[147,221] However, these local treatment recommendations have not been generally accepted. Despite the absence of treatment consensus, the treatment for PHFs has continued to change in recent years, in terms of both the frequency of surgery and the surgical modalities that are used.

5.4.1 Treatment of proximal humeral fractures

Study IV examined treatment trends in a large cohort of consecutively treated patients at a large centre in Sweden during a seven-year period from 2011 to 2017. We found that the proportion of surgically treated patients with a PHF decreased slightly during this time period (from 24% in 2011/2012 to 21% in 2016/2017; p=0.06), although this difference was not statistically significant. The finding of a stable, or slightly decreasing, rate of surgery in recent years follows a decade of increased surgery for PHFs, observed both in Sweden and in most other parts of the western world.[5,44,59] However, from 2010 and onwards, numerous studies have been published reporting non-superior outcome in surgically versus non-surgically treated patients.[15-18,121,131,133,134] This is most probably the reason why enthusiasm for the surgical treatment of PHF has declined. The stable, or slightly decreasing, rate of surgery found in **Study IV** is in accordance with the recommendations of the PROFHER study in 2015, which concluded that an increase in the incidence of surgical treatment for PHF is not warranted.[18]

A wide regional variation in the treatment of PHF has previously existed. In 2011, Bell et al. reported that the number of proximal humeral fractures treated surgically ranged from a low of 0% to a high of 68% in different parts of the USA.[5] Similar diverging rates were reported from different parts of Europe during the latter part of the first decade of this century. Surgical rates as high as 60-80% were reported in studies emanating from Central Europe, while the proportion of surgically treated patients in studies from Northern Europe were more similar to the proportion reported in **Study IV**.[59,148,190,221] This high degree of regional variation is in direct contrast to a number of other geriatric fractures, where there is broad consensus in terms of management.[154] However, during the last decade, the proportion of surgically treated PHF patients appears to have stabilised at around 15-25% in many parts of the world.[6,10,44,190] When Rikli et al. introduced a treatment algorithm for PHF in 2015 at their institution in Switzerland, based on the latest evidence, the rate of surgical treatment decreased from 64% to 22%.[221] Their rate of non-surgical treatment for PHF following the introduction of their algorithm is in accordance with the results in **Study IV**. However, although recent evidence has indicated that, with the current treatment methods available, the overall rate of surgical treatment for PHFs should probably not exceed the current 15-25% of patients, the optimal rate of surgical treatment for PHFs remains unclear.

The observed changes in surgical treatment modalities found in **Study IV** (i.e. decrease in plate fixation and increasing use of IM nails and RSA) are in accordance with reports from other parts of the western world. In particular, the use of RSA in PHF treatment has increased during the last decade. Register data from New Zealand and the USA reveal how RSA surpassed HA as the main arthroplasty treatment for PHFs between 2012 and 2015, and a six- and 13-fold increase in RSA use for PHFs was reported from these respective countries between 2009-2014 and 2009-2016.[222,223] A similar trend was observed in the Nordic countries, with a fivefold increase between 2009 and 2016.[100] In terms of the rate of patients treated with plate osteosynthesis, the reported decrease of almost 50% found in **Study IV** is substantially greater than that reported in other studies. Most studies report only a small yet substantial decline in the use of plates during the same period as in **Study IV**, while others report no change in the incidence of plate fixation.[1,6,224] There are few reports relating to changes in the incidence of osteosynthesis with IM nails. However, following the RCT by Zhu in 2011, where IM nails were shown to be associated with substantially fewer complications and reoperations compared with plates for two-part surgical neck fractures (AO/OTA A2 and A3), IM nails have been recommended when osteosynthesis is considered for these fractures in the elderly.[118,147,221]

5.4.2 Reoperation

Contrary to what we anticipated, the previously described treatment changes did not render lower overall reoperation rates. With advances in surgical techniques and the preferred use of RSA in the elderly, as well as in complex fractures, a reduced failure rate/reoperation rate for plates, IM nails or HAs could be expected. However, no such changes were noted and the observed rate of reoperation for these treatment modalities remained high during the study period. Since plate fixation, IM nails and HAs still accounted for two-thirds (n=159, 67%) of all surgical treatments at the end of the study period, the low reoperation rates following RSA did not result in lower overall reoperation rates.

Study IV examines the reoperation rates in everyday clinical practice. We have found no other study with such a large cohort of consecutive patients that have been individually controlled for reoperations. Although a direct comparison between different treatment modalities is not possible, due to the treatment selection bias in observational studies, the findings are still supportive of previous reports of low rates of unplanned surgery following non-surgical treatment and higher rates associated with surgical treatment. In **Study IV,** only 1.9% of patients treated non-surgically underwent unplanned surgery related to the initial treatment. This is in accordance with previous reports of a reoperation rate of less than 2% in initially non-displaced fractures and 2-5% in initially displaced PHFs.[17,104,105,133,136] The treatment modalities associated with the highest risk of reoperation in **Study IV** were plate osteosynthesis, IM nail fixation and HAs (21%, 18% and 17% respectively). These rates are in general agreement with most previous reports, although the rates of reoperation vary widely between studies due to different patient cohorts (plate 12-40%; IM nail 4-35% and HA 8-20%).[17,44,96,115,117,119,133,145,147] The surgical treatment modality associated with the lowest rate of reoperation in **Study IV** was RSA (6%). This is in harmony with previous reports of rates between 5% and 10%, and substantially lower compared with the traditional surgical treatment modalities for PHFs.[97,99,145] However, the low reoperation rate following RSA in fractures should be interpreted with caution. As few salvage procedures are available and revision surgery following RSA is particularly demanding, hesitation on the part of the surgeon might contribute to the low revision rates. However, two recently published studies have demonstrated superior clinical results in patients treated with RSA compared with HA and plates respectively.[20,132] Taken together with the low revision rates, these results indicate that RSA plays an important role in the surgical management of PHFs

The most common reason for an initial reoperation in **Study IV** was some kind of implant failure (i.e. secondary dislocations with screw penetration, perioperative misplacement of implants, instability and tuberosity absorption/displacement/malfunction; 35%). Another common reason for unplanned secondary surgery in initially plate-fixed fractures was avascular necrosis (AVN). More than 5% (n=17/332) of all fractures initially fixed with a plate were reoperated on due to a symptomatic AVN. The high rate of symptomatic AVNs following fixation with a plate is in agreement with the results presented by Barlow et al., who reported that severe AVNs occurred in 13% of their patients following plate fixation, although not all of them required reoperation.[19] AVN was the most common reason for radiographic failure in their study and the mean time to develop a severe AVN (Cruess ≥ 4) was 16 months, indicating the need for long follow-up periods. The reason for the high rate of AVNs following plate fixation is probably multifactorial. The fracture morphology in this selected group of fractures, commonly a displaced three- or four-part fracture, is obviously a major reason, since the incidence of AVNs increases with the severity of the fracture.[19,96,225] However, the surgical approach with exposure of the fracture fragments and the aim of obtaining exact reduction cannot be fully disregarded. The vascular supply to the humeral head might be compromised during surgery and, in RCTs comparing non-surgical treatment with plate fixation, there is a higher incidence of AVNs in the surgical group, indicating a negative impact of surgery on the risk of AVNs.[17,18,133]

The development of locking plates was the main driving force behind the general increase in surgical treatment for PHF during the first decade of this century. However, due to the high rate of complications associated with this treatment, plate fixation has recently been recommended only to be used in young patients (< 60 years old) with good bone quality or for selected three-part valgus fractures.[147,221] However, even this restricted recommendation could be questioned. Reports are emerging of high failure rates despite strict indications and modern techniques. Barlow et al. reported a failure rate of 34% and a reoperation rate of 11% following plate fixation by experienced surgeons using modern techniques in 193 patients.[19] In a Swiss study, a reoperation rate of 45% was reported following plate fixation or HAs in a cohort of patients treated according to a recently developed, evidence-based treatment algorithm.[147] We observed an almost 50% decrease in patients treated with plate osteosynthesis during the study period of Study IV, but there was no accompanying decrease in reoperation rate, despite the stricter patient selection. As a result, the previous widespread use of locking plates for PHFs will soon be history in the treatment for PHF.

The general burden of unplanned surgery in almost a quarter of all operations for PHFs found in **Study IV** is something that needs to be seriously considered when revising today's PHF treatment protocols. Even though **Study IV** was thought to represent a series with relatively low complication rates, since the department at which this study was conducted has a high volume of PHFs, which are treated by upper-extremity trauma surgeons, high rates of reoperations were observed following plate and IM nail fixation and HAs. The indication and continuous use of these three treatment modalities for PHFs must therefore be questioned further.

Factors associated with reoperation

Older age and poor bone quality have previously been shown to be associated with radiographic failure in surgically treated patients with a PHF.[19,99,109,148,226,227] However, older patients are less likely to undergo further surgery and older age has therefore been associated with fewer reoperations.[19,142,146,228] The findings in Study IV are supportive of this, since younger patients (< 59 years old) were more likely to undergo reoperations than patients aged ≥ 75 years. However, the association between younger age and an increased risk of reoperation was not found if reoperations due to patient demands (i.e. reoperations not deemed "compulsory") were excluded. This indicates that younger patients are more willing to undergo further surgery in order to avoid ongoing dysfunction and pain, whereas elderly patients, due to reduced functional demands, are more inclined to accept dysfunction. The finding of increased fracture complexity as an independent predictor of major reoperations is in agreement with previous reports and this needs to be taken into consideration when treatment is discussed with the patient.[19,113,148]

5.4.3 Treatment recommendations

The unaltered rate of reoperation during the study period in **Study IV** demonstrates that the observed treatment changes are not sufficient. The persistent high rates of reoperation following surgery with plates, IM nails and HAs, despite modern techniques and experienced surgeons, indicate that the use of these treatment modalities should probably be reduced and be restricted to only a few selected cases. On the other hand, the results following RSA for PHFs are promising, which indicates that RSA should be used increasingly instead of plates, IM nails or HAs when surgery is considered. However, it is still unclear which patients benefit most from surgical intervention. The plateauing trend and the surgical rate of approximately 23% observed in **Study IV** might still be too high with the treatment modalities currently available. Soler-Peiro et al. reported a high incidence of healing in non-surgically treated patients, despite initially displaced fractures (i.e. 95% three-part fractures and 91% four-part fractures healed), and, together with the findings in **Study IV** of low reoperation rates in non-surgically treated patients, these findings suggest that most patients could be treated non-surgically.[107] A decreasing incidence of surgical treatment might therefore be warranted. Moreover, a recently published review reports a similar functional outcome in PHF patients treated with acute RSA versus patients treated with delayed RSA for failed non-surgically treated PHFs.[229] This is contrary to the findings of poorer functional results when RSA is used as a salvage procedure following failed osteosynthesis or failed HAs.[128,129] Widening the indication for non-surgical treatment and instead being prepared to perform re-do RSA surgery if the functional outcome is disappointing might therefore be considered. However, these treatment recommendations would need a thorough evaluation.

5.4.4 Strengths, limitations and methodological considerations

Reoperations are widely used as an outcome measurement in register-based studies and they were also used in **Study IV**. However, this must be interpreted with caution. A reoperation is not per se the equivalent of a failed functional outcome and, accordingly, the absence of a reoperation does not equal a successful functional outcome. If a treatment method generates a high rate of reoperations, but the functional result is excellent following that reoperation, the high reoperation rate is probably acceptable. On the other hand, the willingness to undergo further surgery is influenced by a number of underlying factors and many patients with a poor outcome never undergo a reoperation.[19,142] As a result, the actual rate of complications is probably substantially higher than the reported reoperation rates.[19,99,133] Moreover, a reoperation is costly, both for society in financial terms and in terms of patient suffering, and, if different treatment methods report the same functional outcome, reoperations become important as an outcome measurement. The fact that all treatment methods for displaced PHFs have resulted in almost comparable functional results, and reoperations have been shown to be associated with poor outcome, justifies the use of reoperation as an outcome measurement when evaluating PHF treatment.[13,14,19,148]

One important problem with register-based studies is the reporting bias associated with reoperations/revisions.[81,146] Underreporting leads to an underestimation of the risk of reoperations. To address this, all the patients in **Study IV** were reviewed in the Sahlgrenska University Hospital surgery planning system for absent registrations, thereby ensuring that all surgical treatments performed at Sahlgrenska were accounted for. Consequently, reoperations performed elsewhere were not included in the study. Those reoperations are most probably few in number, since only patients primarily treated and eligible for follow-up at Sahlgrenska were included and since Sahlgrenska is the sole provider of fracture care in the area.

A multicentre design or the inclusion of the entire SFR would have provided more generalisable results than the single-centre design in **Study IV**. On the other hand, that would have made it almost impossible to validate and improve the completeness of reoperations and the accuracy of the registrations. Without this process of data completion, the reoperation rates would have been severely underestimated. The single-centre design was therefore selected for **Study IV**.

Even though the SFR collects PROM data, no data on the patient-reported or functional outcome of the patients is present in **Study IV**. As mentioned in the background section, the SFR uses the SMFA and EQ-5D PROMs. Pre-injury data, as well as data one,year post fracture, are collected. However, to the best of our knowledge, the PROM used in the SFR to evaluate function, the SMFA, has not previously been used to evaluate outcome following PHFs. A validation study of the comparability between changes in the SMFA and the most commonly used PROMs for PHFs (e.g. the Constant-Murley score, Disability of the Arm and Shoulder score (DASH) and the Oxford Shoulder Score (OSS)) is needed in order to interpret the result and compare it with previous studies. Moreover, the response rate in the SFR to the pre-injury and one-year post-fracture questionnaires is reported to be around 40%.[76] This raises doubts in terms of the credibility and the representativeness of the PROMs. Juto et al. conducted an analysis of non-responders with an upper extremity fracture and found no statistically significant differences in terms of functional outcome between non-responders and responders.[174] However, their study lacked statistical power since it only included complete answers from 42 non-responders. As a result, a new study of the characteristics of non-responders is warranted before PROM data from the SFR can be used. Consequently, no PROMs were used in **Study IV** or in any other of the investigations in this thesis.

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CONCLUSIONS

→ The NPR grossly overestimates the true number of humeral fractures and is therefore, without appropriate case selection, unsuitable for epidemiological research on fractures. On the other hand, the SFR provides data that have acceptable completeness and perfect accuracy. This indicates that the SFR constitutes a valid tool for epidemiological research **(Study I)**.

→ In **Study II**, the epidemiology and incidence of humeral fractures are described in a consecutive series of prospectively collected data. There was a distinct increase in age-specific incidence from the fifth decade onwards, regardless of fracture site, and the vast majority of humeral fractures occur as a result of low-energy falls. This indicates the influence of age-related risk factors in these fractures **(Study II)**.

→ Patients sustaining proximal humeral fractures (PHFs) have a significantly higher short- and mid-term overall mortality compared with the general population. This indicates that these patients constitute a frail part of the population in need of appropriate management **(Study III)**.

→ Although the overall rate of surgical treatment for PHFs did not change during the study period, the choice of surgical treatment modalities did. However, these changes in treatment had no effect on reoperation rates. The fact that every fourth surgical procedure for a PHF was a reoperation highlights the need of choosing the right treatment to the right patient **(Study IV)**.

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FUTURE PERSPECTIVES

With the SFR, new opportunities for fracture research have emerged. This unique database is dependent on voluntary daily measures taken by Swedish orthopaedic surgeons. It is therefore the responsibility of the profession to make the most of these efforts. The studies included in this thesis are examples of the way data in the SFR can be used. We have demonstrated that the SFR can be used to analyse the treatment of fractures and to provide valuable epidemiological data of high quality. However, several questions remain unanswered and future studies are needed.

The algorithm developed for routine completeness calculations in **Study I** requires validation. Due to the full coverage of Swedish orthopaedic departments reporting to the SFR, evaluations of fracture management and epidemiology throughout the country can now be conducted. However, the completeness needs to be consistently high in order to maintain good internal validity. This therefore needs to be continuously assessed.

Measures to prevent fractures from occurring need to be taken. The SFR already contributes by identifying patients with osteoporosis.[230] In a similar way, the SFR can be used to study other population groups at risk of further fractures. If patients with certain fractures are identified in the SFR and screened, frail patients can be identified and the ongoing physical and mental decline ultimately leading to new fractures, and even premature death, might accordingly be avoided. In this way, the SFR could be an even more valuable tool in preventing fractures from occurring.

In order to use the full potential of the register, PROMs need to be included in outcome analyses. However, non-responders need to be validated prior to the utilisation of PROMs. The PROMs in the SFR are a real treasure chest of already collected material and, to date, large-scale outcome data on fracture patients based on PROMs are lacking. With these data, patient-perceived effects of treatment changes, such as in **Study IV**, can be evaluated and subgroups of patients, for example, patients previously excluded from RCTs, can be extracted from the SFR and evaluated in a way that was previously not possible. This would provide new knowledge which might warrant specific RCTs for these patients. Moreover, the recently developed platform that enables RCTs to be conducted within the SFR (i.e. register-based RCTs; R-RCTs) makes it easier to enrol a large number of patients in various departments in a relatively short period of time.[77,78] In future, this interplay between observational register studies and RCTs, traditional or R-RCTs, will help to clarify how to select the appropriate treatment for each individual patient.

The current status and function of the SFR are merely in the initial stages. It is up to us as orthopaedic surgeons to cherish and further develop this new tool for research on fracture management. This is a challenge and a responsibility, but it is also a great privilege.

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