From THE DEPARTMENT OF CLINICAL SCIENCES,
DANDERYD HOSPITAL
Karolinska Institutet, Stockholm, Sweden

PROXIMAL HUMERAL FRACTURES - OUTCOME OF TREATMENT WITH SHOULDER ARTHROPLASTY

Yilmaz Demir

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PROXIMAL HUMERAL FRACTURES - OUTCOME OF TREATMENT WITH SHOULDER ARTHROPLASTY THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Yilmaz Demir

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Principal Supervisor:
Björn Salomonsson, MD Ph.D.
Karolinska Institutet
Department of Clinical sciences, Danderyd Hospital
Division of Orthopedics

Co-supervisor(s):
Professor Andre Stark, MD Ph.D.
Karolinska Institutet
Department of Clinical sciences, Danderyd Hospital
Division of Orthopedics

Professor Olof Sköldenberg, MD Ph.D.
Karolinska Institutet
Department of Clinical sciences, Danderyd Hospital
Division of Orthopedics

Associate Professor Max Gordon, MD Ph.D.
Karolinska Institutet
Department of Clinical sciences, Danderyd Hospital
Division of Orthopedics

Opponent:
Professor Bo Sanderhoff Olsen, MD Ph.D.
University of Copenhagen, Denmark
Department of Clinical Medicine
Division of Orthopedics

Examination Board:
Associate Professor Richard Wallensten, MD Ph.D.
Karolinska Institutet
Department of Molecular Medicine and Surgery
Division of Emergency and Reparative Medicine

Associate Professor Anders Ekelund, MD Ph.D.
Uppsala University
Department of surgical sciences Uppsala University
Division of Orthopedics and handsurgery

Associate Professor Magnus Forssblad, MD Ph.D.
Karolinska Institutet
Department of MMK Karolinska Institutet
Division of Centrum för idrottsskadeforskning och utbildning

To the four pillars of my life,

My beloved wife, Shamiram, and our three amazing daughters, Therese, Nathalie, and Josefin,

This thesis represents not only my academic achievements but also the unwavering support, love, and sacrifice that each of you has offered me during the arduous path of pursuing a Ph.D. Your belief in me, your patience during long hours of research, and your understanding of the sacrifices required have been the cornerstone of my success.

Shamiram, your strength, encouragement, and resilience have been my constant inspiration. You have not only stood by me but have also pushed me to be the best version of myself.

Therese, Nathalie, and Josefin, your youthful curiosity and boundless enthusiasm have reminded me of the joy in learning and discovery. Your presence in my life has been a source of motivation, reminding me of the importance of setting an example.

This dedication is a small token of my immense gratitude for your love and unwavering support. You have been my anchor, and this achievement is a testament to our collective determination.

With all my love and appreciation,

Yilmaz Demir

POPULAR SCIENCE SUMMARY OF THE THESIS

This thesis is about the treatment of common shoulder fractures, especially in the elderly. The main focus is on a surgical procedure with shoulder joint replacement to repair these fractures. The thesis includes four main studies:

Study I: A Nordic registry study found that infections are the most common cause of a second surgery (revision) for reverse total shoulder arthroplasty (rTSA) and that patients younger than 75 years are at higher risk for revision. Survival rates for shoulder hemiarthroplasty (SHA) were worse in younger patients than in older.

Study II: A validation of the Western Ontario Osteoarthritis of the Shoulder Index (WOOS) for proximal humerus fractures treated with shoulder joint replacement surgery. WOOS is used in the Swedish Shoulder Registry as a 19-question questionnaire to assess how the patient is doing in relation to: physical symptoms, sports/activities, work, lifestyle, and feelings. The study advocates the use of WOOS to assess this fracture treated with joint replacement surgery.

Study III: A randomized controlled trial compared the results of two different types of shoulder joint replacement, reverse total shoulder arthroplasty (rTSA) and hemiarthroplasty (SHA) for 3- and 4-part proximal humeral fractures in elderly patients. Results showed that patients treated with rTSA had better shoulder function and higher patient satisfaction. Adverse events were limited and similar in both groups.

Study IV: The aim of this study was to assess the validity of the national recommendation for surgery within two weeks after proximal humerus fractures with shoulder joint replacement. We found that surgery after two weeks had a negative impact on patient outcomes and that the best results were obtained when surgery was performed between six and ten days after fracture.

In conclusion, these studies provide valuable insight into treatment options and outcomes for proximal humerus fractures, with implications for improving patient care and decision making in clinical practice.

Svensk populärvetenskaplig sammanfattning

Syftet med denna avhandling är att studera olika behandlingar av vanligt förekommande axelfrakturer i överarmen, särskilt förekommande hos äldre människor. Avhandlingens huvudsakliga fokus är av kirurgisk karaktär, med axelledsbyte (axelprotes) som kirurgisk åtgärd av dessa frakturer. Avhandlingen omfattar fyra delarbeten:

Studie I: Är ett samarbete mellan de nordiska skulderregistren. Denna studie visar att infektion var den vanligaste orsaken till en andra operation (utbytesoperation) efter första ingreppet med en så kallad omvänd total axelledsplastik (rTSA). Studien visade att patienter yngre än 75 år hade en högre risk för en andra operation. För de patienter som fick en anatomisk halvprotes (SHA) vid operation, så var överlevnaden sämre för de yngre jämfört med de äldre patienterna.

Studie II: Är en valideringsstudie av ett bedömningsinstrument för proximala humerusfrakturer som behandlades med axelledsbyte där bedömningsinstrument tar hänsyn till mer än ren axelfunktion, så som patientens mentala och fysiska välmående. Detta instrument, Western Ontario Osteoarthritis of the Shoulder Index (WOOS), används i det svenska axelregistret som en enkät med 19 frågor för att utvärdera hur patienten mår med avseende på fysiska symtom, idrott/aktiviteter, arbete, livsstil och känslor. Denna studie stödde en fortsatt användning av WOOS för att bedöma proximala humerus frakturer.

Studie III: En randomiserad kontrollerad studie som jämförde resultaten av två olika typer av axelledsbyten hos äldre patienter där ändan av överarmsbenet mot axeln är kluven i tre eller fyra bitar. De två axelledsbytena är omvänd total axelledsplastik (rTSA) och axelhemiartrplastik (SHA) för proximala humerusfrakturer. Vi kom fram till att patienter som behandlats med rTSA hade en bättre axelfunktion och större patienttillfredsställelse. Båda behandlingsformerna hade få negativa händelser.

Studie IV: Målet var att bedöma aktualiteten hos den nationella rekommendationen att operation med proteskirurgi av proximala humerus frakturer bör ske inom två veckor från skadetillfället. Vi kom fram till att operationer som utfördes senare än två veckor hade sämre resultat. De bästa resultaten var om operationen utfördes mellan 6 och 10 dagar efter frakturdatum och bekräftar den nuvarande rekommendationen.

Sammanfattningsvis ger denna avhandling värdefulla insikter om behandlingen och resultat inom proximala humerusfrakturoperationer med axelledsproteser, med syftet att förbättra vården av patienter med denna typ av skada som behöver operation.

Abstract

Introduction

Proximal humerus fractures are a common injury, particularly in the elderly and especially in women. The preferred treatment approach is usually nonsurgical, with surgery reserved for cases that meet specific fracture patterns and patient-specific criteria.

The aim of this thesis was to study the use of arthroplasty as a treatment option for proximal humeral fractures.

Study I: Revision after shoulder replacement for acute fracture of the proximal humerus. A Nordic registry-based study of 6,756 cases

The aim was to investigate revision rates and reasons for revision after shoulder arthroplasty for acute fractures of the proximal humerus.

Common data sets were collected from the Danish, Norwegian, and Swedish registries which conducted shoulder arthroplasty after acute fractures.

The number and proportion of reverse total shoulder arthroplasties (rTSA) performed during the study period increased steadily. Of the 222 arthroplasties revised between 2004 and 2013, infection was the most common reason. The relative risk of revision due to infection was higher for rTSA than for shoulder hemiarthroplasties (SHA). In addition, patients younger than 75 years had a higher relative risk of revision, and survival with SHA was worse in younger patients than in older patients.

Conclusion: Both SHA and rTSA have similar survival rates. However, the factors leading to a revision decision are not fully known, and reported survival rates may not reflect patients' functional outcomes. Patients with acute fractures often have comorbidities and are less amenable to revision surgery. Inclusion of patient reports in the data set would provide important information. The risk of infection was higher after rTSA than after SHA, and differences in revision rates between systematic reviews and national registries may be due to inclusion criteria. Comparisons between SHA and rTSA should be made with caution.

Study II: Western Ontario Osteoarthritis of the Shoulder Index (WOOS) - a validation for use in proximal humerus fractures treated with arthroplasty.

The objective was to validate the Western Ontario Osteoarthritis of the Shoulder Index (WOOS) as a patient-reported outcome measures (PROM) for use in proximal humeral fractures treated with arthroplasty.

Patients from Swedish Shoulder Arthroplasty registry (SSAR) who underwent surgery after PHF with SHA and had surgery Karolinska hospital and Danderyd hospital were selected. Those who accepted performed shoulder-specific PROM and WOOS retest, and the necessary clinical examinations, Constant score (CS) and American shoulder and elbow Society (ASES), were performed at Danderyd Hospital.

The validity of the WOOS has excellent correlation with all shoulder-specific scores and good correlation with EQ -5D. Test-retest reliability of WOOS overall and in subgroups also shows excellent correlation. Cronbach's alpha supports the construct of WOOS, and no floor or ceiling effects were observed.

Conclusion: WOOS is a reliable tool for assessing patients with SHA after PHF. Our study supports the continued use of WOOS in SSAR and further studies with WOOS and arthroplasty after proximal humerus fractures.

Study III: Reverse total shoulder arthroplasty provides better shoulder function than hemiarthroplasty for displaced 3- and 4-part proximal humeral fractures in patients aged 70 years or older: a multicenter randomized controlled trial.

The aim was to compare the outcomes of 3–4-part fractures of the proximal humerus treated with reverse total shoulder arthroplasty (rTSA) and hemiarthroplasty (SHA) in patients aged ≥70 years in a multicenter randomized controlled trial.

An RCT multicenter study was conducted, and eight hospitals recruited patients for the study.

The rTSA group had a higher mean Constant score (58.7) compared with SHA (47.7), with a mean difference of 11.1 points (95% CI, 3.0–18.9). Patients who underwent rTSA reported greater satisfaction with their shoulders on average and had better range of motion. However, no differences were noted in WOOS, EQ -5D or pain at VAS. We noted three adverse events in the rTSA group and four in the SHA group.

Conclusion: Our study showed that the rTSA group had better shoulder function as measured by the Constant score compared with SHA. This could explain why rTSA patients were more satisfied with their shoulder function. The main difference could be explained by a better range of motion in the rTSA group.

Study IV: Timing of surgery for proximal humeral fracture treated with shoulder hemiarthroplasty, best results with surgery within 2 weeks.

The aim was to evaluate the validity of the national recommendation "surgery with arthroplasty within 2 weeks" by investigating the timing to surgery in patients operated on with shoulder arthroplasty after proximal humerus fractures.

Data was collected from SSAR. In addition, the date of fracture was collected from the hospitals that could provide that information.

Preoperative delay had a negative impact on WOOS, EQ -5D, and patient satisfaction scores. The best outcomes, as measured by the WOOS score at a follow-up of at least 1 year, were observed when surgery was performed within 6-10 days of the reported fracture date. A delay of more than 10 days was associated with a worse outcome.

Conclusion: The current recommendation in Sweden to perform shoulder hemiarthroplasty within two weeks after proximal humerus fracture is considered valid.

LIST OF SCIENTIFIC PAPERS

I. **Revision after shoulder replacement for acute fracture of the proximal humerus. A Nordic registry-based study of 6,756 cases**
Stig Brorson, Björn Salomonsson, Steen L Jensen, Anne Marie Fenstad, **Yilmaz Demir**, and Jeppe V Rasmussen
Acta Orthopaedica 2017; 88 (4): 446–450, doi. 10.1080/17453674.2017.1307032

II. **Western Ontario Osteoarthritis of the Shoulder Index (WOOS) - a validation for use in proximal humerus fractures treated with arthroplasty**
Yilmaz Demir, Hanna Sjöberg, Andre Stark and Björn Salomonsson
BMC Musculoskelet Disord. 2023 Jun 2;24(1):450. doi: 10.1186/s12891-023-06578-5

III. **Reverse total shoulder arthroplasty provides better shoulder function than hemiarthroplasty for displaced 3- and 4-part proximal humeral fractures in patients aged 70 years or older: a multicenter randomized controlled trial**
Eythor O. Jonsson, Carl Ekholm, Björn Salomonsson, **Yilmaz Demir**, Per Olerud, and Collaborators in the SAPF Study Group
Journal of Shoulder and Elbow Surgery Volume 30, Issue 5, May 2021, Pages 994-1006

IV. **Timing of surgery for proximal humeral fracture treated with shoulder hemiarthroplasty, best results with surgery within 2 weeks.**
Yilmaz Demir, Alma Vuorinen, Max Gordon, Anders Nordqvist, Björn Salomonsson
Manuscript, Reserch Square, Submitted 20th of March, 2023, Reviewers agreed 21st of August 2023

CONTENTS

List of abbreviations

AVN	Avascular necrosis
ASES	American shoulder and elbow surgeons standardized shoulder
CCI	Charlson comorbidity index
CI_{95}	95% Confidence intervall
CS	Constant-Murley score
CT	Computer tomography
EQ-5D	Euroqol five dimensions health score
ICC	Intraclass correlation coefficient
IM	Intramedullary nail
LS	Likert scale
ORIF	Open reduction and internal fixation
OSS	Oxford shoulder score
PASS	Patient accepted symptom state
PROM	Patient-reported outcome measurements
PHF	Proximal humerus fracture
RCT	Randomized controlled trial
ROM	Range of motion
SHA	Shoulder hemiarthroplasty
SL	Satisfaction Level
SFR	Swedish fracture registry
SMR	Standardized mortality ratio
SSAR	Swedish shoulder arthroplasty registry
TISS	Mnemomnic for the rotator cuff: teres minor, infraspiantus, suptraspinatus and subscapularis muscle/tendons
rTSA	Reverse total shoulder arthroplasty
WOOS	Western ontario osteoarthritis of the shoulder Index

1 INTRODUCTION

1.1 Epidemiology

Proximal humerus fracture (PHF) is the third most common fracture and accounts for 4-6% of all fractures per year, with the highest incidence in Sweden in December-February (1–11) Figure 1. Up to age 50, the incidence rate is almost equal in men and women, after which women are more susceptible to this injury with a ratio of 4:1 (3/4) Figure 2. The severity of the fracture pattern and additional fractures on the same side increase with age and the severity of the trauma (10,12,13).

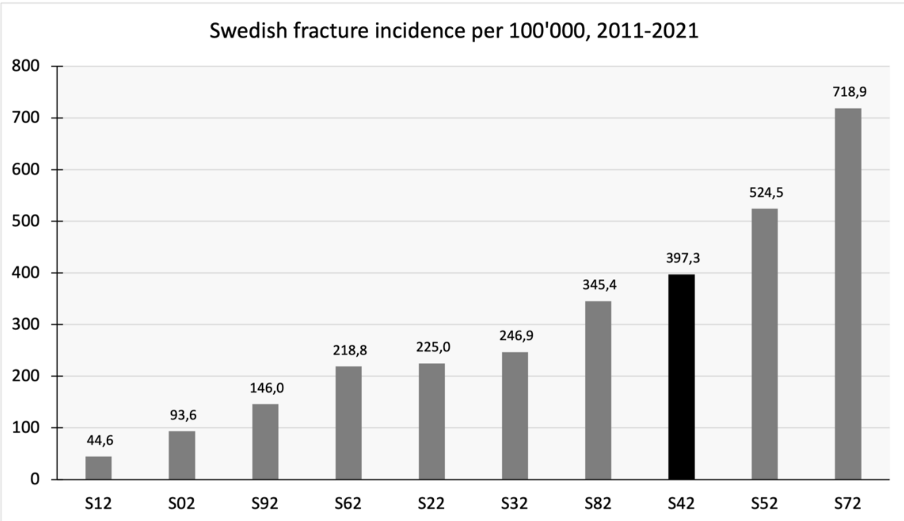

Figure 1. The average incidence of fractures per 100,000 people in Sweden during 2011-2021 for in- and outpatients aged 45 years and older. The y-axis shows incidence, while the x-axis shows diagnoses in order of ascending incidence. The ICD-10 code represents S02 Fracture of skull and face, S12 Fracture of cervical spine and bones, S22 Fracture of ribs, sternum, and thoracic spine, S32 Fracture of lumbar spine and pelvis, **S42 fracture of shoulder and upper arm**, S52 fracture of forearm, S62 fracture of wrist and hand, S72 fracture of thigh, S82 fracture of lower leg including ankle, and S92 fracture of foot without ankle, data was collected from the National Board of Health and Welfare's National Patient Register 4th of September 2023.

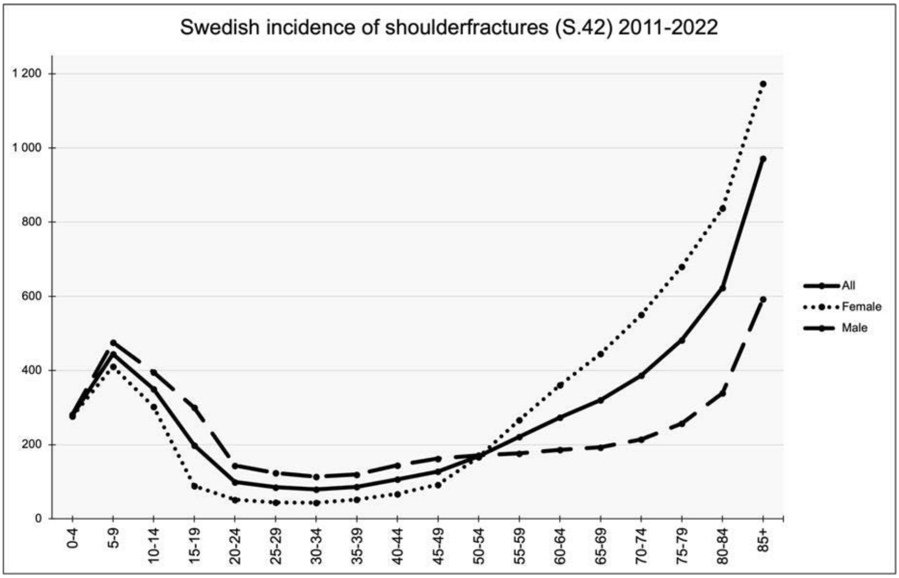

Figure 2. Data from 2011-2022. The y-axis shows the average incidence for in- and outpatients with shoulder fractures per 100,000 population per year in Sweden. The x-axis shows the age of the individuals who suffered the fractures. We observe a bimodal incidence with a peak at younger ages and a second peak starting at age 50 years in women and over 70 years in men, data was collected from the National Board of Health and Welfare's National Patient Register 4th of September 2023.

In general, the main cause of PHF is low-energy falls in an elderly osteoporotic population, Figure 3, which may explain why the incidence rate is higher in women over 50 years of age and in northern countries (10,12). It is important for physicians to evaluate patients for osteoporosis and establish an individualized treatment plan to reduce the risk of fractures related to trauma as well as atypical fractures related to treatment. (The evaluation and treatment of osteoporosis is outside the scope of this thesis and will not be discussed further) (13,14).

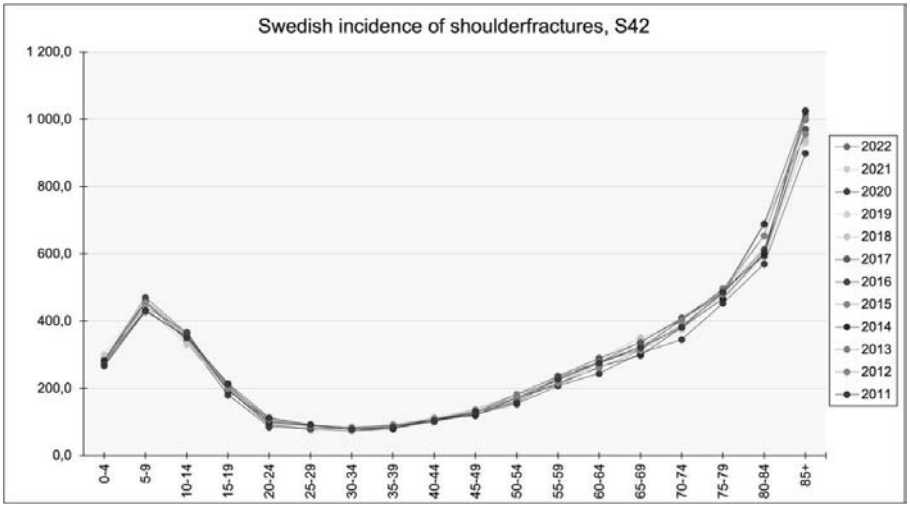

Figure 3. incidence of humerus fractures (ICD-10, S.42) for in- and outpatients in the Swedish population . The **y-axis** is the incidence of fractures of the upper shoulder per 100,000 per year in Sweden. The **x-axis** is the age of the person who had the fracture. The incidence has remained almost the same from 2011 to 2022. We have a bimodal incidence, one at a younger age and a second from the age of 50 when both sexes are included, data was collected from the National Board of Health and Welfare's National Patient Register 4th of September 2023.

The standardized all-cause mortality rate (SMR) within 30 days of trauma is 7-fold and, the SMR within 1 year is twice that in the general population. In elderly patients with severe disease, the mortality rate within the first year after a PHF is 40%, regardless of the severity of the fracture, whereas the same fracture in a healthy elderly person is 8% (15). A study from the Swedish Fracture Registry included a total of 18,452 patients between 2011 and 2017. Bergdahl et al. described a higher mortality rate compared with the general population in patients who had sustained a low-energy proximal humerus fracture. Increasing age and male sex were identified as risk factors for higher mortality. The study aimed to raise awareness of frailty in these patients (16). In addition, individuals who relied on a cane had at least a one-level increase in the Charlson comorbidity index (CCI) (17) one year after trauma, especially if they relied on walkers (18).

PHF in the young population is usually the result of high-energy trauma and is slightly more common in men (1–7), Figure 1 and 3.

1.2 Anatomy

This thesis focuses specifically on the glenohumeral joint and in particular the proximal humerus. The **attachments** in the glenohumeral joint include the capsule with the glenohumeral ligaments and the rotator cuff, which provide stability and motion. The rotator cuff consists of four major muscles: Teres minor, infraspinatus, supraspinatus and subscapularis (TISS).

The rotator cuff **tendons** form elevations on the proximal humerus, namely the lesser tuberosity for the subscapularis muscle and the greater tuberosity for the supraspinatus (upper part), infraspinatus and teres minor (dorsolateral part) muscles. Depending on their position, these tendons have different functions. The suprascapular nerve innervates the supraspinatus muscle and the infraspinatus muscle, while the superior subscapular nerve innervates the upper part of the subscapular muscle, and the inferior subscapular nerve innervates the lower part of the subscapular muscle and the teres minor muscle.

The deltoid and pectoralis major muscles attach to the shaft of the humerus and are critical to understanding the fracture pattern in the proximal humerus.

Important **neural** structures in the shoulder include the axillary nerve (which innervates the deltoid muscle) and the continuation of the nerve plexus, which forms the three major nerves of the upper extremity: Radial, Ulnar, and Median nerves. In this neurovascular bundle you will also find the main artery of the upper extremity, the axillary artery.

The anterior and posterior circumflex humeral arteries are the main blood vessels supplying the proximal humerus, while the arcuate arteries, especially the posterior one, are responsible for supplying blood to the humeral head, Figure 4A (19) and 4B (20). The blood supply through the rotator cuff also contributes to this process. An intact periosteum is also important for proper healing of fractures in the proximal humerus. However, with increasing age and the development of risk factors for atherosclerosis, the blood supply to the humerus tends to decrease.

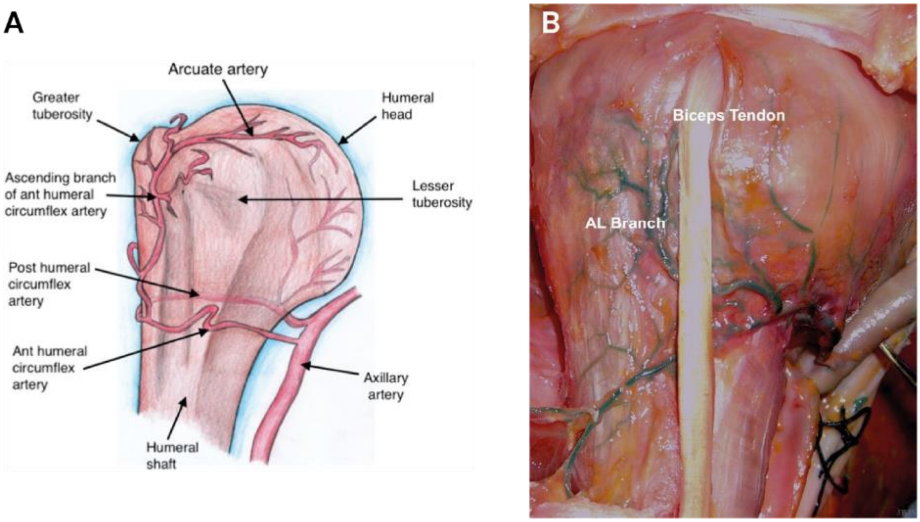

Figure 4. The circulation to the proximal humerus. The circumflex artery comes from the axillary artery. The main branch for circulation to the humeral head comes from the posterior circumflex artery. A. shows the posterior, anterior and ascending branch from the circumflex artery (Reprint with permission Elsevier Ltd.). B. Blue coloring of the anterior humeral circumflex artery, which is intimately adherent to the humeral head. AL Branch = anterolateral branch of the anterior humeral circumflex artery (Reprint with permission Wolters Kluwer Health, Inc).

Numerous studies have been conducted to gain a better understanding of the risk factors for avascular necrosis (AVN) after proximal humerus fractures (PHF) (20–24), Figure 5.

A comprehensive understanding of the normal physiology and anatomy of the glenohumeral joint is critical to understanding the fracture pattern, predicting potential healing complications, and ultimately making treatment decisions. For example, a bipartite fracture of the proximal humerus may be a high-risk fracture that can lead to painful malunion and avascular necrosis (AVN), depending on the location and extent of fracture dislocation.

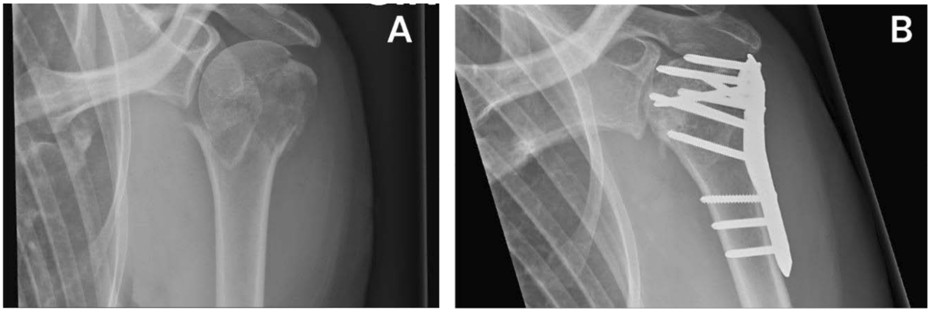

Figure 5. Since the patient was a healthy and active middle-aged woman, I choose to do surgery with ORIF. 7 months later she showed radiologic signs of AVN but had yet not developed pain, but in later follow up the pain was elevated, and she later underwent revision surgery with arthroplasty. A complex PHF (A). AVN with penetration of the screws in the proximal part of the head of the humerus 14 months afteer surgery with ORIF (B). Illustration by Yilmaz Demir.

1.3 General considerations for the treatment of PHF

When evaluating a proximal humerus fracture, there are several factors to consider (23–26) when selecting an appropriate treatment plan, and the choice of treatment involves four main considerations: Fracture type, blood flow, age, and if there is presence of osteoporosis.

1.3.1 Fracture type - radiology

A complete classification system is critical for understanding proximal humeral fractures and determining appropriate treatment. A well-planned surgical approach is necessary if surgery is chosen as a treatment option, Figure 6.

Neer's classification system is commonly used for proximal humerus fractures because of its elegance and logical explanation of fracture parts (27).

Plain radiographs, including the lateral view, transscapular Y view, and true frontal view, are the most common methods for fracture evaluation and classification (28–31). However, in cases of doubt or when a better analysis of the fracture is needed, a shoulder computed tomography scan (CT) can provide additional information and is often used for preoperative planning (24,31,32). Classifications are generally based on plain radiographs.

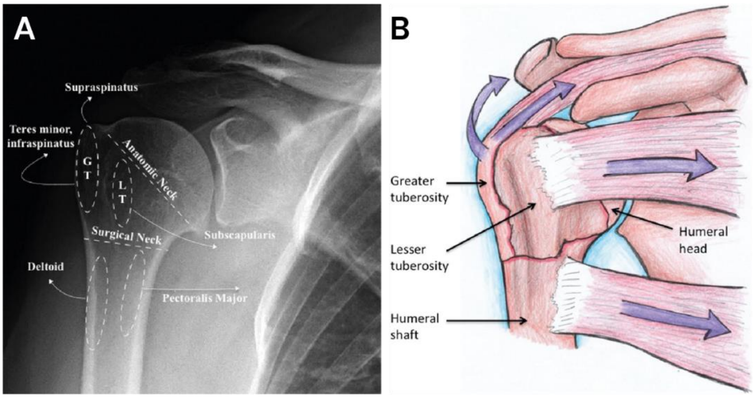

Figure 6. Impact of the soft tissues on the fracture pattern. A. AP view showing attachment points of the tendons *(Reprint with permission SAGE Publications.)*. B. is illustrating the direction of the force from the tendons *(Reprint with permission Elsevier Ltd.)*.

1.3.2 Circulation

Circulation to the humeral head plays a critical role in the development of AVN and pseudarthrosis (20–24,33). As mentioned previously, knowledge of the blood supply to the proximal humerus is critical in predicting the outcome of treatment for PHF. Disruption of blood supply can lead to AVN, a condition characterized by death of bone tissue due to lack of blood supply. This can lead to bone collapse, pain and joint dysfunction. In addition, inadequate blood supply can lead to pseudoarthrosis, in which the bone fails to grow together due to poor healing, resulting in pain, reduced function and instability.

1.3.3 Age and osteoporosis

In health care, decisions about treatment should always take into account the patient's health status and functional requirements. For severe fractures, it is important to ask what the patient's goals are, whether he or she is a candidate for surgery, and what types of surgical options are possible or available. In addition, bone density tends to decrease with age, so it is critical for surgeons to use judicious planning based on bone and tendon quality when choosing between osteosynthesis or joint replacement (7).

Low-energy PHF often correlates with osteoporosis. Therefore, it is important to follow guidelines that recommend immediate treatment or screening for osteoporosis (34–36). These measures can help prevent future fractures and improve patients' overall health.

1.4 Fracture classification

Fracture classification is crucial for the proper treatment of proximal humerus fractures. Various systems have been proposed, such as the Neer, Hertel, and AO classification(8,23,27,37,38). The choice of classification depends on several factors, such as local tradition, physician preference, and choice of reporting registry. The use of a standardized classification system facilitates communication among health care professionals, aids in treatment decisions, and allows for accurate comparison of treatment outcomes across studies. It is important that the treating physician be familiar with the various classification systems and select the most appropriate system for each patient.

All classifications of fractures can be **summarized in a few principles** (8,24,25,27,33,37–40).

a) *How many parts/fragments*: 2-part, 3-part, 4-part or more.

b) *Degree of dislocation?* What structures are pulling the fragments?

c) *Placement of the fracture*: collum chirurgicum, collum anatomicum, head split or tubercle fractures. A combination of fractures is common.

d) Rotation of the head, valgus, or varus impaction?

e) Is the **blood supply** to the head at risk?

g) Is it a combined dislocation of the shoulder and a fracture?

1.4.1 Classification according to Neer

One common classification is Neer's classification, which is primarily based on the number of parts or fragments. Fragments are considered dislocated if they are angled more than 45° and spaced more than 0.5 cm apart (24,25,33,37,40,41).

1.4.2 Classification according to Hertel

This classification is based on the principle established by Codman in 1934 (42), figure 7, and has since been modified and evaluated in several publications describing how a PHF should be evaluated based on radiographs and CT (9,21,23,43). There are four main parts considered in this classification: Head (H), Greater Tuberosity (G), Lesser Tuberosity (L), and the Shaft (S). Hertel et al. have also presented a systematic radiological assessment and intraoperative evaluation of blood flow based on this classification (23).

1.4.3The AO /OTA-Classification

The AO/OTA classification is based on the Codman classification and is divided in: Type A - two-part fracture, Type B – three-part fractures and Type C - four-part fractures, articular fracture or fracture dislocations. All types are also subdivided in more detail (10,27,32,38,44,45). It is a common classificationfor PHF and also used by the Swedish Fracture Register (SFR).

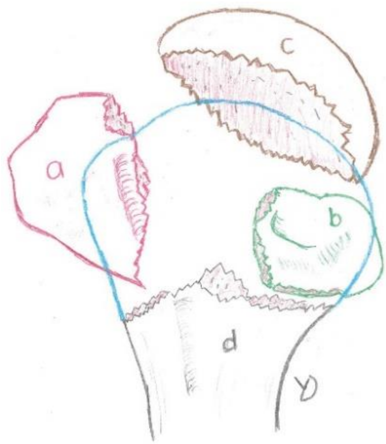

Figure 7. a. tuberculum majus, b. tuberculum minor, c. head of the humerus, d. shaft of the humerus, illustration by Yilmaz Demir

1.5 Common treatments for PHF

Normal shoulder function is rarely restored after a proximal humerus fracture, and it is important to make the patient aware of this, regardless of treatment. Even if treatment can minimize loss of function and pain, patients will still experience consequences after a PHF, and this is not unique to adult patients. It is uncommon for patients to be fully recovered after a fracture, and expectations and demands on the shoulder can vary significantly depending on age, work, and physical activities (46).

Because more than 80% of PHFs are related to osteoporosis, this should be considered when planning the treatment of choice (10,13).

Nonsurgical treatment is the preferred choice if the fracture can be treated with acceptable results, as surgical methods are associated with risks. Further and larger studies are needed to better understand the optimal treatment. Fracture registries can also help understand fracture patterns and determine the outcome related to the treatment.

1.5.1 Nonsurgical treatment

Nonsurgical treatment is the most common for PHF, in almost 4 out of 5 cases. This is because most PHF achieve the same or better results with nonsurgical treatment than with surgery (7,46–52). The choice of nonsurgical or surgical treatment for individual patients on fracture patterns is not a topic of this thesis.

There are several surgical methods for treating PHF. The most common ones will be briefly discussed.

1.5.2 Surgery with osteosynthesis

1.5.2.1 Surgery with humerus nail – intramedullary nail - IM

Indication: 2-part and dislocated fractures. When combined with osteosutures, the nail can also stabilize 3- and 4-part fractures.

Biomechanically, the nail may be more stable in varus impacted fractures, and newer nails have been designed to adapt to the weak fixation in the proximal humerus (51,53).

However, nailing has inferior results in 3–4-part fractures, head split, risk for AVN, and severe osteoporosis (49). Despite correct indications for surgery, incorrect positioning of the nail can lead to a high failure rate, especially in the osteoporotic population (50,54).

1.5.2.2 Surgery with plating – open reduction and internal fixation - ORIF

Plating is a versatile method and can be used for most fractures. However, it gives is suitable in valgus impacted fractures, while there is a high risk of failure in varus impacted fractures because the plate does not biomechanically support these fractures. Plating can minimize malalignment and provide better biomechanics, preferably in younger patients with good bone quality (49,51,54–57). There is evidence that supports plating as a good first operation, and if it fails, revision surgery with joint replacement still has a good chance of success (58).

However, in severe PHF patients undergoing ORIF with a plate, the osteonecrosis rate may range from 0-15% (51). In addition, plating has worse outcomes in head split fractures, high risk of avascular necrosis, co-morbidities, and severe osteoporosis.

1.5.3 Surgery with joint replacement

Indication: severe fractures where plating or nailing does not provide adequate support, and in patients with osteoporotic bone at high risk of failure, high risk of nonunion, and high risk of AVN (21,23,24,26,48–50,59,60,51,57,50).

There are two methods for joint replacement in the shoulder for acute PHF. The first is anatomic shoulder hemiarthroplasty (SHA), in which only the humeral head is replaced with an implant. The second is reverse total shoulder arthroplasty (rTSA), in which both the humeral head and glenoid are replaced with implants.

1.5.3.1 Shoulder hemiarthroplasty

Indication: severe PHF when ORIF is not possible in younger patients and in older patients with high shoulder demands with preserved rotator cuff. Surgery within two weeks of trauma is recommended (61–63).

The reason to opt for SHA is to preserve as much of the "normal anatomy" as possible, which can lead to a better range of motion (ROM) and avoid the risk of dislocation as with rTSA.

Results after SHA can vary greatly depending on the healing of the tuberosity and soft tissues.

1.5.3.2 Reverse total shoulder arthroplasty

In older patients, rTSA is generally preferred as the primary treatment option (57,64–66). This procedure may lead to a good functional outcome, as shown in study III, in which we compared hemiarthroplasty with reverse arthroplasty (66).

1.6 Evaluation of outcomes in this thesis

There are several research methods to evaluate a treatment. This thesis focuses on studies based on registries, RCT, and clinical evaluations.

1.6.1 Registries

In Sweden, there are over 100 national quality registries. Depending on the disease or treatment studied, registries collect different types of data such as laboratory results, blood pressure, BMI, PROM, medication use, implant types, implant survival rates, and birth or death records.

Registries are an important tool for evaluating and monitoring health care outcomes. They provide a cost-effective way to collect and analyze data over a longer period of time than would be possible for a single research team. In addition, with good coverage, registries can detect adverse events and treatments for specific populations.

1.6.1.1 Swedish Shoulder and Arthroplasty Registry

Surgeons register the procedures in the Swedish Shoulder and Arthroplasty Registry (SSAR). After each joint replacement of the shoulder, the surgeon completes a form that includes the date of surgery, diagnosis, If these is type, type of x-ray used, antibiotic use, implant type, and other questions about surgical technique and findings. Outcomes measured in SSAR include implant survival and PROM. Participation in registries is voluntary, and patients can opt out at any time.

For elective procedures, a preoperative PROM is collected, but this is difficult, and not requested for fractures. Follow-up time is 1, 5, and 10 years after surgery. Patients will be given questionnaires, including the Western Ontario Osteoarthritis of the Shoulder Index, (WOOS) the EuroQol five Dimensions health score (EQ-5D), and a self-assessment of Satisfaction Level (SL).

1.6.2 PROM, Patient Reported Outcome Measure

The questionnaires items are designed to capture the effects of treatment on characteristics that are important to patients. WOOS is a shoulder-specific score for osteoarthritis (OA), useful in measuring the outcomes of joint replacement. The questions are stratified so that we can capture the patient's well-being and outcome after surgery as accurately as possible without requiring a clinical examination and asking too many questions. It is a balance between asking too many questions (more details but filling out the form is too tedious) and asking too few questions (better coverage, but with limited information).

WOOS consists of 19 questions divided into four domains (67). The four domains are physical symptoms (6 questions), sports/activities and work (5 questions), lifestyle (5 questions), and emotions (3 questions). Each question is answered on a visual analog scale (VAS) ranging from 0-100, with 0 representing a normal shoulder and 1900 representing the worst possible outcome. The minimum clinically significant difference (MCID) for WOOS is reported as 8% (68).

The advantage of the PROM used by SSAR is that they are filled at the patient's own comfort and do not take up patients' time more than filling out the form. In addition, patients can be honest about their symptoms because they are not face-to-face with their physician (69).

In a clinical trial, function can be measured with specific tests such as range of motion (ROM) and strength. However, these tests require more resources in the clinic. The group studied is usually smaller compared with registries and PROM, and a small error or a few outliers can affect the results and the conclusion of the treatment.

1.7 Validation process

There are several types of shoulder-specific PROM used in studies or registries. Researchers may select a particular questionnaire based on local traditions or its prevalence in the field of study.

Because registries and studies use different PROM, it is important to understand their compatibility to compare results across studies. The registry or author usually explains the one used PROM, but it is advisable to check whether it is a self-assessment or also a clinical examination.

If a measurement is used in a different patient group or diagnosis than it originally designed for it is important to perform a new validation for that purpose.

Several factors should be considered in the validation process, but ultimately the instrument must have a good ***validity*** – the instrument is measuring what it is supposed to, and ***reliability*** - the instrument gives consistent results that could be repeated *(repeatability*).

1.7.1 Validity

Internal *validity* aims to ensure that the measurement has a correct cause-and-effect relationship while minimizing other factors that could influence the results.

To assess internal validity, several methods can examine potential threats, such as temporal and historical effects, maturity effects, test and order effects, changes in instruments, selection bias (including poor or no randomization), mortality or dropouts, and participant or observer bias. Although some of these hazards are more intuitive than others, it is necessary to address them to maintain the internal validity of the study.

External *validity* on the other hand, assesses whether the cause-and-effect relationship is generalizable beyond the study sample. Researchers must assess whether the results can be generalized to the general population or whether they apply only to the study's subgroup. It is important to assess the external validity of a study to determine if its results are applicable to a broader population.

Criterion *validity* answers the questions: "if the instrument agrees with the "truth" and does WOOS measure what it is supposed to measure?". ***Construct*** *validity* answers the question of whether a minor change could affect the outcome. ***Content*** *validity* is the examination of the floor and ceiling effect *(when 15% of the responses reach the minimum or maximum value).* ***Convergent*** *validity* is an assessment if the combination of questions leads to the most meaningful result without the need for questions to be homogeneous.

1.7.2 Reliability

To ensure that the method produces the same or similar results when repeated, researchers may use the following methods for evaluation: Test-Retest, Parallel Form Reliability, Split-Halves Method, Internal Consistency Method, Inter-Observer Reliability, and Inter-Rater Reliability.

1.7.3 Accuracy and Precision

In addition to reliability, other terms are relevant to measurement such as ***accuracy*** - how close the measurement is to the true value, and ***precision*** - how consistent the measurements are when repeated, regardless of proximity to the true value.

The goal is to achieve high accuracy and precision. High precision without hitting the target is meaningless, as is high accuracy with a wide range of values that make interpretation of the measurement difficult.

1.7.4 Bias and Confounders

In any study, it is critical to identify and address potential hazards that may lead to inaccurate measurements or erroneous conclusions before research begins. In this way, researchers can minimize the risks of ***bias***-systematic errors-and ***confounding*** variables-variables that are associated with both the predictor of interest and the outcome. This step is important to ensure that the results of the study are trustworthy and applicable to the target population.

2 LITERATURE REVIEW

In the last decade, there has been a trend toward nonsurgical treatment of PHF because several studies have had difficulty demonstrating the benefit of surgery (63). A major problem is that most (about 80%) of PHF that can be treated without surgery are compared with those that require surgery (52).

The other situation is understanding the personality of PHF, the degree of osteopenia, and biological age of the patient, risk for falling and level of activity in choosing the right surgical intervention (IM, ORIF, SHA, or rTSA).

2.1 Factors in the decision to treatment

2.1.1 Preserved rotator cuff

If the rotator cuff is preserved and the risk for osteopenia is low, the treatment chosen is flexible and depends on other factors, as some treatments are not possible in a degenerative rotator cuff.

If the rotator cuff is degenerative or there are systemic diseases or treatments that put the patient at increased risk for osteopenia and rotator cuff rupture, or if the tendons are at risk for rupture, nonsurgical treatment or treatment with rTSA is an option.

2.1.2 Deforming forces and fracture type

The deforming forces in PHF are due to the tendons attaching to the proximal humerus:

- Anterior and medial displacement of the shaft is caused by the forces of the pectoralis major.
- The dorsal and cranial displacement of the greater tuberosity is caused by the forces of the supraspinatus, infraspinatus, and teres minor.
- Internal rotation of the lesser tuberosity and/or the articular segment is caused by the subscapularis.

Depending on patient-related factors, patients may be treated nonsurgical even though they meet radiographic criteria for surgery. Generally accepted criteria for surgery are 2–4-part fractures with any of the following characteristics (50,70):

- > 10 mm displacement of the head from the shaft
- > 5 mm cranial displacement of the greater tuberosity
- Displaced fracture in the lesser tuberosity
- > 45 degrees of angular displacment of the head
- Loss of medial support/calcar
- Splitting of the humeral joint surface

2.1.3 Age

Biologically 'younger' patients who are active and at low risk for osteopenia are usually under 65 years of age and suitable candidates for PHF surgery. However, biological age can vary significantly depending on factors such as alcohol abuse, smoking, systemic disease, systemic treatments that affect bone and tendon quality, and activity level.

If the risks of surgery outweigh the benefits, surgery is not a recommended option. The treatment approach should be based on the anticipated degree of osteopenia, the degree of glenohumeral OA, and rotator cuff function (57,70,71).

Surgery with ORIF is recommended if the fracture has a good chance of healing and can be placed in a more anatomic position. If this is not possible in biologically younger individuals, SHA is preferred in centers that are comfortable performing the surgery (57,70,72,73). In recent years, rTSA has become more common as a 'safe' method that does not depend on tuberosity healing or rotator cuff condition (74–76).

Stenquist et al (77) compared outcomes in terms of shoulder function, implant survival, and complications with a follow-up of at least 3 years between younger, active patients (mean age 64) and older patients (mean age 78) treated for PHF with rTSA but found no significant differences.

However, it should be emphasized that the durability of rTSA in younger patients remains unknown. In addition, many centers have stopped training their residents in SHA and now prefer rTSA to SHA because of its increasing popularity.

2.1.4 Activity level – ADL

If the patient has low expectations regarding shoulder function, severe dementia, and lives in a nursing home, it is probably best to avoid surgery for an ambulatory PHF, regardless of radiographic findings.

2.1.5 Treatment algorithm

Spross et al. developed a treatment algorithm based on radiology, biological age, activity-level and ADL (57). The choice of treatment should be based on the expected outcome. After a traumatic injury, it is important to balance early motion and healing. Limited range of motion and strength in the shoulder is often due to scarring, altered anatomy, pseudoarthrosis, or post-traumatic OA.

In high-demand patients, early surgery is important to prevent stiffness and loss of muscle function, as reported in many studies. In low-demand patients or patients who require surgery only when needed, it is often better to wait-and-see approach and provide surgery with SHA or rTSA as a last resort to relieve pain.

For younger or active patients with high demands, the primary goals are to relieve pain and restore shoulder function to the greatest extent possible. Our primary goal for older patients with low demands is pain relief, Figure 7.

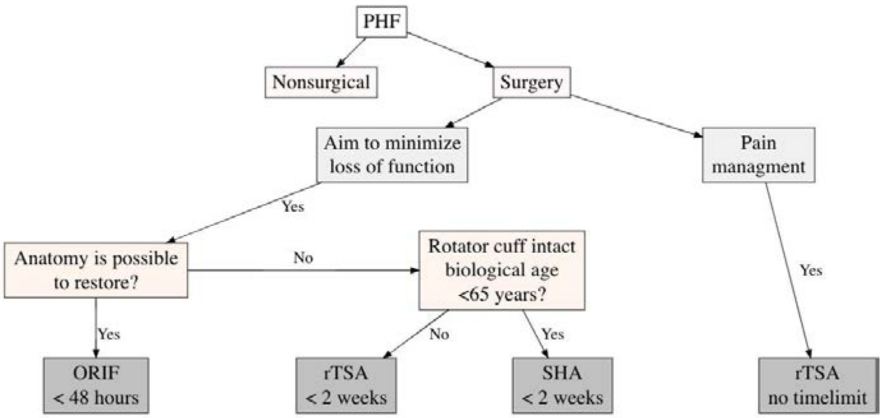

Figure 7. A flowchart to summarize the treatment alternatives and the timing to surgery depending on treatment of choice, the biological age, co-morbidity, and activity level.

2.1.6 Common shoulder specific scores used in follow up in PHF

2.1.6.1 American Shoulder and Elbow Surgeons Score (ASES)

The American Shoulder and Elbow Surgeons Standardized Shoulder Assessment Form (78–80), is a comprehensive instrument for evaluating shoulder function and treatment outcomes. It provides a score between 0 and 100, with higher scores representing better outcomes. ASES is a versatile assessment tool consisting of 17 subjective questions and an objective component that includes a clinical examination. It is important to note that only the subjective responses are considered in calculating the ASES score.

The ASES has proven its usefulness in assessing shoulder disorders and treatment outcomes, particularly in North America, where it is widely recommended and has been in use for some time.

Although the ASES is a valuable tool, there may be a slight "ceiling effect." A ceiling effect suggests that the assessment may have limitations in capturing improvements in individuals with relatively good shoulder function at baseline. The ASES is a well-established and widely accepted shoulder assessment tool that provides valuable insight into patient symptoms and clinical outcomes.

2.1.6.2 Constant-Murley Score (CS)

The Constant-Murley Score (78–83) is a widely used assessment tool to evaluate shoulder function and outcomes, mainly used in Europe. It assigns a score between 0 and 100, with higher scores representing better shoulder function and overall patient well-being. CS's long history of use and support by medical professionals underscores its importance in the field of shoulder assessment and patient care.

The CS score can be divided into two main components: the self-assessment/subjective portion and the objective measurements. The subjective portion is self-report of shoulder-related symptoms, and the objective measurements are assessed by clinical examination.

The CS is a valuable tool for healthcare professionals, common in Europe where it is widely recommended and has been in use for some decades. It serves several purposes, including preoperative assessment, postoperative assessment, and monitoring the progress of nonsurgical treatments for various shoulder conditions.

2.1.6.3 Oxford Shoulder Score (OSS)

The Oxford Shoulder Score (84,85) consists of 12 questions, each with five response levels (from 0 to 4). This PROM is based entirely on self-assessment and does not require clinical examination. The cumulative score is reported as a numerical value between 0 and 48, with lower values representing better outcomes.

3 RESEARCH AIMS

The overall aim of this thesis is to better understand the outcomes of PHF treated with joint replacement. To accomplish this, the more specific aims are broken down into four studies presented in this thesis.

3.1 Specific aims:

In Study I the aim was to investigate revision rates and reasons for revision after shoulder arthroplasty for acute fractures of the proximal humerus.

In Study II the aim was to assess a specific shoulder score, WOOS as PROM for PHF treated with shoulder arthroplasty. Since SSAR uses PROM for all arthroplasty diagnoses, we saw the need to validate WOOS for fracture diagnosis.

In Study III the aim was to analyze if rTSA is the superior treatment for complex PHF compared to SHA.

In study IV the aim was to determine the best timing for surgery with shoulder joint replacement after PHF.

4 MATERIALS AND METHODS

4.1 General material and methods

4.1.1 Patient selection

In Study I the population was selected from the SSAR and corresponding registries in Denmark, Finland, and Norway. We decided on the aim of the study, the compatible data sets, and created a hierarchy of the complications to be studied. The goal of NARA is to share knowledge across the Scandinavian countries to create a better understanding of joint replacement of the shoulder through comparison. The registries submitted the pseudonymized data from the registries that contained the compatible data sets. This was an international collaboration and a registry-only study.

To validate WOOS, we needed a series of patients who had PHF and surgery with joint replacement. After ethical approval, we had access to patients in Stockholm and sent a letter to those who were eligible for the study. The methodology was different from Study I because we used the registry for patient selection for further data collection and examination.

The third methodology was an RCT multicenter study. Participants were included from 8 trauma hospitals, and we had a template for study information. It was important to maintain equipoise between the treatments before surgery, during rehab, and at follow-up.

In the fourth study, the study population was included from SSAR and from the hospitals that could provide the date of trauma and the date of surgery. The sample size was determined from the combination of SSAR and the information from the hospitals that could provide us with the required data.

4.1.2 Sample size

Registries can be considered as large, continuous cohorts that include all individuals who have a disease or treatment. The sample size was determined depending on the data available for the study.

For the RCT study the sample size was determined by a power calculation.

4.1.3 Statistics

In Study I, a survival analysis using Kaplan-Meier was performed and the relative risk between SHA and rTSA was calculated using a Cox proportional hazards regression model.

In Study II, we validated WOOS with shoulder-specific scores and general scores. Because there was no pre-fracture PROM collected, the data was ordinal, not normally distributed, and not binomial, we decided to use Spearman rank correlation and set the level at >0.75 as excellent. Cronbach's alpha was used for internal consistency. An intraclass correlation coefficient (ICC) was used for the test results of WOOS, and we also decided on a lowest level on Satisfaction Level, setting a threshold for an acceptable level for WOOS on PHF with treated with joint replacement.

Study III was an RCT comparison of SHA with rTSA based mainly on functional scores and the Fisher exact test, Fisher nonparametric permutation test, chi-square test, Wilcox signed rank test, and signed test for time-dependent variables were used.

In Study IV the outcomes related to time from trauma to surgery were assessed with WOOS% and were analyzed using linear regression for continuous data and logistic regression for SL since it is binomial.

4.1.4 Ethical considerations

All studies were performed in accordance with the principles of the Helsinki declaration and approved by the regional ethical review board of Karolinska Institutet. In Study I, we used pseudonymized data from Denmark, Finland, Norway, and Sweden. The data was analyzed in Norway, and at the time of publication, the registries were able to share the data. The analyze was approved by the Norsk samfunnsvienskapelig datatjeneste AS in Norway, ref 19860/2LT. In Study II all participants were identified from SSAR and they then gave informed consent to participate in the follow-up and examinations, DNR 2012/1505-31/4. Study III all participants had written informed consent, 2013/1053-31/3, and patients were only included who accepted surgery and met the criteria for joint replacement. Study IV used retrospective observational data from registry and the Swedish social security number to collect the date of trauma from the hospitals, DNR 2012/1505-31/4.

4.2 Specific material methods for the studies

Study I: *Revision after shoulder replacement for acute fracture of the proximal humerus*

The data sets were extracted from the Nordic arthroplasty register association (NARA) to examine 19,857 shoulder arthroplasties performed between 2004 and 2013 in Denmark, Sweden, and Norway, with report completeness ranging from 80% to 95% in the three countries.

The dataset includes information on patient demographics, primary procedure details such as diagnosis, date of surgery, type of joint replacement, brand, and information on revision procedures including revision date, reason for revision, number of revisions, and new type of joint replacement.

Definitions were established for key terms such as acute fracture and fracture sequelae in the NARA consensus (86). An acute fracture was defined as a proximal humerus fracture that was not categorized as a subsequent fracture, regardless of the time between injury and surgery. Fracture sequelae included fractures reported as nonunion, malunion, previous osteosynthesis, OA, and humeral head necrosis when reported with a fracture.

A hierarchy of reasons for revision was used and in cases where more than one reason was reported, only one reason for revision was recorded.

Survival rates were calculated based on reported revisions and by reviewing deaths in each country's national population registry through December 2013.

Study II: *Validation of Western Ontario Osteoarthritis of the Shoulder Index (WOOS) for proximal humerus fractures treated with arthroplasty— A study from the Swedish Shoulder Register*

Patients treated with hemiarthroplasty between 2008 and 2011 after acute PHF were identified, and those with a follow-up of at least one to five years were invited to participate. The questionnaire-only group consisted of 72 subjects who met the inclusion criteria and completed WOOS, OSS, EQ -5D, and SL, while the study group consisted of 43 subjects who also underwent a clinical examination and WOOS retest.

To ***validate*** the construct of WOOS, it was compared with other shoulder-specific scores *(Oxford Shoulder Score, American Shoulder and Elbow Surgeons Score, and Constant Score)* and with generic scores *(EuroQol-5D-3L and Satisfaction Level).*

For the **validity** analysis of *Criterion validity, Construct validity, Content validity and Convergent validity* was performed.

For *Criterion validity*, a comparison of WOOS to other shoulder-specific PROM that either were self-assessment only (WOOS and OSS) or also had a part that included a clinical examination (ASES and CS). For *Construct validity* analysis of the effect of shoulder pain and stiffness was compared to general health, and a change in EQ-5D and SL should also occur with some agreement, but not as much as with the shoulder-specific scores. For *Content validity* the floor and ceiling effect was examined to determine whether the WOOS was relevant and representative. For *Convergent validity* analysis with Cronbach's Alpha (0-1) of WOOS total and within domains was performed. A low alpha value indicates scattered questions, and a high value indicates homogeneity. It is important to understand that the more values the questionnaire contains, the higher the alpha value.

For the **reliability** of the WOOS, the total score and each domain in WOOS were first analyzed for construct reliability. Then, a test-retest was conducted with a minimum interval of 2 weeks to ensure that the symptomatology was unchanged but that subjects would have forgotten their original responses.

All scores were compared with a dichotomized SL to assess responsiveness. The study used the previously reported minimal detectable change (MDC) of 10% and minimal clinically important difference (MCID) of 8% for WOOS % (83). We used the SL score of 3 ("neither satisfied nor dissatisfied") as the Patient Accepted Symptom State (PASS) threshold for PHF treated with joint replacement. PASS for WOOS% was 72 (CI_{95} 62-81.5).

Study III: *Reverse Total Shoulder Arthroplasty Versus Hemiarthroplasty for Displaced 3- and 4-part Proximal Humeral Fractures in Patients Older Than 70 Years. A Multicenter Randomized Controlled Trial*

This is a multicenter, prospective, randomized controlled trial. The inclusion criteria were displaced 3- or 4-part proximal humerus fractures in elderly patients aged ≥70 years, living independently, with a low-energy mechanism of injury. The exclusion criteria were preexisting shoulder condition, cognitive impairment, or comorbidities that significantly affected shoulder rehabilitation.

A total of eight hospitals in Sweden participated in the study, and 17 experienced surgeons performed the procedures. The choice of prosthesis brand was at the discretion of the treating surgeon. The postoperative protocol was that patients wore a **sling** for 2-4 weeks with individualized rehabilitation of **passive** and active-assisted range-of-motion exercises that transitioned to **active exercises** approximately at 4-6 weeks and **strengthening exercises** usually started after 8-12 weeks.

Clinical outcome measures included CS, WOOS, EQ-5D, 10 cm VAS scale for pain and satisfaction of the shoulder, range of motion, and strength, radiographs were taken, and adverse events were recorded 1 year and 2 years postoperatively.

Study IV: *Timing of surgery for proximal humeral fracture treated with shoulder hemiarthroplasty, best results with surgery within 2 weeks.*

This study analyzed a national cohort of 3383 shoulders that underwent shoulder hemiarthroplasty after proximal humerus fractures between 1999 and 2011. Of the 2762 shoulders with an acute fracture diagnosis, 1469 were selected from nine hospitals. After exclusion because of missing follow-up and missing data, 380 shoulders were analyzed.

The exposure variable was timing to surgery, categorized as within 14 days, 14-60 days, or > 60 days after trauma, with weekends and weekdays included. The subset of surgeries > 60 days after trauma was classified as "fracture sequelae".

Primary outcome was measured at least 1 year after surgery using WOOS. Secondary outcomes were EQ -5D and SL.

WOOS scores were converted to a percentage. For analysis we considered MDC of 10% and MCID of 8% for WOOS (83). EQ -5D measured five dimensions and was represented by its specific index. Patient satisfaction was measured by a Likert scale and dichotomized into satisfied and dissatisfied groups.

5 RESULTS

5.1 Study I: *Revision after shoulder replacement for acute fracture of the proximal humerus.*

This study analyzed the use of prostheses for acute fractures of the proximal humerus between 2004 and 2013. A total of 6,756 prostheses were used, with an initial increase in incidence but stabilization over the last 5 years of the study. The proportion of patients treated with rTSA increased steadily, with 8.4% of all prostheses being rTSA. The mean age of patients was 72 years, and 80% of all patients were women.

The study found that the cumulative survival rates of SHA and rTSA were similar, with a 10-year survival rate of 0.95 for SHA and data on rTSA survival rates not yet available. The most common reason for revision in both types of joint replacement was infection. The relative risk of revision due to infection was higher for rTSA than for SHA. The study also found that younger patients had a higher relative risk of revision and worse survival rates than older patients.

The most commonly used SHA brands were Bigliani-Flatow, Global Fx, and Aequalis Fracture stem, while the most commonly used rTSA was Delta Xtend. 3.3% of all prostheses were revised, with infection being the most common reason for revision.

5.2 Study II: *Validation of Western Ontario Osteoarthritis of the Shoulder Index (WOOS) for proximal humerus fractures treated with arthroplasty— A study from the Swedish Shoulder Register*

The ***validity*** of the WOOS % was found to be excellent, as indicated by the Spearman correlation coefficient (R > 0.75) with the shoulder-specific scores.

EQ-5D showed a good correlation (R = 0.68), but 15.7% of the subjects reached a ***ceiling effect***. No floor or ceiling effect was observed for the other scores.

The ***internal consistency*** of the four domains of WOOS was good to excellent, with Cronbach alfa values ranging from 0.894 to 0.965. The test-retest reliability of WOOS % was excellent, with an ICC of 0.970.

The questionnaires, including WOOS%, were ***responsive*** to the level of satisfaction, with a good correlation between satisfaction and the scores obtained.

The mean ***PASS*** of WOOS% with an anchor set at SL = 3 was 72.1 (CI95 62.1, 81.5).

5.3 Study III: *Reverse Total Shoulder Arthroplasty Versus Hemiarthroplasty for Displaced 3- and 4-part Proximal Humeral Fractures in Patients Older Than 70 Years. A Multicenter Randomized Controlled Trial*

Of the 99 patients with proximal humerus fractures that were included, 48 received a rTSA and 51 received a SHA. Fifteen patients did not complete the final follow-up, including 10 patients who died (rTSA = 4, SHA = 6). The patients lost to follow-up were older and had a lower preinjury EQ-5D index score. As a result, 84 patients were analyzed.

The mean follow-up time was 2.4 years in both groups. There were no demographic or clinical characteristic differences between the 41 patients in the rTSA group and the 43 patients in the SHA group. Three patients in the SHA group were treated with rTSA at final follow-up and were analyzed on an intention-to-treat basis. One patient was converted to rTSA perioperatively because of the absence of the supraspinatus tendon, whereas the others two underwent surgery with rTSA due to adverse events.

The rTSA group had a higher mean ***CS*** than the SHA group (58.7 vs. 47.7). There were no differences in ***WOOS*** or ***EQ-5D*** between the treatment groups. Most patients in both groups had a WOOS% score between 80 and 100, and there were patients in both groups with a WOOS% score ≥ 97.

The rTSA patients (79mm) had better shoulder ***SL*** (0-100mm) than for SHA patients (63mm). Both groups had similar levels of ***pain***.

ROM with flexion and abduction was better for rTSA group whereas external rotation was better for SHA group.

The ***radiographic*** parameters showed equal failed union of tubercles in both groups, with a rate of 33% for the rTSA group and 29% for the SHA group. When union and malunion were compared within the groups, they didn't show any clinically relevant differences with CS.

There was no difference in ***adverse events*** between rTSA and SHA. There were four periprosthetic fractures (one in the rTSA group and three in the SHA group). Two patients with SHA underwent surgical revision due to complications, one with a painful rotator cuff and migration of the SHA head, and one due to loosening after a periprosthetic fracture caused by trauma. The rTSA patient with a fracture had a distal humerus fracture that required surgery with ORIF. One rTSA patient died of pneumonia eight days after surgery, and the other deaths were unrelated to the proximal humeral fracture or its treatment.

5.4 Study IV: *Timing of surgery for proximal humeral fracture treated with shoulder hemiarthroplasty, best results with surgery within 2 weeks.*

Of the 380 shoulders studied 81% were women, with the age ranging 42 to 90 in women and 34 to 91 years in men. Most of the patients (82%) underwent surgery within 14 days after their trauma.

The mean overall WOOS% was 63% (±26) and the mean EQ-5D index was 0.67 (±0.3). We found that patients who had surgery within 14 days after the trauma had better outcomes than patients who had surgery later. The mean WOOS % value was highest between days 6-10 after surgery, with a cut-off point at 10 days after which WOOS % decreased by 1.4 WOOS %/day. Patients who underwent surgery 15-60 days after trauma had worse outcomes in all three scores.

The EQ -5D index decreased linearly by 0.03 per day, and satisfaction had a linear decrease with an odds ratio of 0.7 per day.

Subgroup analysis showed that weekday surgeries had better scores compared with weekend surgeries.

6 DISCUSSION

6.1 General discussion

The timing of surgery for orthopedic trauma is important and there are several general considerations, such as:

- the risk of major bleeding from the fracture
- damage to the nerves
- the risks of prolonged immobilization such as deep vein thrombosis, pulmonary embolism, and pressure ulcers
- soft tissue damage that must heal prior to surgery
- open fractures that need to be treated more quickly
- pain management
- functional results
- the general health or fragility of the patient

The same principles apply to PHF as to all orthopedic traumas. The recommendation for timing of surgery with joint replacement after PHF is based on past experience and current knowledge.

Shoulder function depends on the intricate coordination of the shoulder girdle and rotator cuff, and PHF can cause damage to the muscles and tendons. Degeneration and stiffening of soft tissues worsen when the time to surgery is prolonged, and early surgery may be beneficial (87,88). This may reflect the result at follow-up in SSAR of the study IV, in which surgery within 2 weeks with SHA showed better results, compared to later than 2 weeks. The result with rTSA does not seem to have the same effect on time to surgery in the elderly population (>75 years).

The function of a SHA is to replace the humeral head and return the shoulder to its former biomechanics. Therefore, restoration of the anatomy around the joint replacement should provide good pain relief and ROM. Prolonged delay to surgery results in a more difficult surgery to restore the anatomy, difficulty in correcting any malunion, or risk of nonunion at later stages (89). In biologically younger patients' treatment with early surgery and ORIF (<48 hours to enhance healing of the reconstructed tubercles) is recommended if anatomy can be restored, or surgery with joint replacement if the fracture is too severe to restore the anatomy (57).

In the elderly, the rotator cuff is weaker, and the tuberosity healing is uncertain (64,77). The better ROM and higher satisfaction level with rTSA in study III study may reflect the biomechanical properties of the joint replacement. The balance of the shoulder is not as dependent on the rotator cuff in rTSA as in SHA, so the deltoid muscle can transmit more force in a better-balanced shoulder.

The more predictable outcome may be one reason for the increased use of rTSA as a treatment for 3–4-part PHF and revision after osteosynthesis in patients > 65 years. However, in case of complications, revision of rTSA is more complicated than SHA (50,90). In study III there were no adverse effects associated with joint replacement for rTSA. The early pain relief and better ROM could also be due to the different postoperative rehabilitation protocol. Patients who underwent surgery with rTSA were able to actively exercise sooner, compared with SHA where rehab was more cautious to protect tubercle healing.

There is an increased surgery with rTSA in younger individuals with complex PHF, but the long-term complications are unknown (73). In recent years, there have been several publications on the need to reconsider and strengthen the indication of SHA in younger and active people when ORIF is not possible for complex PHF (63,74,91). The long-term risk of SHA has been suggested to be erosion on the glenoid and migration (92), but there are recent studies with follow-up of at least 10 years showing a survival rate at 96.6% (73). The age ranged from 42-90 years in Study IV and in study I the proportion of patients <75 years was 38% thus the majority is on the elderly population and the increased use of rTSA the elderly could be a result of more predictable result of worse healing of the tubercles and weaker rotator cuff in the elderly. The younger population was not separated in the analysis in study IV.

If treatment fails with nonsurgical treatment or ORIF, the choice is to revise the treatment with either ORIF or joint replacement. If SHA fails, revision could be a new SHA or revision to an rTSA. If the failed treatment is an rTSA, there are fewer options and surgery may be more challenging including a salvage SHA. Therefore, the threshold may be higher for revision of an rTSA. Unexplained pain is a reason for revision for anatomic joint replacement but is not common for rTSA (93). In study I, the overall revision rate was 3.3% for SHA and 3.5% for rTSA. The reason for revision "other diagnoses" was 1.8% for SHA and 0.5% for rTSA. This could be a reflection of the complexity in comparing two different methods and the risk for revision and implant survival. The rate and severity of adverse events are important. In study I and IV the choice between SHA and rTSA was in the discretion of the treating surgeon and it is reflecting the.

Revisions due to infection were more frequent with rTSA in study I. One reason for this could be that there are more parts in rTSA than in SHA. It could also be an effect of the learning curve including the longer time to perform the surgery, and the implants available at the time of the study. A limitation of study I is the lack of information on operating room time and surgeon experience. In Study III the attending surgeons were experienced, possibly reflecting the non-existent rate of complications with rTSA.

6.2 Specific discussion

Study I: *Revision after shoulder replacement for acute fracture of the proximal humerus.*

Both SHA and rTSA had high survival rates, but the factors influencing the decision to revise the joint replacement are not fully known in the registry data. In addition, reported survival rates do not necessarily reflect patients' functional outcomes. There are also discrepancies in revision rates between systematic reviews and data from national registries, possibly due to differences in inclusion criteria. It is important to interpret any comparison between SHA and rTSA with caution because rTSA was a newer design at baseline and the indications for its use in the treatment of acute fractures likely changed during the study period. Surgery with rTSA was associated with a higher risk of infection compared with SHA. Periprosthetic infection is a severe complication with long hospitalization and high costs.

Study II: *Validation of Western Ontario Osteoarthritis of the Shoulder Index (WOOS) for proximal humerus fractures treated with arthroplasty— A study from the Swedish Shoulder Register*

SSAR use WOOS as PROM, and until 2021, it was also used in the Danish shoulder registry. It has been translated and validated in Swedish (94) and in Danish (95) for OA. WOOS was originally designed as a specific PROM for OA of the shoulder (67) The research team incorporated additional dimensions to align with the World Health Organization's (WHO) principle that *"Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity"* (96). The total score is converted to a percentage. The total score is converted to a percentage and WOOS% (ranging from 0 to 100) represents the level of satisfaction compared to a healthy shoulder (67).

In cases of shoulder OA, both preoperative and postoperative WOOS scores are obtained. MDC and MCID are used to assess the responsiveness of WOOS scores. However, in the context of PHF, there is no preoperative WOOS available. Therefore, we opt for using PASS as a threshold in WOOS% for patients with PHF treated with joint replacement. This approach allows us to distinguish between poor and acceptable outcomes in the PROM.

A PASS introduces an additional dimension to treatment effectiveness beyond what MDC and MCID provide. While observing a clinical change indicates treatment efficacy, it does not address whether the improvement that is considered as PASS-positive or

PASS-negative (97). The phrasing of the PASS question is critical, and an example is, 'In the next few months, if you were to remain as you were during the last 48 hours, would this be acceptable or unacceptable to you?' However, patients often rephrase it as 'for the rest of your life' and remove the time frame (98). In Study II, the satisfaction level used was 'neither satisfied nor dissatisfied,' with no specified time limit.

We considered a steady state when at least one year has passed after surgery. PASS positive for WOOS% was 72% (62.1-81.5). This threshold holds significance for future studies utilizing WOOS.

Study III: *Reverse Total Shoulder Arthroplasty Versus Hemiarthroplasty for Displaced 3- and 4-part Proximal Humeral Fractures in Patients Older Than 70 Years. A Multicenter Randomized Controlled Trial*

The rTSA group had a mean Constant score of 58.7, significantly better than the HA group of 47.7. Satisfaction (79 mm vs. 63 mm), abduction (112° vs. 83°), and flexion (125° vs. 90°) were significantly improved in the rTSA group. These results are consistent with previous studies. The rTSA patients also achieved better range of motion.

We hypothesize that the greater satisfaction with the shoulder in the rTSA group was due to the improved range of motion, as there were no significant differences in pain or complications. However, rTSA did not prevent the decline in EQ -5D Index scores in either group.

Our study highlights the importance of age on treatment outcomes and the potential for sustained improvement in shoulder function beyond 1 year. Healing of the greater tuberosity did not significantly affect outcomes in either group.

Prior RCT with plating vs non-treatment in elderly patients did not show any clinically significant difference (99). Nor has RCT in the elderly shown any benefit with SHA vs non-surgical treatment (59,100).

We find rTSA provides better shoulder function and satisfaction in elderly patients with proximal humerus fractures, with age playing a critical role in treatment efficacy.

A limitation of this study is that we did not compare surgical treatment with nonsurgical treatment.

Study IV: *Timing of surgery for proximal humeral fracture treated with shoulder hemiarthroplasty, best results with surgery within 2 weeks.*

Surgery with joint replacement within two weeks of PHF compared surgery after two weeks, has a lower revision rate (3.5% vs. 5.8%), better WOOS%, and EQ -5D compared with surgery after two weeks, according to analyzes in SSAR (unpublished data). Late sequelae (*PHF treated nonsurgical or with ORIF that resulted in pain, AVN, posttraumatic* *arthrosis, malunion or nonunion)* after fracture had a worse outcome compared with those who had acute surgery with joint replacement. However, they still had a better quality of life after surgery with joint replacement compared to unpublished data from the registry. Both SHA and rTSA showed a higher revision rate when surgery was performed after two weeks than when it was performed before two weeks. WOOS% showed no significant difference with surgery after two weeks for the rTSA, according to analyzes in SSAR (unpublished data).

For SHA, the WOOS% scores deteriorated with each day of delay beyond two weeks before surgery, in accordance analyzes in SSAR (unpublished data). This is consistent with the IV study, which examined SHA in the timing of surgery with joint replacement.

Our results are consistent with previous studies emphasizing the benefits of early surgery for PHF. Factors such as healing processes, technical difficulties, and soft tissue stiffness may contribute to worse outcomes with delayed surgery (87–89).

Strengths of the study include a large sample (380 patients) representing different types of PHF, with a follow-up period of 1-5 years. Limitations, however, include lack of detailed information on fractures, surgical variations, and limited data on postoperative physical therapy and contralateral shoulder function for comparison.

7 MAIN CONCLUSIONS OF THIS THESIS

Based on Nordic national registries, we found that revisions after joint replacement on acute fractures were rare and survival rates were similar for SHA and rTSA. However, the risk of revision due to infection was higher for rTSA than for SHA. Patient age had a significant effect on the risk for revision, with younger patients having a higher risk of revision.

The use of WOOS can be continued in future studies as it is a valid PROM for PHF treated with joint replacement.

Displaced 3- or 4-part fractures of the proximal humerus treated with rTSA demonstrated a better shoulder function and higher satisfaction level than SHA in the elderly.

Time to surgery is important. In nonurgent cases, it is safe to wait for optimal conditions and patient assessment and to consider patient-related factors in decision making.

Since the goal for treatment in the younger population is to restore function and reduce pain surgery with SHA should not be delayed. If the treatment is delayed more than two weeks rTSA is a good option.

8 POINTS OF PERSPECTIVE

8.1 Prosthetic joint infection

The common bacteria in periprosthetic joint infections are Cutibacterium Acnes (38.9%) Staphylococcus Aureus (14.8%), Staphylococcus Epidermidis (14.5%) and Coagulase-negative Staphylococcus (14%) (101). With more knowledge of the behavior Cutibacterium Acnes the treatment has switched over with time. Prophylaxis with Cloxacillin had a higher relative risk for revision compared to the combination of Cloxacillin and Bensylpenicillin. There was no difference between Clindamycin and the double treatment Cloxacillin and Bencylpenicillin. Between 2013-2019 the use of single Cloxacillin decreased drastically, Clindamycin increased since it covers Cutibacterium, and prophylaxis with the combination Cloxacillin and Bensylpenicillin was the most common in Sweden (102).

Our current recommendation established in collaboration with the infection clinic in Danderyd hospital is Cloxacillin in combination with Bensylpenicillin, since we noticed a development of clindamycin resistent cutibacterium cultures.

Since Cutibacterium Acne hides within the sebaceous glands and can survive the preopretive shower and skin sterilization (103), our patients are currently treated with topical benzoylperoxides. Positive cultures during surgery are decreased from 28% to 8% (104).

A future study could be to better understand surgical site infection in prosthetic joint infection and the effect of topical treatment.

8.2 PASS

To understand further understand the scores in WOOS % and further development of PASS would be to also compare for WOOS with scores such as SF-36, socioeconomic status and co-morbidities.

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10 REFERENCES

1. Kristiansen B, Barfod G, Bredesen J, Erin-madsen J, Grum B, Horsnaes MW, et al. Epidemiology of proximal humeral fractures. Acta Orthopaedica. 1987 Jan;58(1):75–7.

2. Barrett JA, Baron JA, Karagas MR, Beach ML. Fracture Risk in the U.S. Medicare Population. Journal of Clinical Epidemiology. 1999 Mar;52(3):243–9.

3. Court-Brown CM, Garg A, McQueen MM. The epidemiology of proximal humeral fractures. Acta Orthop Scand. 2001 Aug;72(4):365–71.

4. Court-Brown CM, Caesar B. Epidemiology of adult fractures: A review. Injury. 2006 Aug;37(8):691–7.

5. Hansen L, Petersen KD, Eriksen SA, Langdahl BL, Eiken PA, Brixen K, et al. Subsequent fracture rates in a nationwide population-based cohort study with a 10-year perspective. Osteoporos Int. 2014 Sep 4;26(2):513–9.

6. Rosengren BE, Karlsson M, Petersson I, Englund M. The 21st century landscape of adult fractures - Cohort study of a complete adult regional population. J Bone Miner Res. 2014 Oct 3;

7. Schumaier A, Grawe B. Proximal Humerus Fractures: Evaluation and Management in the Elderly Patient. Geriatr Orthop Surg Rehabil [Internet]. 2018 Jan 25 [cited 2019 Mar 7];9. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5788098/

8. Jawa A, Burnikel D. Treatment of Proximal Humeral Fractures: A Critical Analysis Review. JBJS Reviews [Internet]. 2016 Jan 19 [cited 2019 Mar 13];4(1). Available from: https://journals.lww.com/jbjsreviews/fulltext/2016/01000/Treatment_of_Proximal_Humeral_Fractures__A.2.aspx

9. Passaretti D, Candela V, Sessa P, Gumina S. Epidemiology of proximal humeral fractures: a detailed survey of 711 patients in a metropolitan area. Journal of Shoulder and Elbow Surgery. 2017 Dec 1;26(12):2117–24.

10. Bergdahl C, Ekholm C, Wennergren D, Nilsson F, Möller M. Epidemiology and patho-anatomical pattern of 2,011 humeral fractures: data from the Swedish Fracture Register. BMC Musculoskelet Disord. 2016 Apr 12;17:159.

11. Sumrein BO, Huttunen TT, Launonen AP, Berg HE, Felländer-Tsai L, Mattila VM. Proximal humeral fractures in Sweden—a registry-based study. Osteoporos Int. 2017 Mar 1;28(3):901–7.

12. Iglesias-Rodríguez S, Domínguez-Prado DM, García-Reza A, Fernández-Fernández D, Pérez-Alfonso E, García-Piñeiro J, et al. Epidemiology of proximal humerus fractures. J Orthop Surg Res. 2021 Jun 22;16:402.

13. Taskesen A, Göçer A, Uzel K, Yaradılmış YU. Effect of Osteoporosis on Proximal Humerus Fractures. Geriatr Orthop Surg Rehabil. 2020 Dec 23;11:2151459320985399.

14. Dimai HP, Fahrleitner-Pammer A. Osteoporosis and Fragility Fractures: currently available pharmacological options and future directions. Best Practice & Research Clinical Rheumatology. 2022 Sep;101780.

15. Olsson C, Petersson CJ. Clinical Importance of Comorbidity in Patients with a Proximal Humerus Fracture: Clinical Orthopaedics and Related Research. 2006 Jan;442(NA;):93–9.

16. Bergh C, Möller M, Ekelund J, Brisby H. 30-day and 1-year mortality after skeletal fractures: a register study of 295,713 fractures at different locations. Acta Orthop. 92(6):739–45.

17. Brusselaers N, Lagergren J. The Charlson Comorbidity Index in Registry-based Research: Which Version to Use? Methods Inf Med. 2017;56(05):401–6.

18. Myeroff CM, Anderson JP, Sveom DS, Switzer JA. Predictors of Mortality in Elder Patients With Proximal Humeral Fracture. Geriatr Orthop Surg Rehabil. 2018 Jan 1;9:2151458517728155.

19. Gogna R, Bhabra G, Modi CS. Fractures of the proximal humerus: overview and non-surgical management. Orthopaedics and Trauma. 2019 Oct 1;33(5):315–21.

20. Hettrich CM, Boraiah S, Dyke JP, Neviaser A, Helfet DL, Lorich DG. Quantitative Assessment of the Vascularity of the Proximal Part of the Humerus: The Journal of Bone and Joint Surgery-American Volume. 2010 Apr;92(4):943–8.

21. Lambert SM. Ischaemia, healing and outcomes in proximal humeral fractures. EFORT Open Rev. 2018 May 21;3(5):304–15.

22. Gerber C, Hersche O, Berberat C. The clinical relevance of posttraumatic avascular necrosis of the humeral head. Journal of Shoulder and Elbow Surgery. 1998 Nov 1;7(6):586–90.

23. Hertel R, Hempfing A, Stiehler M, Leunig M. Predictors of humeral head ischemia after intracapsular fracture of the proximal humerus. Journal of Shoulder and Elbow Surgery. 2004 Jul 1;13(4):427–33.

24. Resch H, Tauber M, Neviaser RJ, Neviaser AS, Majed A, Halsey T, et al. Classification of proximal humeral fractures based on a pathomorphologic analysis. Journal of Shoulder and Elbow Surgery. 2016 Mar 1;25(3):455–62.

25. Lowry V, Bureau NJ, Desmeules F, Roy JS, Rouleau DM. Acute proximal humeral fractures in adults. Journal of Hand Therapy. 2017 Apr 1;30(2):158–66.

26. Katthagen JC, Grabowski S, Huber M, Jensen G, Voigt C, Lill H. Epidemiology and treatment reality of proximal humeral fractures at a level-1 trauma center. Obere Extremität. 2016 Jun 1;11(2):112–8.

27. Brorson S, Eckardt H, Audigé L, Rolauffs B, Bahrs C. Translation between the Neer- and the AO/OTA-classification for proximal humeral fractures: do we need to be bilingual to interpret the scientific literature? BMC Research Notes. 2013 Feb 25;6(1):69.

28. Koh KH, Han KY, Yoon YC, Lee SW, Yoo JC. True anteroposterior (Grashey) view as a screening radiograph for further imaging study in rotator cuff tear. Journal of Shoulder and Elbow Surgery. 2013 Jul 1;22(7):901–7.

29. Wijdicks CA, Anavian J, Hill BW, Armitage BM, Vang S, Cole PA. The assessment of scapular radiographs. The Bone & Joint Journal. 2013 Aug 1;95-B(8):1114–20.

30. Kristiansen B, Andersen ULS, Olsen CA, Varmarken JE. The Neer classification of fractures of the proximal humerus: An assessment of interobserver variation. Skeletal Radiology. 1988 Sep;17(6):420–2.

31. Bao MH, DeAngelis JP, Wu JS. Imaging of traumatic shoulder injuries – Understanding the surgeon's perspective. Eur J Radiol Open. 2022 Mar 2;9:100411.

32. Gracitelli MEC, Dotta TAG, Assunção JH, Malavolta EA, Andrade-Silva FB, Kojima KE, et al. Intraobserver and interobserver agreement in the classification and treatment of proximal humeral fractures. Journal of Shoulder and Elbow Surgery. 2017 Jun 1;26(6):1097–102.

33. Resch H. Proximal humeral fractures: current controversies. Journal of Shoulder and Elbow Surgery. 2011 Jul 1;20(5):827–32.

34. Gregson CL, Armstrong DJ, Bowden J, Cooper C, Edwards J, Gittoes NJL, et al. UK clinical guideline for the prevention and treatment of osteoporosis. Arch Osteoporos. 2022;17(1):58.

35. Kanis JA, Cooper C, Rizzoli R, Reginster JY. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int. 2019;30(1):3–44.

36. Osteoporos - Viss.nu [Internet]. [cited 2022 Nov 2]. Available from: https://viss.nu/kunskapsstod/vardprogram/osteoporos

37. Brorson S, Bagger J, Sylvest A, Hróbjartsson A. Low agreement among 24 doctors using the Neer-classification; only moderate agreement on displacement, even between specialists. Int Orthop. 2002 Oct;26(5):271–3.

38. Wennergren D, Stjernström S, Möller M, Sundfeldt M, Ekholm C. Validity of humerus fracture classification in the Swedish fracture register. BMC Musculoskelet Disord [Internet]. 2017 Jun 10 [cited 2019 Mar 14];18. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5466790/

39. Hempfing A, Leunig M, Ballmer FT, Hertel R. Surgical landmarks to determine humeral head retrotorsion for hemiarthroplasty in fractures. Journal of Shoulder and Elbow Surgery. 2001 Sep;10(5):460–3.

40. Handoll HHG, Brealey SD, Jefferson L, Keding A, Brooksbank AJ, Johnstone AJ, et al. Defining the fracture population in a pragmatic multicentre randomised controlled trial. Bone & Joint Research. 2016 Oct 1;5(10):481–9.

41. Neer CS. Displaced proximal humeral fractures. I. Classification and evaluation. J Bone Joint Surg Am. 1970 Sep;52(6):1077–89.

42. Wellcome Collection [Internet]. [cited 2023 Sep 27]. The shoulder : rupture of the supraspinatus tendon and other lesions in or about the subacromial bursa / E.A. Codman. Available from: https://wellcomecollection.org/works/k83a3rba

43. Iordens GIT, Mahabier KC, Buisman FE, Schep NWL, Muradin GSR, Beenen LFM, et al. The reliability and reproducibility of the Hertel classification for comminuted proximal humeral fractures compared with the Neer classification. Journal of Orthopaedic Science. 2016 Sep 1;21(5):596–602.

44. Wennergren D, Ekholm C, Sandelin A, Möller M. The Swedish fracture register: 103,000 fractures registered. BMC Musculoskelet Disord. 2015 Nov 6;16:338.

45. Kellam JF, Meinberg EG, Agel J, Karam MD, Roberts CS. Introduction: Fracture and Dislocation Classification Compendium—2018. Journal of Orthopaedic Trauma. 2018 Jan;32:S1–10.

46. Handoll HH, Brorson S. Interventions for treating proximal humeral fractures in adults. Cochrane Database of Systematic Reviews [Internet]. 2015 [cited 2023 Mar 29];(11). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD000434.pub4/full

47. Mellstrand Navarro C, Brolund A, Ekholm C, Heintz E, Hoxha Ekström E, Josefsson PO, et al. Treatment of humerus fractures in the elderly: A systematic review covering effectiveness, safety, economic aspects and evolution of practice. PLoS One. 2018 Dec 13;13(12):e0207815.

48. McLean AS, Price N, Graves S, Hatton A, Taylor FJ. Nationwide trends in management of proximal humeral fractures: an analysis of 77,966 cases from 2008 to 2017. Journal of Shoulder and Elbow Surgery. 2019 Nov;28(11):2072–8.

49. Patel AH, Wilder JH, Ofa SA, Lee OC, Savoie FH, O'Brien MJ, et al. Trending a decade of proximal humerus fracture management in older adults. JSES Int. 2021 Oct 13;6(1):137–43.

50. Baker HP, Gutbrod J, Strelzow JA, Maassen NH, Shi L. Management of Proximal Humerus Fractures in Adults—A Scoping Review. J Clin Med. 2022 Oct 18;11(20):6140.

51. Baker HP, Gutbrod J, Cahill M, Shi L. Optimal Treatment of Proximal Humeral Fractures in the Elderly: Risks and Management Challenges. Orthop Res Rev. 2023 Jun 26;15:129–37.

52. Handoll HH, Elliott J, Thillemann TM, Aluko P, Brorson S. Interventions for treating proximal humeral fractures in adults. Cochrane Database of Systematic Reviews [Internet]. 2022 [cited 2023 Sep 23];(6). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD000434.pub5/full

53. Euler SA, Petri M, Venderley MB, Dornan GJ, Schmoelz W, Turnbull TL, et al. Biomechanical evaluation of straight antegrade nailing in proximal humeral fractures: the rationale of the "proximal anchoring point." International Orthopaedics (SICOT). 2017 Sep;41(9):1715–21.

54. Murena L, Canton G, Ratti C, Hoxhaj B, Giraldi G, Surace MF, et al. Indications and results of osteosynthesis for proximal humerus fragility fractures in elderly patients. Orthop Rev (Pavia). 2020 Apr 28;12(1):8559.

55. Robinson CM, Amin AK, Godley KC, Murray IR, White TO. Modern Perspectives of Open Reduction and Plate Fixation of Proximal Humerus Fractures. Journal of Orthopaedic Trauma. 2011 Oct;25(10):618–29.

56. Attala D, Primavera M, Di Marcantonio A, Broccolo L, Oliverio FP, Zoccali C, et al. The role of minimally invasive plate osteosynthesis (MIPO) technique for treating 3- and 4-part proximal humerus fractures in the elderly. A case study. Acta Biomed. 2021;92(4):e2021251.

57. Spross C, Meester J, Mazzucchelli RA, Puskás GJ, Zdravkovic V, Jost B. Evidence-based algorithm to treat patients with proximal humerus fractures—a prospective study with early clinical and overall performance results. Journal of Shoulder and Elbow Surgery. 2019 Jun 1;28(6):1022–32.

58. Robinson CM, Wylie JR, Ray AG, Dempster NJ, Olabi B, Seah KTM, et al. Proximal humeral fractures with a severe varus deformity treated by fixation with a locking plate. The Journal of Bone and Joint Surgery British volume. 2010 May;92-B(5):672–8.

59. Olerud P, Ahrengart L, Ponzer S, Saving J, Tidermark J. Hemiarthroplasty versus nonoperative treatment of displaced 4-part proximal humeral fractures in elderly patients: a randomized controlled trial. Journal of Shoulder and Elbow Surgery. 2011 Oct;20(7):1025–33.

60. Fialka C, Stampfl P, Arbes S, Reuter P, Oberleitner G, Vécsei V. Primary hemiarthroplasty in four-part fractures of the proximal humerus: Randomized trial of two different implant systems. Journal of Shoulder and Elbow Surgery. 2008 Mar;17(2):210–5.

61. Demir Y. Primary shoulder arthroplasty after proximal humeral fracture, outcome related to waiting time to surgery, and subsequent to a fracture sequelae. -Analyzed from the Swedish shoulder registry. Oral presentation at ISAR presented at: ISAR 2021, International Society of Arthroplasty Registries; 2021 Nov 12; Virtual congres live from Copenhagen.

62. Demir Y. Primary arthroplasty after proximal humeral fracture or sequelae. Outcome related to time to surgery, Analysis from the Swedish shoulder registry. Posterpresentation at SECEC-ESSSE Congress presented at: SECEC-ESSSE Congress; 2022 Sep 7; Dublin.

63. Marigi EM, Bartels DW, Aibinder WR, Cofield RH, Sperling JW, Sanchez-Sotelo J, et al. Hemiarthroplasty for proximal humerus fractures and for fracture sequelae: did not differ in their outcomes. JSES International. 2023 Mar 1;7(2):239–46.

64. Boileau P, Alta TD, Decroocq L, Sirveaux F, Clavert P, Favard L, et al. Reverse shoulder arthroplasty for acute fractures in the elderly: is it worth reattaching the tuberosities? Journal of Shoulder and Elbow Surgery. 2019 Mar;28(3):437–44.

65. Reuther F, Petermann M, Stangl R. Reverse Shoulder Arthroplasty in Acute Fractures of the Proximal Humerus: Does Tuberosity Healing Improve Clinical Outcomes? J Orthop Trauma. 2019 Feb;33(2):e46–51.

66. Jonsson EÖ, Ekholm C, Salomonsson B, Demir Y, Olerud P, Etzner M, et al. Reverse total shoulder arthroplasty provides better shoulder function than hemiarthroplasty for displaced 3- and 4-part proximal humeral fractures in patients aged 70 years or older: a multicenter randomized controlled trial. Journal of Shoulder and Elbow Surgery. 2021 May 1;30(5):994–1006.

67. Lo IK, Griffin S, Kirkley A. The development of a disease-specific quality of life measurement tool for osteoarthritis of the shoulder: The Western Ontario Osteoarthritis of the Shoulder (WOOS) index. Osteoarthr Cartil. 2001 Nov;9(8):771–8.

68. Polk A, Rasmussen JV, Brorson S, Olsen BS. Reliability of patient-reported functional outcome in a joint replacement registry. Acta Orthop. 2013 Feb;84(1):12–7.

69. Black N. Patient reported outcome measures could help transform healthcare. BMJ. 2013 Jan 28;346:f167.

70. Mease SJ, Kraeutler MJ, Gonzales-Luna DC, Gregory JM, Gardner MJ, Choo AM. Current Controversies in the Treatment of Geriatric Proximal Humeral Fractures. Journal of Bone and Joint Surgery. 2021 May 5;103(9):829–36.

71. Jung SW, Shim SB, Kim HM, Lee JH, Lim HS. Factors that Influence Reduction Loss in Proximal Humerus Fracture Surgery. Journal of Orthopaedic Trauma. 2015 Jun;29(6):276.

72. White JJE, Soothill JR, Morgan M, Clark DI, Espag MP, Tambe AA. Outcomes for a large metaphyseal volume hemiarthroplasty in complex fractures of the proximal humerus. Journal of Shoulder and Elbow Surgery. 2017 Mar 1;26(3):478–83.

73. Zhao Y, Zhu Y, Lu Y, Li F, Jiang C. Long-term outcomes of shoulder hemiarthroplasty for acute proximal humeral fractures. International Orthopaedics (SICOT) [Internet]. 2023 Mar 27 [cited 2023 Mar 31]; Available from: https://doi.org/10.1007/s00264-023-05746-5

74. Yahuaca BI, Simon P, Christmas KN, Patel S, Gorman RA, Mighell MA, et al. Acute surgical management of proximal humerus fractures: ORIF vs. hemiarthroplasty vs. reverse shoulder arthroplasty. Journal of Shoulder and Elbow Surgery. 2020 Jul 1;29(7, Supplement):S32–40.

75. Ezuma CO, Kosber RL, Kovacevic D. Biological sex impacts perioperative complications after reverse shoulder arthroplasty for proximal humeral fracture. JSES Int. 2021 Feb 16;5(3):371–6.

76. Patel AH, Wilder JH, Ofa SA, Lee OC, Iloanya MC, Savoie FH, et al. How age and gender influence proximal humerus fracture management in patients older than fifty years. JSES Int. 2021 Dec 17;6(2):253–8.

77. Stenquist DS, Barger J, Mohamadi A, Weaver MJ, Suneja N, Dyer GSM, et al. Impact of Age on Functional Outcome After Reverse Shoulder Arthroplasty Performed for Proximal Humerus Fractures or Their Sequelae. Arch Bone Jt Surg. 2023;11(1):29–38.

78. Richards RR, An KN, Bigliani LU, Friedman RJ, Gartsman GM, Gristina AG, et al. A standardized method for the assessment of shoulder function. Journal of Shoulder and Elbow Surgery. 1994 Nov;3(6):347–52.

79. Wylie JD, Beckmann JT, Granger E, Tashjian RZ. Functional outcomes assessment in shoulder surgery. World Journal of Orthopedics. 2014 Nov 18;5(5):623–33.

80. Kocher MS, Horan MP, Briggs KK, Richardson TR, O'Holleran J, Hawkins RJ. Reliability, Validity, and Responsiveness of the American Shoulder and Elbow Surgeons Subjective Shoulder Scale in Patients with Shoulder Instability, Rotator Cuff Disease, and Glenohumeral Arthritis. JBJS. 2005 Sep;87(9):2006–11.

81. Olerud P, Tidermark J, Ponzer S, Ahrengart L, Bergström G. Responsiveness of the EQ-5D in patients with proximal humeral fractures. Journal of Shoulder and Elbow Surgery. 2011 Dec;20(8):1200–6.

82. Terwee CB, Bot SDM, de Boer MR, van der Windt DAWM, Knol DL, Dekker J, et al. Quality criteria were proposed for measurement properties of health status questionnaires. Journal of Clinical Epidemiology. 2007 Jan 1;60(1):34–42.

83. Hallberg K, Salomonsson B. Validity, reliability, and responsiveness of the Swedish version of Western Ontario Osteoarthritis of the Shoulder index. BMC Musculoskeletal Disorders. 2022 Apr 11;23(1):351.

84. Dawson J, Fitzpatrick R, Carr A. QUESTIONNAIRE ON THE PERCEPTIONS OF PATIENTS ABOUT SHOULDER SURGERY. THE JOURNAL OF BONE AND JOINT SURGERY. 1996;78(4):8.

85. Dawson J, Rogers K, Fitzpatrick R, Carr A. The Oxford shoulder score revisited. Arch Orthop Trauma Surg. 2009 Jan;129(1):119–23.

86. Rasmussen JV, Brorson S, Hallan G, Dale H, Äärimaa V, Mokka J, et al. Is it feasible to merge data from national shoulder registries? A new collaboration within the Nordic Arthroplasty Register Association. Journal of Shoulder and Elbow Surgery. 2016 Dec 1;25(12):e369–77.

87. Abdelhady AM. Timing of shoulder arthroplasty in comminuted proximal humerus fracture, how much does it matter? Eur J Orthop Surg Traumatol. 2013 Jul 1;23(5):515–9.

88. Demirhan M, Kilicoglu O, Altinel L, Eralp L, Akalin Y. Prognostic Factors in Prosthetic Replacement for Acute Proximal Humerus Fractures. Journal of Orthopaedic Trauma. 2003 Mar;17(3):181–8.

89. Boileau P, Krishnan SG, Tinsi L, Walch G, Coste JS, Molé D. Tuberosity malposition and migration: reasons for poor outcomes after hemiarthroplasty for displaced fractures of the proximal humerus. J Shoulder Elbow Surg. 2002;11(5):401–12.

90. Lin CC, Karlin E, Boin MA, Dankert JF, Larose G, Zuckerman JD, et al. Operative Treatment of Proximal Humeral Fractures with Reverse Total Shoulder Arthroplasty in Patients ≥65 Years Old: A Critical Analysis Review. JBJS Reviews [Internet]. 2022 May [cited 2023 Oct 2];10(5). Available from: https://journals.lww.com/10.2106/JBJS.RVW.21.00245

91. Lanzerath F, Loew M, Schnetzke M. Is there still a place for anatomic hemiarthroplasty in patients with high functional demands in primary, nonreconstructable proximal humeral fractures? A clinical and radiographic assessment. Journal of Shoulder and Elbow Surgery. 2023 Sep 1;32(9):1909–17.

92. Grönhagen CM, Abbaszadegan H, Révay SA, Adolphson PY. Medium-term results after primary hemiarthroplasty for comminute proximal humerus fractures: A study of 46 patients followed up for an average of 4.4 years. Journal of Shoulder and Elbow Surgery. 2007 Nov;16(6):766–73.

93. Hao KA, Boschert EN, O'Keefe DS, Saengchote SA, Schoch BS, Wright JO, et al. Comparison of clinical outcomes of revision reverse total shoulder arthroplasty for failed primary anatomic vs. reverse shoulder arthroplasty. JSES Int. 2022 Dec 16;7(2):257–63.

94. Hallberg K, Salomonsson B. Validity, reliability, and responsiveness of the Swedish version of Western Ontario Osteoarthritis of the Shoulder index. BMC Musculoskeletal Disorders [Internet]. 2022 [cited 2022 Oct 31];23. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8996484/

95. Rasmussen JV, Jakobsen J, Olsen BS, Brorson S. Translation and validation of the Western Ontario Osteoarthritis of the Shoulder (WOOS) index – the Danish version. Patient Relat Outcome Meas. 2013 Sep 18;4:49–54.

96. WHO | Basic documents [Internet]. [cited 2023 Oct 7]. Available from: https://apps.who.int/gb/bd/

97. Tran G, Dube B, Kingsbury SR, Tennant A, Conaghan PG, Hensor EMA. Investigating the patient acceptable symptom state cut-offs: longitudinal data from a community cohort using the shoulder pain and disability index. Rheumatol Int. 2020 Apr 1;40(4):599–605.

98. Tubach F, Ravaud P, Beaton D, Boers M, Bombardier C, Felson DT, et al. Minimal clinically important improvement and patient acceptable symptom state for subjective outcome measures in rheumatic disorders. J Rheumatol. 2007 May;34(5):1188–93.

99. Olerud P, Ahrengart L, Ponzer S, Saving J, Tidermark J. Internal fixation versus nonoperative treatment of displaced 3-part proximal humeral fractures in elderly patients: a randomized controlled trial. Journal of Shoulder and Elbow Surgery. 2011 Jul 1;20(5):747–55.

100. Boons HW, Goosen JH, van Grinsven S, van Susante JL, van Loon CJ. Hemiarthroplasty for Humeral Four-part Fractures for Patients 65 Years and Older: A Randomized Controlled Trial. Clinical Orthopaedics and Related Research®. 2012 Dec;470(12):3483.

101. Nelson GN, Davis DE, Namdari S. Outcomes in the treatment of periprosthetic joint infection after shoulder arthroplasty: a systematic review. Journal of Shoulder and Elbow Surgery. 2016 Aug 1;25(8):1337–45.

102. Dettmer A, Melander M, Björnsson Hallgren HC, Adolfsson LE, Salomonsson B. The Choice of Antibiotic Prophylaxis Influences the Infection Reoperation Rate in Primary Shoulder Arthroplasty: Analysis From the Swedish Shoulder Arthroplasty Register. Clin Orthop Relat Res. 2023 Apr 1;481(4):728–34.

103. Lee MJ, Pottinger PS, Butler-Wu S, Bumgarner RE, Russ SM, Matsen FA. Propionibacterium persists in the skin despite standard surgical preparation. J Bone Joint Surg Am. 2014 Sep 3;96(17):1447–50.

104. Sabetta JR, Rana VP, Vadasdi KB, Greene RT, Cunningham JG, Miller SR, et al. Efficacy of topical benzoyl peroxide on the reduction of Propionibacterium acnes during shoulder surgery. Journal of Shoulder and Elbow Surgery. 2015 Jul 1;24(7):995–1004.