# DIAGNOSTIC CHALLENGES IN BONE AND JOINT INFECTIONS

*LESSONS LEARNED FROM INTERNATIONAL COLLABORATIONS*

**Janna van den Kieboom**

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Diagnostic Challenges in Bone and Joint Infections
Lessons learned from international collaborations



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**Diagnostic Challenges in Bone and Joint Infections**
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(met een samenvatting in het Nederlands)

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# Chapter 1

## General introduction and outline of this thesis

## BACKGROUND

Ever since the dawn of mankind, bone fractures and osteoarthritis have plagued our species [1–3]. Archeologists identified prehistoric human bones with fairly aligned, united fractures, highlighting the development of effective non-operative fracture care during primitive times. Nonetheless, it was not until the late 18th and early 19th century that the first operative techniques for the treatment of fractures and osteoarthritis were developed. However, these surgeries were characterized by pain and associated with disastrous results including infections, amputations, or death in the majority of patients [4]. With the introduction of anesthesia in 1846, antisepsis in 1867, asepsis in 1886, the use of X-ray imaging in 1895, and the discovery of penicillin in 1928, internal fixation of fractured bones and joint replacements became possible treatment methods for the first surgeons [4,5]. In 1891, the earliest development of joint replacement using ivory to replace the femoral head was reported [6] and following this, the modern arthroplasty was invented in 1960 [4,5].

Currently, trauma and orthopaedic surgeons across the world use orthopaedic implants on a daily basis. For the treatment of extremity fractures, implantable devices are generally used for the stabilization and fixation of fractures to support bone healing resulting in consolidation. Based on previous reports, it was estimated by a large, worldwide review that 673,141 fractures occurred in the Netherlands and 9,379,391 in the United States in 2019 [7]. The number of surgeries remains unclear, yet it is estimated that one third of fracture patients require admission to the trauma ward [8] and that 82.0% of admitted fractures need operative treatment [9], suggesting that roughly over 180,000 fracture fixations occur in the Netherlands yearly and more than 2,563,000 in the United States. Although favorable results and consolidation of the bone are achieved in most patients, complications can occur any time after surgery. One of the most challenging complications after fracture fixation is fracture-related infection (FRI) [10,11], often incurring high morbidity, limited mobility and function, and in some cases amputation, which decreased the quality of life and renders patients unable to participate in work and social activities [12]. Moreover, FRI is associated with an increase in healthcare costs and considerable socio-economic impact [13]. The exact number of patients suffering from FRI in the Netherlands is not known, but extrapolating from the assumed 180.000 fracture surgeries per year, and a postoperative infection rate of 2-4%, the incidence of FRI in the Netherlands is between 3.600 and 7.200 patients/year.

When treating joint disorders, orthopaedic implants are mainly used to maintain the function and movement of the joints. Osteoarthritis is most frequently encountered [14], and weight-bearing joints including the hip and knee are most commonly affected [15]. The number of total joint arthroplasties in the Netherlands is recorded by the Dutch Implant Registry (Landelijke Registratie Orthopedische Implantaten)

[16]. According to the registry, the number of primary total hip arthroplasties (THAs) was approximately 33,000 in 2019. For total knee arthroplasties (TKAs) this was roughly 26,000. In the United States, the American Joint Replacement Registry (AJRR) registers arthroplasties performed in hospitals. Around 96,000 THAs and 145,000 TKAs were performed in 2019 [17], yet these numbers are likely higher since data from ambulatory surgical centers is not captured. The prevalence of THAs and TKAs is projected to increase substantially over this decade and is expected to reach approximately 4.0 million by 2030 [18]. As the number of arthroplasties continues to rise, it is anticipated that the magnitude of revision surgeries due to complications will increase accordingly [19]. For the elective orthopaedic patient, periprosthetic joint infection (PJI) after hemi- or total joint arthroplasties is among the most severe and difficult complications [20]. PJI often causes functional impairment, high morbidity, and increased treatment costs, straining both the physical and psychological well-being of patients [21], leading to decreased quality of life and patient-reported outcome measures (PROMs) [22,23].



Even though FRI and PJI demonstrate several similarities as they are both biofilm infections in trauma and orthopaedic surgery [24], important differences exist between the trauma and elective arthroplasty patients with regard to the diagnosis, treatment options, and desired outcomes [25,26].

**Definition and diagnosis**

As with most medical disorders, a well-established definition and an accurate diagnosis of FRI and hip and knee PJI are key for a successful treatment outcome. The diagnosis and treatment of these conditions are complex, costly, and eminently multi-disciplinary. It is important that a team of trauma and orthopaedic surgeons, infectious diseases specialists, medical microbiologists, infection preventionists, and plastic surgeons are available for the management of these patients.

*Fracture-related infection*

Until 2017, a uniform definition of infection after surgical fracture care was lacking. As a clear definition would allow for development of international guidelines and research standards, bone infection experts in collaboration with the Arbeitsgemeinschaft für Osteosynthesefragen (AO Foundation) and the European Bone and Joint Infection Society (EBJIS) introduced a consensus definition and diagnostic criteria for FRI in 2018 [27]. The diagnostic features of FRI were either confirmatory (definite infection) or suggestive (potential infection). The confirmatory signs are 1) a fistula, sinus, or wound breakdown with communication to the bone itself or the fixation device, 2) purulent wound drainage or presence of pus during surgery, 3) phenotypically indistinguishable pathogens identified from at least two separate deep tissue/implant cultures taken during operative intervention (including sonication fluid), and/or 4) presence of pathogens on histopathological

examination of deep tissue taken during operative intervention. The diagnosis FRI is definite when one of the confirmatory signs is present. Signs that are suggestive of FRI are 1) clinical infection symptoms such as redness, pain, fever, and new onset swelling, 2) radiological and/or nuclear imaging signs including bone lysis, sequestration, implant loosening, nonunion, and periosteal bone formation, 3) a pathogen identified in one single deep tissue/implant specimen, 4) elevated serum inflammatory markers erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), 5) persistent, increasing, or new onset postoperative wound drainage, and/or 6) new onset joint effusion. In presence of one or more suggestive signs, FRI must be considered [28].

However, the diagnostic workup for FRI is not yet definite [29]. Generally, the diagnostic process with a thorough medical history and clinical examination, in which there is attention for systemic or local infection signs that could indicate presence of FRI. A fistula, sinus, wound breakdown, or purulent drainage are pathognomonic and thus confirmatory signs [27]. Next, serum inflammatory markers can be obtained, yet it is not yet clear to what extent they are useful. It is thought that when the markers are elevated, they can be regarded as suggestive signs [27]. Referring a patient for radiological and nuclear imaging is generally the subsequent step in the diagnosis to establish presence of FRI, anatomic details, and fracture and implant stability [30] on X-ray, magnetic imaging resonance (MRI)-scan, computed tomography (CT)-scan, white blood cell (WBC) or antigranulocyte antibody (AGA) scintigraphy, or fluorodeoxyglucose positron emission tomography (FGD-PET), possibly with CT-scan. However, the usefulness of diagnostic radiology and nuclear imaging techniques has not been fully crystalized [29]. Then, using a low threshold to look for confirmatory signs, the presence of FRI may be considered and surgical exploration follows [11]. Before antibiotic prophylaxis is administered, cultures are obtained. Presence of the same pathogen in at least two separate deep tissue/implant specimens is considered a confirmatory criterion of FRI, while a single culture is considered suggestive [27]. Furthermore, during the surgery, deep tissue is sent for histopathological assessment. The presence of a pathogen or more than five polymorphonuclear neutrophils (PMNs) per high-power field (HPF) are also considered confirmatory [27]. Even if no confirmatory criterion is present, there should be high suspicion of FRI in case of multiple suggestive signs and a single positive deep culture.

The fact that the clinical presentation of FRI varies widely can be challenging for the treating medical team. In early FRI cases, the classical infection signs such as redness, pain, warmth, and swelling with or without fever are more often observed compared to in late FRI patients. These symptoms mostly occur when wound healing is compromised, although they are also frequently observed in non-infected wound healing. Late onset infections generally present with subtle and unspecific clinical

symptoms, though draining sinuses are also often seen. FRI can present with indolent symptoms that can relapse and remit over longer periods of time [31] and might even be present without clinical symptoms and signs of infection at all [32].

*Periprosthetic joint infection*

In 2011, the Musculoskeletal Infection Society (MSIS) defined diagnostic criteria for the diagnosis of PJI based on clinical and intraoperative findings (the presence of purulence or a sinus tract), raised inflammatory markers (serum ESR and CRP or synovial WBC count and polymorpho-nuclear percentage (PMN%)), histology results (neutrophil count), and microbiological culture results [33]. In 2013, adjustments were published and during the most recent international consensus meeting in 2018, experts in the field of prosthetic infection care proposed guidelines for the new definition for hip and knee PJI [33–35]. The 2018 definition encompasses major and minor criteria. The major criteria include 1) a sinus tract communicating with the joint or 2) identical pathogens identified by at least two separately collected culture specimens using standard culture methods. In the presence of at least one of the major criteria, the PJI diagnosis is definite. Furthermore, the minor criteria are classified as preoperative or intraoperative and are individually weighted and scored. The preoperative minor criteria are 1) elevated serum inflammatory markers CRP or D-dimer (2 points), 2) elevated serum ESR (1 point), 3) elevated synovial WBC count or leukocyte esterase (3 points), 4) positive synovial α-defensin (3 points), 5) elevated synovial PMN% (2 points), 6) elevated synovial CRP (1 point). PJI is definitely present with a score of ≥6, possibly present with a score of 2-5, and not present with a score of 0-1. The intraoperative minor criteria are 1) a pathogen in one tissue or fluid sample culture (2 points), 2) more than five PMNs per HPF in five HPFs at x400 magnification on histologic analysis (3 points), and 3) intraoperative purulence (3 points). PJI is definitely present with a score of ≥6, a score of 4-5 is inconclusive, and with a score of ≤3, PJI is not present [36].

Usually, the diagnostic workup for PJI is similar to that for FRI. The orthopaedic surgeon starts with obtaining a thorough medical history and clinical examination. Then, serum inflammatory markers CRP, D-dimer, and ESR are obtained, which when elevated are regarded as minor signs [36]. Subsequently, if possible, an aspiration of the joint is performed and tested for synovial WBC, leukocyte esterase, α-defensin, PMN%, and CRP, which are also minor signs when elevated [36]. Then, using a low threshold to look for major signs, PJI presence is considered and surgical exploration follows [11]. Before antibiotic prophylaxis is administered, cultures are obtained. At least two separate deep tissue specimens with the same pathogen are major signs for PJI, while a single culture is a minor sign [27]. Furthermore, during the surgery deep tissue is sent for histological analysis. Presence of pathogens or more than five PMNs per HPF are also considered minor signs [27]. There should be high suspicion of PJI in case of minor signs and a single deep culture.

## Classification

*Fracture-related infection*

Several classification strategies have been presented to assist in the timely diagnosis and treatment of FRI. One of the previously used is the Cierny Mader classification, utilizing anatomic, clinical, and radiological characteristics [37]. It consists of a combination of two parameters, namely the anatomic infection type, which can be classified as medullary, superficial, localized, or diffuse, and the physiologic class of the patient, which can be classified as Host A (good immune system and delivery), Host B (compromised locally (Bl) or systemically (Bs)), or Host C (treatment worse than disease). Though the Cierny Mader classification evaluates both bone involvement and host condition, it has been partially abandoned for the more extensive BACH classification as this also assesses antibiotic options and wound and soft tissue condition [38]. The individual parameters divide uncomplicated and complex cases in which the most severely classified parameter determines the overall complexity. Initially, the BACH classification was developed for (chronic) osteomyelitis and not specifically for FRI. However, the classification was recently evaluated in a study cohort that mainly comprised of FRI as the osteomyelitis etiology [38]. This indicates that the BACH classification may be useful in cases of FRI. Furthermore, since the time from injury to infection surgery had little impact on the outcome of FRI [39], BACH may be used for both early and chronic FRI. Historically, another classification method for FRI was according to the time of onset after surgery. Some authors divide FRI into early (onset <6 weeks) and late (onset ≥6 weeks) infections [40], while others stratify into early (≤2 weeks), delayed (3 to 10 weeks), and late onset (>10 weeks) infections [41]. Even though the time of onset distinction is arbitrary, many protocols and guidelines still make use of this classification due to differences in treatment approaches and challenges observed in fracture and soft tissue management [42].

*Periprosthetic joint infection*

Over the years, multiple classification systems for PJI have been proposed and most depend on the timing of clinical symptoms. One commonly used method is the extensive Staging System by McPherson et al, which stratifies patients according to infection type, systemic host grade, and local extremity grade [43,44]. Infection type is divided into early postoperative infection (onset <4 weeks), hematogenous infection (<4 weeks duration), and late chronic infection (≥4 weeks duration). Host grade and local extremity grade can both be classified as uncompromised, compromised, and substantially compromised. There are several other classification methods, such as the system proposed by Coventry [45]. This system stratifies PJI based on the time of onset into stage I (acute PJI within the first three months after surgery), stage II (more than three months after surgery), and stage III (two years after surgery). In addition, Tsukayama et al published a different classification

strategy categorizing PJIs into four types: type I: positive intraoperative cultures, type II early infection within four weeks after surgery, type III: late chronic infection at least four weeks after surgery, and type IV: acute hematogenous infection [46].

**Incidence and risk factors**

*Fracture-related infection*
Regardless of antibiotic prophylaxis before the initial fracture surgery and sterile precautions taken in the operating room, incidences of FRI can vary between 1.0% and 5.0% with outliers up to 45.0% depending on soft tissue injury, contamination, fracture type and localization, and patient comorbidities [47–49]. Factors that are known to increase the risk for the development of FRI include male gender, Gustilo-Anderson classification, diabetes mellitus, smoking, lower extremity fracture, contaminated fracture, and polytrauma [49].

*Periprosthetic joint infection*
Hip and knee PJI is relatively uncommon and generally occurs within 1.6% and 3.4% of patients, respectively, even though preoperative antibiotics, antibiotic cement, sterile operative precautions, and irrigation solutions are used [50,51]. PJI is the most common reason for revision after TKA in as many as 25.2% of revision surgeries. For THA, PJI is the third most frequent reason for revision surgery accounting for 14.8% of revision cases [50]. Several modifiable host-related risk factors, including body mass index (BMI), smoking, alcohol consumption, and medical comorbidities such as diabetes and malnutrition were identified [34]. Furthermore, non-modifiable risk factors include higher age, male gender, American Society of Anesthesiologists (ASA) score >2, previous PJI, and low socioeconomic status [52]. In addition, several perioperative factors include the use of potent anticoagulation, allogenic blood transfusion, and general anesthesia [53–55].

**Treatment concepts**
Surgical treatment strategies for the management of FRI and PJI include debridement, antibiotics and implant retention (DAIR), one-stage, or two-stage (revision) surgery. Selection of the appropriate surgery is based on several criteria, such as the onset and duration of the infection.

*Fracture-related infection*
First, for the treatment of early onset FRIs, a DAIR procedure is frequently opted for. As early onset FRIs occur when the fracture is not yet consolidated, implant retention can still lead to successful fracture healing and infection eradication, provided that a stable fracture fixation is in situ and proper antibiotic therapy is in place [42]. During a DAIR operation, the implant is not removed and thus the open reduction and internal fixation (ORIF) procedure and stability are not compromised. Success

rates of DAIR for FRI up to ten weeks after ORIF have been reported in the literature between 57.0% and 100.0% [56], however the outcomes have not been fully clarified. Second, for late FRI with consolidated fracture, or for patients unsuitable for or with failed DAIR, implant removal, debridement and antimicrobial therapy can be considered. If the fracture has not healed, debridement, antimicrobial therapy and implant exchange as one-stage or multiple-stage operation is an option, [26] depending on host and microbiological factors. Stable fracture fixation and adequate soft tissue coverage are required to promote consolidation of the fracture [42]. Eradication of complex FRI is reported in approximately 85.0% of patients [57]. Finally, for the patients not able to undergo surgical intervention, suppressive antibiotic treatment can be an option to prevent adverse outcomes, depending on patient factors and pathogen types and resistances.

*Periprosthetic joint infection*

First, DAIR with modular component exchange is recommended for patients with early hip and knee PJI by the consensus meeting and Infectious Diseases Society of America [33]. With a DAIR procedure, the intra-articular pathogen load can be reduced and extensive debridement can be provided. In combination with postoperative antibiotic therapy, the aim is to retain the prosthesis and avoid more invasive surgery. Successful eradication of PJI has been reported in over 82.0% [58,59]. Second, for late chronic hip and knee PJI, two-stage revision arthroplasty is currently considered the gold standard treatment option for both culture-positive and culture-negative infections [60]. The two-stage revision procedure involves explantation of infected components during the first stage with thorough debridement and the reimplantation of a revision arthroplasty in the second stage after a period of time [61]. During the time interval between the first and second stage operations, patients are generally implanted with an antibiotic-loaded spacer that helps to bridge the joint gap for therapeutic, structural, and functional purposes [62]. The success rate of two stage revision for culture-positive PJI reported in the literature exceed 80.0% [63,64]. For culture-negative infections, this is up to 90.0% [65–67]. An emerging alternative for two-stage revision for hip and knee PJI is one-stage revision. This may reduce patient morbidity and mortality as well as associated healthcare costs since it only involves one surgical procedure with extensive debridement without the need for an antibiotic-loaded spacer [22,68]. Several studies have reported similar eradication rates, function, and patient-reported outcomes of this procedure for both hip and knee PJI [63,64]. Therefore, one-stage revision may be a viable surgical option for chronic PJI in selected patients [69]. The choice between one- or two-stage revision is made based upon predefined criteria reported in previous research. However, the selection criteria for one-stage revision are not fully elucidated. Finally, for PJI patients unfit for surgical intervention, suppressive antibiotic treatment is available to prevent adverse outcomes. If re-

implantation of a prosthesis is not possible, permanent implant removal may be performed.

**Striving to continuously improve trauma and orthopaedic infection care**

Even after the recent development and implementation of definitions and guidelines, the diagnosis and treatment of FRI and PJI remain challenging. A successful treatment starts with an accurate diagnosis and it is therefore important that all steps in the workup and management plans remain under constant review. Although uniform definitions led to multi-institution collaborations and an increasing body of standardized literature, knowledge gaps still exist. This is only logical as both conditions were clearly defined eleven and four years ago, respectively, yet it is imperative to act upon them. Since the presentations of FRI and PJI vary widely, atypical forms of the disorders are not uncommon. In order to optimize patient-specific treatment plans for all patients, it is important to further develop the known guidelines and perform more inclusive research.

## AIMS AND OUTLINE OF THE THESIS

The aim of this thesis is to contribute to the diagnostic process and to present treatment outcomes for infections in trauma and orthopaedic surgery in order to optimize outcomes for all patients. To improve holistic care for these patients, it is important to 1) address and define diagnostic knowledge gaps, 2) assess tailored treatment options and complications, and 3) analyze the patiens who are at risk of infection. Since trauma and orthopaedic infections can comprise of both FRIs and PJIs, the thesis is divided into two parts.

**Part I** (Chapter 2 -6) reports on fracture-related infection.

First, the predictive value of serum inflammatory markers for the diagnosis of fracture-related infections is evaluated in **Chapter 2**. Next, in **Chapter 3**, a systematic review and meta-analysis is performed to assess the diagnostic accuracy of serum inflammatory markers for late fracture-related infection. In **Chapter 4**, the diagnostic accuracy of $^{18}$F-FDG PET/CT is investigated for diagnosing fracture-related infections. The patient characteristics, need for additional procedures, and recurrence predictors for early onset fracture-related infection treated with DAIR are studied in **Chapter 5**.

**Part II** (Chapter 6-9) focuses on periprosthetic joint infection.

First, **Chapter 6** investigates the diagnostic utility of serum and synovial markers in hip and knee periprosthetic joint infection in patients presenting with a periprosthetic fracture. In **Chapter 7**, the outcome of one-stage and two-stage revision arthroplasty for chronic culture-negative periprosthetic joint infection is explored. The outcome of two-stage revision total hip and knee arthroplasty as a salvage procedure for deep infection of peri-articular fracture fixation is evaluated using a propensity score-matched study setup in **Chapter 8**. Finally, in **Chapter 9**, the reasons for failure after revision arthroplasty for periprosthetic fractures are explored.

## TABLES AND FIGURES

**Table 1.** Summary of research questions addressed in the thesis.

| Chapter | Research Questions |
|---|---|
| 2 | - What is the diagnostic accuracy of the three commonly used serum inflammatory markers, C-reactive protein (CRP), leukocyte count (LC), and erythrocyte sedimentation rate (ESR), in patients presenting with suspected FRI? |
| 3 | - What is the current evidence on the diagnostic value of CRP, leukocyte count and erythrocyte sedimentation rate (ESR) in FRI? |
| 4 | - What is the diagnostic performance of 18F-FDG-PET/CT for diagnosing FRI?<br>- What is the diagnostic performance of Standardized Uptake Values (SUVs) in 18F-FDG-PET/CT for diagnosing FRI, and what are their associated cut-off values?<br>- Which variables are independent predictors of a false-positive or false-negative test result in patients with suspected FRI? |
| 5 | - What is the recurrence rate after treatment of early onset FRI?<br>- What is the number of additional procedures (re-debridement and/or washout) needed to gain control of the initial infection in the same treatment period as the first FRI?<br>- What are predictors for recurrence of infection in early FRI patients? |
| 6 | - What is the individual diagnostic performance of the commonly used inflammatory markers serum ESR and CRP, and synovial fluid white blood cell (WBC) count and percentage polymorphonuclear neutrophils (PMN%) for patients with concomitant PJI and periprosthetic fracture of a total hip arthroplasty (THA) and total knee arthroplasty (TKA)? |
| 7 | - What are the outcomes for one- and two-stage exchange arthroplasty for patients with chronic culture-negative PJI? |
| 8 | - What are the results and complications of revision total hip and knee arthroplasty as a salvage procedure for deep infection of peri-articular fracture fixation? |
| 9 | - What are the outcomes and risk factors for re-revision surgery following failure of revision for periprosthetic fracture of THA and TKA? |

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# PART I

## FRACTURE-RELATED INFECTION

# CHAPTER 2

## Limited predictive value of serum inflammatory markers for diagnosing fracture-related infections: results of a large retrospective multicenter cohort study

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## ABSTRACT

**Introduction**

Diagnosing Fracture-Related Infections (FRI) based on clinical symptoms alone can be challenging and additional diagnostic tools such as serum inflammatory markers are often utilized. The aims of this study were 1) to determine the individual diagnostic performance of three commonly used serum inflammatory markers: C-Reactive Protein (CRP), Leukocyte Count (LC) and Erythrocyte Sedimentation Rate (ESR), and 2) to determine the diagnostic performance of a combination of these markers, and the additional value of including clinical parameters predictive of FRI.

**Methods**

This cohort study included patients who presented with a suspected FRI at two participating level I academic trauma centers between February 1st 2009 and December 31st 2017. The parameters CRP, LC and ESR, determined at diagnostic work-up of the suspected FRI, were retrieved from hospital records. The gold standard for diagnosing or ruling out FRI was defined as: positive microbiology results of surgically obtained tissue samples, or absence of FRI at a clinical follow-up of at least six months. The diagnostic accuracy of the individual serum inflammatory markers was assessed. Analyses were done with both dichotomized values using hospital thresholds as well as continuous values. Multivariable logistic regression analyses were performed to obtain the discriminative performance (Area Under the Receiver Operating Characteristic, AUROC) of 1) the combined inflammatory markers, and 2) the added value of these markers to clinical parameters.

**Results**

A total of 168 patients met the inclusion criteria and were included for analysis. CRP had a 83% sensitivity, 34% specificity, 42% positive predictive value (PPV) and 78% negative predictive value (NPV). For LC this was 39%, 74%, 46% and 67% and for ESR 62%, 64%, 45% and 76% respectively. The diagnostic accuracy was 52%, 61% and 80% respectively. The AUROC was 0.64 for CRP, 0.60 for LC and 0.58 for ESR. The AUROC of the combined inflammatory markers was 0.63. Serum inflammatory markers combined with clinical parameters resulted in AUROC of 0.66 as opposed to 0.62 for clinical parameters alone.

**Conclusion**

The added value of CRP, LC and ESR for diagnosing FRI is limited. Clinicians should be cautious when interpreting the results of these tests in patients with suspected FRI.

## INTRODUCTION

Fracture-Related Infection (FRI) is a challenging complication after surgical fracture treatment (1, 2). Consequences include reoperations, prolonged treatment with antibiotics, prolonged immobilization, inability to participate in social and work-related activities, increased medical costs, loss of function and even amputation (3-5). As with most medical conditions, a successful treatment outcome starts with an accurate diagnosis. The fact that the clinical presentation of infection can be obscured by apparently normal wound healing is one of the difficulties of diagnosing FRI. When wound healing is compromised, and the classical infection symptoms such as pain, increased temperature, local erythema and swelling are present, FRI is usually easy to recognize. However, FRI can also present less apparent with symptoms mimicking those of delayed- or non-union, such as pain, implant failure and impaired fracture healing. It might even be present without any clinical signs and symptoms at all (1, 6, 7).



Another difficulty has been that until recently, the literature regarding the diagnosis and treatment of FRI was hampered by the lack of a clear definition (4). However, in 2017, the characteristics of a FRI were clearly defined in a consensus meeting between experts in the field of bone infection in collaboration with the Arbeitsgemeinschaft für Osteosynthesefragen (AO Foundation) and the European Bone and Joint Infection Society (EBJIS) (2). Two levels of certainty around diagnostic features were defined. Signs that are suggestive of FRI can be clinical signs of infection (such as redness, fever and new onset of joint effusion), radiological signs (for example bone lysis, sequestration, implant loosening, nonunion and periosteal bone formation), wound drainage and elevated serum inflammatory markers. Confirmatory clinical signs are a fistula, sinus, purulent drainage or wound breakdown which communicates to the bone itself or to the fixation device. In absence of these confirmatory clinical signs, the diagnosis can be confirmed by either microbiology (with phenotypically indistinguishable pathogens identified by culture from at least two separate deep tissue/implant specimens) or histology (presence of microorganisms in deep tissue taken during an operative intervention) (2).

Elevated serum inflammatory markers are often used as diagnostic parameters for postoperative infections after orthopedic trauma surgery and are mainly investigated in PJIs (8, 9). Although they are considered to be indicative for the presence of FRI according to the aforementioned consensus meeting, research focusing on the added value of these parameters for diagnosing FRI is limited (10-13). In a recent survey amongst medical specialists involved in the care for patients with FRI, C-reactive protein (CRP) was regarded to be the most valuable tool for diagnosing FRI, followed by the Erythrocyte Sedimentation Rate (ESR) and Leucocyte Count (LC), respectively (14). However, the added value of serum inflammatory markers is still

under debate. Large cohort studies which tell us whether these markers are capable of distinguishing a bacterial infection from a normal inflammatory response due to the injury, tissue damage, fracture healing, or the fracture surgery, are lacking so far (15-19). It is therefore mandatory to assess the role of these serum inflammatory markers in the decision-making process for diagnosing FRI.

The two aims of the current study were:
1) To determine the individual diagnostic performance of the three commonly used serum inflammatory markers, CRP, LC and ESR, in FRI.
2) To assess the diagnostic value of a combination of these markers, and their value in addition to clinical parameters predictive of FRI.

## PATIENTS AND METHODS

**Study design**
This is a retrospective cohort study performed at the University Medical Center Utrecht (UMCU) and the University Medical Center Groningen (UMCG), two Level I academic trauma centers in the Netherlands.

**In- and exclusion criteria**
In order to be able to calculate the accuracy of serum inflammatory markers in both patients with and without FRI, patients from a previous assembled database on medical imaging for suspected FRI were included. This database comprised of all patients who underwent nuclear medical imaging for suspected FRI between February 1st 2009 and December 31st 2017 of the UMCU and UMCG. In accordance with clinical practice, where serum inflammatory markers are ordered when an infection is suspected, blood sampling had to be obtained within a range of seven days around the date an FRI was first considered (mostly at the outpatient department). Cases missing inflammatory markers or outcome data due to incomplete reporting were excluded from the analyses. In uncomplicated orthopedic- and traumatologic cases, levels of CRP peak at the second postoperative day. In uneventful cases, the CRP returns to normal values between day two to twelve postoperatively (20-25). Maximum values of LC are seen on day one to three postoperatively and decline to normal values between day four to six (26). Values of ESR peak at day seven to eleven postoperatively and decrease gradually until after week six (19). Therefore, patients were excluded who underwent surgery in 14 days preceding testing for CRP, 7 days for LC and 6 weeks for ESR testing. In- and exclusion criteria are presented in Table 1.

**Table 1.** Inclusion and exclusion criteria.

| Inclusion | Exclusion |
|---|---|
| 1. Patients with a suspected Fracture-Related Infection. | 1. Patients who underwent surgery in the fourteen days preceding collection of the blood sample for determining the serum inflammatory markers<br>2. Pathologic fractures<br>3. Prosthetic joint infection (PJI)<br>4. Haematogenous infection<br>5. Patients with (auto-)immune diseases<br>6. Patients with (pre-)malignancies<br>7. Concomitant use of corticosteroids<br>8. Evident other focus of infection<br>9. No reference standard available (representative cultures or at least six months follow-up) |



**Ethical approval**

The study protocol was evaluated by the institutional review board (medical ethical research commission, METC) of the UMCU and found to be exempted from further approval requirements (METC-17-694).

**Serum inflammatory markers**

The index test comprised of CRP, LC and ESR. Analysis was done similarly in both participating centers. In the UMCU, blood was drawn into a 2.0 mL vacuum tube (BD Vacutainer; BD Medical Systems, Franklin Lakes, NJ, USA) containing K2-EDTA as an anticoagulant for blood cell analysis and a 4.0 mL vacuum tube Lithium-Heparin as an anticoagulant for CRP measurement.

The UMCG used standard 4.0 mL K2 EDTA and 4.5 mL Lithium-Heparin tubes. All blood samples were analyzed in the central diagnostic laboratories of the UMCU and UMCG (both with full ISO-15189 accreditation). C-reactive protein (CRP) was measured using a turbidimetric immunoassay on a DxAU 5811 automated chemistry analyzer (Beckman-Coulter, Brea, CA, USA). Similar analysis was done in the UMCG using a Roche CRPL3 analyzer with wide range assay (Roche, Mannheim, Germany). LC was measured using a Cell-Dyn Sapphire hematology analyzer (Abbott Diagnostics, Santa Clara, CA, USA). This analyzer uses spectrophotometry, electrical impedance and laser light scattering (multi angle polarized scatter separation, (MAPPS)) to classify blood cells (27, 28). In the UMCG, similar analysis was done using a Sysmex XN-20 Automated hematology analyzer (Sysmex, Kobe, Japan). The validity of all test results was checked with built-in quality flags, daily quality control samples and external quality assessment schemes. The ESR was measured using a method according to Westergren. The UMCU uses whole blood anticoagulated with sodium citrate 3,2% (4:1) in combination with a ESR analyzer (Monitor V100, Vital Diagnostics, SrL, Forli, Italy), in the UMCG the ESR was measured in EDTA whole blood in diluted with

sodium citrate 3,2% (4:1) combination with the Starrsed interrliner (Mechatronics, Zwaag, the Netherlands) (29).

Although analyses of blood samples were done in a similar set-up, both participating centers used slightly different threshold values for the serum makers. Since statistical calculations in this paper were performed on data from both centers to improve the possible predictive performance, common threshold values used in clinical practice and reported in medical literature were used to reflect the current performance of the separate parameters. The threshold in this study for CRP was less than 5.0 mg/L and leukocyte count less than 10.0 x $10^9$/L. For ESR, the threshold for men was 11 mm/h and for women 24 mm/h.

**Clinical parameters**
The clinical parameters included in the multivariate analysis were Gustilo-Anderson classification, ISS, diabetes mellitus, smoking status and lower extremity fractures. These parameters were used as these are known to increase the risk of a FRI (30).

**Reference standard**
The gold standard in the final diagnosis of FRI was based on the outcome of medical microbiology (MMB) results of at least two separate samples of deep tissue taken during a surgical intervention (2). Two experienced trauma surgeons (GG and FIJ, >5 years board certified) assessed the validity of the MMB results. Only if two or more deep samples were taken from the suspected area of bone infection, the MMB results were regarded as relevant. Only when two or more samples were positive with both morphologically the same organism, the MMB results were regarded as positive. In case of no surgery (and therefore no intra-operative cultures), the definite diagnosis was based on a clinical follow-up of at least six months. Throughout the follow-up, a final diagnosis was made on basis of positive clinical confirmatory criteria. When the aforementioned confirmatory signs were present perioperatively, the patient was also considered to be suffering from FRI (2).

**Data collection**
The electronic patient files of all included patients were scrutinized on when an infectious complication was first suspected and data was collected on demographics, type of fracture according to the Müller AO Classification of Fractures (31), Gustilo Anderson classification in case of an open fracture (32), date, trauma mechanism, fracture type and surgical management of the index trauma, laboratory findings, microbiology results, final diagnosis and clinical outcome during follow-up.

**Statistical analysis**
Continuous data are presented as mean and standard deviation (SD) in case of normal distributions or median and interquartile range (IQR) when not normally

distributed. The baseline characteristics per center were compared to analyze whether there were any substantial differences between the centers. Hypothesis testing was done using independent t-test or Mann-Whitney U test for the continuous values and Chi-squared test or Fisher's exact test for the dichotomized values. A p-value of <0.05 was considered significant.

In the first analysis, the serum markers were dichotomized using the aforementioned threshold values, as this reflects the diagnostic performance in current clinical practice. For each parameter, true positive (TP), true negative (TN), false positive (FP) and false negative (FN) results were described. Contingency tables were constructed. Sensitivity and specificity, positive and negative predictive values (PPV and NPV), positive and negative likelihood ratio's (LR+ and LR) were calculated. Second, to assess the maximal predictive performance, separate continuous values were used.



Third, to assess the diagnostic performance of the combination of the inflammatory markers, a multivariable logistic regression model including the inflammatory markers was fitted. Subsequently, two models were fitted to determine the added value of the inflammatory markers to the clinical parameters. The first one included the clinically predetermined parameters. The second one included these parameters, and also the combined inflammatory markers. To reduce the risk of overfitting, a maximum of one predictor per 5-10 events was used.

The diagnostic performance of these continuous models was assessed using the AUROC as a measure of discrimination. The Q-point method, which determines the threshold value closest to the upper left corner of the AUROC, was used to deduct the optimal threshold, for which the sensitivity and specificity were calculated.

Sensitivity analyses were performed to 1) assess whether the diagnostic performance of the multivariable logistic regression analysis differs per center, 2) whether the time interval (<14 days versus ≥14 days between inflammatory markers and intra-operative cultures) affects the diagnostic performance and 3) to assess whether the linearity assumption of the combined markers with the (logit) outcome affects the performance, through log-transforming the variables.

All data analyses were performed using the Statistical Package for Social Sciences (SPSS®) statistics for Windows (version 20.0.0.0, IBM, Armonk, NY, USA). Where applicable, the reporting of this study followed the Transparent Reporting of a multivariable Prediction Model for individual diagnosis or prognosis (TRIPOD statement) (33).

## RESULTS

The cohort consisted of 365 patients who underwent medical imaging for suspected FRI. A total of 197 patients were excluded from analyses due to missing data on serum inflammatory markers (n=171) or other parameters. After exclusion, a total of 168 patients were included in this study. Basic demographics and clinical characteristics of the included patients from both participating centers are shown in Table 2. The cohort consisted predominantly of male patients (n=115, 68.5%) with a median age of 54 (IQR 40-62). Fractures were most commonly located in the lower extremity (n=140, 83.4%). The study population consisted of patients who were suspected to suffer from long standing FRI. The median interval between initial fracture surgery and nuclear imaging for a suspected FRI was 480 (IQR 229-1312) days.

**Table 2.** Baseline characteristics of study population.

| | Both centers | UMCU (n=41) | UMCG (n=127) | p-value |
|---|---|---|---|---|
| **Age (median (IQR))** | 54 (40-64) | 58 (47-63) | 54 (38-64) | 0.27 |
| **Age at onset (median (IQR))** | 51 (36-59) | 53 (45-59) | 51 (36-62) | 0.26 |
| **Sex** | | | | |
| Male | 115 (68.5%) | 26 (63.4%) | 89 (70.1%) | 0.44 |
| **Comorbidities** | | | | |
| Diabetes mellitus | 13 (7.7%) | 5 (12.2%) | 8 (6.3%) | 0.31 |
| Psychiatric disorder | 11 (6.5) | 2 (4.9%) | 9 (7.1%) | 0.47 |
| Obesity | 21 (12.5%) | 2 (4.9%) | 19 (15.0%) | 0.11 |
| Osteoporosis | 5 (3.0%) | 5 (12.2%) | 0 (0.0%) | 0.35 |
| Hypothyroidism | 3 (1.8%) | 1 (2.4%) | 2 (1.6%) | 0.57 |
| **Risk factors** | | | | |
| Smoking | 63 (37.5%) | 14 (34.1%) | 49 (38.6%) | 0.71 |
| NSAIDs | 31 (18.5%) | 5 (12.2%) | 26 (20.5%) | 0.26 |
| Soft drugs | 6 (3.6%) | 2 (4.9%) | 4 (3.1%) | 0.64 |
| Hard drugs | 6 (3.6%) | 2 (4.9%) | 4 (3.1%) | 0.64 |
| Alcohol abuse | 7 (4.2%) | 2 (4.9%) | 5 (3.9%) | 0.68 |
| **ASA classification** | | | | 0.40 |
| I | 58 (35.5%) | 14 (34.1%) | 44 (39.3%) | |
| II | 72 (42.9%) | 20 (48.8%) | 52 (46.4%) | |
| III | 20 (11.9%) | 4 (9.8%) | 16 (14.3%) | |
| IV | 1 (0.6%) | 1 (2.4%) | 0 (0.0%) | |
| Unknown | 17 (10.1%) | 2 (4.9%) | 15 (11.8%) | |

**Table 2.** Baseline characteristics of study population. (continued)

| | Both centers | UMCU (n=41) | UMCG (n=127) | p-value |
|---|---|---|---|---|
| **BMI, n = 150 (mean (SD))**<br>Unknown (n= ) | 28,18 (5.38)<br>18 (10.7%) | 26.91 (4.68)<br>1 (2.4%) | 28,77 (5.54)<br>17 (13.4%) | 0.06 |
| **ISS** | | | | **<0.001** |
| <16 | 115 (68.5%) | 16 (39.0%) | 99 (78.0%) | |
| >16 | 39 (23.2%) | 18 (43.9%) | 21 (16.5%) | |
| Unknown | 14 (8.3%) | 7 (17.1%) | 7 (5.5%) | |
| **Fracture location** | | | | **0.002** |
| Upper extremity | 18 (10.7%) | 1 (2.4%) | 17 (13.4%) | |
| Lower extremity | 140 (83.3%) | 33 (80.5%) | 107 (84.3%) | |
| Spine | 7 (4.2%) | 5 (12.2%) | 2 (1.6%) | |
| Pelvis | 3 (1.8%) | 2 (4.9%) | 1 (0.8%) | |
| **Fracture type** | | | | 0.85 |
| Open | 80 (47,6%) | 18 (43.9%) | 62 (48.8%) | |
| Closed | 79 (47.0%) | 16 (39.0%) | 63 (49.6%) | |
| Unknown | 9 (5.4%) | 7 (17.1%) | 2 (1.6%) | |
| **Gustilo-Anderson Classification** (32) | | | | **0.04** |
| Grade 1 | 16 (9.5%) | 3 (7.3%) | 13 (10.2%) | |
| Grade 2 | 12 (7.1%) | 0 (0.0%) | 12 (9.4%) | |
| Grade 3 | 43 (19.7%) | 11 (26.8%) | 22 (17.4%) | |
| Unknown | 19 (11.3%) | 4 (9.8%) | 15 (11.8%) | |

**FRI in study population**

Overall, FRI was present in 61 patients (36%). In the cohort, 41 patients were diagnosed with FRI on basis of MMB results. Twenty patients with negative or without MMB results developed FRI during the follow up. The median clinical follow up in the cohort was 53 (IQR 45-134) weeks. Median interval between blood sampling for laboratory analysis and operatively obtained samples for MMB was 49 (IQR 19-85) days.

**Diagnostic performance of serum inflammatory markers**

Details on the serum markers are shown in Table 3. For CRP, there were 49 TP, 36 TN, 69 FP and 10 FN results. This corresponds to 83% sensitivity and 34% specificity. When considering CRP as a continuous variable, an AUROC of 0.64 (0.55-0.72) was found. The optimum threshold was 10.5 mg/L, with a corresponding 61.0% sensitivity and 62.9% specificity. For leukocyte count, there were 22 TP, 72 TN, 26 FP and 35 FN results. This resulted in a 39% sensitivity and 74% specificity. When analyzed as a

continuous variable the AUROC was 0.60 (0.50-0.69). The optimum threshold was 8.6 x$10^9$/L, with a corresponding 60.0% sensitivity and 61.2% specificity. Regarding ESR, there were 18 TP, 35 TN, 11 FP and 22 FN results. This is consistent with 45% sensitivity and 76% specificity. When analyzed as a continuous variable, the AUROC was 0.58 (0.46-0.71). At the optimum threshold (10.0), sensitivity was 72.4% specificity 50.1%. The results are presented in Table 4 and Table 5.

**Table 3.** CRP, LC and ESR.

| | **FRI** | | | | **No FRI** | | | |
|---|---|---|---|---|---|---|---|---|
| | TP | TN | Median | IQR | FP | FN | Median | IQR |
| CRP | 49 | 36 | 15.0 mg/L | 5.0-60.0 mg/L | 69 | 10 | 7.0 mg/L | 4.1-18.5 mg/L |
| LC | 22 | 72 | 9.3 x$10^9$/L | 7.1-12.4 x$10^9$/L | 26 | 35 | 8.1 x$10^9$/L | 6.7-10.2 x$10^9$/L |
| ESR | 18 | 35 | 18.0 mm/h | 7.0-36.0 mm/h | 11 | 22 | 11.0 mm/h | 5-31.5 mm/h |

**Table 4.** Diagnostic accuracies for CRP, LC and ESR.

| **Test** | **CRP** | **LC** | **ESR** |
|---|---|---|---|
| Sensitivity (95% CI) | 83.1% (71.0%-91.6%) | 38.6% (22.0%-52.4%) | 45.0% (29.3% - 61.5%) |
| Specificity (95% CI) | 34.3% (25.3%-44.2%) | 73.5% (63.6%-81.9%) | 76.1% (61.2% - 87.4%) |
| PPV (95% CI) | 41.5% (37.2%-46.0%) | 45.8% (34.7%-57.4%) | 62.1% (46.8% - 75.2%) |
| NPV (95% CI) | 78.3% (65.9%-87.0%) | 67.3% (61.9%-72.3%) | 61.4% (53.5% - 68.7%) |
| LR+ (95% CI) | 1.26 (1.06-1.51) | 1.45 (0.91-2.31) | 1.88 (1.01 - 3.49) |
| LR- (95% CI) | 0.49 (0.26-0.92) | 0.84 (0.66-1.06) | 0.72 (0.52 - 1.00) |
| Accuracy | 51.8% (43.9%-59.7%) | 60.7% (52.5%-68.4%) | 79.6% (64.7% - 90.2%) |

**Table 5.** Diagnostic accuracies for continuous variables CRP, LC, ESR and CRP + LC.

| **Test** | **CRP** | **LC** | **ESR** | **CRP + LC** |
|---|---|---|---|---|
| AUROC | 0.64 (95% CI 0.55-0.72) | 0.60 (95% CI 0.50-0.69) | 0.58 (95% CI 0.46-0.71) | 0.63 (95% CI 0.54-0.73) |
| Sensitivity | 61.0% | 60.0% | 72.4% | 60.0% |
| Specificity | 62.9% | 61.2% | 50.1% | 63.9% |

**Multivariable logistic regression analysis**

ESR was left out of these analyses as this marker was missing in half of the patients (n=86, 51.2%). The AUROC of CRP and LC combined was 0.63 (95% CI 0.54-0.73). At the Q-point, there were 33 TP, 62 TN, 35 FP and 22 FN, with a sensitivity and specificity of 60% and 64% (Table 4 and Table 5). The model with clinical parameters and combined inflammatory markers had an AUROC of 0.66 (95% CI 0.55-0.77), as compared to 0.62 (95% CI 0.51-0.72) without inflammatory markers.

The AUROC of the combined markers per center was 0.63 (0.54-0.73) for the UMCG, and 0.68 (0.51-0.87) for the UMCU. The AUROC was 0.64 (0.34-0.93) <14 days and 0.61 (0.48-0.75) ≥14 days. The AUROC of the model with log-transformed CRP and LC was 0.63 (0.54-0.73)

## DISCUSSION

This study focused on the diagnostic accuracy of the serum inflammatory markers CRP, LC and ESR in patients who were suspected of FRI. It is the first study to include clinical parameters proven to be predictive of FRI in its analysis. Although most clinicians regard serum inflammatory markers to be part of the general work-up of suspected FRI, the results of this study indicate that they should be cautious when interpreting their results, as was published in the Consensus definition on FRI (2).



The majority of the literature on inflammatory markers in orthopedic infection has focused on periprosthetic joint infections (PJI) and osteomyelitis of the diabetic foot (34-37). CRP has been proven to be useful in both (38, 39). Moreover, the value of LC is less well established (9, 40). In early postoperative infections after fracture surgery, continuous elevation or a secondary rise might be expected in CRP and LC (24, 41). Levels of serum CRP, LC and ESR have been shown to be significantly lower in FRI than in hematogenous osteomyelitis and osteomyelitis of the diabetic foot (42, 43).

Studies on the diagnostic value of serum inflammatory markers in FRI are limited, and their methodology is heterogeneous. Different serum marker thresholds are used, and study populations vary. As in the current study, the study population of Buhl et al. consisted of patients who underwent nuclear medical imaging for suspected FRI or infected prosthesis (44). They reported a sensitivity and specificity for ESR of 84% and 29% respectively, and 56% and 35% for CRP. These results differ from those in the current study. This may be due to PJI being excluded in the current study and the use of different thresholds. Most studies on serum markers in FRI have focused on subgroups of FRI, such as infected non-union or patients undergoing conversion surgery. One study reported on the value of CRP and ESR in diagnosing infection in patients undergoing conversion from internal fixation of a femoral neck fracture to total hip arthroplasty (45). The authors reported a higher diagnostic accuracy than the current study, with an AUROC of 0.89 for both markers. Unfortunately, their study has a high risk of overfitting due to the inclusion of only six patients with FRI. Therefore, the true AUROC, obtained after (internal and) external validation, will be much lower (46). Several studies have focused on the value of inflammatory markers in diagnosing infection in patients presenting with mal- or non-union (11-13). The diagnostic accuracy of individual serum inflammatory markers in this sub-group of FRI is low. Some of these studies have looked at the

diagnostic accuracy of combined serum markers. Similar to the results of the current study, combining markers was found to increase the diagnostic accuracy for FRI only marginally (11, 13).

With an accuracy of 79.6%, the diagnostic value of ESR in the current study appears to be high. However, the large overlap in the IQR of the FRI and non-FRI groups shows the discriminative value of ESR to be low.

The differences in results between the literature and the current study may be caused by several factors. Most importantly, several different thresholds are used to define elevation of serum inflammatory markers. This makes a valid comparison of results impossible, especially when only sensitivity and specificity are reported. Furthermore, FRI is a heterogeneous disease, with tissue involvement varying in location and severity. Some studies focus on all patients with FRI, others choose subgroups to increase population homogeneity. These differences in study populations further complicate comparing results and it is therefore imperative that international lab protocols are being developed and uniform diagnostic criteria including threshold values and timing for obtaining serum inflammatory markers regarding FRI are being established and implemented. Finally, most studies have looked at serum markers taken between 1 to 14 days prior to obtaining intra-operative cultures. The current study focused on inflammatory markers when infection was first suspected, with a median of 48.5 days between index- and reference test. This is in concordance with clinical practice, as the clinician will obtain serum inflammatory markers at the time an FRI has to be confirmed or ruled out. The actual surgery often follows at a later point, when additional diagnostic work, such as imaging, has been completed. This difference may have influenced the results.

Strengths of this study are that it is one of the largest cohorts investigating the diagnostic performance of individual and combined serum inflammatory markers in FRI. The inclusion of combined markers is important, as in clinical practice, inflammatory markers are never interpreted individually. Furthermore, they are always interpreted in combination with clinical parameters. Therefore, information from multiple markers was combined with clinical parameters that are associated with FRI to estimate the probability of infection.

This study does have some limitations. First of all, all patients with suspected FRI were collectively analyzed, and thus these results may not be applicable to all possible subgroups. Furthermore, due to its retrospective nature, there was no uniform time interval between index- and reference test. However, this is in accordance with clinical practice. In addition, the laboratory measurements have been performed using different methods, however due to laboratory standardization and internal

and external quality control schemes differences due to measurement methods are negligible. Also, the outcome of this study might be affected by selection bias as the patients undergoing advanced nuclear imaging could have been selected based on the outcome of their serum inflammatory marker testing. This could potentially alter the true NPV of the markers.

## CONCLUSION

The outcome of this retrospective study indicates that the added diagnostic value of CRP, LC and ESR seems to be limited for FRI. FRI can still be present when serum inflammatory markers are within normal range. Therefore, clinicians should be cautious when interpreting the results of these tests in patients with suspected FRI.

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**Appendix table 1.** Models multivariable logistic regression analyses.

| | AUROC | 95% CI | n = | Intercept | Gustilo 0-1+2 | Gustilo 0-3 | DM | ISS | Smoking | Lower extremity | LC | CRP |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 0.63 | 0.54 - 0.73 | 152 | -1.179 | N/A | N/A | N/A | N/A | N/A | N/A | 0.005 | 0.048 |
| 2 | 0.62 | 0.51 - 0.72 | 134 | 0.357 | 0.496 | 0.212 | -0,158 | -0.066 | 0.282 | -0.811 | N/A | N/A |
| 3 | 0.66 | 0.55 - 0.77 | 123 | -1.050 | 0.479 | -0.101 | 0,804 | -0.139 | 0.370 | -0.746 | 0.044 | 0.007 |

# CHAPTER 3

## Diagnostic accuracy of serum inflammatory markers in late fracture-related infection: a systematic review and meta-analysis

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## ABSTRACT

**Aims**
To assess the diagnostic value of C-reactive protein (CRP), leucocyte count (LC), and erythrocyte sedimentation rate (ESR) in late fracture-related infection (FRI).

**Methods**
PubMed, Embase, and Cochrane databases were searched focusing on the diagnostic value of CRP, LC, and ESR in late FRI. Sensitivity and specificity combinations were extracted for each marker. Average estimates were obtained using bivariate mixed effects models.

**Results**
A total of 8284 articles were identified but only six were suitable for inclusion. Sensitivity of CRP ranged from 60.0% to 100.0% and specificity from 34.3% to 85.7% in all publications considered. Five articles were pooled for meta-analysis, showing a sensitivity and specificity of 77.0% and 67.9%, respectively. For LC, this was 22.9% to 72.6%, and 73.5% to 85.7%, respectively, in five articles. Four articles were pooled for meta-analysis, resulting in a 51.7% sensitivity and 67.1% specificity. For ESR, sensitivity and specificity ranged from 37.1% to 100.0% and 59.0% to 85.0%, respectively, in five articles. Three articles were pooled in meta-analysis, showing a 45.1% sensitivity and 79.3% specificity. Four articles analyzed the value of combined inflammatory markers, reporting an increased diagnostic accuracy. These results could not be pooled due to heterogeneity.

**Conclusion**
The serum inflammatory markers CRP, LC, and ESR are insufficiently accurate to diagnose late FRI, but they may be used as a suggestive sign in its diagnosis.

## INTRODUCTION

Fracture-related infection (FRI) is a challenging complication in orthopaedic trauma surgery and uncertainties exist in both diagnostic and treatment strategies [1]. Regardless of antibiotic prophylaxis and sterile precautions observed at operation, the incidence of infection after fracture treatment is relatively high, generally varying between 1% and 30% depending on comorbidities, fracture type, and soft-tissue injury [2–5]. FRIs often result in multiple re-operations, long antibiotic treatment, immobilization, and restrictions in work and social activities [6–9].

Although classical clinical signs typically seen in infection (such as redness, swelling, pain, and warmth) are often more prominent in early compared with late cases, symptoms can be subtle in both groups and may be relapsing and remitting over long periods of time [10]. Accordingly, dedicated imaging [11] and histological testing [12] are advised. In the FRI Consensus Definition, criteria to establish the presence or absence of FRI may be considered as confirmatory (infection definitely present) or suggestive (infection possibly present) [13]. Suggestive diagnostic criteria include elevated CRP, leucocyte count (LC), and/or ESR. Although these markers are part of the FRI Consensus Definition and commonly used as a diagnostic and severity parameter for postoperative infections after orthopaedic trauma surgery, their accuracy has mainly been investigated in prosthetic joint infections (PJI) and patients with osteomyelitis due to diabetic foot disease [14–19].



Generally, raised inflammatory markers are considered to be suggestive of infection when a secondary rise occurs after an initial decrease, or when a consistent elevation is present over a long period of time [13]. In FRI, elevations in inflammatory markers may be more subtle compared with PJI or diabetic foot osteomyelitis [20]. In addition, an elevation in these markers may be seen in trauma patients due to a systemic inflammatory response, postoperative or post-trauma tissue damage or other, non-surgical infections during the postoperative period [21–24]. It is this clinical variation, together with limited evidence in the literature, that makes the exact role of serum inflammatory markers, as part of the diagnostic algorithm for FRI, unclear.

The aim of this study was to assess the diagnostic value of CRP, LC, and ESR in late fracture-related infection.

## MATERIALS AND METHODS

**Search strategy**

On 26 March 2018, a computer-aided systematic literature search was performed in the PubMed, EMBASE, and Cochrane libraries. Articles in the English, Dutch, and

German language were included. No time limitation was applied. Search terms were defined by the authors and reviewed by a professional information retrieval specialist. The search strings are available in Supplementary Table i. Articles were first screened on title and abstract. Two reviewers (JK and PB) scored all articles independently. A third reviewer (GG) was consulted in the event of uncertainty to assess whether the articles met the inclusion criteria. Subsequently, the full-text of the included articles was reviewed by all three reviewers. In addition, cross-reference checking of included articles and of relevant review articles was performed.

**Study selection**

This review focuses on the diagnostic accuracy of the most commonly utilized serum inflammatory markers for detecting late FRI, namely CRP, LC, and ESR, individually or combined. Therefore, information on other diagnostic inflammatory markers was disregarded. Articles solely reporting on early FRI (onset less than six weeks after the operation) [10] were excluded as: 1) early FRI usually poses a less complex diagnostic dilemma; and 2) it was felt by the authors that early and late infections are different entities and should be analyzed separately to prevent confounding bias. Patients with or without fracture fixation in situ were eligible for inclusion. Articles solely reporting on other types of bone or non-trauma related infections such as PJI, diabetic feet, spondylodiscitis, and haematogenous osteomyelitis were excluded. Furthermore, articles without a definitive reference test, defined as intraoperative cultures or clinical follow-up of at least five months, for confirmation of the infection, were excluded. Papers reporting on the results of a heterogeneous patient population were included, as long as separate analyses for FRI were provided. This accommodation is specifically stated in the results section if applicable. No concessions were made for non-trauma-related articles. The inclusion and exclusion criteria are presented in Table I.

**Data collection and extraction**

From all included articles, the following data were extracted: 1) author; 2) year of publication; 3) study type and population; 4) number of patients included; 5) results of index test; 6) results of reference test; 7) diagnostic accuracy (any measures) of the serum inflammatory markers for late FRI. Data were extracted by two reviewers independently (JK and PB). All authors were contacted when raw data were not reported in the articles.

**Table 1.** Inclusion and exclusion criteria.

| Criteria |
|---|
| **Inclusion criteria** |
| 1. The study must analyze serum inflammatory parameters C-reactive protein (CRP), leucocyte count (LC) (or: white blood cell count), and erythrocyte sedimentation rate (ESR).<br>2. The study must evaluate late fracture-related infection (or a synonym), defined as onset later than six weeks after surgical intervention.<br>3. A valid reference test must be used in the study defined as intraoperative cultures or clinical follow-up of at least five months.<br>4. The study must provide a clear analysis of the investigated serum inflammatory parameters in order to construct contingency tables of relevant results.<br>5. The study must be conducted on humans. |
| **Exclusion criteria** |
| 1. Articles that investigate forms of non-traumatic osteomyelitis, such as acute osteomyelitis and osteomyelitis due to prosthetic infections, diabetic feet, and haematogenous infections.<br>2. Articles that included fewer than five participants.<br>3. Articles not written in the English, Dutch, or German language.<br>4. Poster/conference papers. |



### Methodological quality assessment

Assessment of risk of bias and applicability of the study design of the included articles was performed using the QUADAS-2 tool (Quality Assessment of Diagnostic Accuracy Articles, version 2). The QUADAS-2 tool consists of four domains: patient selection, index test, reference standard, and flow and timing [25]. The methodological quality of the articles was assessed by two reviewers independently (JK and PB). A third reviewer (GG) confirmed the outcomes of the QUADAS-2 tool for the included articles. Since one selected study [26] was (co-)authored by the same authors as the current review, its methodological quality was assessed by an independent author (WJM). Authors were contacted when information regarding the quality of the study was not provided in the articles.

### Statistical analysis

To assess the diagnostic performance per study, first the sensitivity and specificity were calculated from the (reconstructed) 2×2 contingency tables from the included articles. These were graphically visualized in a forest plot, along with their 95% confidence interval (CI). The individual sensitivities and specificities in summary measurement were not directly pooled, because the included articles are likely to have used different (explicit or implicit) threshold values. Explicitly, researchers often use the threshold that is in use at their institution and these thresholds often differ between institutions.

Implicitly, there could be variations in the thresholds (even if they are explicitly the same) due to differences in observers, laboratory protocols, or equipment. These threshold values are a problem in obtaining pooled estimates of sensitivity and specificity as the natural trade-off between sensitivity and specificity means that a lower used threshold for an inflammatory marker leads to a higher sensitivity but lower specificity for FRI, and vice versa [27].

The reported pairs of sensitivity and specificity were graphically visualized. These plots were used to assess heterogeneity in discriminative performances between the articles. If the amount of clinical and statistical heterogeneity was considered acceptable, a summary measurement and expected Receiver Operating Characteristic (ROC) curve of the sensitivities and specificities was obtained. This was done while accounting for the (explicitly and implicitly) different thresholds, using a bivariate mixed effects model [27,28]. This model first jointly incorporates both the degree of inter- and intra-study variation in sensitivity and specificity to calculate the corresponding confidence intervals per study. Second, these parameters were combined to obtain the summary ROC curve as a measure of the average discriminative performance. Summary ROC plots were obtained for both the separate and the combined inflammatory markers.

All analyses were performed using R software for statistical computing version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria) with the additional package 'mada' [29] and 'forestplot' [30]. This systematic review was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [31] and its 'Explanation and Elaboration' [32].

## RESULTS

### Included articles

The search flow diagram is displayed in Figure 1. A total of 9860 articles met the search criteria. Additional data were provided by three authors [33–35]. Ultimately, six articles remained for qualitative assessment [26,33–37]. No articles were excluded after qualitative assessment, and all six articles were included in this systematic review [26,33–37], drawing on information on 582 patients. All included articles covered late FRI.

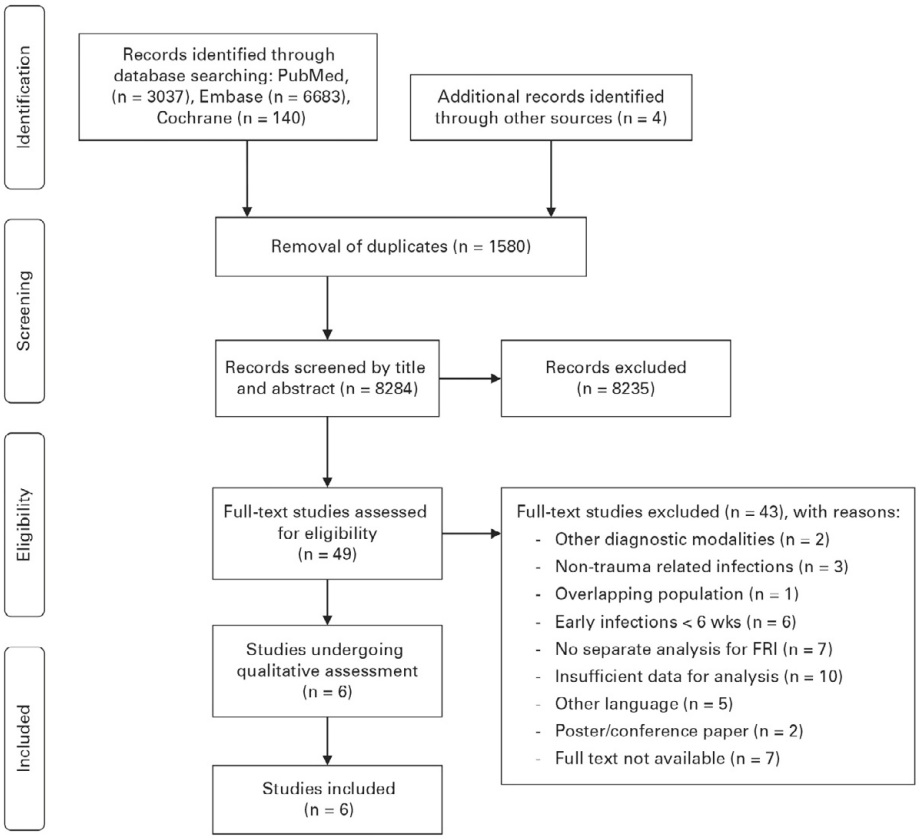


**Figure 1.** Flow Diagram (PRISMA).

**Study quality**

The results of the risk of bias and applicability assessment are presented in Figure 2. Concerns were mainly raised in regard to index- and reference test, and study flow and timing.

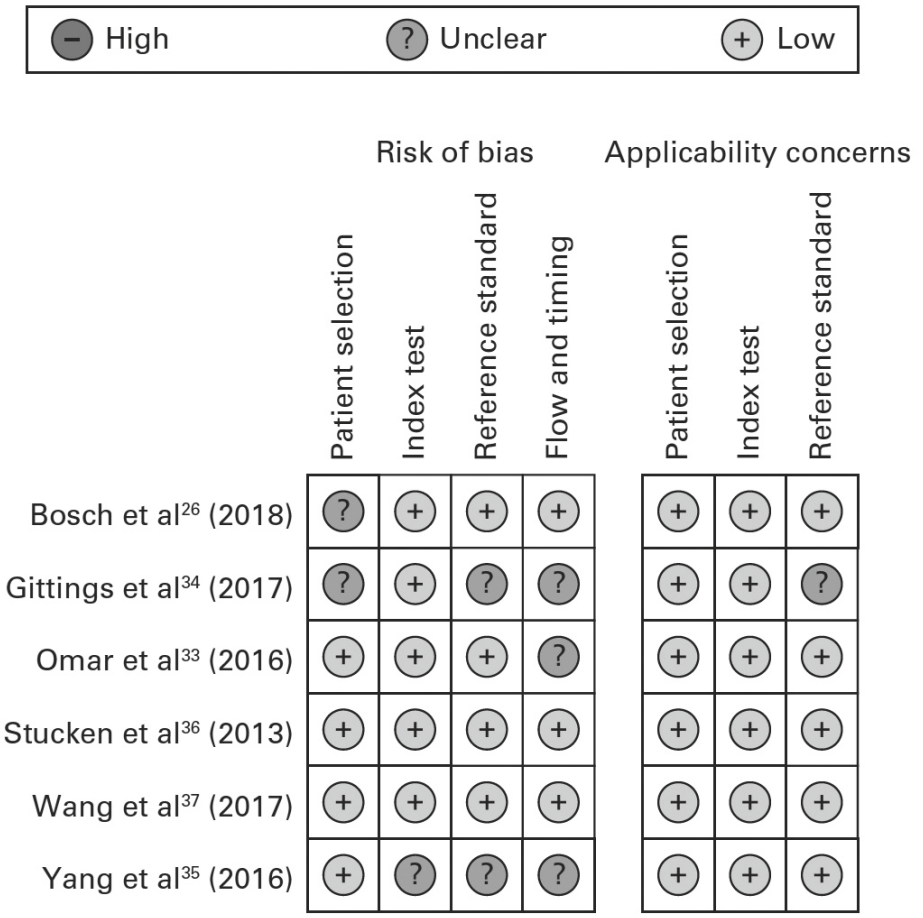


**Figure 2.** QUADAS-2 assessment for risk of bias and applicability.

**Study characteristics**

The characteristics of the included studies are presented in Table II. Four articles focused on the value of combining markers [26,34,36,37].

**C-reactive protein**

All six included articles reported on CRP in their analysis. Three had populations consisting of patients with ununited fractures [35–37], two focused on patients undergoing revision surgery after initial internal fixation [33,34], and one investigated patients undergoing nuclear medical imaging for suspected FRI [26]. The results can be found in Table II and Figure 3. Thresholds used to define elevation varied between 5.0 mg/l to 10.0 mg/l, and all articles used intraoperative cultures as a reference test. Overall, the sensitivity for detecting FRI varied between 60.0% and 100.0%, and specificity varied between 34.3% and 85.7%.

**Table 2.** Characteristics and results of included articles

| Author | Study type and population | Sample size, n | FRI, n | Reference test | Markers | Thresholds | Sensitivity, % | Specificity, % |
|---|---|---|---|---|---|---|---|---|
| Bosch et al [26] (2018) | Retrospective cohort. Nuclear medical imaging for suspected FRI. | 168 | 61 | Intra-operative cultures with at least two sites revealing the same pathogen, presence of sinus tract, or intra-operative purulence, or >6 months follow up. | CRP<br>LC<br>ESR | 5 mg/L<br>10 x $10^9$ cells/L<br>11 mm/h (male)<br>24 mm/h (female) | 83.1%<br>38.6%<br>45.0% | 34.3%<br>73.5%<br>76.1% |
| Gittings et al [34] (2017) | Retrospective cohort. Conversion to total hip arthroplasty after initial internal fixation. | 33 | 6 | Intra-operative cultures or pre-operative diagnosis using MSIS criteria for PJI. | CRP<br>ESR | 7 mg/L<br>30 mm/h | 100.0%<br>100.0% | 81.0%<br>85.0% |
| Omar et al [33] (2016) | Prospective cohort. Revision surgery after initial internal fixation. | 62 | 51 | Intra-operative cultures with at least two sites revealing the same pathogen, presence of sinus tract or intra-operative purulence. | CRP<br>LC | 5 mg/L<br>10.2 x $10^9$ cells/L | 78.4%<br>72.6% | 72.7%<br>81.8% |
| Stucken et al [36] | Prospective cohort. Un-united fractures. | 93 | 30 | Positive intra-operative cultures or gross infection at time of surgery or in the immediate post-operative period. | CRP<br>LC<br>ESR | 10 mg/L<br>10 x $10^9$ cells/L<br>30 mm/h | NE<br>NE<br>NE | NE<br>NE<br>NE |
| Wang et al [37] (2017) | Retrospective cohort. Un-united fractures. | 42 | 35 | Intra-operative cultures with at least two sites revealing the same pathogen. | CRP<br>LC<br>ESR | 8 mg/L<br>10 x $10^9$ cells/L<br>20 mm/h | 60.0%<br>22.9%<br>37.1% | 85.7%<br>85.7%<br>71.4% |
| Yang et al [35] (2016) | Retrospective cohort. Un-united fractures. | 184 | 96 | Intra-operative cultures, presence of a sinus tract, or purulence. | CRP<br>LC<br>ESR | 8 mg/L<br>9.15 x $10^9$ cells/L<br>15 mm/h (male)<br>20 mm/h (female) | 68.8%<br>40.9%<br>74.2% | 81.8%<br>79.4%<br>59.0% |

FRI, fracture-related infection; CRP, C-reactive protein; LC, leucocyte count; ESR, erythrocyte sedimentation rate; MSIS, Musculoskeletal Infection Society; PJI, prosthetic joint infection; N/E, not estimable

**Leukocyte count**

Five articles included LC in their analysis [26,33,35–37]. Three focused on patients presenting with ununited fractures [35–37]. The other two investigated patients undergoing revision surgery after initial internal fixation [33] and patients who underwent nuclear imaging for suspected FRI [26]. Thresholds used were comparable, ranging from $9.15 \times 10^9$ cells/l to $10.2 \times 10^9$ cells/l, and all articles used intraoperative cultures as a reference test. Reported sensitivity varied between 22.9% and 72.6%, and specificity varied between 73.5% and 85.7%.

**Erythrocyte sedimentation rate**

Five articles reported on ESR in their analysis [26,34–37]. Three included ESR in their analysis on diagnosing infection in patients with ununited fractures [35–37], one studied the value of ESR in diagnosing infection in patients undergoing nuclear imaging for suspected FRI [26], and one focused on patients undergoing conversion to total hip arthroplasty after failed initial internal fixation [34]. Thresholds varied between 11.0 mm/h and 30.0 mm/h, with two articles using different threshold for men and women [26,35]. All articles used intraoperative cultures as a reference test [36]. Overall, the reported sensitivity varied between 37.1% and 100.0%, and specificity varied between 59.0% and 85.0%.

**Combined scores**

Four articles reported on the added value of combining markers [26,34,36,37]. Two reported on combining up to four markers without specifying which markers [36,37]. One study reported a predicted probability value of two and three combined positive tests [36]. They found a predicted probability of 56.0% when combining any two markers, and 100.0% when all three markers (CRP, LC, and ESR) are elevated. Another study also reported on combining CRP, LC, and ESR [37]. With any two markers combined, a predicted probability of 90.9% was calculated. When all three markers were elevated, a combined predicted probability of 100.0% was found. One study reported on the combination of CRP and ESR with a 83.0% sensitivity and 88.0% specificity [37]. One study reported on CRP and LC finding a 60.0% sensitivity and 64.0% specificity [26].

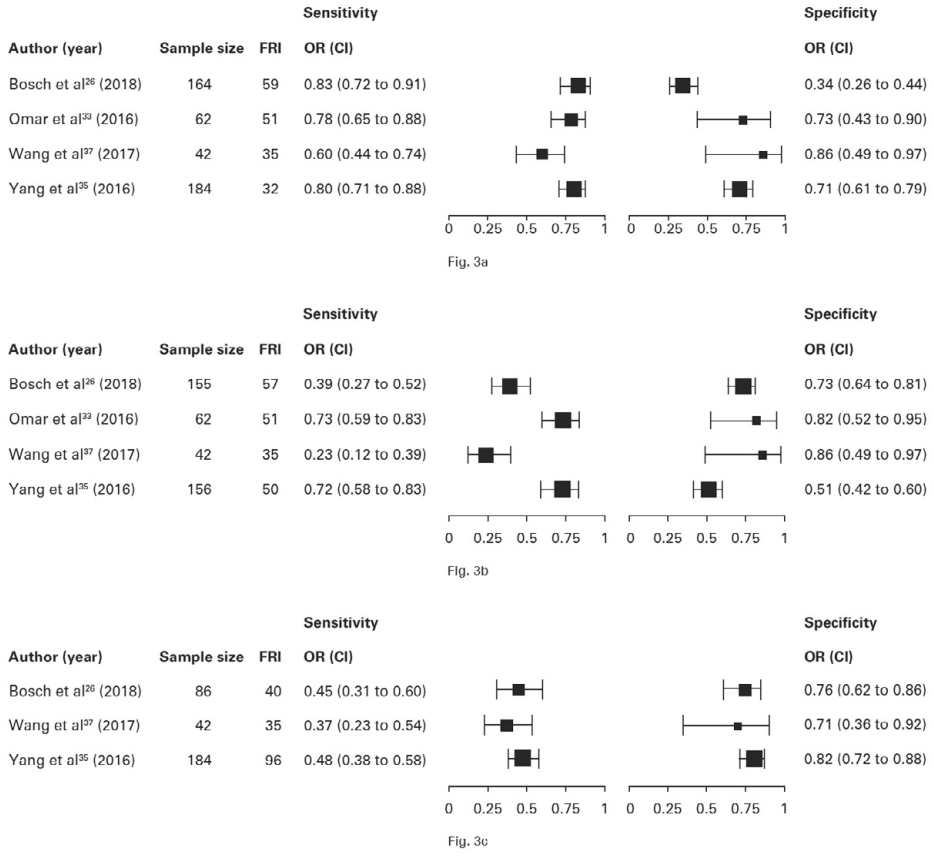


**Figure 3.**
Forest plots sensitivity and specificity markers: a) C-reactive protein (CRP), b) leucocyte count (LC), and c) erythrocyte sedimentation rate (ESR). FRI, fracture-related infection; OR, odds ratio; CI, confidence interval.

## Meta-analysis

Articles were grouped per individual marker. Two-by-two contingency tables (true positive (TP), false negative (FN), false positive (FP), true negative (TN)) could be constructed from the pooled results of four articles for CRP (n = 452) [26,33,35,37], of four articles for LC (n = 415) [26,33,35,37], and of three articles for ESR (n = 312) [26,35,37]. The sensitivities and specificities of the articles within the analysis of each serum marker showed acceptable comparability and could therefore be pooled. This resulted in a sensitivity and specificity of 77.0% (95% CI 66.5 to 85.0) and 67.9% (95% CI 38.7 to 87.6) for CRP, 51.7% (95% CI 27.2 to 75.5) and 67.1% (95% CI 19.3 to 50.2) for LC, and 45.1% (95% CI 37.8 to 52.6) and 79.3% (95% CI 71.7 to 85.2) for ESR (Fig. 4).

Due to heterogeneity, the articles reporting on combined markers could not be pooled (Fig. 5).

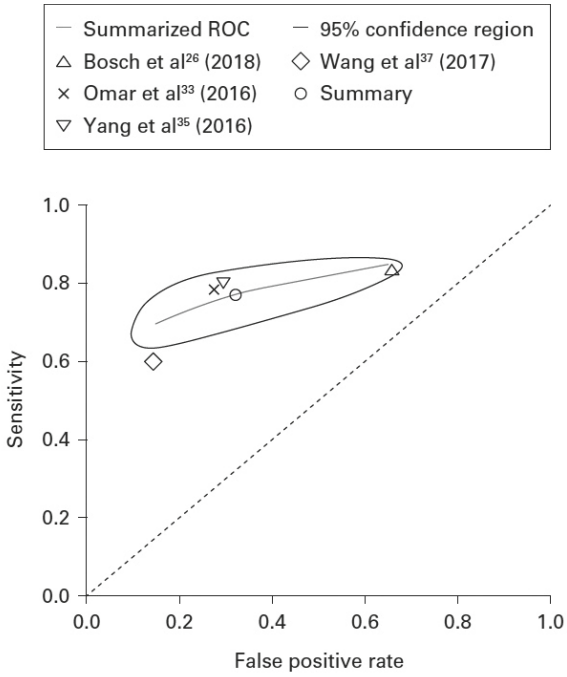
Summarized ROC
95% confidence region
Bosch et al[26] (2018)
Wang et al[37] (2017)
Omar et al[33] (2016)
Summary
Yang et al[35] (2016)
Sensitivity
False positive rate
0.0
0.2
0.4
0.6
0.8
1.0

Fig. 4a

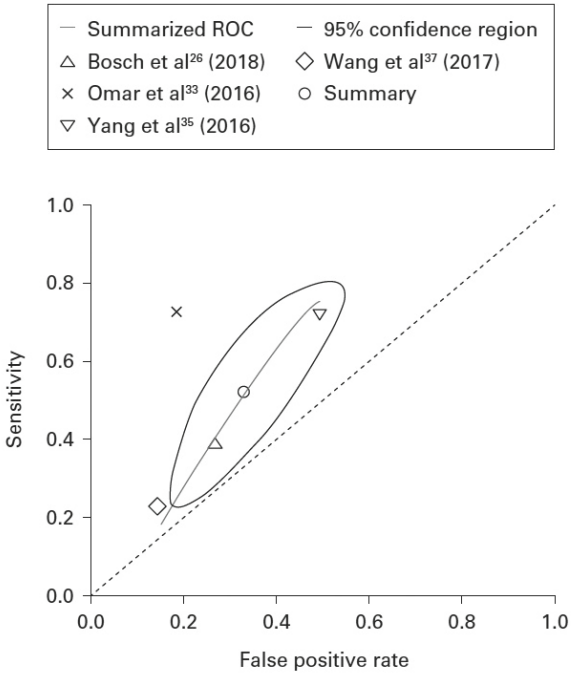
Summarized ROC
95% confidence region
Bosch et al[26] (2018)
Wang et al[37] (2017)
Omar et al[33] (2016)
Summary
Yang et al[35] (2016)
Sensitivity
False positive rate
0.0
0.2
0.4
0.6
0.8
1.0

Fig. 4b

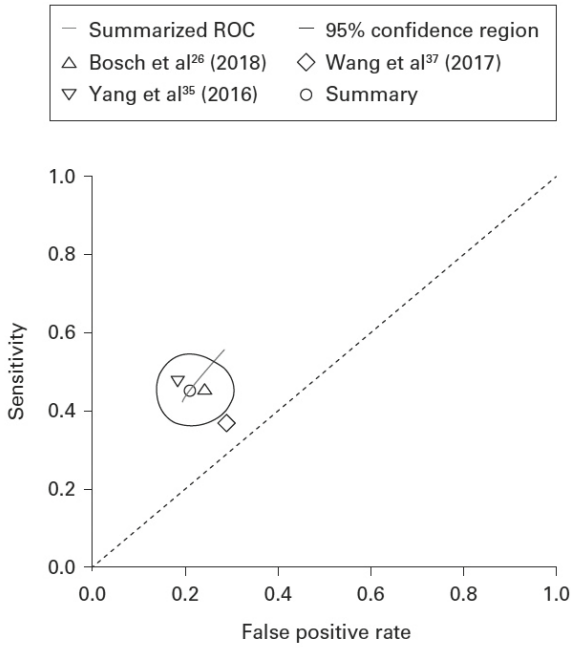


Fig. 4c

**Figure 4.**
Summary receiver operating characteristic (ROC) curves individual markers: a) C-reactive protein (CRP), b) leucocyte count (LC), and c) erythrocyte sedimentation rate (ESR).

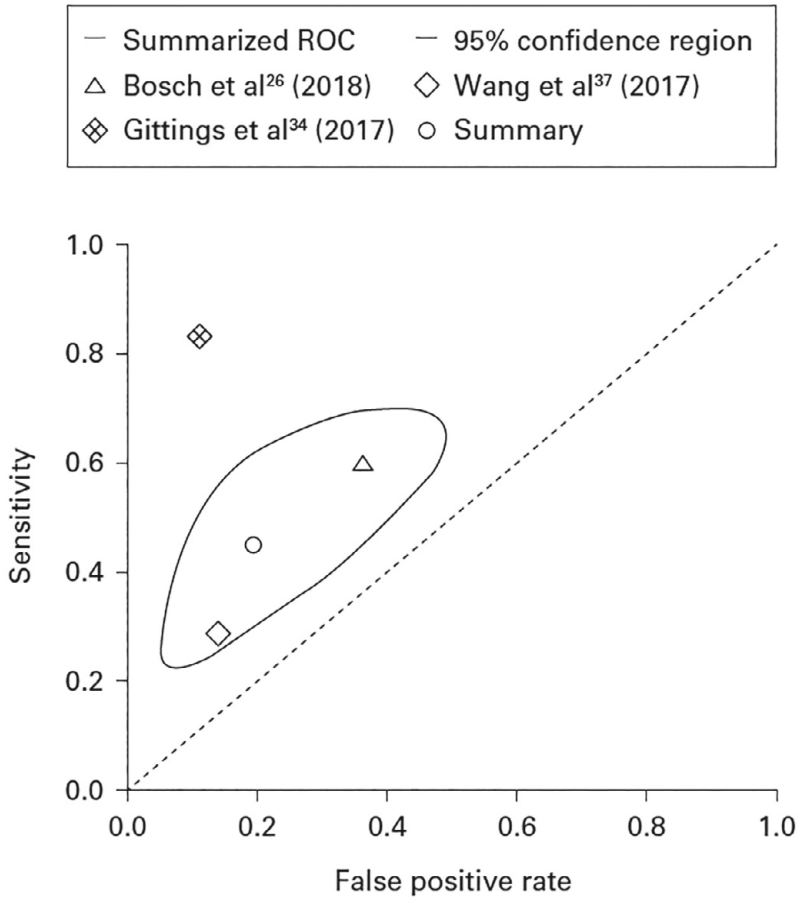


**Figure 5.** Summary receiver operating characteristic (ROC) curve combined markers.

## DISCUSSION

This review presents the current evidence on the diagnostic value of the serum inflammatory markers CRP, LC, and ESR for late FRI. Meta-analysis of the pooled results showed limited diagnostic value of all three markers individually. Combined scores are shown to increase diagnostic performance, yet the accuracy remains insufficient in most articles.

Overall, the results of all markers vary greatly between the included articles. One of the difficulties that we encountered in this review was the fact that serum inflammatory markers were measured using different apparatus and methods. Also, the articles included in this review used several different thresholds when dichotomizing the serum inflammatory markers. The use of different thresholds complicates direct comparison of diagnostic performance between articles. Also,

as these markers are measured on a continuous scale, dichotomization decreases their diagnostic potential. Therefore, articles on their diagnostic performance should analyze these markers continuously in order to assess their potential and, subsequently, determine ideal threshold values. The value at which a sensitivity of > 90% is reached should serve as the threshold in suspected late FRI.

FRI encompasses a broad spectrum of manifestations, which can vary greatly in severity, location, and duration. Study populations often consist of sub-groups of FRI, like infected nonunion, patients undergoing revision surgery, or certain types of medical imaging without specifying the pre-test probability. This results in heterogenic study populations being analyzed, further complicating comparison of diagnostic performance between articles.



All of the included articles used intraoperative cultures as a reference test. However, there were variations in the specific culture methods used. Differences were seen in the number of samples taken, ranging from three to five. Some articles consider FRI to be present when the culture result of a single sample was positive [34,36], while others require the same pathogen to be present in at least two different samples [26,33,37]. Also, details on collecting and culturing protocols were not always provided. Until the FRI Consensus Definition, there was no uniform definition for FRI [13]. Since then, agreement has been reached on a reference standard and protocols for collecting intraoperative cultures have been formed [13,37].

Since serum inflammatory markers are used in clinical practice to rule out FRI, a high sensitivity is needed. A high specificity is needed in order to prevent unnecessary invasive surgery and anti-microbial therapy in patients with a false positive diagnosis. Only one study found a sensitivity > 90%. However, they included only six patients with FRI, increasing the risk of overfitting (the inclusion of too many variables in the statistical model compared with the number of included cases of FRI, the one-in-ten rule) [34]. Specificity was generally low in all articles, increasing the risk of over-treatment when inflammatory markers are relied upon.

Although the results of this review show that dichotomized results of individual serum inflammatory markers have insufficient diagnostic performance, they may still be a suggestive sign of FRI. One way of increasing the diagnostic performance is by combining markers. This resembles clinical practice, where inflammatory markers are rarely interpreted on a stand-alone basis. Usually, multiple markers are interpreted in addition to clinical signs when estimating the likelihood of FRI. Only one study assessed the combination CRP, LC, ESR, and clinical parameters predictive of FRI, and reported a limited added value of these inflammatory markers [26]. The other articles reported increased diagnostic performance when combining

markers [34,36,37]. However, the diagnostic performance remains insufficient in most articles.

We recommend that international laboratory protocols for serum inflammatory markers become standardized in order to compare articles in a more reliable way and improve the diagnosis of late FRI in a clinical setting. Furthermore, uniform definitions and diagnostic criteria, as recently published in the FRI Consensus Definition [13], should be implemented in both clinical practice and research.

This review has some limitations. Most articles on this topic suffer from small and heterogeneous patient populations, under reporting regarding laboratory techniques, different thresholds used and lack of a reference standard. Therefore, only six articles could be included. Furthermore, slight differences existed in the reference tests used by the included articles. Finally, it needs to be mentioned that a cut-off, time-based division between early and late infections remains arbitrary and therefore subject to on-going discussion [13].

In conclusion, the serum inflammatory markers CRP, LC and ESR are insufficiently accurate to diagnose late FRI. These markers cannot confirm or rule out the presence of FRI, and should therefore be used as a suggestive sign in the diagnosis of late FRI.

## TAKE HOME MESSAGE

The diagnostic accuracy of the serum inflammatory markers C-reactive protein, leucocyte count, and erythrocyte sedimentation rate is insufficient to diagnose or exclude late fracture-related infection. These markers should therefore be used only as a suggestive sign in the diagnostic work-up of suspected late fracture-related infection.

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# APPENDIX

**Appendix 1.** Search strings for PubMed and Embase.

| **PubMed** |
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| (((surgical wound infection[MeSH] OR infectious bone disease[MeSH] OR infect*[tiab] OR osteitis[tiab]) OR infectious bone disease[tiab]) AND (bone fracture[MeSH] OR broken bone[tiab] OR fracture*[ tiab] OR trauma*[tiab])) OR (osteomyelitis[MeSH] OR osteomyelitis[tiab])) AND (((biologic*[tiab] OR immunologic*[tiab] OR inflammat*[tiab] OR laboratory[tiab] OR serum[tiab]) AND (marker*[tiab] OR parameter*[tiab] OR mediator*[tiab]) OR (blood sedimentation[MeSH] OR c reactive protein[MeSH] OR leukocyte count[MeSH] OR inflammation mediators[MeSH] OR biomarkers[MeSH] OR blood sedimentation[tiab] OR sedimentation rate[tiab] OR c reactive protein[tiab] OR C-reactive protein[tiab] OR leukocyte*[tiab] OR leucocyte*[tiab] OR leukocytosis[tiab] OR leucocytosis[tiab] OR blood cell count[tiab] OR white blood cell*[tiab] OR CRP[tiab] OR ESR[tiab] OR immune marker*[tiab] OR erythrocyte sedimentation[tiab] OR biomarker*[tiab])) NOT (animals[MeSH] NOT humans [MeSH]) |
| **Embase** |
| (((‘surgical infection’/exp OR infect*:ab,ti OR osteitis:ab,ti OR ‘infectious bone disease’:ab,ti) AND (‘fracture’/exp OR ‘broken bone’:ab,ti OR fracture*:ab,ti OR trauma*:ab,ti)) OR (‘chronic osteomyelitis’/exp OR osteomyelitis:ab,ti)) AND (((biologic*:ab,ti OR immunologic*:ab,ti OR inflammat*:ab,ti OR laboratory:ab,ti OR serum:ab,ti) AND (marker*:ab,ti OR parameter*:ab,ti OR mediator*:ab,ti)) OR (‘erythrocyte sedimentation rate’/exp OR ‘c reactive protein’/exp OR leukocyte/exp OR ‘autacoid’/exp OR ‘biological marker’/exp OR ‘blood sedimentation’:ab,ti OR ‘sedimentation rate’:ab,ti OR ‘c reactive protein’:ab,ti OR leukocyte*:ab,ti OR leucocyte*:ab,ti OR leukocytosis:ab,ti OR leucocytosis:ab,ti OR ‘blood cell count’:ab,ti OR ‘white blood cell’:ab,ti OR crp:ab,ti OR esr:ab,ti OR ‘immune marker*’:ab,ti OR ‘erythrocyte sedimentation’:ab,ti)) AND [humans]/lim |

# CHAPTER 4

## The diagnostic accuracy of $^{18}$F-FDG-PET/CT in diagnosing fracture related infections: a retrospective dual center cohort study

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## ABSTRACT

### Introduction

$^{18}$F-Fluorodeoxyglucose positron emission tomography ($^{18}$F-FDG PET/CT) is frequently used to diagnose fracture-related infections (FRIs), but its diagnostic performance in this field is still unknown. The aims of this study were: 1) to assess the diagnostic performance of qualitative assessment of $^{18}$F-FDG PET/CT scans in diagnosing FRI, 2) to establish the diagnostic performance of standardized uptake values (SUVs) extracted from $^{18}$F-FDG PET/CT scans and to determine their associated optimal cut-off values, and 3) to identify variables that predict a false-positive (FP) or false-negative (FN) $^{18}$F-FDG PET/CT result.

### Methods

This retrospective cohort study included all patients with suspected FRI undergoing $^{18}$F-FDG PET/CT between 2011 and 2017 in two level-1 trauma centers. Two nuclear medicine physicians independently reassessed all $^{18}$F-FDG PET/CT scans. The reference standard consisted of the result of at least two deep, representative microbiological cultures or the presence/absence of clinical confirmatory signs of FRI (AO/EBJIS consensus definition) during a follow-up of at least 6 months. Diagnostic performance in terms of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) was calculated. Additionally, SUVs were measured on $^{18}$F-FDG PET/CT scans. Volumes of interest were drawn around the suspected and corresponding contralateral areas to obtain absolute values and ratios between suspected and contralateral areas. A multivariable logistic regression analysis was also performed to identify the most important predictor(s) of FP or FN $^{18}$F-FDG PET/CT results.

### Results

The study included 156 $^{18}$F-FDG PET/CT scans in 135 patients. Qualitative assessment of $^{18}$F-FDG PET/CT scans showed a sensitivity of 0.89, specificity of 0.80, PPV of 0.74, NPV of 0.91 and diagnostic accuracy of 0.83. SUVs on their own resulted in lower diagnostic performance, but combining them with qualitative assessments yielded an AUC of 0.89 compared to an AUC of 0.84 when considering only the qualitative assessment results ($p = 0.007$). $^{18}$F-FDG PET/CT performed <1 month after surgery was found to be the independent variable with the highest predictive value for a false test result, with an absolute risk of 46% (95% CI 27–66%), compared with 7% (95% CI 4–12%) in patients with $^{18}$F-FDG PET/CT performed 1–6 months after surgery.

### Conclusion

Qualitative assessment of $^{18}$F-FDGPET/CT scans had a diagnostic accuracy of 0.83 and an excellent NPV of 0.91 in diagnosing FRI. Adding SUV measurements to qualitative assessment provided additional accuracy in comparison to qualitative assessment alone. An interval between surgery and $^{18}$F-FDG PET/CT of <1 month was associated with a sharp increase in false test results.

## INTRODUCTION

Fracture-related infection (FRI) is a serious complication following trauma surgery and can lead to increased morbidity and high medical costs [1,2]. Clinical symptoms are not always evident, therefore diagnosing FRI can be challenging. This problem was worsened by the fact that, until recently, there was no uniform definition of FRI [3]. Recently, the AO Foundation (Arbeitsgemeinschaft für Osteosynthesefragen) and the European Bone and Joint Infection Society (EBJIS) published a consensus definition comprising confirmatory and suggestive criteria for diagnosing FRI [4]. Medical imaging is considered to be only an adjunct to the diagnosis of FRI (i.e. a suggestive criterion). The reason for this is that the evidence for its accuracy in diagnosing FRI is limited. Moreover, such evidence as is available was obtained mainly from studies investigating other causes of bone infection such as diabetic foot infection, periprosthetic joint infection (PJI) and haematogenous osteomyelitis [5]. Most previous studies on diagnostic imaging of FRI have been hampered by small patient cohorts, unclear reference standards and heterogeneous patient populations [5,6]. Recently, our group found that white blood cell (WBC) scintigraphy has a high accuracy (0.92) when diagnosing FRI [7]. To compare imaging modalities, we used the same study design to evaluate the diagnostic performance of $^{18}$F-fluorodeoxyglucose positron emission tomography/ computed tomography ($^{18}$F-FDG PET/CT).



The aims of the current study were:

1) To establish the performance of qualitative assessment of $^{18}$F-FDG PET/CT scans in diagnosing FRI
2) To establish the performance of standardized uptake values (SUVs) from $^{18}$F-FDG PET/CT in diagnosing FRI and to determine their optimal associated cut-off values
3) To determine which variables are independent predictors of a false positive (FP) or false negative (FN) $^{18}$F-FDG PET/CT test result in patients with suspected FRI

## METHODS

### Ethical approval

Due to the observational nature of this study the need for informed consent was waived by the Medical Ethics Review Committee (METC) of the University Medical Center Utrecht (METC 17-475).

### Study design and eligibility criteria

This was a two-center, retrospective cohort study that included patients from two large level-1 trauma centers in the Netherlands: the University Medical Center Utrecht and the University Medical Center Groningen. All consecutive patients

undergoing $^{18}$F-FDG PET/CT for diagnosing (or excluding) FRI between January 2011 and November 2017 were eligible for inclusion. FRI was considered as either an infection following an open fracture (irrespective of type of treatment), an infection following fracture surgery, or an infection following instrumented fusion for spinal fractures. Skeletally immature patients (<16 years old) and patients undergoing $^{18}$F-FDG PET/CT for reasons other than diagnosing FRI (such as PJI, nontraumatic osteosyntheses or haematogenous osteomyelitis) were excluded. Patients in whom the reference test did not meet the criteria for validity, as described in the section Reference test, were also excluded.

**Index test**

The index test was the $^{18}$F-FDG-PET/CT scan. Scanning protocols were similar in both centres. Scans were acquired approximately 60 min after intravenous administration of 2–3 MBq/kg $^{18}$F-FDG according to existing European Association of Nuclear Medicine (EANM) guidelines for $^{18}$F imaging [8]. Scans were acquired on either a Biograph mCT 64-slice or a Biograph mCT 40-slice PET/CT system (Siemens, Knoxville, TN, USA). No metal artefact reduction algorithm was used in either centre.

After anonymization, the scans were independently reassessed by two experienced nuclear medicine physicians (M.G.G.H. and A.W.J.M.G.). Both the attenuation-corrected images and the images without attenuation correction were reviewed. Both nuclear medicine physicians were blinded to the reference test result. Nuclear imaging signs were documented for each of the scans on a case report form (CRF). These signs included uptake location, uptake pattern (multifocal, heterogeneous, diffuse homogeneous), uptake grade (0: no uptake, 1: higher uptake in the side with suspected infection than in the contralateral side, 2: much higher uptake in the side with suspected infection than in the contralateral side), involvement of osteosynthesis material, and soft-tissue and bone involvement. Disagreements were resolved through discussion until consensus was reached. A clinical case example of the use of $^{18}$F-FDG PET/CT for diagnosing FRI is provided in Figure 1.

For semiquantitative analysis, SUVs were also measured on $^{18}$F-FDG-PET/CT scans reconstructed according to EANM EARL protocols. SUVs correspond to the extent of $^{18}$F-FDG uptake and consequently reflect cellular glucose metabolism. Because glucose metabolism is increased in infected tissues, higher measured SUVs correspond to a greater risk of FRI than lower SUVs [9]. SUVs were determined by drawing a spherical volume of interest (VOI) on both the target area with suspected infection and a corresponding anatomical reference area on the contralateral side. Additionally, a VOI was drawn on nearby muscle for background comparison. For all VOIs, both $SUV_{max}$ (single-pixel value) and $SUV_{peak}$ (average value in a high-uptake part of the VOI) were calculated. For both $SUV_{max}$ and $SUV_{peak}$, the ratios between the suspected infected side and contralateral side were also calculated ($SUV_{maxratio}$

and $SUV_{peakratio}$). To correct for background $^{18}$F-FDG uptake, ratios between SUVs of the suspected infected site and the SUVs of nearby muscles ($SUV_{maxmuscleratio}$ and $SUV_{peakmuscleratio}$) were calculated. These data were reported in a separate CRF as continuous measurements. All SUV measurements were corrected for body weight and blood glucose level and were performed with *syngo*.via software (Siemens Healthineers, Forchheim, Germany).

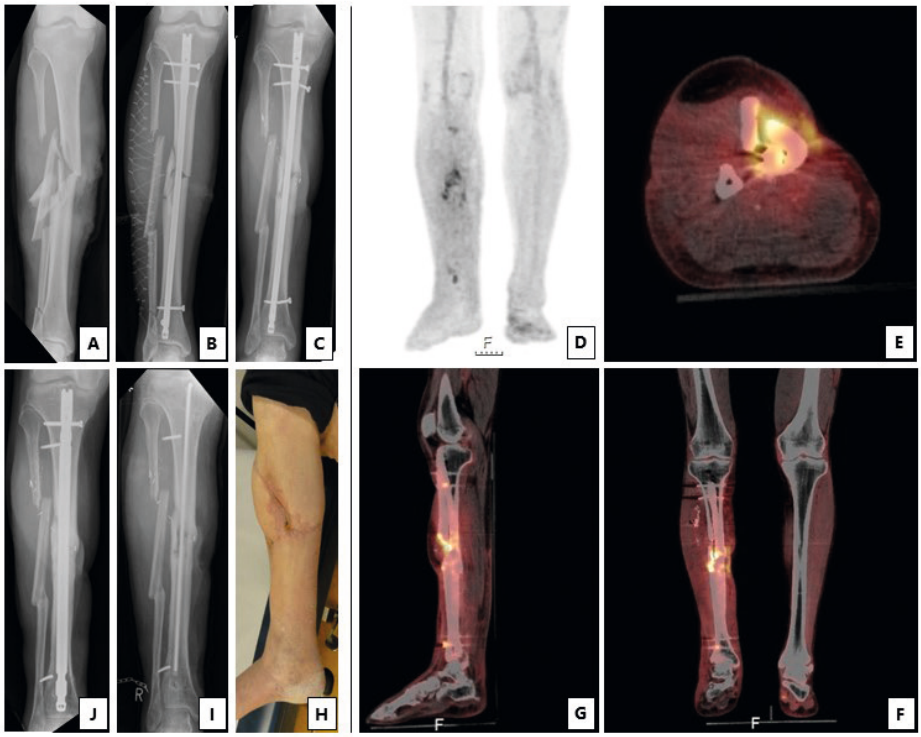


**Figure 1:** Clinical example
Fig. 1 A 59-year-old man sustained a right-sided Gustilo grade IIIB open crural fracture (**a**) which was treated with intramedullary nailing and a fasciotomy (**b**). After several soft-tissue debridement procedures, the remaining soft tissue defect was eventually closed with a free musculocutaneous flap. After 20 months, there was a non-union with "autodynamization" of the intramedullary nail, demonstrated by broken interlocking screws (**c**). The $^{18}$F-FDG PET image (**d**) shows increased uptake around the fracture site in the tibial shaft and around the proximal and distal screws. The hybrid $^{18}$F-FDG PET/CT images (**e** axial, **f** coronal, **g** sagittal) localize the suspected fracture-related infection (FRI) not only to the fracture site but also to the surrounding bone of the tibia around the fracture site which corresponds to the unstable scar overlapping the area of the non-union (**h**). The intramedullary nail was removed, the tibia was reamed, the fracture site was debrided and an in- house, custom-made antibiotic nail was inserted (**i**). FRI was confirmed by microbiological cultures and the patient was subsequently treated with antibiotics. One year after exchange nailing, fracture healing was successful (**j**)

**Reference test**

The final diagnosis of FRI (reference test) was based on the outcome of medical microbiological (MMB) culture results in patients with surgical intervention, or – if unavailable – on clinical follow-up of at least 6 months. Because this study involved the retrospective analysis of culture results obtained in an era when no uniform culturing protocol existed, strict criteria for judging the validity of the reference test were applied. All MMB results were judged by an experienced trauma surgeon on their ability to correctly detect FRI. The microbiological results from swabs and cultures of fistulas were disregarded due to relatively low accuracy [10–12]. The MMB results were only considered representative if cultures of at least two surgically obtained deep-tissue samples from the site of suspected infection were available. A positive FRI result was defined as at least two positive representative MMB cultures with the same microorganism according to the microbiological criteria outlined in the AO/EBJIS consensus definition [4]. FRI during clinical follow-up was defined according to the clinical confirmatory criteria of the AO/EBJIS consensus definition as any wound breakdown, purulent drainage or the presence or development of a sinus tract (communicating with the implant material) [4]. If culture results were negative but confirmatory criteria for FRI were met (e.g. pus, fistula) peroperatively when cultures were taken, FRI was deemed to be present (and the culture result was considered to be erroneous). Culture-negative FRIs are known to be caused by bacteria with low virulence such as coagulase- negative *Staphylococcus* species [13].

## STATISTICAL ANALYSES

To assess the diagnostic performance of the $^{18}$F-FDG PET/CT scan, the number of true-positive (TP), FP, true-negative (TN) and FN test results were obtained. From this, sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV), positive and negative likelihood ratios and diagnostic odds ratios with 95% confidence intervals (CI) were calculated. A sensitivity analysis was performed including only the first scan in each patient to determine whether selection bias of patients undergoing multiple scans may have contributed to differences in diagnostic parameters.

All SUVs were compared between groups using Student's t test (if normally distributed) or the Mann-Whitney *U* test (if not normally distributed). Normality of the data was determined by visual inspection of normality plots. The sensitivity and specificity of the separate SUV measurements were plotted as receiver operating characteristic (ROC) curves and for each curve, the area under the curve (AUC) was calculated. The Q-point on each curve (i.e. the point at which sensitivity and specificity were maximized) was determined and the associated cut-off value was extracted. In addition, an ROC curve was plotted combining the diagnostic performance of SUV measurements with the performance of qualitative assessment. The difference between the ROC curve from the combined analysis and the ROC

curve with only the qualitative assessment was analysed using the test described by DeLong et al. [14]. To ensure that this test was appropriately applied in this situation of nested models, we investigated whether the added variable "combined SUV measurements" in the combined model was independently associated with the outcome [15].

Consequently, a backward stepwise multivariable logistic regression analysis was performed to determine which variables were independent predictors of a false (i.e. FP or FN) test result. Removal testing was performed with the probabilities of the likelihood ratio statistic based on the maximum partial likelihood estimates. Multiple variables suggested in the literature to influence $^{18}$F-FDG-PET/CT accuracy were included in the model [16]. The variables entered were: interval between the last operative procedure (or date of trauma if no operation was performed) and the $^{18}$F-FDG PET/CT scan (ordinal; <1 month, between 1 and 6 months and >6 months), body mass index (continuous), presence of diabetes mellitus (dichotomous), smoking history (dichotomous), nonsteroidal anti-inflammatory drug (NSAID) use at the time of $^{18}$F-FDG PET/CT (dichotomous) and antibiotic use at the time of 18F- FDG PET/CT (dichotomous). Using the final model, the probabilities of false test results were obtained (with 95% CIs) for the different variables. Additionally, the diagnostic performance of qualitative assessment was calculated excluding scans with a high risk of a false test result. All statistical analyses were performed with SPSS Statistics version 25.0 (IBM Corp., Armonk, NY).



## RESULTS

In the study period, 154 patients underwent 176 $^{18}$F-FDG PET/ CT scans for suspected FRI. The reference test was not performed in 18 patients and these patients were excluded. Two $^{18}$F-FDG PET/CT scans in skeletally immature patients were also excluded. A total of 135 patients who underwent 156 $^{18}$F-FDG PET/CT scans were ultimately included. The patient characteristics are summarized in Table 1. The fracture specifics are presented in Table 2, and the types of index operation in Table 3.

**Table 1:** Baseline characteristics.

| Characteristic | Value |
|---|---|
| Age (years), mean (range) | 46.7 (16–76) |
| Sex (male), *n* (%) | 112 (71.8) |
| Body mass index (kg/m$^2$), mean (range) | 27.1 (15.3–48.1) |
| ASA score, *n* (%) | |
| 1 | 58 (37.2) |
| 2 | 73 (46.8) |
| 3 | 10 (6.4) |
| 4 | 1 (0.6) |
| Unknown | 14 (9.0) |
| Injury severity score, *n* (%) | |
| <16 | 91 (58.3) |
| ≥16 | 58 (37.2) |
| Unknown | 7 (4.5) |
| Comorbidities/risk factors at time of $^{18}$F-FDG PET/CT, *n* (%) | |
| Diabetes mellitus | 16 (10.3) |
| Psychiatric disease | 15 (9.6) |
| Obesity | 31 (19.9) |
| Hypothyroidism | 4 (2.6) |
| Hypertension | 19 (12.2) |
| Tobacco use | 63 (40.4) |
| Alcohol abuse | 11 (7.1) |
| Drug abuse | 9 (5.8) |
| NSAID use | 34 (21.8) |
| Corticosteroid use | 3 (1.9) |
| Antibiotic use | 35 (22.4) |

*BMI* Body mass index *ASA* American Society of Anesthesiologists, *ISS* Injury severity score, *NSAID* nonsteroidal anti-inflammatory drug

**Table 2:** Fracture Characteristics.

| Classification | Number (%) of scans |
|---|---|
| AO classification[†] | |
| 1: Humerus fractures | 5 (3.2) |
| 13: Distal | 1 (0.6) |
| 15: Clavicle | 4 (2.6) |

**Table 2:** Fracture Characteristics. (continued)

| Classification | Number (%) of scans |
|---|---|
| 2: Radius/ulna fractures | 8 (5.1) |
| 21: Proximal | 3 (1.9) |
| 22: Diaphyseal | 3 (1.9) |
| 23: Distal | 2 (1.3) |
| 3: Femur fractures | 25 (16.0) |
| 31: Proximal | 1 (0.6) |
| 32: Diaphyseal | 18 (11.5) |
| 33: Distal | 6 (3.8) |
| 4: Tibia/fibula fractures | 88 (56.4) |
| 41: Proximal | 12 (7.7) |
| 42: Diaphyseal | 48 (30.8) |
| 43: Distal | 16 (10.3) |
| 44: Malleolar | 12 (7.7) |
| 5: Spine fractures | 14 (9.0) |
| A: Compression injury | 9 (5.8) |
| B: Distraction injury | 1 (0.6) |
| C: Dislocation injury | 3 (1.9) |
| Unknown | 1 (0.6) |
| 6: Pelvis/sacrum fractures | 5 (3.2) |
| 8: Foot fractures | 11 (7.1) |
| 81: Talus | 3 (1.9) |
| 82: Calcaneus | 6 (3.8) |
| 83: Navicular | 1 (0.6) |
| Unknown | 1 (0.6) |
| Gustilo-Anderson classification¥ | |
| Closed fractures | 68 (43.6) |
| Open fractures | 76 (48.7) |
| Type I | 13 (8.3) |
| Type II | 11 (7.1) |
| Type IIIA | 20 (12.8) |
| Type IIIB | 6 (3.8) |
| Type IIIC | 3 (1.9) |
| Unknown | 23 (14.7) |
| Unknown | 12 (7.7) |

*AO* Arbeitsgemeinschaft für Osteosynthesefragen, † AO Spine Injury Classification was used, ¥ Gustillo-Anderson classification was used

**Table 3:** Index procedures

| Procedure | Number (%) of scans |
|---|---|
| Operative | 150 (96.2) |
| Plate | 53 (34.0) |
| Screw(s) | 16 (10.3) |
| Intramedullary nail | 35 (22.4) |
| Arthrodesis (including spinal fusion) | 14 (9.0) |
| Amputation | 1 (0.6) |
| External fixator | 31 (19.9) |
| followed by: | |
| Plate | 17 (10.9) |
| Screw | 1 (0.6) |
| Intramedullary nail | 5 (3.2) |
| Conservative | 2 (1.3) |
| Unknown | 6 (3.8) |
| Closed reduction/conservative | 5 (3.2) |
| Unknown | 1 (0.6) |

For 67 $^{18}$F-FDG PET/CT scans (43%), a representative MMB culture result was available. These scans were obtained from patients with a median clinical follow-up of 13 months (IQR 20 months), 33 of these scans (49%) were obtained from patients that had a MMB culture-confirmed FRI. *Staphylococcus* species were most commonly cultured (Table 4). In 11 patients, culture results were negative but there were peroperative confirmatory signs of FRI, including purulent drainage, wound breakdown or a fistula communicating with implant material. These patients were scored as positive for FRI.

For 89 $^{18}$F-FDG PET/CT scans (57%), representative MMB culture results were not available. These scans were obtained from patients with a median clinical follow-up of 16 months (IQR 23 months), 18 of these scans were obtained from patients that showed clinical confirmatory signs of FRI, the remainder of these patients had an uneventful clinical follow-up. The 71 remaining patients had an uneventful clinical follow-up. In total, 62 patients were diagnosed with FRI. In 55 of these 62 patients, $^{18}$F-FDG PET/CT was positive for FRI (TP). In 75 of 94 patients negative for FRI, $^{18}$F-FDG PET/CT correctly ruled out an FRI (TN). The $^{18}$F-FDG PET/CT result was FP in 19 patients and FN in 7 patients. Thus, $^{18}$F-FDG PET/CT showed a diagnostic sensitivity of 0.89 (95% CI 0.78–0.95), specificity of 0.80 (95% CI 0.70–0.87), PPV of 0.74 (95% CI 0.66–0.81), NPV of 0.91 (95% CI 0.84–0.96), positive likelihood ratio of 4.39 (95% CI 2.91–6.62), negative likelihood ratio of 0.14 (95% CI 0.07–0.29), and diagnostic odds ratio of 31.0 (95% CI 12.2–78.9). The accuracy of $^{18}$F- FDG PET/CT for diagnosing FRI

was 0.83 (95% CI 0.77– 0.89). The sensitivity analysis including only the first $^{18}$F- FDG PET/CT scan in each patient (n = 135) resulted in similar diagnostic parameters: sensitivity 0.91 (95% CI 0.80– 0.97), specificity 0.81 (95% CI 0.70–0.89), PPV 0.77 (95% CI 0.68–0.84), NPV 0.93 (95% CI 0.84–0.97) and diagnostic accuracy 0.85 (95% CI 0.78–0.91).

**Table 4:** Microbiological findings in 33 patients with MMB culture- confirmed FRI in relation to the $^{18}$F-FDG PET/CT result.

| **Species cultured** | **$^{18}$F-FDG PET/CT result** | |
|---|---|---|
| | **True-positive** | **False-negative** |
| | **(N = 31)** | **(N = 2)** |
| *Staphylococcus aureus* | 12 | 1 |
| Coagulase-negative *Staphylococcus* spp | 10 | |
| *Streptococcus* spp. | 4 | |
| *Corynebacterium* spp. | 2 | |
| *Enterococcus* spp. | 4 | |
| *Finegoldia magna* | | 1 |
| *Actinomyces neuii* | 1 | |
| *Propionibacterium acnes* | 1 | |
| *Pseudomonas aeruginosa* | 4 | |
| *Escherichia coli* | 2 | |
| *Enterobacter cloacae* | 2 | |
| *Serratia marcescens* | 1 | |
| *Fusobacterium gonidiaformans* | 1 | |
| *Bacteroides thetaiotaomicron* | 1 | |
| *Proteus vulgaris* | 1 | |
| *Klebsiella oxytoca* | 1 | |
| *Morganella morganii* | 1 | |
| *Bacteroides fragilis* | 1 | |
| Polymicrobial | 11 | 1 |

**Semiquantitative measurements**

Semiquantitative measurements are presented in Table 5. Patients with FRI had a median $SUV_{max}$ of 5.9 (IQR 3.5) and median $SUV_{peak}$ of 4.7 (IQR 2.4) in the area with suspected infection. Patients without FRI had a median $SUV_{max}$ of 3.2 (IQR 2.5)

and a median $SUV_{peak}$ of 2.6 (IQR 1.9) in the area initially suspected of infection. The differences in both $SUV_{max}$ and $SUV_{peak}$ between the groups were significant (both $p < 0.001$). In patients with FRI, the SUV ratios for the area with suspected infection in relation to the contralateral area were 3.0 (IQR 2.1) for $SUV_{max}$ and 2.9 (IQR 2.0) for $SUV_{peak}$. In patients without FRI, the ratios were 1.9 (IQR 1.4) and 1.8 (IQR 1.4), respectively. Both ratios were significantly different between patients with and without FRI ($p < 0.001$). In patients with FRI, the SUV ratios for the area with suspected infection in relation to nearby muscle were 6.4 (IQR 4.9) for $SUV_{max}$ and 5.5 (IQR 3.6) for $SUV_{peak}$. In patients without FRI, the ratios were 3.5 (IQR 3.0) and 3.3 (IQR 2.9), respectively. These ratios were also significantly different between patients with and without FRI ($p < 0.001$)

**Table 5:** Semi-quantitative measurement data

| | **All $^{18}$F-FDG PET/CT scans (N = 155)[a]** | **$^{18}$F-FDG PET/CT scans positive for FRI (N = 61)[a]** | **$^{18}$F-FDG PET/CT scans negative for FRI (N =94)** | **p value** |
|---|---|---|---|---|
| $^{18}$F-FDG dose (MBq) | 193.0 (77.0) | 199.0 (132.0) | 192.0 (70.0) | 0.287 |
| Blood glucose (mmol/l) | 5.6 (1.0) | 5.7 (0.9) | 5.5 (1.1) | 0.241 |
| $SUV_{max}$ | | | | |
| Infection location | 4.2 (3.4) | 5.9 (3.5) | 3.2 (2.5) | < 0.001 |
| Contralateral location | 1.7 (0.7) | 1.8 (0.9) | 1.7 (0.7) | 0.039 |
| Ratios[b] | | | | |
| Infection/Contralateral | 2.1 (1.8) | 3.0 (2.1) | 1.9 (1.4) | < 0.001 |
| Infection/Muscle | 4.6 (3.9) | 6.4 (4.9) | 3.5 (3.0) | < 0.001 |
| $SUV_{peak}$ | | | | |
| Infection location | 3.5 (2.7) | 4.7 (2.4) | 2.6 (1.9) | < 0.001 |
| Contralateral location | 1.4 (0.7) | 1.5 (0.7) | 1.4 (0.7) | 0.070 |
| Ratios[b] | | | | |
| Infection/Contralateral | 2.1 (1.8) | 2.9 (2.0) | 1.8 (1.4) | < 0.001 |
| Infection/Muscle | 4.1 (3.4) | 5.5 (3.6) | 3.3 (2.9) | < 0.001 |

Data are presented as medians (interquatile range (IQR))
*FRI* fracture-related infection
[a] SUV measurements could not be retrieved in one patient for technical reasons.
[b] Ratios were calculated by dividing the SUV of the suspected infected area by the SUV of the contralateral area / nearby muscle; a value of >1 signifies higher uptake in the suspected infected area.

ROC curves for the semiquantitative SUV data are shown in Figure 2. The area's under the curve were 0.80 (95% CI 0.73-0.88) for $SUV_{max}$, 0.73 (95%CI 0.64-0.81) for $SUV_{maxratio}$ and 0.77 (95% CI 0.70-0.85) for $SUV_{maxmuscleratio}$. Optimal sensitivity and specificity for $SUV_{max}$ were 0.80 and 0.72 at a cut-off value of 4.2. The PPV and NPV for

$SUV_{max}$ at this cut- off value were 0.65 and 0.85, respectively. For $SUV_{maxratio}$, sensitivity was 0.75 and specificity was 0.62 at a cut-off value of 2.0, and for $SUV_{maxmuscleratio}$, sensitivity was 0.74 and specificity was 0.68 at a cut-off value of 4.7. The diagnostic parameters and associated cut-off values for $SUV_{peak}$ were similar to those for $SUV_{max}$ and are also shown in Figure 2.

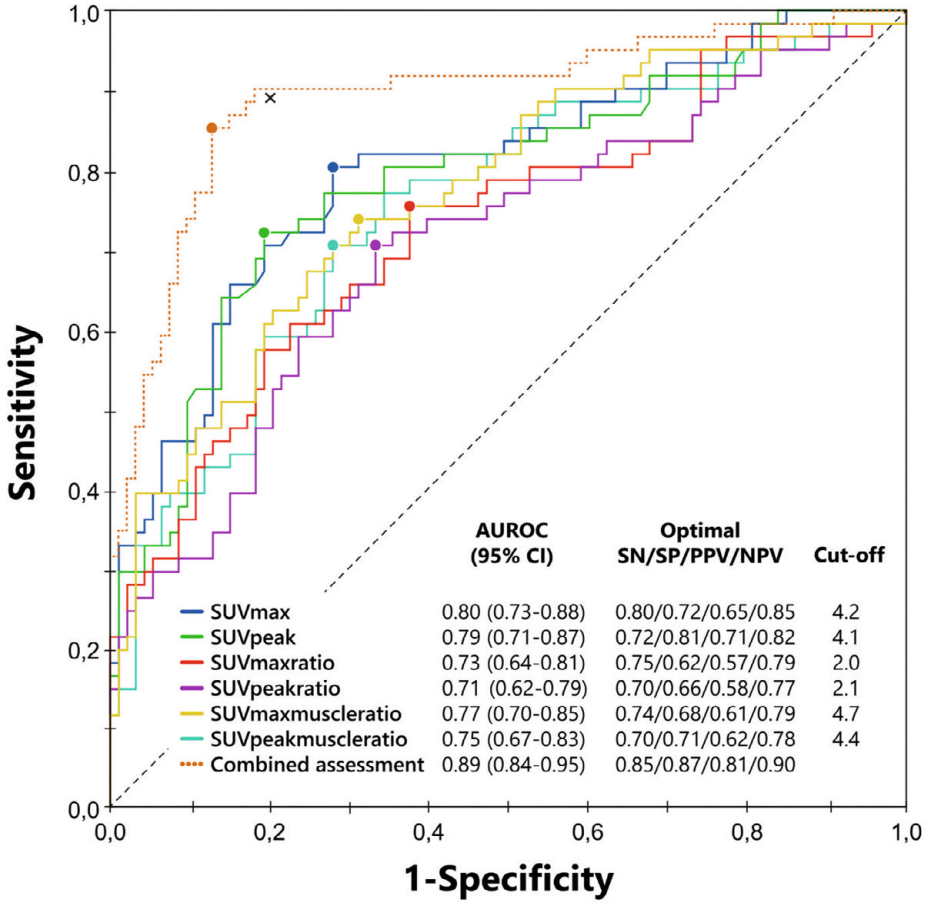


**Figure 2.** Receiver operating characteristics (ROC) curves for the semiquantitative SUV measurements analysed separately and in combination with the qualitative $^{18}$F-FDG PET/CT assessment data. The *circles* on the curves represent the Q-points (i.e. the optimum between sensitivity and specificity at a specific cut-off value). The *cross* represents the sensitivity and specificity of the qualitative $^{18}$F-FDG PET/CT assessment. This point is higher than any of the Q-points for the semiquantitative measurements alone. The area under the curve for the combined qualitative and semi-quantitative assessment (dotted line) is 0.89, higher than the areas under the curve for the semiquantitative measurements analysed separately and also higher than the AUC of the qualitative assessment alone. *AUROC* area under the receiver operator characteristics curve, *SN* sensitivity, *SP* specificity, *PPV* positive predictive value, *NPV* negative predictive value.

Combining the SUV measurement data with the qualitative assessment of $^{18}$F-FDG PET/CT scans in a separate ROC curve yielded an AUC of 0.89 (95% CI 0.84–0.95) and a diagnostic accuracy of 0.86 (sensitivity 0.85, specificity 0.87, PPV 0.81, NPV 0.90), in contrast to an AUC of 0.84 (95% CI 0.78–0.91) and a diagnostic accuracy of 0.83 for the qualitative assessment on its own. The added explanatory variable "combined SUV measurements" was independently associated with the presence/absence of FRI and comparison of the ROC curves was deemed appropriate. The AUC of the combined assessment was 0.05 (95% CI 0.01–0.09) greater than the AUC of the qualitative assessment alone (p = 0.007).

**False negative/false positive patient characteristics**

Seven patients were included with a FN test result. Two patients had positive intraoperative cultures, while five patients showed confirmatory signs peroperatively or during the 6-month follow-up. Two patients had (low-grade) infection of a non-union (both ankle fractures). Another patient (with two scans) showed peroperative signs of FRI in the tibia (infected tissue and pus) despite microbiological cultures remaining negative. There were 19 patients with a FP test result. These included two patients with a lower arm fracture, two with a femoral fracture, two with a tibial plateau fracture, seven with a lower leg fracture, two with an ankle fracture, two with a talar fracture and two with a spinal fracture. Eight patients had a negative intraoperative culture, 11 had no cultures taken but showed no signs of FRI during the 6-month follow-up. Five patients (26%) with a FP result underwent surgery during the week before the $^{18}$F-FDG PET/CT scan (one with a tibial fracture, one with a talar fracture, one with an ankle fracture, and two with a tibial plateau fracture). These scans were performed to determine if the FRI had receded or was still advancing in patients who underwent surgery for suspected FRI shortly before the scan.

**Predictors of a false test result**

The most important predictor of a false test result was an interval of <1 month between the last operative procedure and the $^{18}$F-FDG-PET/CT scan (*B* = 2.461; intercept = -2.615). The associated absolute predicted risk of a false result with this variable was 46% (95% CI 27–66%) compared with an absolute predicted risk of the reference group (with an interval of 1–6 months) of 7% (95% CI 4–12%). In patients with an interval of >6 months, the absolute risk was 17% (95% CI 10–29%). The test result was erroneous in 6 of 14 patients (42.9%) undergoing $^{18}$F-FDG PET/CT within 1 month (FP in all six patients). The rate of erroneous test results reduced to 8.9% (4 of 45 patients) in those with an interval between 1 and 6 months, and showed a slight increase to 16.8% (16 out of 95 patients) in those with an interval of more than 6 months. Omitting the results from the early $^{18}$F- FDG PET/CT scans (performed within 1 month of surgery) led to an increase in diagnostic accuracy of the qualitative assessment to 0.86 (95% CI 0.79–0.91) with a sensitivity and specificity of 0.88 (95% CI 0.76–0.95) and 0.85 (95% CI 0.76–0.92), respectively.

## DISCUSSION

The current study showed that qualitative assessment of $^{18}$FDG-PET/CT scans has good performance in diagnosing FRI with a diagnostic accuracy of 0.83 (95% CI 0.77-0.89) and an AUC of 0.84 (95% CI 0.78–0.91). The NPV (0.91) was notably higher than that of most other imaging modalities, and makes $^{18}$FDG PET/CT an excellent tool for use in patients with chronic or low-grade infections [5]. Combining the results of qualitative assessment and SUV measurements resulted in an even higher diagnostic accuracy (0.86) and an AUC of 0.89 (95% CI 0.84–0.95), which shows that including SUV measurements increased diagnostic accuracy, although the increase was relatively small.

The sensitivity and specificity rates found in this study are in line with those found in other studies on the accuracy of $^{18}$F-FDG PET/CT in diagnosing FRI [5,9]. However, this study also included semiquantitative measurements and used strict $^{18}$F-FDG PET/CT assessment and reference test criteria (based on the recently released AO/EBJIS consensus definition of FRI) [4]. It also included the largest series to date of patients with suspected FRI undergoing hybrid $^{18}$F-FDG PET/ CT imaging. One systematic review and meta-analysis investigating the accuracy of different imaging modalities for diagnosing chronic osteomyelitis showed higher diagnostic accuracy of $^{18}$F-FDG PET with a pooled sensitivity of 0.96 and a specificity of 0.91 [6]. That study, however, included only studies published before 2003 and investigated only $^{18}$F- FDG PET without fusion CT images, which is now rarely used following the advent of $^{18}$F-FDG PET/CT scanners. In addition, reference test criteria were unclear in some of the studies reviewed and the studies included few patients and a relatively large number of spinal $^{18}$F-FDG PET/CT scans. A more recent systematic review found that the sensitivities and specificities of $^{18}$F-FDG-PET/CT in diagnosing FRI ranges between 0.86–0.94 and 0.76–1.00, respectively [5]. These results, as well as the methodology used (patient population and reference standard) are comparable to those used in our study.

There is only limited research on the accuracy of quantification in diagnosing FRI. A recent study on the accuracy of SUV measurements from $^{18}$F-FDG PET/CT for diagnosing FRI found a sensitivity of 0.65 and specificity of 0.77 at a $SUV_{max}$ cut-off value of 4.0 [17]. These values are lower than those published previously for qualitative assessment of $^{18}$F-FDG PET/CT scans [5]. The reason for this could be that the previous SUV measurement study used only $^{18}$F-FDG PET/CT to differentiate between infected non-unions and aseptic non-unions. In both circumstances, increased bone metabolism will often be found, and thus differences between $^{18}$F-FDG uptake will be limited. The cut-off value of 4.0 used in the previous study is similar to the $SUV_{max}$ cut-off value found in the current study (4.2). Unfortunately, the validity of the results is difficult to compare between our study and the previous

study, because it is unclear whether the standardized EARL scanning protocols were used in the latter [18]. Additionally, only semiquantitative measurements, and no qualitative criteria (such as uptake pattern and grade) for diagnosing FRI were used. SUV measurements do not take into account the activity pattern and uptake location, and can be positive as a consequence of both bone healing and/or non-union. Therefore, using only semiquantitative data might lead to misclassification of some patients. This is supported by the results of our study, in which the diagnostic accuracy of the qualitative assessment by the nuclear medicine physicians was higher than the accuracy when using SUVs alone. This phenomenon was also seen in a large study of patients with FRI which demonstrated a diagnostic accuracy of 0.82 with qualitative assessment of $^{18}$F-FDG PET(/CT) scans and a lower accuracy with only semiquantitative measurements ($SUV_{max}$ sensitivity 0.69, specificity 0.66 using a cut-off value of 3.9) [9]. Another study investigating SUVs in histologically proven culture-positive and culture-negative patients with FRI showed that SUVs in both groups of patients were similar ($SUV_{max}$ 3.73 in culture-positive patients, 2.81 in culture-negative patients) [19]. The findings of these studies, as well as those of the current study, add to the mounting evidence that semiquantitative measurements can be used as additional diagnostic tools for diagnosing FRI.

WBC scintigraphy has been more thoroughly investigated as an imaging modality for diagnosing FRI. Our previous study of WBC scintigraphy found a diagnostic accuracy of 0.92, which is higher than the diagnostic accuracy found in the current study for $^{18}$F-FDG PET/CT [7]. However, $^{18}$F-FDG PET/CT does have several advantages over WBC scintigraphy. First, there is no need for manipulation of leukocytes, which is a labourious and expensive part of WBC scintigraphy [20]. Second, $^{18}$F-FDG PET/CT can be performed much more quickly (1 h following radionuclide injection) and takes only one scanning session, as opposed to WBC scintigraphy, which takes at least two scans (4 h and 20–24 h after radionuclide injection) on two consecutive days [20]. Third, WBC scintigraphy has lower accuracy when used for diagnosing infections in the axial skeleton due to physiological uptake in the bone marrow, while $^{18}$F-FDG PET/CT does not have this limitation [16]. $^{18}$F-FDG PET/CT has the disadvantage that implants negatively affect diagnostic accuracy, although in some studies, this effect has not been shown [5,9]. With the recent onset of several techniques for metal artefact reduction in the newest generation PET/CT camera systems, the diagnostic performance of both qualitative assessment and quantification in patients with an implant and suspected FRI can probably be improved further. Ultimately, both imaging modalities have their specific advantages and limitations and although $^{18}$F-FDG PET/CT has lower accuracy than WBC scintigraphy, its advantages in terms of logistics and patient comfort make it a good alternative to WBC scintigraphy as the first nuclear imaging modality to perform when diagnosing FRI. Thus, both modalities can be used to diagnose FRI depending on physician/hospital preference, financial considerations, and/or experience with either technique.

We found that performing the $^{18}$F-FDG PET/CT scan <1 month following surgery was correlated with a FP $^{18}$F-FDG PET/CT result. It is known that operative procedures cause tissue damage and inflammation/regeneration, and affected tissue shows increased uptake of $^{18}$F-FDG, especially when the interval between the $^{18}$F-FDG PET/CT and surgery is short [16]. Five of the FP $^{18}$F-FDG PET/CT scans were performed within a week of an operative procedure. Both nuclear medicine physicians reassessing these scans for this study agreed that in some of these scans, inflammation due to surgery was indistinguishable from FRI. We conclude that $^{18}$F-FDG PET/CT should therefore not be performed as a diagnostic tool within a month of surgery. If (per protocol) early (<1 month after surgery) $^{18}$F-FDG PET/CT scans for suspected FRI are no longer performed, diagnostic accuracy can be expected to improve, in this study exclusion of such early scans led to an increase in accuracy from 0.83 to 0.86.

The strengths of the current study are the large cohort size, and the fact that a robust, standardized and repeatable scan assessment was performed by two independent nuclear medicine physicians (one from each hospital) who were blinded to the reference standard. We also used strict reference standard criteria to determine whether FRI was present or not, based on the recently published FRI consensus definition [4]. Finally, the addition of SUV measurements and SUV analysis provided additional insight into its merits and its performance compared to standard qualitative assessments.

The limitations of the current study include its retrospective design, with the associated risks of selection- and differential misclassification bias. Patients were recruited in two different teaching hospitals, thus there may have been differences in the diagnostic work-up and treatment of FRI, as each hospital has its own standard of care. Also, in some patients, FRI had already been diagnosed and the $^{18}$F-FDG PET/CT scans were used for treatment follow-up. This mainly occurred at the beginning of the study period; since then, stricter protocols have been adopted, which aim to standardize both $^{18}$F-FDG PET/CT indications and microbiological culture acquisition and treatment regimens. Finally, it is important to remember that the combined assessment by two nuclear medicine specialists might have led to a higher diagnostic accuracy than can be obtained in the normal clinical situation, in which only one nuclear medicine physician reviews a scan. Further prospective studies to compare different imaging modalities for diagnosing FRI are warranted.

**Conclusion**

The results of the study can be summarized as follows:

1. Qualitative assessment of $^{18}$F-FDG PET/CT scans has good accuracy (0.83) for diagnosing FRI, with an excellent NPV of 0.91.
2. SUV measurements provide additional diagnostic accuracy when added to qualitative assessment of $^{18}$F-FDG PET/CT scans.
3. $^{18}$F-FDG PET/CT should not be performed for diagnosis within a month of surgery.

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# CHAPTER 5

## Outcome and risk factors for recurrence of early onset fracture-related infections treated with debridement, antibiotics and implant retention: results of a large retrospective multicentre cohort study

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## ABSTRACT

**Introduction**

Early Fracture-Related Infections (FRIs) are a common entity in hospitals treating trauma patients and are often treated with a Debridement, Antibiotics and Implant Retention (DAIR) procedure. Aims of this study were to 1) evaluate the recurrence rate after DAIR procedures for early onset FRI, 2) establish the number of surgical procedures to gain control of the initial infection and 3) identify independent predictors for recurrence in this cohort.

**Methods**

A retrospective multicentre cohort study was conducted in two level 1 trauma centres. Consecutive patients who underwent a DAIR procedure between January 1st 2015 and July 1st 2020 for confirmed FRI with an onset of <6 weeks after the latest osseous operation were included. Recorded data included patient demographics, treatment characteristics and follow-up. Univariate and multivariate logistic regression analyses were performed to assess predictors for recurrent FRI.

**Results**

A total of 141 patients with early FRI were included in this study with a median age of 54.0 years (interquartile range (IQR) 34.5-64.0). The recurrence rate of FRI was 13% (n = 19) at one year follow-up and 18% (n = 25) at 23.1 months (IQR 15.3-36.4) follow-up. Infection control was achieved in 94% (n = 127/135) of cases. In total, 73 patients (52%) underwent at least two surgical procedures to treat the ongoing initial episode of FRI, of whom 54 patients (74%) required two to three procedures and 17 patients (23%) four to five procedures. Predictors for recurrent FRI were use of an intramedullary nail during index operation (odds ratio (OR) 4.0 (95% confidence interval (CI) 1.1-13.8)), need for additional surgical procedures to treat ongoing infection during the treatment period following the first presentation of early FRI (OR 1.9 (95% CI 1.1-3.5)) and a decreased Injury Severity Score (ISS) (inverted OR 1.1 (95% CI 1.0-1.1)).

**Conclusion**

The recurrence rate after treatment of early onset FRI in patients treated with a DAIR procedure was 18% at 23.1 months follow-up. At least two surgical procedures to gain control of the initial infection were needed in 52% of patients. Independent predictors for recurrent FRI were the use of an intramedullary nail during index operation, need for additional surgical procedures and a decreased ISS.

## INTRODUCTION

Fracture-Related Infections (FRIs) are among the most challenging complications in fracture care [1]. As the clinical presentations of FRI vary widely, the FRI Consensus Group proposed a consensus-based definition for this disease [2]. Classification methods, such as by infection location, duration or onset, were not included in this consensus definition. Historically however, based on the clinical differences, the presentation of FRI was related to the time of onset of infection after the initial surgery [3]. One approach was to divide FRIs in early (<6 weeks) and late onset (≥6 weeks) infections [4], another is to divide FRI in early (≤2 weeks), delayed (3 to 10 weeks) and late onset (>10 weeks) infections [5]. Even though these distinctions are arbitrary, they are still used in many protocols to guide treatment as challenges in terms of fracture and soft tissue management are thought to be important [3]. For example, due to the maturation of the biofilm over time and increasing osteolysis and necrosis of the affected bone, late onset FRIs are generally considered to be more difficult to eradicate compared to early onset FRIs [6].



In general, early onset FRIs occur at a time when fracture healing is still ongoing and therefore the stability of the fracture depends on the additional strength of an implant [7]. As a result, complete removal of the implant is often not an option in early FRI which forces the surgeon to decide whether the implant can be retained or should be exchanged for another fixation device [7]. Due to reduced maturation of the biofilm and generally healthier appearing bone and soft tissues in early FRIs, this results in a more frequent consideration of implant retention in cases with stable fracture fixation and good fracture reduction [7,8]. In these cases, an often challenging Open Reduction and Internal Fixation (ORIF) procedure is compromised by the chance of losing reduction and stability when an implant is (temporarily) removed. A so-called DAIR (Debridement, Antibiotics and Implant Retention) procedure, which is often performed for treatment of both early onset FRIs and Periprosthetic Joint Infections (PJIs) [9,10], is preferred in these cases. Besides stability of the fracture, other important factors such as vital soft tissues, the technical ability to perform a proper debridement, susceptibility of the pathogen and absence of major impairments regarding the host physiology determine whether a DAIR procedure can be performed [11,12].

Although recent literature has given more insight regarding the management of early onset FRI and the outcome of DAIR procedures for these patients [12], it remains challenging to accurately counsel patients about the expected course of their disease [2,4]. Therefore, the aims of this study were to 1) evaluate the recurrence rate after DAIR procedures for early onset FRI, 2) establish the number of surgical procedures needed to gain control of the initial infection in the same treatment period as the first FRI and 3) identify predictors for FRI recurrence in the cohort.

## PATIENTS AND METHODS

### Study design

A retrospective multicentre cohort study was performed. All consecutive patients diagnosed with FRI between January 1st 2015 to July 1st 2020 treated in either the University Medical Centre Utrecht (UMCU) or the University Medical Centre Groningen (UMCG), both level 1 trauma centres in the Netherlands, were eligible for inclusion in this study. A waiver was granted by the Medical Ethics Review Committee (METC-20-004/C) of the UMCU.

### In- and exclusion criteria

Patients of at least 16-years of age with early onset FRI of <6 weeks after the latest osseous operation were eligible for inclusion. The latest osseous operation was defined as the intervention that most likely caused the FRI, which could therefore be the surgical fracture stabilisation procedure, but also a revision operation or removal of implants only. Solely patients who underwent a DAIR procedure for the (suspected) early onset FRI were included in this study. Additionally, during the first DAIR procedure, at least three separate intraoperative deep tissue cultures had to be obtained. FRI was defined according to the FRI consensus criteria and at least one confirmatory criterion had to be met (Table 1) [2,13–15]. Lastly, patients with spinal or skull fractures and fractures of the small bones of the hand or foot were not eligible for inclusion. All patients who did not meet these criteria were excluded. Moreover, patients with inadequate availability of data needed for this study were excluded, as well as patients who were lost to follow-up within <12 months after treatment of the initial FRI. Discharge from follow-up by the treating medical team, death or amputation within <12 months was not defined as loss to follow-up and these patients will therefore be included in this study. Patients discharged from follow-up were required to have complete fracture consolidation, absence of both confirmatory and suggestive criteria, and were instructed to contact the treating centre if recurrence of symptoms occurred.

### Early FRI and DAIR treatment protocol

A treatment protocol for the management of patients with early onset FRI was used in both centres. All surgical interventions were performed or supervised by an experienced board-certified trauma surgeon. According to these protocols, the preferred treatment method in case of early onset FRI with a stable fracture fixation was a DAIR procedure [3,11]. Ensuring adequate soft tissue coverage was considered an essential part of the operative procedure [3]. Intravenous (IV) empiric antimicrobial therapy was started immediately after surgical debridement and tissue sampling for microbiological culturing [14]. Based on the definitive microbiological results, targeted antimicrobial treatment was initiated in consultation with Infectious Diseases specialists. Biofilm targeting antibiotic therapy such as Rifampicin was

added if deemed appropriate. Antimicrobial treatment was continued for a duration of twelve weeks following any procedure where implants remained in situ [11].

**Table 1.** Confirmatory and suggestive FRI [1] consensus criteria.

| **Confirmatory and suggestive FRI consensus criteria** | |
|---|---|
| **Confirmatory criteria** | **Suggestive criteria** |
| *Fistula, sinus tract or wound breakdown* | *Clinical signs (local & systemic) ** |
| *Presence of pus in the fracture* | *Radiological signs and/or nuclear imaging signs *** |
| *Phenotypically indistinguishable organisms identified from two or more separate deep tissue specimens* | *Pathogen identified from a single deep tissue specimen* |
| *Visible microorganisms on histological analysis* | *Elevated serum inflammatory markers:*<br>*Erythrocyte sedimentation rate (ESR)*<br>*Leukocyte count (LC)*<br>*C-reactive protein (CRP)* |
| *Presence of five or more neutrophils per high power field on histology* [2] | *Persistent wound drainage* |
| | *New onset of joint effusion* |

** Clinical signs (local & systemic): redness, pain, swelling, fever (>38.3 °C), persistent/ increasing or new onset wound drainage, increased local temperature*
*** Failure of progression of bone healing (nonunion), implant loosening, bone lysis, sequestration, periosteal bone formation, cloacae, sinus tracts, and/or subcortical abscesses and increased tracer uptake*

Adapted from McNally M, Govaert G, Dudareva M, Morgenstern M, Metsemakers W-J. Definition and diagnosis of fracture-related infection. EFFORT Open Reviews 2020;5:614–9 [13].

[1] Fracture-Related Infection [2] Only a confirmatory criterion in FRI with an onset ≥ 8 weeks [13]

**Data collection**

Data was collected using the combined FRI database of both study centres and additionally by reviewing electronic patient files of the included patients. All relevant data with regard to the management of FRI were collected, including patient demographics, treatment characteristics and outpatient follow-up along with documentation of all re-admissions and re-operations for each patient. All data was entered and stored in the data capturing program Castor EDC (Castor Electronic Data Capture, v2021.5.3) and was pseudonymised [16].

Patient characteristics were identified, including sex, age, Body Mass Index (BMI), American Society of Anaesthesiologists (ASA) classification, comorbidities such as diabetes mellitus and obesity, and possible risk factors such as alcohol abuse, smoking and drug use [11,17,18]. The Injury Severity Score (ISS) was used to assess

the severity of the trauma that caused the fracture [19]. Fractures were classified according to the Arbeitsgemeinschaft für Osteosynthesefragen/Orthopaedic Trauma Association (AO/OTA) fracture classification [20]. Furthermore, open fractures were classified according to the Gustilo-Anderson classification [21]. Thresholds of 5.0 mg/L and $10 \cdot 10^9$/L were utilised to assess C-reactive protein (CRP) and Leukocyte Count (LC), respectively [22].

**Study outcomes**

The primary endpoint of this study was the recurrence rate after early onset FRI in patients treated with a DAIR procedure. A recurrent FRI was defined as the re-appearance of at least one confirmatory FRI criterion after completion of the surgical and antibiotic treatment of the initial early onset FRI. Infection control was defined as absence of amputation, absence of confirmatory FRI criteria and absence of ongoing treatment with antimicrobials at the last follow-up appointment. The secondary endpoint was to establish the number of surgical procedures. Need for additional surgical procedures was defined as the need for any extra operative washout and/or debridement procedure(s) to treat ongoing infection during the treatment period following the first presentation of early FRI, frequently due to persisting wound leakage. This could either be executed as an additional DAIR or a non-DAIR procedure. The tertiary endpoint was the identification of possible predictors of a recurrent FRI.

**Statistical analysis**

Data was either presented as dichotomised variables in counts and percentages (n (%)) or as continuous variables with mean and standard deviation (SD) when normally distributed, or as median and interquartile range (IQR) when not normally distributed. A Chi-Squared test or Fisher's exact test was performed for dichotomised values according to the estimated cell size. An independent t-test or Mann-Whitney U test were performed for continuous variables, depending on the normality test of the variable.

A univariate analysis was performed to identify possible predictors that could lead to a recurrent FRI. Variables that were previously thought to contribute to an increased recurrence rate [23] were selected and tested individually against the primary outcome in a logistic regression model. All variables demonstrating a p-value of <0.10 after univariate analysis were selected and included in the initial model. If overfitting of the model was imminent when using the selected variables at a p-value of <0.10, a lower p-value was used, so that a minimum of 5-10 events per predictor were utilised. A backward, stepwise logistic method was subsequently used, excluding variables from the multivariate model until only variables with a p-value of <0.05 remained [24]. The corresponding odds ratio (OR) with 95% confidence interval (95% CI) were calculated for each parameter to demonstrate

its contribution to FRI recurrence. A p-value of <0.05 was considered as statistically significant. All data analyses were executed in Statistical Package for the Social Sciences (SPSS®) statistics (version 26.0, Armonk, NY, USA: IBM Corp.).

## RESULTS

### Baseline characteristics

The FRI database used for this study consisted of 352 patients and 141 patients were ultimately included in this study. Of these 141 patients, whom all underwent a DAIR procedure as per study protocol, 101 patients (72%) were treated in the UMCU and 40 (28%) in the UMCG. The flow diagram of the in- and exclusion process is shown in Figure 1.

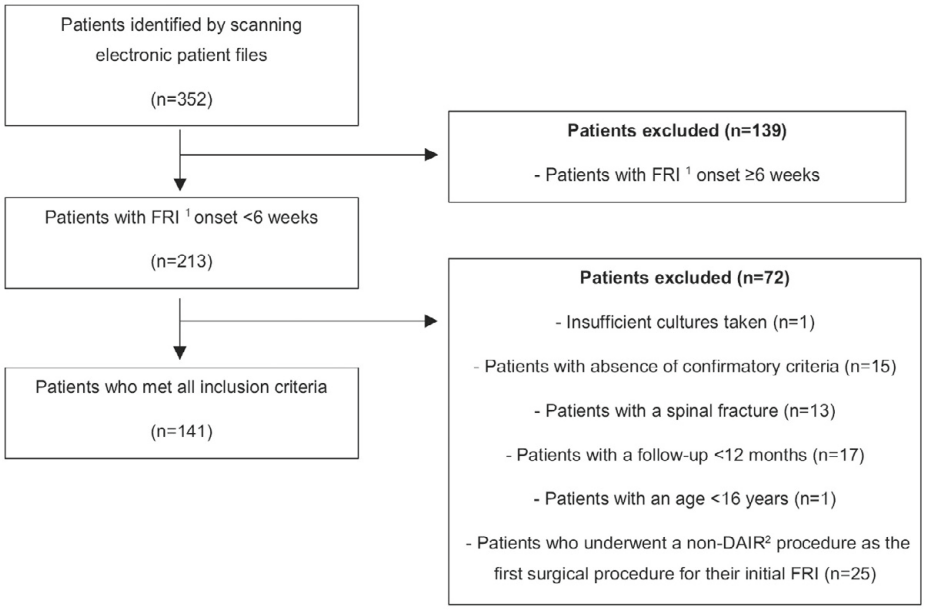


**Figure 1.** In- and exclusion diagram of early onset FRI [1] patients.

The baseline characteristics are displayed in Tables 2 and 3. The cohort consisted of a majority of males (64%, n=90). The median age was 54.0 years (IQR 34.5-64.0). The most common fracture sites were the tibia/fibula (48%, n = 67), femur (20%, n = 28) and pelvis (15%, n = 21). Of all fractures, 71% (n=100) were closed fractures. The median timeframe between the latest osseous operation and onset of FRI symptoms was 14.0 days (IQR 10.0-19.0) (Table 2). In total, 129 patients (91%) started immediately with empiric broad spectrum IV antimicrobial therapy, which was subsequently narrowed according to the microbiological results. Out of the 12 patients (9%) that were not started on IV antimicrobial therapy immediately, nine patients (6%) received IV antimicrobial therapy as soon as the obtained cultures became positive, two patients (1%) received oral antimicrobial therapy

only and one patient (1%) did not receive antimicrobial therapy due to amputation of the affected limb. The total duration of the initial course of antimicrobial therapy was 12.0 weeks (IQR 11.0-13.0), as per institutional protocol. Addition of Rifampicin during the treatment of the initial FRI was common and administered to 65% (n = 91) of patients.

**Table 2.** Baseline patient- and fracture characteristics.

| | All patients (n=141) | No recurrent FRI (n=116) | Recurrent FRI (n=25) | p-value |
|---|---|---|---|---|
| **Patient characteristics** | | | | |
| *Sex (male)* | 90 (64%) | 74 (64%) | 16 (64%) | 0.98 |
| *Age (years)* | 54.0 (34.5-64.0) | 53.5 (34.3-65.0) | 57.0 (38.5-60.5) | 0.60 |
| *Body Mass Index (kg/m²) (n=140)* | 26.4 (23.4-30.3) | 26.4 (23.4-30.6) | 26.4 (23.5-30.2) | 0.98 |
| *Injury Severity Score (n=122)* | 13.0 (9.0-22.0) | 13.0 (9.0-22.0) | 10.0 (6.5-15.0) | 0.06 |
| *Injury Severity Score categorised (n=122)* | | | | 0.23 |
| *<16* | 75 (61%) | 56 (58%) | 19 (76%) | |
| *16-24* | 25 (20%) | 21 (22%) | 4 (16%) | |
| *>24* | 22 (18%) | 20 (21%) | 2 (8%) | |
| *Follow-up (months)* | 23.1 (15.3-36.4) | 21.8 (14.7-33.5) | 27.6 (20.5-43.1) | **0.008** |
| *Comorbidities* | | | | |
| *Diabetes mellitus* | 17 (12%) | 15 (13%) | 2 (8%) | 0.78 |
| *Obesity (n=140)* | 37 (26%) | 30 (26%) | 7 (28%) | 0.84 |
| *Risk factors* | | | | |
| *Smoking (n=136)* | 39 (29%) | 34 (31%) | 5 (20%) | 0.29 |
| *Drugs (n=132)* | 7 (5%) | 7 (7%) | 0 (0%) | 0.35 |
| *Alcohol abuse (n=139)* | 9 (6%) | 9 (8%) | 0 (0%) | 0.36 |
| *ASA classification* [1] | | | | |
| *ASA 1* | 34 (24%) | 28 (24%) | 6 (24%) | 0.28 |
| *ASA 2* | 75 (53%) | 58 (50%) | 17 (68%) | |
| *ASA 3* | 29 (21%) | 27 (23%) | 2 (8%) | |
| *ASA 4* | 3 (2%) | 3 (3%) | 0 (0%) | |

**Table 2.** Baseline patient- and fracture characteristics. (continued)

| | All patients (n=141) | No recurrent FRI (n=116) | Recurrent FRI (n=25) | p-value |
|---|---|---|---|---|
| **Fracture characteristics** | | | | |
| *Fracture location* | | | | |
| *Humerus/clavicle/scapula/chest* | 9 (6%) | 8 (7%) | 1 (4%) | 0.46 |
| *Forearm* | 6 (4%) | 6 (5%) | 0 (0%) | |
| *Femur* | 28 (20%) | 24 (21%) | 4 (16%) | |
| *Tibia/fibula* | 67 (48%) | 51 (44%) | 16 (64%) | |
| *Pelvis* | 21 (15%) | 17 (15%) | 4 (16%) | |
| *Foot* | 10 (7%) | 10 (9%) | 0 (0%) | |
| *Open fracture* | 41 (29%) | 31 (27%) | 10 (40%) | 0.19 |
| *Gustilo-Anderson classification (n=41)* | | | | |
| *Grade I* | 4 (10%) | 3 (10%) | 1 (10%) | 0.55 |
| *Grade II* | 10 (24%) | 9 (29%) | 1 (10%) | |
| *Grade III* | 27 (66%) | 19 (61%) | 8 (80%) | |
| *Implant used at index operation* | | | | |
| *Dynamic Hip Screw or similar* | 3 (2%) | 3 (3%) | 0 (0%) | 0.85 |
| *G-nail, PFNA [2] or similar* | 13 (9%) | 10 (9%) | 3 (12%) | |
| *Intramedullary nail* | 19 (13%) | 13 (11%) | 6 (24%) | |
| *Plate* | 91 (65%) | 76 (66%) | 15 (60%) | |
| *Screws or K-wires* | 8 (6%) | 8 (7%) | 0 (0%) | |
| *External fixation as definite treatment* | 2 (1%) | 1 (1%) | 1 (4%) | |
| *Implant removal only* | 5 (4%) | 5 (4%) | 0 (0%) | |
| *External fixation before index surgery* | 36 (26%) | 30 (26%) | 6 (24%) | 0.43 |
| *Time between latest osseous operation and FRI suspicion (days)* | 14.0 (10.0-19.0) | 14.0 (10.0-18.0) | 16.0 (11.0-23.5) | 0.14 |
| *Dichotomised variables: n (%)*<br>*Continuous variables: median (IQR)* | | | | |

[1] American Society of Anaesthesiologists, [2] Proximal Femoral Nail Antirotation

**Clinical confirmatory and suggestive criteria**

Clinical and operative confirmatory signs were present in 48% (n = 68) and 50% (n = 71) of patients, respectively. Purulent discharge (29%, n = 41) and wound dehiscence (23%, n = 32) were the most common confirmatory clinical signs. Suggestive clinical signs were common, redness (64%, n = 90) and persistent wound leakage (49%, n = 69) were the most frequently described symptoms. Elevated CRP and LC was seen in 95% (n = 124/131) and 53% (n = 75/129) of the patients, respectively. Radiological signs such as implant loosening or breakage, sequestrae and halo-signs around implants were present in 22% (n = 16/74) of the cases. During the operation, an abscess was the most frequently seen (47%, n = 66) confirmatory criterion. A more in-depth view of the confirmatory and suggestive criteria is available in Appendix 1.

**Microbiology results**

A total of 135 patients (96%) demonstrated at least two phenotypically identical cultures obtained during the operative intervention, the remaining six patients were diagnosed based on other confirmative criteria. Just over half of the patients with confirmatory positive cultures (52%, n = 70/135) had a polymicrobial FRI. Staphylococcus aureus, Staphylococcus epidermidis and Enterobacter cloacae complex were most frequently cultured in monomicrobial early onset FRI. Staphylococcus aureus and Staphylococcus epidermidis were also the most common causative pathogens in polymicrobial FRI. Furthermore, in comparison to the monomicrobial FRI group, Corynebacterium species, Enterococcus faecalis and Escherichia coli were more often detected in the polymicrobial group. An overview of the microbiology results is available in Appendix 2.

**Clinical outcomes**

The FRI recurrence rate at one year follow-up was 13% (n = 19). The overall recurrence rate in our cohort was 18% (n = 25) within a median follow-up of 23.1 months (IQR 15.3-36.4). In total, 122 patients (87%) had a follow-up of at least 12 months. A total of 19 patients (13%) did not complete the 12-month follow-up term because of discharge from follow-up after healing of the fracture and curation of the FRI (63% (n = 12/19)), death (none related to the FRI) (32% (n = 6/19)) or amputation of the affected limb (5% (n = 1/19)). These patients were not lost to follow up and were therefore included in this study. As per both hospital's policies, all patients who were discharged from follow-up received strict instructions to contact the treating centre in case of recurrence of symptoms. Overall infection control was achieved in 94% (n = 127/135) of cases, excluding deceased patients. Only 93 patients underwent imaging during follow-up, in this group complete fracture consolidation was seen in 65 patients (70%) at 12.0 months and 74 patients (80%) at 23.1 months. 19 patients (20%) did not achieve complete fracture consolidation. Consolidation rates were higher in the polymicrobial group (84%) compared to the monomicrobial

group (72%). The median length-of-stay (LOS) in hospital after the diagnosis of FRI was 21.0 days (IQR 13.5-31.5) (Table 3). A total of 73 patients (52%) underwent at least two surgical procedures in order to treat the ongoing infection during the first presentation of early FRI (Table 4). The overall recurrence rate after completion of the surgical and antimicrobial treatment was 12% (n = 8/68) for patients who were treated with only one initial FRI procedure, 19% (n = 10/54) for patients with two to three surgical procedures and 41% (n = 7/17) for patients with four to five surgical procedures.

**Table 3.** FRI [1] and microbiological characteristics.

| | **All patients (n=141)** | **No recurrent FRI (n=116)** | **Recurrent FRI (n=25)** | **p-value** |
|---|---|---|---|---|
| **FRI signs** | | | | |
| *Confirmatory clinical signs* | 68 (48%) | 55 (47%) | 13 (52%) | 0.35 |
| *Only suggestive clinical signs* | 71 (50%) | 60 (52%) | 11 (44%) | 0.35 |
| **Operative findings & procedure** | | | | |
| *Soft tissue reconstruction (n=30)*<br>*Free/local flap*<br>*Split Skin Graft only* | 24 (80%)<br>6 (20%) | 19 (83%)<br>4 (17%) | 5 (71%)<br>2 (29%) | 0.60 |
| **Microbiology & antimicrobial therapy** | | | | |
| *At least two phenotypically identical cultures* | 135 (96%) | 112 (97%) | 23 (92%) | 0.29 |
| *Polymicrobial (n=135)* [2] | 70 (52%) | 55 (49%) | 15 (65%) | 0.16 |
| *Immediate start empiric IV antimicrobial therapy* | 129 (91%) | 106 (91%) | 23 (92%) | 1.00 |
| *Duration IV antimicrobial therapy (days) (n=129)* | 14.0 (10.0-21.0) | 14.0 (10.0-20.3) | 13.0 (10.0-21.0) | 0.71 |
| *Total duration initial antimicrobial therapy (weeks) (n=131)* | 12.0 (11.0-13.0) | 12.0 (12.0-13.0) | 12.0 (11.0-14.0) | 0.99 |
| **Duration of admission** | | | | |
| *Length-of-stay in hospital (days)* | 21.0 (13.5-31.5) | 21.5 (14.0-31.0) | 20.0 (13.0-38.0) | 0.69 |

*Dichotomised variables: n (%)*
*Continuous variables: median (IQR)*

[1] Fracture-Related Infection, [2] Polymicrobial infection was defined as the presence of at least two pathogens cultured from at least two cultures obtained during the operation [2]

**Table 4.** Correlation of need for additional surgical procedures during the primary FRI [1] treatment plan and overall recurrence rate.

| | All patients (n=141) | Recurrence rate |
|---|---|---|
| *Number of surgical procedures* [2] | 68 (48%) | 8 (12%) |
| *1 procedure* | 54 (38%) | 10 (19%) |
| *2 to 3 procedures* | 17 (12%) | 7 (41%) |
| *4 to 5 procedures* | 2 (1%) | 0 (0%) |
| *6+ procedures* | | |
| *Total number of patients* | 141 | 25 |
| *Dichotomised variables: n (%)* | | |

[1] Fracture-Related Infection, [2] Additional procedures are re-operations that can either be a washout and/or debridement procedure during the primary FRI treatment or a complete revision with exchange of implant after initial DAIR

### Risk factor analysis

A total of 32 variables were included in the univariate analysis (Table 5). One variable was statistically significant (p-value of <0.05), which was the need for additional washout and debridement procedures to treat the ongoing infection during the first presentation of early FRI (p = 0.033). Four additional variables demonstrated a p-value of <0.10, which were a decreased ISS (p = 0.054), a tibia/fibula fracture (p = 0.073), a Gustilo-Anderson grade 3 open fracture (p = 0.078) and use of an intramedullary nail during the index operation (p = 0.097). The five aforementioned variables were included in the multivariate logistic regression analysis. Overfitting was taken into account, due to the number of variables with a p-value <0.10, adjustment of this p-value was not required. Other variables were not eligible for inclusion in this analysis due to their insignificant value.

**Table 5.** Univariate analysis of predictors for recurrent FRI [1].

| | OR (95% CI) [2] | p-value |
|---|---|---|
| **Patient- and fracture characteristics** | | |
| *Sex (male)* | 1.0 (0.4-2.5) | 0.98 |
| *Age (years)* | 1.0 (1.0-1.0) | 0.74 |
| *Body Mass Index (kg/m²)* | 1.0 (0.9-1.1) | 0.73 |
| *ASA classification* [3] | 0.7 (0.4-1.3) | 0.21 |
| Fracture location | | |
| *Humerus/clavicle/scapula/chest* | 0.6 (0.1-4.7) | 0.60 |
| *Forearm* | 0.0 (0.0-0.0) | 1.00 |
| *Femur* | 0.7 (0.2-2.3) | 0.60 |
| *Tibia/fibula* | 2.3 (0.9-5.6) | 0.073 |
| *Pelvis* | 1.1 (0.3-3.6) | 0.86 |
| *Foot* | 0.0 (0.0-0.0) | 1.00 |

**Table 5.** Univariate analysis of predictors for recurrent FRI [1]. (continued)

| | OR (95% CI) [2] | p-value |
|---|---|---|
| *Open fracture* | 0.5 (0.2-1.3) | 0.19 |
| *Gustilo-Anderson classification* | 1.6 (0.2-15.7) | 0.70 |
| *Grade I* | 0.5 (0.1-4.1) | 0.52 |
| *Grade II* | 2.4 (0.9-6.4) | 0.078 |
| *Grade III* | | |
| *Injury Severity Score (per point decrease)* | 1.1 (1.0-1.1)* | 0.054 |
| Implant used at index operation | | |
| *Dynamic Hip Screw or similar* | 0.0 (0.0-0.0) | 1.00 |
| *G-nail, PFNA [4] or similar* | 1.4 (0.4-5.7) | 0.60 |
| *Intramedullary nail* | 2.5 (0.8-7.4) | 0.097 |
| *Plate* | 0.8 (0.3-1.9) | 0.60 |
| *Screws or K-wires* | 0.0 (0.0-0.0) | 1.00 |
| *External fixation as definite treatment* | 4.8 (0.3-79.3) | 0.27 |
| *Implant removal only* | 0.0 (0.0-0.0) | 1.00 |
| *External fixation before index surgery* | 1.1 (0.4-3.0) | 0.85 |
| **Risk factors and comorbidities** | | |
| *Diabetes mellitus* | 0.6 (0.1-2.7) | 0.50 |
| *Obesity* | 1.1 (0.4-2.9) | 0.84 |
| *Smoking* | 0.6 (0.2-1.6) | 0.29 |
| *Drugs* | 0.0 (0.0-0.0) | 1.00 |
| *Alcohol abuse* | 0.0 (0.0-0.0) | 1.00 |
| **FRI and operation characteristics** | | |
| *Soft tissue reconstruction* | 1.9 (0.3-13.5) | 0.52 |
| *Need for additional surgical procedures* | 1.8 (1.0-3.2) | **0.033** |
| **Microbiology & antimicrobial therapy** | | |
| *Polymicrobial* | 1.9 (0.8-4.9) | 0.16 |
| *Immediate start empiric IV antimicrobial therapy* | 0.9 (0.2-4.5) | 0.92 |

[1] Fracture-Related Infection, [2] Odds Ratio and 95% Confidence Interval, [3] American Society of Anaesthesiologists, [4] Proximal Femoral Nail Antirotation, * Inverted Odds Ratio

The multivariate logistic regression was executed with the five aforementioned variables, which are need for additional surgical procedures, a decreased ISS, tibia/fibula fracture, a Gustilo-Anderson grade 3 fracture and use of an intramedullary nail. After a backward selection of the variables with a p-value >0.05 ((Gustilo-Anderson grade 3 fracture (OR 1.4 (95% CI 0.4-4.8), p = 0.55) and (tibia/fibula fracture (OR 1.9 (95% CI 0.7-5.1), p = 0.21))), only three variables with a p-value

<0.05 remained, which were the use of an intramedullary nail during the index operation (OR 4.0 (95% CI 1.1-13.8), p = 0.030), the need for additional washout and debridement procedures during the first presentation of early FRI (OR 1.9 (95% CI 1.1-3.5), p = 0.029) and a decreased ISS (inverted OR 1.1 (95% CI 1.0-1.1), p = 0.040).

**Table 6.** Multivariate analysis of predictors for recurrent FRI [1].

| | **OR (95% CI) [2]** | **p-value** |
|---|---|---|
| **Selected patients (n=122)** | | |
| *Need for additional surgical procedures* | 1.9 (1.1-3.5) | **0.029** |
| *Use of an intramedullary nail* | 4.0 (1.1-13.8) | **0.030** |
| *Injury Severity Score (per point decrease)* | 1.1 (1.0-1.1)* | **0.040** |

[1] Fracture-Related Infection, [2] Odds Ratio and 95% Confidence Interval, * Inverted Odds Ratio

## DISCUSSION



In our study, the FRI recurrence rate in patients with early onset FRI treated with a DAIR procedure was 13% and 18% after a median of 12.0 and 23.1 months, respectively. Overall infection control was achieved in 94% of cases. A total of 73 patients (52%) underwent at least two surgical procedures in order to treat the ongoing infection during the first presentation of early FRI. The recurrence rate significantly correlated with the use of an intramedullary nail during the index operation, the need for additional surgical procedures and a decreased ISS. It is important to realise that this study does not provide information on the development of FRI. This study focuses on infection control, ongoing infection and recurrence rate after treatment of early onset FRI in patients who underwent a DAIR procedure. It is, to our knowledge, one of the first studies that focuses on the expected course of this disease in this subgroup of patients. Factors that may have contributed to the overall recurrence rate of 18%, as well as the need for additional surgical procedures in 52% of cases will be discussed along with the results of the multivariate analysis.

The recurrence rate in the present cohort demonstrated to be in line with the majority of recent literature, reported between 8%-43% [12,25,26]. However, it is difficult to exactly compare the results of those studies with our study, especially due to the differences between study populations. In addition, neither of these studies focuses on the early onset FRI population. This allows us to consider the outcomes of our study, in particular with regard to the recurrence rate and the number of surgical procedures, as new data for early onset (<6 weeks) FRI. In our study, a cut-off of 6 weeks was preferred over the classification of Willenegger et al. in which FRI are divided in early (≤2 weeks), delayed (3 to 10 weeks) and late onset

(>10 weeks) infections [5]. This preference was related to the fact that UMCU and UMCG guidelines use an arbitrary cut-off of 6 weeks for the treatment of early FRI [3].

In our multivariate analysis, the use of an intramedullary nail during the index operation, the need for additional surgical procedures and a decreased ISS remained significant independent predictors for recurrent FRI. Firstly, the use of an intramedullary nail was a significant predictor of recurrence (OR 4.0) in this cohort of early FRI patients treated with a DAIR procedure. This can also be explained by the fact that it is more challenging to adequately debride the medullary canal when the implant remains in situ [11]. This observation is confirmed by the findings of Berkes et al. in their study regarding predictors for recurrent FRI in early FRI patients, in which an intramedullary nail was also identified as a predictor of recurrent FRI [27].

Secondly, the recurrence rate increased in relation to the number of surgical procedures that were needed to control the infection after the initial FRI operation (12% for one procedure vs. 19% for two to three procedures vs. 41% for four to five procedures). This finding is not surprising as it is understandable that more severe infections have a higher risk of incomplete debridement in a DAIR procedure, which could consequently lead to the need for additional surgical procedures and development of recurrent FRI.

Lastly, when considering the ISS, it shows that the recurrence rate for patients with an ISS of <16 was 25%, for an ISS of 16-24 16% and for an ISS of >24 9%, respectively. This implies that a lower ISS is associated with a higher FRI recurrence rate. Previous studies demonstrated an opposite correlation between lower ISS and the occurrence of both FRI and recurrent FRI [28,29], so this finding is remarkable. An explanation for the higher recurrence rate in patients with a lower ISS in our cohort might be that there were more tibia/fibula fractures in the group with an ISS of <16 (52% ISS <16 vs. 32% ISS ≥16). Although these injuries are commonly present in low-energy injuries [30], they often have a challenging soft tissue status which makes them prone for the development of FRI [26]. It is possible that this influenced the results of the multivariate risk factor analysis in which the ISS was the dominant overlapping parameter. An alternative hypothesis is that the association between an increase in ISS and a lower recurrence rate might be related to the altered immune response of polytrauma patients, although underlying mechanisms need to be further elucidated [31–33]. In addition, it can be hypothesised that severely injured patients receive antimicrobial therapy more frequently during the course of their overall treatment for other infections [34] which might have acted as suppressive antibiotic therapy in case of FRI.

The diagnosis FRI was confirmed by the presence of one of the confirmatory consensus criteria, including two phenotypically identical pathogens in deep tissue/implant samples taken during the operative intervention [13]. This criterion was met by 96% of all patients in our study, the remaining 4% of patients were diagnosed based on other confirmatory FRI criteria alone. The top three pathogens in our study, Staphylococcus aureus, Staphylococcus epidermidis and Enterobacter cloacae complex, are in accordance with the literature [35,36].

After the operative intervention, 91% of the patients were immediately started on empiric broad spectrum IV antimicrobial therapy. Empiric therapy was replaced by targeted antimicrobial therapy when culture results and antibiogram were available and, as per protocol, continued for a total duration of 12.0 weeks. The total duration of the antimicrobial treatment in our study was in line with the recommendations of the Fracture-Related Infection Group [6,15] and the Dutch FRI Guideline and common practice in both study centres [3]. The percentage of patients with immediate start of IV antibiotics should ideally be higher in case of FRI suspicion [6], yet in our cohort this was possibly influenced by the assumed absence of clinical signs of infection during the FRI operation in several patients. Furthermore, intravenous antimicrobial therapy was given for an average of 14.0 days, which was in accordance with the FRI treatment protocols at that time [11]. Results of the Oral versus Intravenous Antibiotics for Bone and Joint Infection (OVIVA) trial have affected the average duration of IV antimicrobial therapy due to an earlier switch to oral antimicrobial therapy after publication of that study [37]. The duration of administration of IV antibiotics was adapted in the UMCU on April 15th 2019, which reduced the use of IV antibiotics with a median of 2.0 days in this specific subgroup.



Complete fracture consolidation was seen in 65 of the 93 patients who underwent radiographic follow-up (70%) at 12 months and was achieved in 74 patients (80%) overall. These numbers are similar to the results of Müller et al., where fracture consolidation was achieved in 74% of patients nine months after soft tissue reconstruction due to FRI [38]. Their study identified polymicrobial infection as a possible risk factor for the absence of fracture consolidation [38]. In the present cohort, this finding was not confirmed as higher consolidation rates were seen in the polymicrobial group (84%) in comparison with the monomicrobial group (72%). It is possible that incomplete fracture consolidation is potentially caused by the presence of a low-grade (chronic) infection in patients without clinical signs of infection. This was demonstrated by recent research of Hackl et al., in which time to complete fracture consolidation was significantly increased in patients with low-grade infection [39].

This study is subject to several limitations. First, due to the retrospective nature of this study, there may be selection bias and missing data. Patients were selected

after the outcome was known, therefore the results may not apply to the entire early onset FRI population treated with a DAIR procedure. However, selection bias is thought to be limited due to the use of consecutive patients. In addition, 87% of patients had a follow-up duration of at least 12 months and follow-up data was regularly updated during the course of this study. Secondly, the sample size of this cohort may be considered limited. Nevertheless, this is one of the largest series evaluating risk factors and treatment outcome of early onset FRI. Lastly, with this being a multicentre study, it is possible that the centres differed in both fracture- and infection treatment. However, due to the use of the same national guidelines and standardised protocols [3], this difference is also thought to be minor.

In conclusion, results of this study can be used for management and preoperative counselling of early onset FRI patients. Patients can be informed that a recurrence rate of 13% at one year follow-up and an overall recurrence rate of 18% were seen in our cohort. At least two surgical procedures to gain control of the initial infection were needed in 52% of patients. Independent predictors for developing recurrent FRI were the use of an intramedullary nail during the index operation, need for additional surgical procedures and a decreased ISS.

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**Appendix 1.** Specification of confirmatory and suggestive signs.

| | All patients (n=141) | No recurrent FRI (n=116) | Recurrent FRI (n=25) | p-value |
|---|---|---|---|---|
| *Confirmatory clinical signs* | | | | |
| *Fistula* | 8 (6%) | 6 (5%) | 2 (8%) | 0.63 |
| *Wound dehiscence* | 32 (23%) | 24 (21%) | 8 (32%) | 0.22 |
| *Purulent discharge* | 41 (29%) | 34 (29%) | 7 (28%) | 0.90 |
| *Exposed implant* | 4 (3%) | 4 (3%) | 0 (0%) | 1.000 |
| *Suggestive clinical signs* | | | | |
| *Redness* | 90 (64%) | 76 (66%) | 14 (56%) | 0.37 |
| *Warmth* | 34 (24%) | 29 (25%) | 5 (20%) | 0.60 |
| *Pain* | 68 (48%) | 56 (48%) | 12 (48%) | 0.98 |
| *Swelling* | 61 (43%) | 53 (46%) | 8 (32%) | 0.21 |
| *Fever (>38.3 °C)* | 27 (19%) | 22 (19%) | 5 (20%) | 1.000 |
| *Persistent wound leakage* | 69 (49%) | 55 (47%) | 14 (56%) | 0.44 |
| *Elevated serum inflammatory markers* | | | | |
| *C-reactive protein ≥5.0 mg/L (n=131)* | 124 (95%) | 103 (94%) | 21 (95%) | 1.000 |
| *Leukocyte count ≥10·10$^9$/L (n=129)* | 75 (53%) | 64 (60%) | 11 (50%) | 0.40 |
| *Radiological signs (n=74)* * | 16 (22%) | 14 (22%) | 2 (22%) | 1.000 |
| *Confirmatory operative signs* | | | | |
| *Abscess* | 66 (47%) | 56 (48%) | 10 (40%) | 0.45 |
| *Sinustract/fistula* | 15 (11%) | 12 (10%) | 3 (12%) | 0.81 |
| *Suggestive operative signs* | | | | |
| *Sequestrum* | 5 (4%) | 5 (4%) | 0 (0%) | 0.59 |
| *Cavitary defect* | 1 (1%) | 1 (1%) | 0 (0%) | 1.000 |
| *Medical microbiology results* | | | | |
| *At least two phenotypically identical cultures* | 135 (96%) | 112 (97%) | 23 (92%) | 0.29 |
| *Pathogen isolated in only one sample* | 2 (1%) | 1 (1%) | 1 (4%) | 0.29 |
| *Dichotomised variables: n (%)* | | | | |

* Failure of progression of bone healing (nonunion), implant loosening, bone lysis, sequestration, periosteal bone formation, cloacae, sinus tracts, and/or subcortical abscesses and increased tracer uptake [13]

**Appendix 2.** Medical microbiology results – common pathogens.

| | All patients (n=141) | No recurrent FRI (n=116) | Recurrent FRI (n=25) |
|---|---|---|---|
| **Monomicrobial infection (n=65)** [1] | | | |
| *Staphylococcus aureus* | 38 (58%) | 33 (58%) | 5 (63%) |
| *Staphylococcus epidermidis* | 8 (12%) | 8 (14%) | 0 (0%) |
| *Enterobacter cloacae complex* | 5 (8%) | 4 (7%) | 1 (13%) |
| *Enterococcus faecalis* | 2 (3%) | 2 (4%) | 0 (0%) |
| *Enterococcus faecium* | 2 (3%) | 2 (4%) | 0 (0%) |
| *Corynebacterium species* | 2 (3%) | 2 (4%) | 0 (0%) |
| *Candida albicans* | 2 (3%) | 1 (2%) | 1 (13%) |
| *Escherichia coli* | 1 (2%) | 1 (2%) | 0 (0%) |
| *Streptococcus dysgalactiae* | 1 (2%) | 0 (0%) | 1 (13%) |
| *Enterobacterales other* [2] | 1 (2%) | 1 (2%) | 0 (0%) |
| *Pseudomonas aeruginosa* | 1 (2%) | 1 (2%) | 0 (0%) |
| *Rhodococcus equi* | 1 (2%) | 1 (2%) | 0 (0%) |
| *Proteus mirabilis* | 1 (2%) | 1 (2%) | 0 (0%) |
| *Polymicrobial infection* | 70 (52%) | 55 (49%) | 15 (65%) |
| *Pathogen isolated in only one sample* | 2 (1%) | 1 (1%) | 1 (4%) |
| *Culture-negative infection* | 4 (3%) | 3 (3%) | 1 (4%) |

[1] Two phenotypically identical pathogens, [2] Category not further specified

# PART II

## PERIPROSTHETIC JOINT INFECTION

# CHAPTER 6

## Concomitant hip and knee periprosthetic joint infection in periprosthetic fracture: diagnostic utility of serum and synovial fluid markers

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## ABSTRACT

**Background**

Diagnosing periprosthetic joint infection (PJI) in patients with a periprosthetic fracture can be challenging due to concerns regarding the reliability of commonly used serum and synovial fluid markers. This study aimed at determining the diagnostic performance of serum and synovial fluid markers for diagnosing PJI in patients with a periprosthetic fracture of a total joint arthroplasty.

**Methods**

A total of 144 consecutive patients were included: (1) 41 patients with concomitant PJI and periprosthetic fracture and (2) 103 patients with periprosthetic fracture alone. Serum markers erythrocyte sedimentation rate (ESR) and C-reactive Protein (CRP), and synovial markers white blood cell (WBC) count and polymorphonuclear percentage were assessed.

**Results**

ESR demonstrated 87% sensitivity and 48% specificity at the Musculoskeletal Infection Society threshold, area under the curve (AUC) of 0.74, and optimal threshold of 45.5 mm/h (76% sensitivity, 68% specificity). CRP showed 94% sensitivity and 40% specificity, AUC of 0.68 with optimal threshold of 16.7 mg/L (84% sensitivity, 51% specificity). Synovial WBC count demonstrated 87% sensitivity and 78% specificity, AUC of 0.90 with optimal threshold of 4552 cells/μL (86% sensitivity, 85% specificity). Polymorphonuclear percentage showed 79% sensitivity and 63% specificity, AUC of 0.70 with optimal threshold of 79.5% (74% sensitivity, 63% specificity). The AUC of all combined markers was 0.90 with 84% sensitivity and 79% specificity.

**Conclusion**

The diagnostic utility of the serum and synovial markers for diagnosing PJI was lower in the setting of concomitant periprosthetic fracture compared to PJI alone. Using the Musculoskeletal Infection Society thresholds, ESR, CRP, and WBC count showed high sensitivity, yet low specificity, thus higher thresholds and utilizing all serum and synovial markers in combination should be considered.

## INTRODUCTION

Periprosthetic fracture and periprosthetic joint infection (PJI) are among the most challenging complications after hip and knee total joint arthroplasty requiring a complex surgical treatment. The occurrence of concomitant PJI has been reported in 11.6% to 25.3% of patients with a periprosthetic fracture [1,2] and is associated with a challenging treatment focus of infection control alongside stabilization of the fracture [3]. To optimize the treatment outcome, an accurate PJI diagnosis is essential. The workgroup of the Musculoskeletal Infection Society (MSIS) defined several criteria to correctly diagnose PJI, in which perioperatively obtained serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), and synovial fluid white blood cell (WBC) count and polymorphonuclear percentage (PMN%) serve as minor criteria suggestive of infection [4,5]. The use of laboratory markers as assisting modalities to diagnose PJI has been well established in the literature [6,7]. Recently, a meta-analysis focusing on PJI after total hip arthroplasty (THA) and total knee arthroplasty (TKA) demonstrated good discriminative ability for serum ESR (81.6% sensitivity; 79.0% specificity) and CRP (84.5% sensitivity; 81.3% specificity), as well as very good discriminative ability for synovial fluid WBC count (90.1% sensitivity; 92.5% specificity) and PMN% (90.7% sensitivity; 87.8% specificity) [8].



Diagnosis of PJI in the setting of periprosthetic fracture, however, can be challenging. As timely fixation of the periprosthetic fracture yields better surgical outcomes [9], the interval in which testing for PJI takes place may be short. Furthermore, concerns exist regarding the reliability of serum and synovial inflammatory markers in the setting of periprosthetic fractures as recent trauma may influence infection response and elevation of the inflammatory markers for 2-3 weeks [10–12]. Although the use of serum and synovial fluid markers has been extensively assessed in cases of PJI, there is a paucity of studies reporting on the individual utility of these diagnostic markers to accurately diagnose PJI in the setting of periprosthetic fracture [1,13,14]. As per the 2018 evidence-based definition for diagnosing PJI of a THA and TKA, clinicians are recommended to rely on a combination of multiple clinical and laboratory findings for PJI, including the serum and synovial markers [5]. Previous literature has elucidated that combining the serum and synovial markers substantially improves the diagnostic accuracy [15–18] compared to using these inflammatory markers individually [8]. However, their added value for diagnosing PJI in patients with periprosthetic fractures remains largely unelucidated [14]. Therefore, the aims of this study were to determine (1) the individual diagnostic performance of the commonly used inflammatory markers: serum ESR and CRP, and synovial fluid WBC count and PMN%, and (2) the diagnostic performance of a combination of these markers in the diagnosis of PJI for patients with concomitant periprosthetic fracture of a THA and TKA.

## METHODS

### Patients

After approval of the institutional review board, a retrospective cohort study was conducted at a large tertiary institution. Patients who underwent revision surgery for a periprosthetic fracture with or without PJI were reviewed. Patients were included if a periprosthetic fracture after THA or TKA was treated with revision surgery. Cases missing serum and synovial fluid markers (n = 3; 7% of cohort) due to incomplete reporting were not included. Patients who previously underwent revision surgery were excluded from the study. In addition, patients (n = 1; 2% of cohort) who were suspected with having PJI but did not meet the criteria of the workgroup of the MSIS were excluded from analysis [4,5].

A total of 144 consecutive cases of revision hip (n = 101) and knee (n = 43) total joint arthroplasty for periprosthetic fracture with or without PJI and with available serum and synovial fluid markers met the inclusion criteria. The cohort was divided into two groups: (1) 41 patients with a concomitant PJI and periprosthetic fracture, and (2) 103 patients with solely a periprosthetic fracture (Table 1). The diagnosis of PJI of the hip or knee was defined using the guideline proposed by the workgroup of the MSIS. The criteria include the presence of at least 1 of the major criteria, specifically a sinus tract communicating with the prosthesis or 2 positive cultures with same pathogen collected separately, or the presence of at least 4 minor criteria, specifically elevated ESR and CRP, elevated synovial WBC count, elevated synovial PMN%, presence of purulence in the affected joint during surgery, isolation of microorganism in one culture of a joint tissue or fluid sample, or histologic analysis of periprosthetic tissue demonstrating more than 5 neutrophils per high-power field in 5 high-power fields at ×400 magnification [4,5].

### Data collection

Electronic patient charts were retrospectively reviewed for all included patients. Data on patient demographics, including age, gender, body mass index, several comorbidities, and American Society of Anesthesiologists classification score at the time of the revision were collected. In addition, data on the fracture characteristics and revision surgery type, medical microbiology culture results, and final infection diagnosis were obtained. The diagnostic markers serum ESR and CRP, and synovial WBC count and PMN% were retrieved from electronical hospital records. All culture data were confirmed through medical microbiology records for the aspiration and tissue samples obtained at the revision surgery.

### Statistical analysis

Binary data were analyzed using Fisher's exact test or chi-squared test, and continuous data were analyzed using independent Student's t-test or Mann-Whitney

U test. The diagnostic accuracy of the individual markers was first evaluated with dichotomized values using the thresholds as proposed by the MSIS workgroup (ESR ≥ 30 mm/hr, CRP ≥ 10 mg/L, WBC count ≥ 3000 cells/μL, and PMN% ≥ 80%). The sensitivity and specificity, positive and negative predictive values, and positive and negative likelihood ratios were calculated with corresponding 95% confidence interval (95% CI) [19]. Second, the maximal predictive performance of the markers was assessed using receiver operating characteristic (ROC) analysis. The discriminative power of the test is estimated by the shape of the ROC curve and the area under the curve (AUC). The closer the curve is to the upper-left hand corner and the larger the AUC, the better the test is at discriminating between both patients with PJI and patients without PJI. A perfect test has an AUC of 1.0, whereas a non-discriminative test has an AUC of 0.5, which is represented by the diagonal line. The Q-point method, which determines the threshold value closest to the upper-left corner of the ROC curve, was used to deduct the optimal threshold values [20]. Third, for the diagnostic performance of multiple inflammatory markers combined, a maximum of one predictor per 5-9 PJI events was used to reduce the risk of overfitting [21]. The sensitivity and specificity for the optimal threshold were calculated. Sensitivity analyses were performed to assess whether the diagnostic performance of the markers differed for the patients in the THA and TKA subgroups. All data analyses were performed using the Statistical Package for Social Sciences (SPSS®) statistics for Windows (version 26.0.0.0, IBM Corp, Armonk, NY) [22].



## RESULTS

### Patient cohorts

The gender distribution was predominantly female in both cohorts, namely 68.3% in the infected fracture group and 62.1% in the fracture-only group ($p$ = 0.43). The mean age was significantly lower in the infected fracture group compared to the fracture only group (67.7 ± 14.1 vs. 73.2 ± 13.5 years, $p$ = 0.04). Compared to the fracture-only cohort, there were significantly more smokers in the infected fracture cohort (22.0% vs. 2.9%, $p$ = 0.001). A trend towards a higher body mass index was seen for the infected fracture compared to the fracture-only cohort, however this difference was not significant (32.3 ± 8.6 vs. 29.8 ± 8.0, $p$ = 0.08). Furthermore, there were no significant differences for laterality, alcohol use, and comorbidities between the 2 cohorts (Table 1). The fracture characteristics and revision types are shown in Table 2. Subsequently, the demographics for the THA and TKA subgroups were compared. For the THA subgroup, similar to the full cohort, patients with an infected fracture were significantly younger (67.7 vs. 73.2 years, $p$ = 0.005) and smoked more frequently (24.2% vs. 4.5%, $p$ = 0.005). For the TKA subgroup, patients with an infected fracture suffered more frequently from cardiovascular disease (12.5% vs. 0.0%, $p$ = 0.045).

**Table 1.** Patient Demographics.

| Characteristic | Total (n=144) | Infected Fracture (n=41) | Fracture only (n=103) | P-value |
|---|---|---|---|---|
| Age (mean ± SD) | 71.8 ± 13.8 | 67.7 ± 14.1 | 73.2 ± 13.5 | **0.04** |
| BMI (median ± SD) | 30.4 ± 8.2 | 32.3 ± 8.6 | 29.8 ± 8.0 | 0.08 |
| *ASA* | | | | 0.89 |
| 1 | 6 (4.2%) | 2 (4.9%) | 4 (3.9%) | |
| 2 | 95 (66.0%) | 25 (61.0%) | 70 (68.0%) | |
| 3 | 40 (27.8%) | 13 (31.7%) | 27 (26.2%) | |
| 4 | 3 (2.1%) | 1 (2.4%) | 2 (1.9%) | |
| *Joint* | | | | 0.07 |
| Hip | 101 (70.1%) | 34 (82.9%) | 67 (65.0%) | |
| Knee | 44 (29.9%) | 8 (17.1%) | 36 (35.0%) | |
| *Laterality* | | | | 0.75 |
| Left | 72 (49.3%) | 20 (46.3%) | 52 (50.5%) | |
| Right | 73 (50.7%) | 22 (53.7%) | 51 (49.5%) | |
| *Gender* | | | | 0.43 |
| Male | 52 (36.1%) | 13 (31.7%) | 139 (37.9%) | |
| Female | 93 (63.9%) | 29 (68.3%) | 64 (62.1%) | |
| *Risk factors* | | | | |
| Smoking | 12 (8.3%) | 9 (22.0%) | 3 (2.9%) | **0.001** |
| Alcohol | 50 (34.7%) | 15 (36.6%) | 35 (34.0%) | 0.84 |
| Drugs | 7 (4.9%) | 4 (9.8%) | 3 (2.9%) | 0.11 |
| *Comorbidities* | | | | |
| Vascular | 60 (41.7%) | 20 (48.8%) | 40 (38.8%) | 0.33 |
| Hypertension | 71 (49.3%) | 19 (46.3%) | 52 (50.5%) | 0.57 |
| Diabetes Mellitus | 22 (15.3%) | 5 (12.2%) | 17 (16.5%) | 0.61 |
| Malignant tumor | 14 (9.7%) | 2 (4.9%) | 12 (11.7%) | 0.35 |
| Inflammatory disease | 14 (9.7%) | 4 (9.8%) | 10 (9.7%) | 1.00 |

SD, standard deviation; BMI, body mass index; ASA, American Society of Anesthesiologists. Bold values indicate statistically significant values (P < .05).

**Table 2.** Fracture and Revision Surgery Characteristics.

| Characteristic | Total (n=144) | Infected Fracture (n=41) | Fracture Only (n=103) | P-value |
|---|---|---|---|---|
| *Fracture Site* | | | | |
| Acetabulum | 9 (6.3%) | 4 (9.7%) | 5 (4.9%) | 0.27 |
| Proximal Femur | 90 (62.5%) | 30 (73.2%) | 60 (58.3%) | 0.10 |
| Distal Femur | 33 (22.9%) | 4 (9.8%) | 29 (28.1%) | **0.02** |
| Proximal Tibia | 12 (8.3%) | 3 (7.3%) | 9 (8.7%) | 0.78 |
| *Revision Type* | | | | |
| Revision and Cerclage | 66 (45.8%) | 16 (39.0%) | 50 (48.5%) | 0.32 |
| Revision and Plate Fixation | 23 (16.0%) | 0 (0.0%) | 23 (22.3%) | **0.003** |
| Revision with Plate Fixation and Cerclage | 14 (9.7%) | 5 (12.2%) | 9 (8.7%) | 0.27 |
| Revision and Screw Fixation | 3 (2.1%) | 1 (2.4%) | 2 (2.0%) | 1.00 |
| Spacer Implantation Only | 12 (8.3%) | 12 (29.3%) | 0 (0.0%) | **<0.001** |
| Revision Only | 19 (13.2%) | 0 (0.0%) | 19 (18.5%) | **0.002** |
| Resection Arthroplasty | 7 (4.9%) | 7 (17.1%) | 0 (0.0%) | **<0.001** |

Bold values indicate statistically significant values (P < .05).



**Serum and synovial fluid markers**

The infected fracture cohort (n = 41) included 26 patients who met the major MSIS criteria and 15 patients who met the minor MSIS criteria. Of these 41 patients, 29 (79%) had positive intra-operative cultures that were isolated from at least two separate tissue or fluid samples, while 12 patients (21%) had negative intra-operative cultures. Using the MSIS threshold, the serum marker ESR had 86.5% sensitivity, 47.6% specificity, and 62.0% accuracy (Table 3). When evaluating ESR as a continuous variable, an AUC of 0.74 (95% CI 0.64-0.85) was plotted. The optimal threshold value was 45.5 mm/h with 75.7% sensitivity and 68.3% specificity (Table 4; Figure 1). CRP showed 93.6% sensitivity, 40.0% specificity, and 58.2% accuracy using the MSIS threshold. When analyzing CRP as a continuous variable, an AUC of 0.69 (95% CI 0.57-0.80) was established. The optimal threshold value was 16.7 mg/L with 83.9% sensitivity and 50.8% specificity.

For the synovial markers, using the MSIS threshold for WBC count, 87.0% sensitivity, 77.9% specificity, and 80.2% accuracy were established (Table 3). When considering WBC count as a continuous variable, an AUC of 0.90 (95% CI 0.83-0.97) was plotted. The optimal threshold value was 4552 cells/μL with 86.4% sensitivity and 85.3%

specificity (Table 4; Figure 1). PMN% had 79.0% sensitivity, 63.2% specificity, and 66.7% accuracy using the MSIS threshold. When assessing PMN% as a continuous variable, an AUC of 0.70 (95% CI 0.57-0.82) was plotted. The optimal threshold was 79.5% with 73.7% sensitivity and 63.2% specificity.

Combining synovial fluid markers provides high sensitivity and specificity for diagnosing PJI, which is almost as high as the diagnostic performance for combining both serum and synovial markers. Given the utility of ESR and CRP baseline levels for the diagnosis of PJI, combining serum and synovial markers is currently recommended by clinical guidelines [5,23]. Accordingly, combinations of sets of serum and synovial markers at the MSIS thresholds were analyzed. The AUC of serum ESR and CRP combined was 0.71 (95% CI 0.61-0.82) with 80.6% sensitivity and 56.4% specificity. The AUC of synovial WBC count and PMN% combined was 0.83 (95% CI 0.74-0.93) with a sensitivity of 84.2% and specificity of 77.9%. The model with all 4 serum and synovial fluid markers combined had an AUC of 0.90 (95% CI 0.80-0.99) with 84.2% sensitivity and 79.3% specificity. The ROC curve parameters for the combinations of markers are shown in Table 4 and Figure 1.

**Sensitivity analyses of THA and TKA patients**

For both THA and TKA subgroups, sensitivity analyses were performed to assess the discriminative performance of the individual serum and synovial markers. The results for the subgroups were similar to the full cohort. The WBC count demonstrated the highest AUC of 0.91 (95% CI 0.82-0.99) with corresponding 81.3% sensitivity and 94.9% specificity for the THA subgroup, and a similar AUC of 0.90 (95% CI 0.78-1.00) with 100.0% sensitivity and 75.9% specificity for the TKA subgroup.

**Table 3.** Diagnostic Accuracies of Inflammatory Markers using MSIS Thresholds.

| | ESR | CRP | WBC count | PMN% |
|---|---|---|---|---|
| Sensitivity (95% CI) | 86.5% (71.2%-95.5%) | 93.6% (78.6%-99.2%) | 87.0% (66.4%-97.2%) | 79.0% (54.4%-94.0%) |
| Specificity (95% CI) | 47.6% (34.9%-60.6%) | 40.0% (27.6%-53.5%) | 77.9% (66.2%-87.1%) | 63.2% (50.7%-74.6%) |
| PPV (95% CI) | 49.2% (42.6%-55.9%) | 44.6% (39.1%-50.3%) | 57.1% (45.4%-68.2%) | 37.5% (28.9%-47.0%) |
| NPV (95% CI) | 85.7% (71.8%-93.4%) | 92.3% (75.2%-97.9%) | 94.6% (85.9%-98.1%) | 91.5% (81.5%-96.3%) |
| LR+ (95% CI) | 1.65 (1.26-2.16) | 1.56 (1.24-1.96) | 3.94 (2.45-6.33) | 2.15 (1.46-3.17) |
| LR− (95% CI) | 0.28 (0.12-0.67) | 0.16 (0.04-0.64) | 0.17 ( 0.06-0.48) | 0.33 (0.14-0.81) |
| Accuracy | 62.0% (51.8%-71.5%) | 58.2% (47.4%-68.5%) | 80.2% (70.6%-87.8%) | 66.7% (55.8%-76.4%) |

MSIS, Musculoskeletal Infection Society; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; WBC count, white blood cell count; PMN%, polymorphonuclear percentage; 95% CI, 95% confidence interval; PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR−, negative likelihood ratio.

**Table 4:** ROC Curve Parameters for Predicting PJI in Patients With a Periprosthetic Fracture Using Individual Markers and Combinations at MSIS Threshold Values.

| ROC Curve Parameters | AUC (95% CI) | Sensitivity | Specificity | Threshold at optimal cutoff |
|---|---|---|---|---|
| ESR, mm/hr | 0.741 (0.637-0.845) | 75.7% | 68.3% | 45.5 |
| CRP, mg/L | 0.687 (0.574-0.800) | 83.9% | 50.8% | 16.7 |
| WBC count, cells/μL | 0.898 (0.828-0.968) | 86.4% | 85.3% | 4552 |
| PMN%, percent | 0.696 (0.568-0.824) | 73.7% | 63.2% | 79.5 |
| Combined ESR, CRP | 0.713 (0.607-0.820) | 80.6% | 56.4% | - |
| Combined WBC, PMN% | 0.832 (0.737-0.927) | 84.2% | 77.9% | - |
| Combined ESR, CRP, WBC, PMN% | 0.895 (0.804-0.985) | 84.2% | 79.3% | - |

ROC, receiver operating characteristic; PJI, periprosthetic joint infection; AUC, area under the curve; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; WBC count, white blood cell count; PMN%, polymorphonuclear percentage.

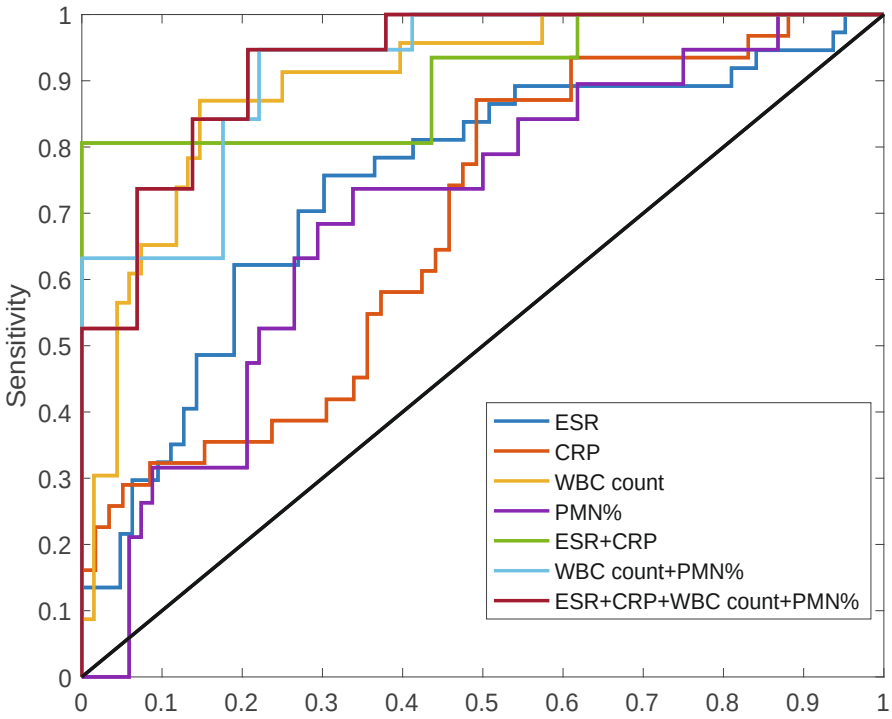


**Figure 1.** ROC curve analysis for predicting PJI in patients with periprosthetic fracture using ESR, CRP, WBC count, PMN%, and these markers in conjunction at the MSIS thresholds.*

* ROC, receiver operating characteristic; PJI, periprosthetic joint infection; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; WBC count, white blood cell count; PMN%, polymorphonuclear percentage; MSIS, Musculoskeletal Infection Society.

## DISCUSSION

Diagnosing concomitant PJI in patients with a periprosthetic fracture can be challenging due to concerns regarding the reliability of commonly used serum and synovial fluid markers. Although a substantial number of reports in the literature have assessed inflammatory markers for diagnosing PJI in THA and TKA patients, limited studies analyzed these markers in the setting of concomitant periprosthetic fracture. As the trauma related to periprosthetic fractures might obscure the test results and inflammation could elevate the inflammatory markers [1], the applicability of the MSIS thresholds defined for the diagnostic algorithm of PJI without periprosthetic fracture remains unclear. This study aimed at evaluating the discriminative performance of commonly used serum and synovial inflammatory markers to diagnose PJI in periprosthetic fractures at the MSIS and optimal thresholds. The results indicate that the overall diagnostic performance of

the serum and synovial markers using the MSIS threshold was lower in the setting of periprosthetic fracture compared to PJI alone. The diagnostic performance of the inflammatory markers in the setting of periprosthetic fracture improved with higher thresholds in addition to utilizing all serum and synovial markers in combination.

A limited number of studies have assessed serum and synovial markers for PJI in the setting of periprosthetic fracture. Chevillotte et al. studied the serum markers ESR, CRP, and WBC in a cohort of 204 periprosthetic fractures, with 21 cases of true PJI [1]. All markers showed poor diagnostic performance, even when combined, and were perceived not reliable for the diagnosis of PJI. Joint aspiration was performed only in 41 patients; moreover, obtained fluid was not used to analyze synovial markers. In contrast, synovial WBC count was evaluated by Preston et al., reporting an excellent 100% sensitivity with only moderate specificity to diagnose infection in periprosthetic fracture [13]. However, their study was limited by a small sample size of two confirmed PJI cases in a subgroup of 27 patients undergoing joint aspiration. Subsequently, Shah et al. analyzed a cohort of 121 periprosthetic fractures, of which 14 patients had a true PJI [14]. Optimal threshold values similar to the MSIS thresholds were derived from ROC curves, demonstrating an AUC of 0.84 for both WBC count and PMN%. The performance of the serum markers was suboptimal as the AUC for ESR was 0.76 and for CRP 0.63. The authors reported that the accuracy did not improve by combining multiple markers, yet not all tests were available for all patients, potentially inducing the risk of overfitting their analyses and compromising the reproducibility of the results.



In our study, the diagnostic accuracy for the individual inflammatory markers at the MSIS and optimal thresholds were analyzed. For the serum markers, both ESR and CRP showed good ability to diagnose infection using the thresholds as proposed by the MSIS workgroup with 86.5% and 93.6% sensitivity, respectively. However, the specificities for ESR and CRP in our study were, with 47.6% and 40.0%, respectively, substantially lower compared to the pooled results of a large meta-analysis on markers for PJI without periprosthetic fracture by Carli et al., who reported 81.6% sensitivity and 79.0% specificity for ESR, and 84.5% sensitivity and 81.3% specificity for CRP [8]. The results of our study indicate that the serum markers were elevated for both the infected fracture and the fracture-only groups. Low specificities were observed in our study due to a large proportion of patients in the fracture only cohort with elevated ESR and CRP values, potentially in response to the fracture [1]. When compared to studies focusing solely on PJI, the optimal threshold for both ESR (45.5 mm/hr) and CRP (16.7 mg/L) in our study were high, indicating that the threshold of the serum markers is elevated in PJI cases with concomitant periprosthetic fracture. Multiple reports on PJI without fracture defined optimal thresholds for ESR between 10.0 mm/hr and 34.5 mm/hr, with corresponding sensitivity ranging from 76.7% to 93.0% and specificity from 68.6% to 90.9% [24–28].

For CRP, the reported thresholds varied between 5.0 mg/L and 16.5 mg/L, with corresponding sensitivity ranging from 78.3% to 95.0% and specificity from 63.3% to 90.9% [24–31]. In our study, both ESR and CRP demonstrated high sensitivity at the MSIS threshold; however the overall utility was low. The use of higher optimal thresholds improved the overall diagnostic accuracy of both serum markers, yet their performance remained lower compared to the diagnostic utility reported for PJI without periprosthetic fracture at the MSIS threshold.

For the synovial markers, only WBC count in the present study demonstrated good discriminative performance for diagnosing PJI in the setting of periprosthetic fracture at the MSIS threshold. However, both 87.0% sensitivity and 77.9% specificity were lower compared to those reported for PJI without fracture with 90.1% sensitivity and 92.5% specificity [8]. The optimal threshold for WBC count in our study of 4552 cells/μL was considerably higher than in studies focusing on PJI without fracture, though the corresponding 86.4% sensitivity and 85.3% specificity at this threshold showed comparable to the literature. Optimal thresholds for WBC count have been reported between 1590 cells/μL and 3450 cells/μL, with corresponding 85.0% to 94.7% sensitivity and 90.1% to 95.0% specificity [25–27,32,33]. In contrast, PMN% at the MSIS threshold in our study underperformed substantially compared to the literature on PJI without fracture, which reported 90.7% sensitivity and 87.8% specificity [8]. Similar to the MSIS threshold for PMN%, the optimal threshold in our study was 79.5%. However, this was higher compared to reported threshold in PJI without fracture, which varied between 64.5% and 78.0% [25–27,32,33]. Our study demonstrated 73.7% sensitivity and 63.2% specificity at the optimal threshold, and these were low compared to reported sensitivity between 89.7% and 95.5% and specificity between 86.0% and 91.1% for PJI alone [25–27,32,33]. The optimal cutoff values for both synovial markers in our study were substantially higher compared to the literature on PJI without fracture, indicating elevated thresholds for the synovial markers in periprosthetic fracture. This might, in part, be due to inflammation of the surrounding joint tissue and hemarthrosis after fracture causing an elevation in the synovial markers for all patients with periprosthetic fractures [14]. Although the diagnostic utility of the synovial markers improved using the higher optimal threshold, the performance of both the best individual marker WBC count and PMN% were lower compared to PJI without periprosthetic fracture at the MSIS threshold.

As utilizing combined inflammatory markers improves the performance for diagnosing PJI [15–18] and is recommended by the 2018 evidence-based PJI definition [5], our study assessed the potential added value of multiple markers in conjunction in the setting of periprosthetic fracture. In agreement with a study on PJI in periprosthetic fracture by Chevillotte et al. [1], combining serum ESR and CRP in our study did not increase the AUC for diagnosing PJI in the setting of fracture.

This finding is in contrast with the performance of combined ESR and CRP in PJI without periprosthetic fracture. Ghanem et al. found 87.8% sensitivity and 88.1% specificity [34], and Greidanus et al. reported a sensitivity and specificity of 88.0% and 93.0%, respectively [28]. When combining the 2 synovial markers WBC count and PMN% in our study cohort, the diagnostic accuracy did not exceed that of WBC count alone. However, the overall accuracy of the markers improved when utilizing a combination of all 4 markers, demonstrating 0.90 AUC with 84.2% sensitivity and 79.3% specificity. Although the sensitivity of all markers in conjunction in the present study was not as high as 99.7% previously reported by McArthur et al. for diagnosing PJI without fracture [15], an excellent AUC was found in our study, suggesting that few infections will be missed and most uninfected fractures will be correctly identified. While combining sets of t2 markers was not as effective, combining all 4 markers resulted in the highest utility exceeding that of using higher threshold values alone.

As the results of this study demonstrate that the overall utility of the commonly used serum and synovial markers for diagnosing PJI was lower in the setting of periprosthetic fracture, it would suggest to considering alternative diagnostic tests. Multiple promising alternative biomarkers have been proposed in recent literature for diagnosing PJI, including synovial alpha defensin (100.0% sensitivity; 96.0% specificity) [35], synovial leukocyte esterase (81.0% sensitivity; 97.0% specificity) [35], serum D-dimer (97.7% sensitivity; 99.5% specificity) [36], synovial CRP (92.0% sensitivity; 90.0% specificity) [37], and interleukin-6 (81.0% sensitivity; 94.0% specificity) [38]. These new tests have not yet been reported in the setting of fracture, and future studies might elucidate the utility of these alternative test for the diagnosis of PJI in concomitant periprosthetic fracture.

The findings of this study should be interpreted in light of its limitations. First, the retrospective character of the study has several inherent limitations, including potential selection and misclassification bias. Second, concerns may rise to the sample size of the cohort. However, due to the nature of concomitant PJI and periprosthetic fracture, this represents one of the largest series reported in the literature. Third, several alternative diagnostic tests that have been proposed for the diagnosis of PJI were not assessed by our study. These markers were beyond the scope of the current study as this study focused on commonly used, and readily available, serum and synovial markers. Finally, the time frame that serum markers remain elevated following fracture which may influence cutoff levels and combinations of markers was beyond the scope of the present study. However, recent studies suggest that inflammatory markers may be elevated for 2-3 weeks following fracture [10–12].

In conclusion, the results of this study indicate that the diagnostic performance of the serum and synovial markers for diagnosing PJI was lower in the setting of concomitant periprosthetic fracture compared to PJI alone. Using the MSIS thresholds, ESR, CRP, and synovial WBC count showed high sensitivity, yet low specificity. In order to improve the diagnostic performance of the inflammatory markers in patients with concomitant periprosthetic fracture, higher thresholds and utilizing all serum and synovial markers in combination should be considered.

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# CHAPTER 7

## One-stage revision is as effective as two-stage revision for chronic culture-negative periprosthetic joint infection after total hip and knee arthroplasty

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## ABSTRACT

**Aims**

Removal of infected components and culture-directed antibiotics are important for the successful treatment of chronic periprosthetic joint infection (PJI). however, as many as 27% of chronic PJI patients yield negative culture results. Although culture negativity has been thought of as a contraindication to one-stage revision, data supporting this assertion are limited. the aim of our study was to report on the clinical outcomes for one-stage and two-stage exchange arthroplasty performed in patients with chronic culture-negative PJI.

**Patients and Methods**

A total of 105 consecutive patients who underwent revision total joint arthroplasty for chronic culture-negative PJI were retrospectively evaluated. One-stage revision arthroplasty was performed in 30 patients, while 75 patients underwent two-stage exchange, with a minimum of one year's follow-up. Reinfection, re-revision for septic and aseptic reasons, amputation, readmission, mortality, and length of stay were compared between the two treatment strategies.

**Results**

The patient demographic characteristics did not differ significantly between the groups. At a mean follow-up of 4.2 years, the treatment failure for reinfection for one-stage and two-stage revision was five (16.7%) and 15 patients (20.0%) ($p = 0.691$), and for aseptic re-revision was four (13.3%) and 11 patients (14.7%) ($p = 0.865$), respectively. No significant differences were observed between one-stage and two-stage revision for 30-, 60-, and 90-day readmissions (10.0% vs 8.0%; $p = 0.715$; 16.7% vs 9.3%; $p = 0.321$; and 26.7% vs 10.7%; $p = 0.078$), one-year mortality (3.3% vs 4.0%; $p > 0.999$), and amputation (3.3% vs 1.3%; $p = 0.496$).

**Conclusion**

In this non-randomized study, one-stage revision arthroplasty demonstrated similar outcomes including reinfection, re-revision, and readmission rates for the treatment of chronic culture-negative PJI after TKA and THA compared to two-stage revision. this suggests culture negativity may not be a contraindication to one-stage revision arthroplasty for chronic culture-negative PJI in selected patients.

## INTRODUCTION

Periprosthetic joint infection (PJI) is a challenging complication following total hip and knee arthroplasty and may result in high patient morbidity and an increased economic burden to the healthcare system [1]. A substantially higher patient mortality is associated with PJI (3% to 18%) when compared to aseptic revisions (2% to 7%) [2,3]. PJI is a relatively uncommon complication, occurring in approximately 1.6% to 3.4% of patients [4–6]. However, it is the most frequent indication for revision after total knee arthroplasty (TKA) — in approximately 25% of all revision cases; and the third most frequent indication for total hip arthroplasty (THA) — in 15% of cases [4,7]. Whereas patients with acute PJI generally present with evident clinical signs of local and systemic inflammation, the symptoms for chronic PJI can be more indolent, such as persistent joint pain [8]. Diagnostic criteria for PJI have been defined by the workgroup of the Musculoskeletal Infection Society (MSIS) based on clinical findings (such as the presence of purulence or a sinus tract), raised inflammatory markers (such as ESR and CRP), histology results (such as neutrophil count), intraoperative findings (such as frozen sections), and medical microbiological culture results [9,10].

Identification of microorganisms responsible for infection is important for selection of the most suitable treatment option. Culture-negative PJI is frequently encountered when antimicrobial agents are used prior to obtaining culture samples [11,12]. Culture-negative PJI accounts for approximately 16% of the cases in the USA [13], while between 7% and 27% of microbiological cultures sent from patients with PJI yield negative results [11,12,14–18]. Two-stage revision arthroplasty is commonly performed for culture-negative PJI, with reported eradication rates up to 90% [16,19,20]. The first stage provides an opportunity for taking further samples which may yield a postive microbiological diagnosis. However, this treatment strategy requires a second definitive intervention, so the potential disadvantages include an increased burden to the patient, higher healthcare costs, and substantial morbidity and mortality rates [21–23]. An emerging alternative is one-stage revision for PJI, with several studies reporting comparable infection eradication rates to two-stage revision for both THA and TKA [24,25] with less patient morbidity, improved functional outcomes, and lower costs [26,27]. Culture negativity has been thought of as a relative contraindication to one-stage revision. However, there is limited published data supporting this assertion [5,27,28]. On the contrary, several case series [29,30] and a recent systematic review [31] suggest that PJI can be effectively eradicated with a one-stage revision strategy [29,30], including in patients with culture-negative PJI [29,32,33]. As there is a paucity of literature in this field, the aim of the present study was to evaluate the outcomes for one- and two-stage exchange arthroplasty for patients with chronic culture-negative PJI.

## METHODS

**Patients**

A retrospective cohort study was performed at a large tertiary institution (institutional review board #2019P002677). All consecutive patients who underwent revision of TKA or THA between 2010 and 2018 for chronic culture-negative PJI were eligible for inclusion and identified through operative notes and International Classification of Diseases of the World Health Organization (ICD)-9 codes [10]. Culture samples from both preoperative joint aspiration and intraoperative periprosthetic tissues from the affected joint at the time of revision surgery at our institution were obtained, and those tissue specimens were sent for aerobic, anaerobic, fungal, and acid-fast bacterial (AFB) cultures using both solid media and broth (Becton-Dickinson, Franklin Lakes, New Jersey, USA) for a minimum of 14 days. Fungal/AFB cultures were held for six weeks. The culture results were regarded as negative when neither preoperative and intraoperative tissue samples showed growth of pathogens. Antibiotics were held until the periprosthetic tissues were obtained in all culture-negative cases.

The final diagnosis of culture-negative PJI was defined based on modified MSIS major and minor criteria, except for scoring the presence of microorganisms in deep tissue samples taken during joint aspiration or revision surgery [9,10,34]. A PJI was present if a sinus tract communicating with the prosthesis was seen, or if three of the minor criteria existed: elevated serum inflammatory markers ESR (≥ 30 mm/h) and CRP (≥ 10 mg/L); elevated synovial white blood cell (WBC) count (≥ 3,000 WBC/μL), 3) elevated synovial neutrophil percentage (PMN%; ≥ 80%); presence of purulence in the joint space; or more than five neutrophils per high-power field (HPF) observed during histopathological analysis. A chronic PJI was regarded as an infection occurring later than four weeks after the index arthroplasty and for which complaints had been present for a duration of more than four weeks [35]. Patients were included if they underwent one-stage revision or two-stage revision for the treatment of chronic culture-negative PJI. One-stage revision consisted of debridement with exchange of all components, and two-stage revision consisted of removal of all components and placement of antibiotic-loaded cement spacers followed by reimplantation of components after completing antibiotic treatment.

In agreement with previous studies, the general indications for one-stage revision for culture-negative PJI included the absence of previous revision surgery and an evaluation of the patient's general medical condition. Patients with the poorly regulated diabetes mellitus, end-stage renal failure, co-existing active long-term local infection, or immunocompromised status were not surgical candidates [29,30,36]. The general indications for two-stage revision for culture-negative PJI included the ability to tolerate two separate surgeries, controlled medical comorbidities [33],

and patients with poor bone stock or compromised soft tissue [16]. Patients with prior revision surgery for infection reasons, PJI of a hemiarthroplasty, or patients who underwent isolated bearing component exchange were excluded. In addition, cases not meeting the PJI criteria or with missing outcome data due to incomplete reporting were excluded.

The electronic patient files of all included patients were reviewed. data were collected on patient demographics, including age, sex, American Society of Anesthesiologists classification (ASA) score [37], and body mass index (BMI), index surgery type and date, time from index surgery until infection, laboratory findings, and final diagnosis of PJI. Additionally, the type of revision surgery and data on treatment outcomes, including reinfection, length of hospital stay, complications, readmission rates, amputation, and one-year mortality were retrieved from the patient records. Subgroup analyses were performed to assess whether the outcomes differed between THA and TKA patients.

**Antibiotic therapy**

The antibiotic treatment protocol was determined in consultation with infectious diseases specialists. In all cases of PJI, medical therapy was initiated using broad-spectrum antibiotics (typically vancomycin and ceftriaxone) after intraoperative samples were taken. Empirical antibiotic therapy (typically cefazolin and amoxicillin/clavulanic acid) was continued when the definitive tissue sample cultures did not yield a growth of any pathogens.



**Sample processing**

The institutional protocol for specimen sampling and processing was performed in concordance with previous literature [38,39]. Multiple tissue samples (typically three) were obtained for culture and histology, using separate instruments for each sample and avoiding contact with the skin to minimize cross-contamination. Each tissue sample was disrupted by vortexing with sterile glass beads in sterile saline [39]. Bactec bottles (Trypticase; Becton-Dickinson) were incubated at 37°C for a minimum of 14 days or until a growth was observed. The maximum length of incubation time was between four and six weeks.

**Outcome measures**

A successful outcome was defined as retainment of the prosthesis without clinical signs of PJI. The treatment was deemed a failure if the patient had undergone a surgical procedure for the treatment of PJI after the completion of the one- or two-stage revision surgery, including debridement, antibiotics and implant retention (DAIR) with modular exchange, subsequent one- or two-stage revision, or resection arthroplasty or amputation. In addition, data on re-revision for aseptic reasons, 30-, 60-, and 90-day readmission rates, length of stay in hospital (the time period

the patient was in hospital from admission to discharge), one-year mortality, and amputation rates were collected.

**Statistical analysis**

Continuous data are presented as mean and standard deviation (SD) and binary data are presented as counts and percentages. For the determination of treatment failure, the reinfection rates for the two treatment groups were assessed using univariate analysis. For comparison of the additional treatment outcomes, the reoperation, 30-, 60-, and 90-day readmission, amputation, and mortality rates were analyzed. An independent-samples *t*-test or Mann-Whitney U test was used for continuous values, and a chi-squared test or Fisher's exact test for dichotomized values according to the estimated cell size. The significance of the p-value was set to $p < 0.05$. All data analyses were performed using the Statistical Package for Social Sciences (SPSS) software for Windows (v. 26; IBM, Armonk, New York, USA) [40].

## RESULTS

A total of 140 consecutive patients underwent a revision for chronic culture-negative PJI. Four patients were excluded due to prior revision for infection. An infected hemiarthroplasty was present in one patient and isolated bearing exchange was performed in five patients, and those patients were therefore excluded. A total of 25 patients did not receive reimplantation after resection and were thus excluded from analyses. After exclusion, a total of 105 patients (30 one-stage and 75 two-stage revision) meeting the modified MSIS criteria were included in this study.

The baseline demographics and patient characteristics for the two groups were assessed (Table 1). The full study cohort consisted of patients with a mean age of 65.9 (SD 10.9) years. The mean clinical follow-up was 4.4 years (2.5 to 22.9). A sinus tract communicating with the joint was present in 19 patients (17.5%). PJI was more commonly located in the knee (62.9, n = 66) than the hip (37.1%, n = 39) in both groups, and this difference was not statistically significant ($p = 0.706$, chi-squared test). There were more female patients in the one-stage revision group (70.0%) compared to the two-stage revision group (45.3%; $p = 0.023$). No significant differences were observed between the one-stage and two-stage cohorts regarding ASA score (mean of 2.43 vs 2.27; $p = 0.467$), smoking status (13.3% vs 9.3%; $p = 0.519$), alcohol intake (43.3% vs 28.0%; $p = 0.137$), or comorbidities including vascular disease (43.3% vs 49.3%; $p = 0.585$), diabetes mellitus (10.0% vs 18.7%; $p = 0.386$), malignant tumour (13.3% vs 4.0%; $p = 0.104$), and systemic inflammatory disease (6.7% vs 9.3%; $p > 0.999$).

**Table 1.** Baseline Characteristics.

| Characteristic | Total (n=105) | One-stage (n=30) | Two-stage (n=75) | p-value* |
|---|---|---|---|---|
| Age (SD) | 65.9 (10.9) | 67.9 (10.6) | 65.0 (11.0) | 0.232 |
| BMI (SD) | 31.0 (6.4) | 29.1 (5.2) | 31.9 (6.8) | 0.096 |
| Follow up (range) | 4.4 (2.5-22.9) | 3.2 (2.5-15.7) | 5.0 (2.8-22.9) | 0.490 |
| **ASA score** | | | | 0.467 |
| 1 | 8 (7.6%) | 1 (3.3%) | 7 (9.3%) | |
| 2 | 57 (54.3%) | 15 (50.0%) | 42 (56.0%) | |
| 3 | 39 (37.1%) | 14 (46.7%) | 25 (33.3%) | |
| 4 | 1 (1.0%) | 0 (0.0%) | 1 (1.3%) | |
| **Joint** | | | | 0.706 |
| Hip | 39 (37.1%) | 12 (40.0%) | 27 (36.0%) | |
| Knee | 66 (62.9%) | 18 (60.0%) | 48 (64.0%) | |
| **Laterality** | | | | 0.361 |
| Left | 53 (50.5%) | 13 (43.3%) | 40 (53.3%) | |
| Right | 52 (49.5%) | 17 (56.7%) | 35 (46.7%) | |
| **Gender** | | | | **0.023** |
| Male | 50 (47.6%) | 9 (30.0%) | 41 (54.7%) | |
| Female | 55 (52.4%) | 21 (70.0%) | 34 (45.3%) | |
| **Risk factors** | | | | |
| Smoking | 11 (10.5%) | 4 (13.3%) | 7 (9.3%) | 0.519 |
| Alcohol | 34 (32.4%) | 13 (43.3%) | 21 (28.0%) | 0.137 |
| Drugs | 6 (5.7%) | 2 (6.7%) | 4 (5.3%) | > 0.999 |
| **Comorbidities** | | | | |
| Vascular Disease | 50 (47.6%) | 13 (43.3%) | 37 (49.3%) | 0.585 |
| Hypertension | 64 (61.0%) | 15 (50.0%) | 49 (65.3%) | 0.151 |
| Diabetes Mellitus | 17 (16.2%) | 3 (10.0%) | 14 (18.7%) | 0.386 |
| Malignant Tumor | 7 (6.7%) | 4 (13.3%) | 3 (4.0%) | 0.104 |
| Inflammatory Disease | 9 (8.6%) | 2 (6.7%) | 7 (9.3%) | > 0.999 |

*Chi-squared test.

ASA, American Society of Anesthesiologists; BMI, body mass index; SD, standard deviation

### Antibiotic Therapy

For both the one-stage and two-stage revision groups, empirical therapy consisted of broad-spectrum antibiotics, most frequently vancomycin (66.7%, n = 70) and ceftriaxone (21.0%, n = 22). Parenteral antibiotics were administered for a duration of six weeks in 29 one-stage (96.7%) and 65 two-stage patients (86.7%), and more

than six weeks in one of the one-stage (3.3%) and ten of the two-stage patients (13.3%). Following the completion of the intravenous therapy, oral antibiotics were used for a duration of at least six weeks in the one-stage and two-stage revision cohorts for all patients. The most frequently used agents were doxycycline (47.4%, n = 50), trimethoprim-sulfamethoxazole (21.1%, n = 22), and amoxicillin with clavulanate (18.4%, n = 19).

**Clinical outcomes**

Of the 105 included patients with chronic culture-negative PJI, five patients (16.7%) in the one-stage cohort and fifteen patients (20.0%) in the two-stage cohort developed a reinfection at the latest follow-up which required further surgical intervention (Table II). This difference was not statistically significant (p = 0.691, chi-squared test). In the one-stage cohort, four patients sustained a deep reinfection. These were treated with DAIR and modular exchange (two patients) or two-stage revision (two patients). There was one superficial infection which was treated with irrigation and debridement (I&D). In the two-stage cohort, 14 patients sustained a deep infection. These were treated with DAIR and modular exchange (nine patients), additional repeat two-stage revision (two patients), arthrodesis (two patients), or with implantation of a cement spacer with subsequent amputation (one patient). There was one superficial infection which was treated with I&D (Table II). There was no difference in risk between patients treated with monotherapy or combination antibiotic therapy (odds ratio (OR) 0.679 (95% confidence interval 0.207 to 2.227); p = 0.524, chi-squared test).

**Table 2.** Clinical outcomes.

| Outcome | Total (n=105) | One-stage (n=30) | Two-stage (n=75) | p-value* |
|---|---|---|---|---|
| **Reinfection, n (%)** | 20 (19.0%) | 5 (16.7%) | 15 (20.0%) | 0.691 |
| Deep Infection | 18 (17.1%) | 4 (13.4%) | 14 (18.7%) | |
| Superficial Infection | 2 (1.9%) | 1 (3.3%) | 1 (1.3%) | |
| **Re-revision, n (%)** | 15 (14.3%) | 4 (13.3%) | 11 (14.7%) | 0.865 |
| Periprosthetic Fracture | 1 (6.7%) | 0 (0.0%) | 1 (9.1% | |
| Instability | 1 (6.7%) | 1 (25.0%) | 0 (0.0%) | |
| Wound Healing | 1 (6.7%) | 0 (0.0%) | 1 (9.1%) | |
| Aseptic Loosening | 3 (20.0%) | 1 (25.0%) | 2 (18.2%) | |
| Dislocation | 3 (20.0%) | 1 (25.0%) | 2 (18.2%) | |
| Arthrofibrosis | 2 (13.3%) | 0 (0.0% | 2 (18.2%) | |
| Extensor Mechanism | 2 (13.3%) | 1 (25.0%) | 1 (9.1%) | |
| Mechanical Complication | 1 (6.7%) | 0 (0.0%) | 1 (9.1%) | |
| Other | 1 (6.7%) | 0 (0.0%) | 1 (9.1%) | |

**Table 2.** Clinical outcomes. (continued)

| Outcome | Total (n=105) | One-stage (n=30) | Two-stage (n=75) | p-value* |
|---|---|---|---|---|
| **30-day Readmission, n (%)** | 9 (8.6%) | 3 (10.0%) | 6 (8.0%) | 0.715 |
| **60-day Readmission, n (%)** | 12 (11.4%) | 5 (16.7%) | 7 (9.3%) | 0.321 |
| **90-day Readmission, n (%)** | 16 (15.2%) | 8 (26.7%) | 8 (10.7%) | 0.078 |
| **1-year Mortality, n (%)** | 4 (3.8%) | 1 (3.3%) | 3 (4.0%) | > 0.999 |
| **Amputation, n (%)** | 2 (1.9%) | 1 (3.3%) | 1 (1.3%) | 0.496 |
| **Length of Stay, days (SD)** | 7.3 (6.1) | 7.8 (8.0) | 7.2 (5.3) | 0.760 |

*Pearson chi-squared test
SD, Standard Deviation

In addition, four patients (13.3%) in the one-stage and eleven (14.7%) in the two-stage cohort underwent re-revision surgery for aseptic reasons (p = 0.865, chi-squared test). In the one-stage cohort, one patient developed aseptic loosening, two patients had recurrent dislocations of the hip, and one patient sustained a patellar tendon injury. In the two-stage cohort, two patients developed aseptic loosening, two patients suffered recurrent dislocations, two patients presented with arthrofibrosis, one patient suffered a periprosthetic fracture of the distal femur requiring fixation, one patient had delayed wound healing of the hip, and one patient sustained a fracture of the femoral stem. Lastly, one patient underwent one-stage revision for suspected PJI, though there was no evidence of infection during revision surgery and all pre- and intraoperative culture results were sterile. The readmission rates at 30-, 60-, and 90 days postoperatively did not differ significantly between the one-stage and two-stage cohorts (10.0% vs 8.0%; p = 0.715 and 16.7% vs 9.3%; p = 0.321; and 26.7 vs 10.7%; p = 0.078, respectively). Furthermore, no significant differences were seen between the cohorts with regards to one-year mortality (3.3% vs 4.0%; p > 0.999) or amputation rates (3.3% vs 1.3%, p = 0.496; all p-values calculated using chi-squared test) (Table II).

The mean time from index procedure to reinfection was 1.2 years (0.3 to 4.2) after single-stage revision, and 1.5 years (0.6 to 5.8) for two-stage revision. The mean time from index procedure to re-revision was 2.8 years (0.2 to 8.9) for single-stage, and 3.3 years (0.2 to 7.9) for two-stage revision. The mean time between explantation and reimplantation for two-stage revision was 4.5 months (2.5 months to 16.0 months).

Subgroup analyses for the hip and knee were performed. For the THA patients, one-stage compared to two-stage revision was not associated with significantly higher reinfection (16.7% vs 11.1%; p = 0.631) or re-revision rates (16.7% vs 7.4%; p = 0.574). The TKA patients undergoing one-stage revision sustained a similar rate of complications requiring reoperation compared to two-stage revision (16.7% vs 25.0%; p = 0.782) and re-revision (11.1% vs 18.8%; p = 0.707; all p-values calculated using chi-squared test). Additional outcome measures for the THA and TKA subgroups are summarized in Tables III and IV, respectively.

**Table 3.** Subgroup analysis of total hip arthroplasty patients.

| Outcome | Total (n=39) | One-Stage (n=12) | Two-Stage (n=27) | p-value* |
|---|---|---|---|---|
| Reinfection, n (%) | 5 (12.8%) | 2 (16.7%) | 3 (11.1%) | 0.631 |
| Re-revision, n (%) | 4 (10.3%) | 2 (16.7%) | 2 (7.4%) | 0.574 |
| 30-day Readmission, n (%) | 5 (12.8%) | 2 (16.7%) | 3 (11.1%) | 0.632 |
| 60-day Readmission, n (%) | 8 (20.5%) | 4 (33.3%) | 4 (14.8%) | 0.196 |
| 90-day Readmission, n (%) | 9 (23.1%) | 5 (41.7%) | 4 (14.8%) | 0.063 |
| 1-year Mortality, n (%) | 3 (7.7%) | 1 (8.3%) | 2 (7.4%) | > 0.999 |
| Amputation, n (%) | 1 (2.6%) | 1 (8.3%) | 0 (0.0%) | 0.315 |
| Length of Stay, days (SD) | 9.0 (7.9) | 10.0 (10.8) | 8.5 (6.4) | 0.826 |

*Chi-squared test
SD, Standard Deviation

**Table 4.** Subgroup analysis of total knee arthroplasty patients.

| Outcome | Total (n=66) | One-Stage (n=18) | Two-Stage (n=48) | p-value* |
|---|---|---|---|---|
| Reinfection, n (%) | 15 (22.7) | 3 (16.7%) | 12 (25.0%) | 0.782 |
| Re-revision, n (%) | 11 (16.7%) | 2 (11.1%) | 9 (18.8%) | 0.707 |
| 30-day Readmission, n (%) | 4 (6.1%) | 1 (5.6%) | 3 (6.3%) | > 0.999 |
| 60-day Readmission, n (%) | 4 (6.1%) | 1 (5.6%) | 3 (6.3%) | > 0.999 |
| 90-day Readmission, n (%) | 7 (10.6%) | 3 (16.7%) | 4 (8.3%) | 0.171 |
| 1-year Mortality, n (%) | 4 (6.1%) | 1 (5.6%) | 3 (6.3%) | > 0.999 |
| Amputation, n (%) | 3 (4.5%) | 0 (0.0%) | 3 (6.3%) | > 0.999 |
| Length of Stay, days (SD) | 6.3 (4.3) | 6.0 (3.9) | 6.4 (4.5) | 0.606 |

*Fisher's exact test
SD, Standard Deviation

## DISCUSSION

There remains uncertainty over whether chronic culture-negative PJI after TKA and THA can be managed by one-stage rather than two-stage revision arthroplasty. This retrospective cohort study evaluated the outcomes of these two treatment strategies. Chronic culture-negative PJI occurred more commonly after primary TKA than THA. Patients were multi-morbid, and diagnosis and management is complex. The rates of infection eradication, and patient morbidity and mortality for one-stage revision were comparable to two-stage revision.

There is renewed interest in one-stage revision for PJI as it may reduce morbidity and healthcare costs compared to two-stage revision [41–43]. In a recent systematic review on chronic PJI in TKA patients, Pangaud et al. [24] compared 14 one-stage revision studies to 18 studies on the gold standard of two- stage revision. There were similar eradication rates, function, and patient-reported outcomes for the two treatment options. A recent systematic review and meta-analysis on chronic PJI in THA patients by Kunutsor et al. [25] analyzed a total of 44 articles, pooling and comparing 13 studies on one-stage revision and 31 studies two-stage revision THA. Their results suggested that one-stage revision may be similarly effective compared to two- stage revision. However, evaluation of the treatment outcomes for culture-negative PJI was not included in these analyses.



Although the outcomes after one-stage revision surgery have been evaluated previously, the studies reporting on these measures mainly investigated culture-positive PJI. Cases that did not yield growth of pathogens were often excluded from the analysis [26,27,44]. Several series on the efficacy of one-stage revision have included a selection of patients suitable to undergo one-stage revision surgery according to predefined criteria, including well-identified causative pathogens with appropriate antibiotics available [5,27,28]. However, the evidence supporting such selection criteria is limited, and several recent studies have applied broader inclusion criteria for patients undergoing one-stage revision. The results of a systematic review by Thakrar et al. [31] indicate that a preoperatively unknown microbiological diagnosis may not be a contraindication for one-stage revision THA and TKA. In addition, a study by Jenny et al. [45] demonstrated that patient selection (suspicion or diagnosis of chronic infection with contraindications being fungal infections, repeat failure of previous infection treatments) prior to one-stage revision did not yield superior outcomes, suggesting that those patients not meeting pre-existing criteria may also benefit from one-stage revision TKA. Ji et al. [32] utilized broad inclusion criteria (severely compromised immune system, severely compromised local limb status) for one-stage revision and reported reinfections in four out of 23 culture-negative cases, stating there is a need to reconsider culture negativity as a contraindication for one-stage revision THA. Lange et al.

[29] questioned the importance of preoperatively determined pathogens in one-stage revision surgery, reporting 91% infection eradication for a cohort consisting of 56 THA patients, among whom 15 patients had negative cultures. This suggests an unknown causative pathogen might not be an exclusion criterion for one-stage revision.

Our study represents one of the first series reporting the outcomes of one-stage and two-stage revision for culture-negative PJI. The results demonstrate infection eradication in 83.3% of the one-stage and 80.0% of the two-stage revision cases, suggesting that these two strategies are similarly effective for the treatment of chronic culture-negative PJI in selected patients. Although the general inclusion criteria were similar to those used by several other studies that reported on one-stage revision for culture-negative PJI, there were no significant differences between the two groups in age, BMI, ASA score, comorbidities, and risk factors such as smoking and alcohol intake [29,30,36]. Previous studies have reported infection eradication rates of 78.0% to 100.0% after two-stage revision [11,12,15,16,19,33], and infection eradication rates between 86.0% and 100.0% after one-stage revision, in cases of culture-negative PJI [29,32,33]. However, Huang et al. [33] and Lange et al. [29] did not assess the one-stage revision outcomes for patients with culture-negative PJI separately. Furthermore, several studies included subgroups of patients with negative cultures during preoperative assessment, who subsequently had a causative pathogen identified from intraoperative samples. This allowed the antibiotic treatment to be tailored specifically to the culture results, and resulted in infection eradication rates of 87.0% to 100.0% after one-stage revision [30,36,46]. In our study, all fluid and intraoperative culture results remained negative throughout the course of treatment, thus representing a cohort of true culture-negative PJI.

The findings of present study should be interpreted in the context of its limitations. Firstly, although the general indications for the use of one-stage revision are included, it remains unclear how much weight and emphasis the operating surgeons put on each criterion including soft tissue quality, medical comorbidities, and bone stock for individual patients due to the retrospective and non-randomized study design. Secondly, even though the two groups were generally similar, the male sex percentage was notably lower in the one-stage group. This discrepancy may have influenced the results of our study, though the potential influence of this factor is thought to be small [47,48]. Thirdly, the sample size of the one-stage cohort is small, though this study represents one of the largest series in the body of literature to evaluate one-stage and two-stage revision arthroplasty for chronic culture-negative PJI. Finally, our institutional protocol does not routinely include sonication in order to confirm culture negativity. However, this represents a common limitation in similar studies on this topic [29,30].

In conclusion, culture negativity in the treatment of chronic PJI after TKA and THA remains challenging. The results of this study indicate that the clinical outcomes after one-stage revision are similar to those after two-stage revision for chronic culture-negative PJI. This suggests culture negativity may not be a contraindication to one-stage revision arthroplasty for chronic PJI, and that one-stage revision surgery may be a viable alternative to two-stage revision in selected patients. Future longer-term and randomized clinical studies are needed to further characterize the viability of single-stage revision arthroplasty compared to two-stage revision for the treatment of chronic culture-negative PJI after TKA and THA.

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# CHAPTER 8

## Outcome of two-stage revision total hip and knee arthroplasty as a salvage procedure for deep infection of peri-articular fracture fixation: propensity score-matched study

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## ABSTRACT

**Background**

Failed open reduction internal fixation (ORIF) of peri-articular fractures due to deep infection is associated with decreased functional outcomes and increased mortality rates. Two-stage revision total joint arthroplasty (TJA) is often needed as a salvage procedure. The aim of this study was to evaluate the outcome of two-stage revision total hip and knee arthroplasty as a salvage procedure for the treatment of deep infection of peri-articular fracture fixation.

**Methods**

Using propensity score-matching, a total of 120 patients was evaluated: 1) 40 consecutive patients were treated with planned salvage two-stage revision for the treatment of deep peri-articular infection, and 2) a control group of 80 patients who underwent two-stage revision for periprosthetic joint infection (PJI) after non-internal fixation (IF) TJA. An infection occurred after a fracture of the acetabulum (27.5%), femoral neck (22.5%), intertrochanteric femur (15.0%), subtrochanteric femur (5.0%), femoral shaft (7.5%), distal femur (5.0%), tibia (15.0%), and patella (2.5%).

**Results**

At an average follow up of 4.5 years (range, 1.0-25.8), the overall failure rate was 42.5% for the IF group compared to 21.3% for the non-IF group (P=0.03). There was a significantly higher reinfection rate for the IF group compared to the non-IF group (group (35.0% vs. 11.3%, P=0.005). Tissue cultures for the IF patients demonstrated significantly higher polymicrobial growth (30.0% vs. 11.2%, P=0.01) and methicillin-resistant Staphylococcus aureus (20.0% vs. 7.5%, P=0.04).

**Conclusion**

Salvage two-stage revision arthroplasty for infected IF of peri-articular fractures was associated with poor outcome. The overall post-operative complications after salvage two-stage revision for infected IF of peri-articular fractures was high with 35% reinfection rates associated with the presence of mixed and resistant pathogens.

## INTRODUCTION

Closed reduction and internal fixation (CRIF) and open reduction and internal fixation (ORIF) represent treatment options for patients with a peri-articular fracture of the hip or knee [1,2]. ORIF of peri-articular fractures of the hip or knee can fail due to complications including nonunion and infection [2,3]. When deep infection after fracture fixation occurs, it is typically associated with decreased functional outcomes and an increased mortality [4]. Furthermore, deep infection can lead to delayed- or non-union of the fracture [4]. Even though peri-articular fractures are not always intracapsular, the hip or knee joint space may be involved when fixation of peri-articular regions of the acetabulum, femur, tibia, or patella fails [4]. Deep infection occurs in approximately 3.9% of peri-articular hip fractures treated with internal fixation (IF), and septic arthritis in 2.4% of peri-articular knee fractures [5,6]. The infection rates after IF of peri-articular fracture are similar to those for periprosthetic joint infection (PJI) after primary TJA, with reported rates between 1.6% to 3.4% of patients [6].

Treatment options for infected IF of peri-articular fractures include resection arthroplasty, arthrodesis, and salvage one-stage or two-stage TJA [7,8]. To optimize patient outcomes and infection control, a salvage two-stage revision is often performed following removal of all hardware and thorough irrigation and debridement (I&D) of all infected and necrotic tissue [9]. A two-stage approach allows to eradicate the infection before the definitive prosthesis is implanted, and thus to reduce the recurrence rate [8]. A similar two-stage approach is applied for patients with PJI after TJA for non-traumatic indications, with recent meta-analyses demonstrating successful infection eradication rates in approximately 85% of patients [10]. Deep articular infection after IF for peri-articular fractures is an important complication associated with serious consequences, and a limited number of studies has assessed the outcomes of complex salvage TJA for the treatment of these infections after failed ORIF of the hip or knee [11]. Therefore, the aim of this study was to evaluate the results and complications of two-stage revision total hip and knee arthroplasty as a salvage procedure for deep infection of peri-articular fracture fixation.



## MATERIALS AND METHODS

**Patients**

Following approval of the Institutional Review Board, all patients who underwent a planned two-stage revision arthroplasty for infection of the hip and knee joint were selected from a prospectively maintained institutional database at a large tertiary referral center. The diagnosis of infection was defined according to the criteria proposed by the workgroup of the Musculoskeletal Infection Society

(MSIS) [12]. This includes the presence of at least one of the major criteria (a sinus tract communicating with the prosthesis or 2 positive cultures with the same pathogen collected separately), or the presence of at least 4 minor criteria (elevated Erythrocyte Sedimentation Rate (ESR) and C-reactive Protein (CRP), elevated synovial White Blood Cell (WBC) count, elevated synovial Polymorphonuclear percentage (PMN%), presence of purulence in the affected joint, isolation of microorganism in 1 culture of a tissue or fluid sample, or histologic analysis of periprosthetic tissue demonstrating more than 5 neutrophils per high-power field at ×400 magnification [12]. In accordance with institutional clinical practice, a two-stage revision consisted of a first stage open procedure with debridement and removal of all prostheses generally followed by placement of antibiotic-loaded cement spacers. The type and amount of antibiotic included vancomycin (2g; 104 patients) and gentamicin (2g; 16 patients). The second stage consisted of extraction of any cement spacers and reimplantation of revision TJA components. Patients in both cohorts underwent the same treatment protocol for two-stage revision surgery. In consultation with infectious disease specialists, patients were treated with organism-specific intravenous antibiotics for a minimum six weeks followed by serum inflammatory markers to ensure normalization prior to reimplantation. In culture-negative infections, intravenous (IV) combination antibiotic therapy was used, consisting of vancomycin and cefepime. Oral antibiotics were used for a duration of at least six weeks in the culture-positive and culture-negative cohorts. The mean duration between first and second-stage reimplantation was 108 days for patients treated with planned salvage two-stage revision for the treatment of deep-peri-articular infection (IF group) as well as 99 days for patients who underwent two-stage revision for PJI after non-IF TJA (non-IF group). Cases not meeting the MSIS criteria, patients who did not undergo two-stage revision, and cases with missing outcome data due to incomplete reporting were excluded.

**Propensity score matching**

A total of 40 patients who underwent planned two-stage revision as a salvage procedure for deep infected IF of a peri-articular fracture of the acetabulum, femur, tibia, or patella (IF group) were identified. Furthermore, a total of 471 patients who underwent planned two-stage revision for PJI of the hip or knee after non-traumatic TJA (non-IF group) were selected. The raw cohorts demonstrated significant differences in age, body mass index (BMI), gender, joint, smoking status, and comorbidities. In order to reduce bias due to the large number of potential confounders, propensity score-matching was used [13]. Propensity scores were determined for each patient in order to achieve balance on the confounding covariates between the IF- and non-IF groups. The propensity score estimate was derived using factors related to the infection outcome, including patient age, BMI, gender, joint, smoking status, cardiovascular disease, diabetes mellitus, and inflammatory disease as covariates. A generalized overlap weighting scheme was

then applied to the distribution of independent propensity scores to check and ensure that patients after matching have approximately the same probabilities of being assigned to all other cohorts [14]. This process ensured to obtain a naturally representative subsample from the 471 patients who underwent planned two-stage revision for PJI of the hip or knee after non-traumatic TJA. A control group was created using propensity score-matching in a 1:2 sampling ratio, as this will result in optimal estimation of treatment effects [13]. All of the 40 patients were matched to 2 controls who sustained a PJI after non-traumatic TJA, resulting in a control group of 80 patients.

The electronic hospital files were reviewed for all included patients. Data was collected on patient demographics, including age, gender, BMI, and American Society of Anesthesiologists classification (ASA) score. Moreover, the files were evaluated for data on the index surgery, fracture type and date, revision surgery type, laboratory findings, and final infection diagnosis. Outcomes including length of hospital stay, reinfection, and re-revision, were retrieved from electronic medical hospital records.

**Fracture types and treatment**

The internal fixation (IF) group consisted of 40 fractured joints (3 patients were excluded due to loss of follow-up), including 27 hips and 13 knees. A total of 11 patients (27.5%) experienced a fracture of the acetabulum, all were treated with plate fixation. An intertrochanteric fracture was observed in 6 patients (15.0%), of which 5 were treated with an intramedullary (IM) nail and 1 with a dynamic hip screw (DHS). A femoral neck fracture was encountered in 9 patients (22.5%), of which 7 were treated with a DHS and 2 with cannulated screws. Two patients (5.0%) sustained a subtrochanteric fracture, of whom 1 was treated with a DHS and 1 with an IM nail. A fracture of the femoral shaft occurred in 3 patients (7.5%), of whom 2 were treated with a retrograde femur nail and 1 with plate fixation. A distal femur fracture was encountered in 2 patients (5.0%), 1 was treated with plate fixation and one with an expert tibia nail (ETN). Six patients (15.0%) experienced a fracture of the proximal tibia, of whom 5 patients with tibia plateau fractures were treated using plate fixation and 1 patient with a proximal tibia fracture using an ETN. Lastly, 1 patient (2.5%) sustained a fracture of the patella and this was treated with cerclage wiring. The fracture types and treatments are summarized in [Table 1].

**Table 1.** Index fracture types and treatments.

| **Infected Internal Fixation (n=40)** | |
|---|---|
| Acetabulum | 11 (27.5%) |
| *Plate Fixation* | 11 |
| Intertrochanteric Femur | 6 (15.0%) |
| *Intramedullary Nail* | 5 |
| *Dynamic Hip Screw* | 1 |
| Femoral Neck | 9 (22.5%) |
| *Dynamic Hip Screw* | 7 |
| *Cannulated Screws* | 2 |
| Subtrochanteric Femur | 2 (5.0%) |
| *Dynamic Hip Screw* | 1 |
| *Intramedullary Nail* | 1 |
| Femoral Shaft | 3 (7.5%) |
| *Retrograde Femur Nail* | 2 |
| *Plate Fixation* | 1 |
| Distal Femur | 2 (5.0%) |
| *Plate Fixation* | 1 |
| *Expert Tibia Nail* | 1 |
| Proximal Tibia | 6 (15.0%) |
| *Plate Fixation* | 5 |
| *Expert Tibia Nail* | 1 |
| Patella | 1 (2.5%) |
| *Cerclage Wiring* | 1 |

**Clinical outcomes**

Post-operative follow-up was scheduled at 2 months, 1 year, 2 years, 5 years, and every 5 years after surgery. The clinical follow-up for all patients was a minimum of 1 year, until subsequent re-revision due to failure, or until death. The outcome was defined as successful when there were no clinical signs of infection during follow up. Moreover, the outcome was successful when no subsequent surgical interventions were necessary, such as debridement, antibiotics and implant retention (DAIR) with modular exchange, additional one- or two-stage revision was not needed, and no successive amputation occurred. If any additional surgical procedure took place for infection control, the treatment was defined as failure [15].

**Statistical analysis**

Propensity score-matching was performed using greedy nearest-neighbor matching technique without replacement in a 1:2 sampling ratio [14]. For the comparison of the treatment outcomes, the reinfection, re-revision, readmission, 2-year mortality, and amputation rates were compared. The propensity score-matched data were compared using a dependent t-test or Wilcoxon signed-rank test for continuous values, and a conditional logistic regression was fitted to test the hypothesis for binary values. All data analyses were performed using the Statistical Package for Social Sciences (SPSS®) statistics for Windows (version 26.0, Armonk, NY, USA: IBM Corp.).

## RESULTS

**Patient cohort**

After propensity score-matching, the study cohort consisted of 120 patients who underwent planned two-stage revision arthroplasty for the treatment of an infected hip or knee joint consisting of two groups: 1) 40 patients with deep infection of peri-articular IF, and 2) 80 patients with PJI after non-IF TJA. The baseline characteristics of the patients did not differ significantly between the two groups [Table 2]. The mean age was 64.1 (SD ± 13.3) years and the mean BMI was 32.1 (SD ± 7.5). Patients presented more often with an infected hip than knee, with infected hips accounting for 67.5% in the ORIF group and 68.8% in the non-IF group (P=0.83). The propensity matched covariates with corresponding standardized mean differences before and after matching are summarized in [Table 3]. There was no significant difference between both cohorts in terms of duration between first and second stage revision surgery (99 days vs 108 days; P=0.23).

**Table 2.** Patient demographics.

| | Total (n=120) | Infected Internal Fixation (n=40) | Infected Non-Internal Fixation (n=80) | P-value |
|---|---|---|---|---|
| Age (mean ± SD) | 64.1 ± 13.3 | 63.2 ± 14.4 | 64.1 ± 13.3 | 0.86 |
| BMI (mean ± SD) | 32.1 ± 7.5 | 31.0 ± 7.8 | 30.9 ± 7.4 | 0.87 |
| Follow up (mean (range)) | 4.5 (1.0-25.8) | 5.0 (1.0-25.8) | 4.2 (1.0-14.5) | 0.18 |
| ASA score | | | | 0.30 |
| 1 | 11 (9.2%) | 1 (2.5%) | 10 (12.5%) | |
| 2 | 61 (50.8%) | 21 (52.5%) | 40 (50.0%) | |
| 3 | 47 (39.2%) | 18 (45.0%) | 29 (36.3%) | |
| 4 | 1 (0.8%) | 0 (0.0%) | 1 (1.3%) | |
| Joint | | | | 0.89 |
| Hip | 82 (68.3%) | 27 (67.5%) | 55 (68.8%) | |
| Knee | 38 (31.7%) | 13 (32.5%) | 25 (31.2%) | |
| Laterality | | | | 0.36 |
| Right | 68 (56.7%) | 25 (62.5%) | 43 (53.8%) | |
| Left | 52 (43.3%) | 15 (37.5%) | 37 (46.2%) | |
| Gender | | | | 0.87 |
| Male | 59 (49.2%) | 20 (50.0%) | 39 (48.7%) | |
| Female | 61 (50.8%) | 20 (50.0%) | 41 (51.3%) | |
| Risk factors | | | | |
| Smoking | 34 (28.3%) | 11 (27.5%) | 23 (28.8%) | 0.84 |
| Alcohol | 42 (35.0%) | 14 (35.0%) | 28 (35.0%) | 1.00 |
| Drugs | 9 (7.5%) | 3 (7.5%) | 6 (7.5%) | 1.00 |
| Comorbidities | | | | |
| Cardiovascular Disease | 44 (36.7%) | 14 (35.0%) | 30 (37.5%) | 0.64 |
| Renal Disease | 7 (5.8%) | 3 (7.5%) | 4 (5.0%) | 0.60 |
| Diabetes Mellitus | 26 (21.7%) | 9 (22.5%) | 17 (21.3%) | 0.85 |
| Malignant tumor | 15 (12.5%) | 3 (7.5%) | 12 (15.0%) | 0.21 |
| Inflammatory Disease | 14 (11.7%) | 4 (10.0%) | 10 (12.5%) | 0.64 |

BMI, Body Mass Index; ASA, American Society of Anesthesiologists classification; SD, Standard Deviation

**Table 3.** Propensity Matched Covariates.

| Covariates | Means IF | | Means Non-IF | | SD Non-IF | | Std. Mean Diff. | |
|---|---|---|---|---|---|---|---|---|
| | Before | After | Before | After | Before | After | Before | After |
| Propensity Score | 0.152 | 0.152 | 0.091 | 0.150 | 0.067 | 0.095 | 0.633 | 0.019 |
| Age | 63.163 | 63.163 | 65.190 | 64.519 | 11.095 | 12.867 | -0.141 | -0.094 |
| Gender | 0.500 | 0.500 | 0.567 | 0.488 | 0.496 | 0.503 | -0.132 | 0.025 |
| BMI | 30.962 | 30.962 | 31.356 | 30.798 | 7.078 | 7.255 | -0.051 | 0.021 |
| Joint | 0.675 | 0.675 | 0.420 | 0.663 | 0.494 | 0.476 | 0.538 | 0.026 |
| Smoking | 0.275 | 0.275 | 0.104 | 0.288 | 0.306 | 0.455 | 0.378 | -0.028 |
| Cardiovascular Disease | 0.350 | 0.350 | 0.548 | 0.375 | 0.498 | 0.487 | -0.410 | -0.052 |
| Diabetes Mellitus | 0.225 | 0.225 | 0.225 | 0.213 | 0.418 | 0.412 | 0.001 | 0.030 |
| Inflammatory Disease | 0.100 | 0.100 | 0.086 | 0.125 | 0.280 | 0.333 | 0.048 | -0.082 |

BMI, Body Mass Index; SD, Standard Deviation; Std. Mean Diff., Standardized Mean Difference

**Clinical outcomes**

At an average follow up of 4.5 years (range, 1.0-25.8), the overall failure rate was 42.5% for IF patients and 21.3% for non-IF patients (P=0.03). Reinfection was the most common indication for failure, occurring in 14 out of 40 IF patients (35.0%) and 9 out of 80 non-IF patients (11.3%, P=0.005). Of those 14 IF patients, 10 out of 14 sustained a deep recurrent infection, which were treated with DAIR and modular exchange (5 patients), implant removal (3 patients), or one-stage revision (2 patients). One patient ultimately underwent amputation due to continued infection. Four patients sustained a superficial reinfection not communicating with the joint, and these were treated with I&D. In the non-IF group, 9 patients developed a deep reinfection, which were treated with DAIR and modular exchange (5 patients), implant removal (3 patients), or additional two-stage revision (1 patient).

Aseptic failures requiring re-revision occurred in 2 out of 40 IF patients (5.0%) compared to 7 out of 80 non-IF patients (8.8%, P=0.49). In the IF group, 2 patients underwent re-revision for recurrent dislocation. In the non-IF group, there were 3 patients who underwent re-revision for recurrent dislocation, 1 patient with adverse local tissue reaction, 1 patient with aseptic loosening, 1 patient with THA malalignment, and 1 patient developed painful effusion and underwent modular exchange. Length of hospital stay after the first stage was longer for the IF group compared to the non-IF group, however not significant (13.5 ± 8.6 days vs. 10.5 ± 7.5 days, P=0.09). Length of stay after second stage surgery did not significantly differ between the groups (6.8 ± 3.2 vs. 6.2 ± 4.2, P=0.50). No significant differences were observed for 30; 60; and 90-day

readmission rates between the IF and non-IF groups (15.0% vs. 11.3%, P=0.56; 20.0% vs. 15.0%, P=0.37; and 20.0% vs. 18.8%, P=0.66). No significant differences were observed for amputation rates (2.5% vs. 1.3%, P=0.62) [Table 4].

**Table 4.** Comparison of postoperative complication rates and clinical outcomes between both study cohorts.

| | **Total (n=120)** | **Infected Internal Fixation (n=40)** | **Infected Non-Internal Fixation (n=80)** | **P-value** |
|---|---|---|---|---|
| Overall Complication Rate | 34 (28.3%) | 17 (42.5%) | 17 (21.3%) | **0.03** |
| Reinfection | 23 (19.2%) | 14 (35.0%) | 9 (11.3%) | **0.005** |
| Re-revision | 9 (7.5%) | 2 (5.0%) | 7 (8.8%) | 0.49 |
| 30-day Readmission | 15 (12.5%) | 6 (15.0%) | 9 (11.3%) | 0.56 |
| 60-day Readmission | 20 (16.7%) | 8 (20.0%) | 12 (15.0%) | 0.37 |
| 90-day Readmission | 23 (19.2%) | 8 (20.0%) | 15 (18.8%) | 0.66 |
| 2-year Mortality | 6 (5.0%) | 2 (5.0%) | 4 (5.0%) | 1.00 |
| Amputation | 2 (1.7%) | 1 (2.5%) | 1 (1.3%) | 0.62 |
| Length of Stay 1, days (mean ± SD) | 10.0 ± 7.3 | 13.5 ± 8.6 | 10.5 ± 7.5 | 0.09 |
| Length of Stay 2, days (mean ± SD) | 6.0 ± 4.0 | 6.8 ± 3.2 | 6.2 ± 4.2 | 0.50 |

SD, Standard Deviation

Subgroup analyses to assess the outcomes for the hip and knee cohorts were performed. In the hip subgroup, higher failure due to reinfection was encountered for IF patients compared to non-IF patients (29.6% vs. 9.1%, P=0.02). In the IF group, there were 6 deep and 2 superficial reinfections, and in the non-IF group there were 5 deep reinfections. For the knee subgroup, more reinfections occurred for the IF patients compared to the non-IF patients (46.2% vs. 16.0%, P=0.04). In the IF group, there were 4 deep and 2 superficial reinfections, and in the non-IF group there were 4 deep reinfections [Tables 5; 6].

**Table 5.** Clinical outcomes for the hip subgroup.

| | Total (n=82) | Infected Internal Fixation (n=27) | Infected Non-Internal Fixation (n=55) | P-value |
|---|---|---|---|---|
| Reinfection | 13 (15.9%) | 8 (29.6%) | 5 (9.1%) | **0.02** |
| Re-revision | 5 (6.1%) | 2 (7.4%) | 3 (5.5%) | 0.73 |
| 30-day Readmission | 13 (15.9%) | 5 (18.5%) | 8 (14.5%) | 0.90 |
| 60-day Readmission | 16 (19.5%) | 7 (25.9%) | 9 (16.4%) | 0.47 |
| 90-day Readmission | 20 (24.4%) | 7 (25.9%) | 13 (23.6%) | 0.82 |
| 2-year Mortality | 2 (2.4%) | 1 (3.7%) | 1 (1.8%) | 1.00 |
| Amputation | 1 (1.2%) | 1 (3.7%) | 0 (0.0%) | 0.61 |
| Length of Stay 1, days (mean ± SD) | 9.9 ± 6.9 | 13.3 ± 8.6 | 8.1 ± 5.1 | 0.31 |
| Length of Stay 2, days (mean ± SD) | 5.8 ± 3.1 | 6.4 ± 3.3 | 5.5 ± 2.9 | 0.82 |

SD, Standard Deviation

**Table 6.** Clinical outcomes for the knee subgroup.

| | Total (n=38) | Infected Internal Fixation (n=13) | Infected Non-Internal Fixation (n=25) | P-value |
|---|---|---|---|---|
| Reinfection | 10 (26.3%) | 6 (46.2%) | 4 (16.0%) | **0.04** |
| Re-revision | 4 (10.5%) | 0 (0.0%) | 4 (16.0%) | 0.28 |
| 30-day Readmission | 6 (15.8%) | 1 (7.7%) | 5 (20.0%) | 0.56 |
| 60-day Readmission | 8 (21.1%) | 1 (7.7%) | 7 (28.0%) | 0.34 |
| 90-day Readmission | 9 (23.7%) | 1 (7.7%) | 8 (32.0%) | 0.22 |
| 2-year Mortality | 1 (2.6%) | 1 (7.7%) | 0 (0.0%) | 0.61 |
| Amputation | 1 (2.6%) | 0 (0.0%) | 1 (4.0%) | 1.00 |
| Length of Stay 1, days (mean ± SD) | 10.2 ± 8.1 | 13.5 ± 8.7 | 8.8 ± 5.4 | **0.04** |
| Length of Stay 2, days (mean ± SD) | 6.4 ± 5.3 | 6.5 ± 3.4 | 6.4 ± 5.1 | 0.13 |

SD, Standard Deviation



**Microbiology Results**

Significantly higher polymicrobial growth (30.0% vs. 11.2%, P=0.01), methicillin-resistant Staphylococcus aureus (MRSA) (20.0% vs. 7.5%, P=0.04), and other Gram-positive organisms (7.5% vs. 0.0%, P=0.04) were encountered for the IF cohort, when compared to the non-IF cohort [Table 7]. For patients sustaining a recurrent

infection, patients in the IF group demonstrated higher rates of MRSA (21.5% vs. 11.1%), Staphylococcus species (14.3% vs. 0.0%) and polymicrobial growth (21.5% vs. 0.0%), whereas the non-IF group demonstrated a higher prevalence of MSSA (33.3% vs. 7.1%), Propionibacterium acnes (22.2% vs. 0.0%), and culture-negative infections (33.3% vs. 14.3%) [Table 8].

**Table 7.** Overview of causative pathogens at salvage two-stage revision.

| Pathogens | Total (n=120) | Infected Internal Fixation (n=40) | Infected Non-Internal Fixation (n=80) | P-value |
|---|---|---|---|---|
| Staphylococcus aureus | 19 (15.8%) | 5 (12.5%) | 14 (17.5%) | 0.48 |
| Methicillin-resistant Staphylococcus aureus | 14 (11.7%) | 8 (20.0%) | 6 (7.5%) | **0.04** |
| Streptococcus species | 8 (6.7%) | 2 (5.0%) | 6 (7.5%) | 0.61 |
| Staphylococcus species | 5 (4.2%) | 1 (2.5%) | 4 (5.0%) | 0.37 |
| Coagulase-negative Staphylococci | 9 (7.5%) | 2 (5.0%) | 7 (8.8%) | 0.46 |
| Propionibacterium acnes | 3 (2.5%) | 0 (0.0%) | 3 (3.8%) | 0.55 |
| Other gram positive organisms | 3 (2.5%) | 3 (7.5%) | 0 (0.0%) | **0.04** |
| Other gram negative organisms | 5 (4.2%) | 0 (0.0%) | 5 (6.3%) | 0.17 |
| Anaerobes | 1 (0.8%) | 0 (0.0%) | 1 (1.2%) | 1.00 |
| Other | 1 (0.8%) | 0 (0.0%) | 1 (1.2%) | 1.00 |
| Negative culture | 31 (25.8%) | 7 (17.5%) | 24 (30.0%) | 0.11 |
| Cultures with Mixed growth | 21 (17.5%) | 12 (30.0%) | 9 (11.2%) | **0.01** |

**Table 8.** Overview of causative pathogens for patients sustaining a reinfection.

| Pathogens | Total (n=23) | Infected Internal Fixation (n=14) | Infected Non-Internal Fixation (n=9) | P-value |
|---|---|---|---|---|
| Staphylococcus aureus | 4 (17.5%) | 1 (7.1%) | 3 (33.3%) | 0.26 |
| Methicillin-resistant Staphylococcus aureus | 4 (17.5%) | 3 (21.5%) | 1 (11.2%) | 0.63 |
| Streptococcus species | 1 (4.3%) | 1 (7.1%) | 0 (0.0%) | 1.00 |
| Staphylococcus species | 2 (8.7%) | 2 (14.3%) | 0 (0.0%) | 0.50 |
| Coagulase-negative Staphylococci | 1 (4.3%) | 1 (7.1%) | 0 (0.0%) | 1.00 |
| Propionibacterium acnes | 2 (8.7%) | 0 (0.0%) | 2 (22.2%) | 0.14 |
| Pseudomonas aeruginosa | 1 (4.3%) | 1 (7.1%) | 0 (0.0%) | 1.00 |
| Negative culture | 5 (21.7%) | 2 (14.3%) | 3 (33.3%) | 0.34 |
| Cultures with Mixed growth | 3 (13.0%) | 3 (21.5%) | 0 (0.0%) | 0.25 |

## DISCUSSION

Deep infection involving the hip or knee joint is a complication that may occur after failed IF for periarticular fracture, for which treatment consists of resection arthroplasty, arthrodesis, and salvage one-stage or two-stage TJA [10,12]. Similar to PJI after non-traumatic TJA, these joint infections are often treated with revision arthroplasty using a two-stage approach. Aseptic failures of peri-articular IF have been reported to show high complication rates after salvage THA and TKA. However, the outcomes of salvage two-stage revision for deep infected peri-articular fracture remain largely unknown. This study aimed to analyze the outcomes of revision arthroplasty as a salvage procedure for deep infection after peri-articular fracture fixation in comparison with a propensity score-matched cohort of patients who underwent two-stage revision for PJI after non-traumatic TJA. Both patient groups underwent the same treatment protocol and surgical approach in order to allow a comparison. The findings of this study demonstrate high overall post-operative complications after salvage two-stage revision for infected IF of peri-articular fractures with 35% reinfection rates and the presence of mixed and resistant pathogens.

Treatment failure of a peri-articular fracture presents a difficult challenge to the orthopaedic surgeon. It is estimated that approximately 14.3% and 7.3% of patients

with failed ORIF of hip and knee fractures respectively require salvage TJA [16,17]. The majority of the literature on conversion TJA after failed ORIF has focused on aseptic failures of fracture fixation, reporting high postoperative complication rates for these patients when compared to patients undergoing elective TJA [18,19]. Studies assessing the outcomes of salvage two-stage TJA for failed infected ORIF of the hip and knee are limited. Few series have described two-stage revision for the treatment of infected ORIF of a combined total of 25 intracapsular femur fractures and 2 studies evaluated a combined total of 34 extracapsular fractures of the femur [5,8,10]. One study included 4 intracapsular and 1 acetabular fracture in their analysis of salvage two-stage revision for septic hip arthritis in 13 patients [20]. For the treatment of infected ORIF of the knee, 1 case-control study was identified reporting on the outcomes for 6 tibia plateau fractures [21]. However, different treatment strategies were used and study populations varied. The present study aimed to address the outcomes for salvage two-stage revision arthroplasty for deep infection after IF of peri-articular fractures of both the hip and knee.

After two-stage revision for non-IF PJI in the present study, complications were observed in 21.3% of patients, with reinfection accounting for 11.3%. The reinfection rate presented in our study is comparable to the results reported in recent meta-analyses on PJI, ranging from 8% to 13.5% of patients [22]. The overall failure rate after salvage two-stage revision for the IF group in our study was significantly higher (42.5%), with reinfection presenting the most common complication observed in 32.5% of patients. Patients in the knee IF subgroup demonstrated a high recurrent infection rate of 46.2%, with deep and superficial reinfection occurring in 30.8% and 15.4% of patients, respectively. This finding is similar to Larson et al., who reported on the occurrence of a reinfection in 2 of the 6 patients that underwent two-stage revision for infected failed tibia plateau fixation in their study [21]. Furthermore, the reinfection rate for the hip subgroup was 29.6%, with deep reinfection in 18.5% of patients and superficial reinfection in 11.1%. This finding is in accordance with 2 previous studies reporting reinfections in 20.0% to 26.0% of patients after two-stage revision for infected hip IF [21,23]. Conversely, Hsieh et al. reported no recurrent infection in 12 patients with antibiotic-loaded cement spacers [5], and Mohanty et al. described 20 consecutive patients who underwent revision THA, in which only 1 superficial reinfection occurred [8]. Moreover, Ebied et al. reported on 26 two-stage procedures for intracapsular and extracapsular femur fractures, with no recurrence of infection or further revision surgery [10].

The microbiology results in our study may have attributed to the high reinfection rates of the IF group, as polymicrobial growth was encountered in 30% of patients and MRSA in 20% of patients. These pathogens are associated with worse outcomes for fracture fixation infections, and their incidence rates in the United States have been reported in up to 35% of patients for polymicrobial infections and in up to 32%

for MRSA [24]. However, few studies on salvage two-stage revision arthroplasty have reported on microbiology results. One study demonstrated high infection control rates in 19 out of 20 patients with coagulase-negative Staphylococcus in 9, MSSA in 5, MRSA in 1, and Gram-negative pathogens in 5 cases [8]. Furthermore, 1 study demonstrated infection eradication in all patients, even though high polymicrobial and MRSA rates were encountered [10]. However, no cases with negative cultures were present, yet this occurred in 17.5% of our IF group. Moreover, when assessing the outcomes for two-stage revision, multiple studies demonstrated the presence of MRSA and cases with polymicrobial growth to be at increased risk for reinfection [25]. This is potentially due to the high virulence pathogens and the need for antibiotic selection in patients with cultures demonstrating mixed growth, highlighting the importance to identify causative pathogens for culture-guided antibiotic therapy and treatment planning.

The findings of the present study should be interpreted in the context of its limitations. Firstly, due to the retrospective nature of the study, possible selection- and misclassification bias for the different indications may have occurred. However, in an effort to alleviate this risk, all patients who underwent planned two-stage revision TJA for any joint infection of the hip or knee were identified and reviewed for inclusion. Secondly, the sample size of the study may be regarded as limited. However, this study represents one of the largest series on salvage two-stage revision for infected peri-articular IF, utilizing a propensity score-matched control group consisting of patients who underwent two-stage revision for PJI after non-traumatic TJA. This limitation in sample size has further not allowed the separate comparison of outcomes for patients with hip and knee arthroplasties.



In conclusion, salvage two-stage revision arthroplasty for infected IF of peri-articular fractures was associated wit hpoor outcome. The overall post-operative complications after salvage two-stage revision for infected IF of peri-articular fractures was high with 35% reinfection rates associated with the presence of mixed and resistant pathogens.

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# CHAPTER 9

## *Based on* Periprosthetic joint infection is the main reason for failure in patients following periprosthetic fracture treated with revision arthroplasty

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## ABSTRACT

**Introduction**

Periprosthetic fracture after primary total hip and knee arthroplasty (THA; TKA) can be challenging, requiring open reduction internal fixation (ORIF), revision, or both. The aim of this study was to evaluate the outcomes and risk factors associated with re-revision surgery following failed revision arthroplasty for periprosthetic fracture.

**Methods**

A total of 316 consecutive THA patients and 79 consecutive TKA patients underwent a revision for periprosthetic fracture, of which 60 THA patients (19.0%) and 23 TKA patients (29.1%) underwent re-revision surgery. The most common indication for hip and knee re-revision was periprosthetic joint infection (PJI) in 25 THA patients (41.6%) and 14 TKA patients (60.7 %).

**Results**

The complication rates of THA and TKA revision were 22.2% and 31.6% respectively, and 35.0% and 39.1% respectively for re-revision surgery at an average follow-up of 4.7 years. Periprosthetic joint infection was the most common indication for THA and TKA re-revision (7.9%; 17.7%) and third revision surgery (10.0%; 17.4%). Factors significantly contributing to an increased risk of THA and TKA re-revision included revision with plate fixation and revision with combined ORIF.

**Conclusion**

The overall complication rate of THA and TKA re-revision surgery following failed revision surgery for periprosthetic fracture was higher than of revision surgery. The most common indication for re-revision and third revision was periprosthetic joint infection. These findings may assist surgeons in the management and preoperative counseling of patients undergoing THA and TKA revision surgery for a periprosthetic fracture to optimize the outcomes for these patients.

## INTRODUCTION

Hip and knee total joint arthroplasty (TJA) is a commonly performed orthopaedic procedure with a prevalence that is projected to increase substantially over the next decade, reaching approximately 4.0 million by 2030 [1]. As the number of TJAs performed continues to rise, it is anticipated that the magnitude of revision surgeries associated with complications will increase accordingly [2]. Periprosthetic fracture associated with TJA of the hip or knee is a challenging complication [3]. Currently, incidences for periprosthetic fracture have been reported to be as high as 5.5% after primary total knee arthroplasty (TKA) and 18.0% after total hip arthroplasty (THA) [4], and those are projected to rise even further due to an increasingly elderly, osteoporotic population [5]. Moreover, a higher body mass index (BMI), osteoporosis, and higher postoperative activity levels in patients younger than 60 years increase the risk of periprosthetic fractures [6,7]. The management of periprosthetic fractures requires expertise of both osteosynthesis and joint reconstruction techniques, as treatment strategies include open reduction internal fixation (ORIF), revision surgery, or a combination of both management options [8]. Generally, ORIF of a periprosthetic fracture is indicated for a well-fixed implant and revision arthroplasty with or without ORIF is indicated in cases with a loose implant [9].

The outcomes for patients with periprosthetic fractures have been reported to be poor and complications requiring readmission are frequently encountered, enhancing the associated cost to the health care system [10]. Following revision surgery for periprosthetic fracture, an increased perioperative complication rate is observed, which is illustrated by the annual proportion of admissions ranging from 4.2 to 7.4%, a longer length of hospital stay, higher discharge rates to specialized care facilities, and increased mortality rates [11]. Furthermore, long-term failure rates after revision surgery for periprosthetic fracture have been described to range from 12.0 to 31.0% [3,8,12,13]. The rate of re-operation has been reported to be 17.1% for patients treated with revision arthroplasty and 18.7% for patients treated with revision and ORIF [8], with the most common indications for re-revision surgery including re-fracture, loosening, nonunion, and periprosthetic joint infection (PJI) [3,7,14,15]. In particular, PJI was highlighted as a devastating complication as it is associated with significant morbidity and mortality, when compared to the other indications [3,16]. Additionally, the treatment outcomes following PJI are deteriorating with each episode of PJI, highlighting the importance for appropriate PJI treatment protocols [17,18]. However, even though it has been reported that patients requiring revision for periprosthetic fracture have high rates of re-revision, the outcomes and characteristics of patients undergoing re-revision surgery for complications after revision for periprosthetic fracture remain largely unelucidated. Therefore, the aim of this study was to evaluate the outcome of re-revision surgery

following the failure of revision for periprosthetic fracture of THA and TKA. This study hypothesizes that PJI is likely to account for a large number of re-revisions and third revision surgeries.

## METHODS

### Patients

Following approval of the Institutional Review Board, all patients who underwent revision surgery with or without additional ORIF for the treatment of a periprosthetic fracture of a primary THA and TKA were identified from a prospectively maintained institutional database at a tertiary referral center. Patients were eligible for inclusion when a clinical follow-up of at least 1 year was completed. A total of 421 patients were identified, and the electronic hospital charts were manually reviewed for those patients. Thirteen patients were excluded due to previously undergoing revision arthroplasty for periprosthetic fracture at an outside hospital and 13 patients were excluded due to incomplete documentation. Ultimately, a total of 395 patients fulfilled the inclusion criteria and were included in the final analyses (Tables 1, 2). Data were collected on patient demographics including age, gender, BMI, American Society of Anesthesiologists classification (ASA) score, and comorbidities at the time of re-revision surgery were collected. In addition, fracture and revision surgery type, and clinical outcomes including length of hospital stay, reinfection, complications, 1-year mortality were retrieved from the patient records.

**Table 1.** Univariate analysis of patient demographics (THA cohort).

| | **Full THA revision cohort (n = 316)** | **THA re-revision (n= 60)** | **No THA re-revision (n = 256)** | **p value** |
|---|---|---|---|---|
| Age (mean ± SD) | 73.8 ± 12.3 | 69.3 ± 11.8 | 74.9 ± 12.1 | **0.001** |
| BMI (mean ± SD) | 27.8 ± 5.9 | 28.9 ± 6.9 | 27.5 ± 5.6 | 0.18 |
| Follow up (mean, range) | 4.6 (1.0–23.0) | 5.9 (1.0–23.5) | 4.3 (1.0–18.0) | **0.04** |
| ASA score | | | | 0.35 |
| 1 | 19 (6.0%) | 6 (10.0%) | 13 (5.1%) | |
| 2 | 200 (63.3%) | 35 (58.3%) | 165 (64.5%) | |
| 3 | 93 (29.4%) | 19 (31.7%) | 74 (28.9%) | |
| 4 | 4 (1.3%) | 0 (0.0%) | 4 (1.6%) | |
| Laterality | | | | 0.97 |
| Left | 152 (48.1%) | 29 (48.3%) | 123 (48.0%) | |
| Right | 164 (51.9%) | 31 (51.7%) | 133 (52.0%) | |
| Gender | | | | 0.72 |
| Male | 133 (42.1%) | 24 (40.0%) | 109 (42.6%) | |
| Female | 183 (57.9%) | 36 (60.0%) | 147 (57.4%) | |
| Intoxications | | | | |
| Smoking | 28 (8.9%) | 8 (13.3%) | 20 (7.8%) | 0.18 |
| Alcohol | 122 (38.6%) | 21 (35.0%) | 101 (39.5%) | 0.52 |
| Drugs | 4 (1.3%) | 0 (0.0%) | 4 (1.3%) | 1.00* |
| Comorbidities | | | | |
| Renal disease | 21 (6.6%) | 2 (3.3%) | 19 (7.4%) | 0.39* |
| Cardiovascular disease | 104 (32.9%) | 15 (25.0%) | 89 (34.8%) | 0.15 |
| Hypertension | 169 (53.5%) | 32 (53.3%) | 137 (53.5%) | 0.98 |
| Diabetes mellitus | 35 (11.1%) | 9 (15.0%) | 26 (10.2%) | 0.28 |
| Malignant tumor | 28 (8.8%) | 4 (6.7%) | 24 (9.4%) | 0.51 |
| Inflammatory disease | 27 (8.5%) | 6 (10.0%) | 21 (8.2%) | 0.65 |
| Depression | 30 (9.5%) | 10 (16.7%) | 20 (7.8%) | **0.04** |
| Hematological disease | 28 (8.9%) | 4 (6.7%) | 24 (9.4%) | 0.51 |
| Neurological disease | 47 (14.9%) | 9 (15.0%) | 38 (14.8%) | 0.98 |
| Pulmonary disease | 28 (8.9%) | 7 (11.7%) | 21 (8.2%) | 0.40 |

Bold values indicate statistical significance ($p < 0.05$); *SD* standard deviation; * Fisher's Exact Test

**Table 2.** Univariate analysis of patient demographics (TKA cohort).

| | **Full TKA revision cohort (n = 79)** | **TKA re-revision (n = 23)** | **No TKA re-revision (n = 56)** | **p value** |
|---|---|---|---|---|
| Age (mean ± SD) | 70.4 ± 13.4 | 66.2 ± 13.7 | 72.2 ± 13.0 | 0.07 |
| BMI (mean ± SD) | 33.0 ± 10.2 | 33.7 ± 8.9 | 32.7 ± 10.8 | 0.77 |
| Follow up (mean, range) | 5.1 (1.0–25.0) | 8.1 (1.0–25.0) | 3.7 (1.0–11.0) | **0.02** |
| ASA score | | | | 0.58 |
| 1 | 1 (1.3%) | 0 (0.0%) | 1 (1.8%) | |
| 2 | 47 (59.4%) | 12 (52.2%) | 35 (62.5%) | |
| 3 | 30 (38.0%) | 11 (47.8%) | 19 (33.9%) | |
| 4 | 1 (1.3%) | 0 (0.0%) | 1 (1.8%) | |
| Laterality | | | | 0.45 |
| Left | 35 (44.3%) | 12 (52.2%) | 23 (41.1%) | |
| Right | 44 (55.7%) | 11 (47.8%) | 33 (58.9%) | |
| Gender | | | | 0.92 |
| Male | 20 (25.3%) | 6 (26.1%) | 14 (25.0%) | |
| Female | 59 (74.7%) | 17 (61.9%) | 42 (75.0%) | |
| Intoxications | | | | |
| Smoking | 3 (3.8%) | 1 (4.3%) | 2 (3.6%) | 1.00* |
| Alcohol | 20 (25.3%) | 5 (21.7%) | 15 (26.8%) | 0.53 |
| Drugs | 1 (1.3%) | 0 (0.0%) | 1 (1.8%) | 1.00* |
| Comorbidities | | | | |
| Renal disease | 7 (8.9%) | 2 (8.7%) | 5 (8.9%) | 1.00* |
| Cardiovascular disease | 28 (35.4%) | 7 (30.4%) | 21 (37.5%) | 0.55 |
| Hypertension | 44 (55.7%) | 12 (52.2%) | 32 (57.1%) | 0.69 |
| Diabetes mellitus | 20 (25.3%) | 4 (17.4%) | 16 (28.6%) | 0.30 |
| Malignant tumor | 5 (6.3%) | 0 (0.0%) | 5 (8.9%) | 0.31* |
| Inflammatory disease | 13 (16.5%) | 4 (17.4%) | 9 (16.0%) | 1.00* |
| Depression | 9 (11.4%) | 2 (8.7%) | 7 (12.5%) | 0.63 |
| Hematological disease | 10 (12.7%) | 2 (8.7%) | 8 (14.3%) | 0.72* |
| Neurological disease | 13 (16.5%) | 2 (8.7%) | 11 (19.6%) | 0.33* |
| Pulmonary disease | 10 (12.7%) | 4 (17.4%) | 6 (10.7%) | 0.47* |

Bold values indicate statistical significance ($p < 0.05$); *SD* standard deviation; * Fisher's Exact Test

**Revision surgery**

The indication for the initial revision surgery was a periprosthetic fracture of a THA or TKA in all 395 included patients (316 THA patients; 79 TKA patients; Tables 1, 2). A periprosthetic fracture of the acetabulum occurred in 29 THA patients (9.2%), a fracture of the proximal femur in 282 THA patients (89.2%), a fracture of the femoral shaft in 5 THA patients (1.6%), a fracture of the distal femur in 52 TKA patients (65.8%), a fracture of the proximal tibia in 19 TKA patients (24.1%), and a fracture of the patella in eight TKA patients (10.1%; Tables 3, 4). The fractures of the proximal femur were grouped according to the Vancouver classification. Fracture fixation using revision arthroplasty with additional ORIF was used in 291 THA patients (92.1%) and 44 TKA patients (55.7%), and revision arthroplasty alone in 25 THA patients (7.9%) and 35 TKA patients (44.3%; Tables 3, 4).

**Table 3.** Fracture and revision surgery characteristics (THA cohort).

| | **Full THA revision cohort (n = 316)** | **THA re-revision (n= 60)** | **No THA re-revision (n = 256)** | **p value** |
|---|---|---|---|---|
| Fracture site | | | | |
| Acetabulum/pelvis | 29 (9.2%) | 9 (15.0%) | 20 (7.8%) | 0.08 |
| Proximal femur | 282 (89.2%) | 49 (81.7%) | 233 (91.0%) | **0.04** |
| Vancouver A | 41 (13.0%) | 11 (18.3%) | 30 (11.7%) | 0.17 |
| Vancouver B1 | 2 (0.6%) | 0 (0.0%) | 2 (0.8%) | 1.00* |
| Vancouver B2 | 204 (64.6%) | 33 (55.0%) | 171 66.8%) | 0.08 |
| Vancouver B3 | 34 (10.8%) | 5 (8.3%) | 29 (11.3%) | 0.50 |
| Vancouver C | 1 (0.3%) | 0 (0.0%) | 1 (0.4%) | 1.00* |
| Femoral shaft | 5 (1.6%) | 2 (3.3%) | 3 (1.2%) | 0.24 |
| Fixation type | | | | |
| Revision only | 25 (7.9%) | 3 (5.0%) | 22 (8.6%) | 0.35 |
| Revision and ORIF | 291 (92.1%) | 57 (95.0%) | 234 (91.4%) | |
| Revision and cerclage | 188 (59.5%) | 29 (48.3%) | 159 (62.1%) | **0.05** |
| Revision and plate fixation | 11 (3.5%) | 3 (5.0%) | 8 (3.1%) | 0.44* |
| Revision and screw fixation | 1 (0.3%) | 1 (1.7%) | 0 (0.0%) | 0.19* |
| Revision and combined ORIF | 84 (26.6%) | 23 (38.3%) | 61 (23.8%) | **0.02** |
| Revision and other | 7 (2.2%) | 1 (1.7%) | 6 (2.3%) | 1.00* |

Bold values indicate statistical significance ($p < 0.05$); *ORIF* open reduction internal fixation; Combined ORIF refers to combination of cerclage and plate fixation; no additional nailing techniques were used for the 'Revision and ORIF' cohort; * Fisher's Exact Test

**Table 4.** Fracture and revision surgery characteristics (TKA cohort).

| | Full TKA revision cohort (n = 79) | TKA re-revision (n = 23) | No TKA re- revision (n = 56) | p value |
|---|---|---|---|---|
| Fracture site | | | | |
| Distal femur | 52 (65.8%) | 16 (69.6%) | 36 (64.3%) | 0.65 |
| Supracondylar | 39 (49.4%) | 14 (61.0%) | 25 (44.6%) | 0.19 |
| Intercondylar | 13 (16.4%) | 2 (8.7%) | 11 (19.6%) | 0.33* |
| Proximal tibia | 19 (24.1%) | 5 (21.7%) | 14 (25.0%) | 0.76 |
| Tibia plateau | 12 (15.2%) | 2 (8.7%) | 10 (17.9%) | 0.49* |
| Adjacent to stem | 7 (8.9%) | 3 (13.0%) | 4 (7.1%) | 0.41* |
| Patella | 8 (10.1%) | 2 (8.7%) | 6 (10.7%) | 1.00* |
| Fixation type | | | | |
| Revision only | 35 (44.3%) | 2 (8.7%) | 33 (58.9%) | **< 0.001** |
| Revision and ORIF | 44 (55.7%) | 21 (91.3%) | 23 (41.1%) | |
| Revision and cerclage | 6 (7.6%) | 1 (4.3%) | 5 (8.9%) | 0.67 |
| Revision and plate fixation | 24 (30.4%) | 14 (60.9%) | 10 (17.9%) | **< 0.001** |
| Revision and screw fixation | 2 (2.5%) | 1 (4.3%) | 1 (1.8%) | 0.50 |
| Revision and combined ORIF | 11 (13.9%) | 4 (17.4%) | 7 (12.5%) | 0.72 |
| Revision and other | 1 (1.3%) | 1 (4.3%) | 0 (0.0%) | 0.29 |

Bold values indicate statistical significance ($p < 0.05$); *ORIF* open reduction internal fixation; Combined ORIF refers to combination of cerclage and plate fixation; no additional nailing techniques were used for the 'Revision and ORIF' cohort; * Fisher's Exact Test

**Re-revision surgery**

Re-revision surgery was performed when treatment failure due to a complication occurred that necessitated the exchange of arthroplasty components. After initial revision surgery for periprosthetic fracture, complications were recorded in a total of 70 THA patients (22.2%) and 25 TKA patients (31.6%; Table 5). Re-revision surgery with component exchange was performed in 83 patients (21.0% of the full cohort), including 60 THA patients (19.0%) and 23 TKA patients (29.1%; Table 5). Of these, the most common indication for both THA and TKA re-revision surgery was PJI in 25 THA patients (41.6%) and 14 TKA patients (60.9%; Table 6), followed by aseptic loosening which was observed in 6 THA patients (10.0%) and 4 TKA patients (17.4%), and dislocation in 10 THA patients (12.1%). An overview of the re-revision indications

and treatments for both the THA and TKA cohorts is summarized in Table 6. The diagnosis of PJI was determined according to the criteria defined by the workgroup of the Musculoskeletal Infection Society (MSIS) [19,20]. Complications that did not necessitate re-revision arthroplasty included periprosthetic fracture treated with ORIF without component revision (5 THA patients; 1 TKA patient), superficial infection treated with irrigation and debridement (I and D) of the wound (3 THA patients; 1 TKA patient), pain treated with removal of ORIF (1 THA patient; 1 TKA patient), and dislocation treated with closed reduction (2 THA patients).

**Table 5.** Complications and clinical outcomes of revision arthroplasty.

| | **Full revision cohort (n = 395)** | **THA revision cohort (n = 316)** | **TKA revision cohort (n = 79)** | **p value** |
|---|---|---|---|---|
| Overall complication rate | 95 (24.1%) | 70 (22.2%) | 25 (31.6%) | 0.08 |
| Re-revision | 83 (21.0%) | 60 (19.0%) | 23 (29.1%) | **0.048** |
| Periprosthetic joint infection | 39 (9.9%) | 25 (7.9%) | 14 (17.7%) | **0.009*** |
| Aseptic indications | 44 (11.1%) | 35 (11.1%) | 9 (11.4%) | 0.94 |
| 30 day readmission | 43 (10.9%) | 34 (10.7%) | 9 (11.4%) | 0.87 |
| 60 day readmission | 53 (13.4%) | 39 (12.3%) | 14 (17.7%) | 0.21 |
| 90 day readmission | 64 (16.2%) | 48 (15.2%) | 16 (20.2%) | 0.28 |
| Mortality (1 year) | 18 (4.6%) | 14 (4.4%) | 4 (5.1%) | 0.79 |
| Length of stay, days (mean ± SD) | 7.3 ± 4.7 | 7.2 ± 4.3 | 7.6 ± 6.1 | 0.58 |

Bold values indicate statistical significance ($p < 0.05$); *SD* standard deviation; * Fisher's Exact Test

**Table 6.** Re-revision indications and surgery characteristics.

| | Full re-revision cohort (n = 83) | THA re-revision cohort (n = 60) | TKA re-revision cohort (n = 23) |
|---|---|---|---|
| Re-revision indication | | | |
| Periprosthetic joint infection | 39 (47.0%) | 25 (41.6%) | 14 (60.9%) |
| Periprosthetic fracture or nonunion | 9 (10.8%) | 5 (8.3%) | 4 (17.4%) |
| Dislocation | 10 (12.1%) | 10 (16.7%) | 0 (0.0%) |
| Instability | 3 (3.6%) | 3 (5.0%) | 0 (0.0%) |
| Debilitating pain | 2 (2.4%) | 1 (1.7%) | 1 (4.3%) |
| Component failure | 3 (3.6%) | 3 (5.0%) | 0 (0.0%) |
| Heterotopic ossification | 1 (1.2%) | 1 (1.7%) | 0 (0.0%) |
| Wear and osteolysis | 3 (3.6%) | 3 (5.0%) | 0 (0.0%) |
| Adverse local tissue reaction | 2 (2.4%) | 2 (3.3%) | 0 (0.0%) |
| Deep hematoma | 1 (1.2%) | 1 (1.7%) | 0 (0.0%) |
| Aseptic loosening | 10 (12.1%) | 6 (10.0%) | 4 (17.4%) |
| Re-revision surgery | | | |
| Component revision | 36 (43.4%) | 28 (46.7%) | 8 (34.8%) |
| Revision and ORIF | 5 (6.0%) | 4 (6.7%) | 1 (4.3%) |
| DAIR with modular exchange | 17 (20.5%) | 15 (25.0%) | 2 (8.7%) |
| One-stage revision | 5 (6.0%) | 1 (1.7%) | 4 (17.4%) |
| Two-stage revision | 10 (12.1%) | 5 (8.3%) | 5 (21.8%) |
| Resection arthroplasty | 5 (6.0%) | 5 (8.3%) | 0 (0.0%) |
| Spacer placement | 5 (6.0%) | 2 (3.3%) | 3 (13.0%) |

Bold values indicate statistical significance ($p < 0.05$); *ORIF* open reduction internal fixation; *DAIR* debridement, antibiotics and implant retention; * Fisher's Exact Test

**Revision and re-revision outcomes**

To evaluate the outcomes after THA and TKA revision surgery for periprosthetic fracture and subsequent re-revision surgery due to treatment failure, the outcomes for both revision and re-revision cohorts were described. First, the baseline characteristics for the patients with a failure requiring re-revision surgery (re-revision group) were compared to the THA and TKA revision patients who did not necessitate re-revision (no re-revision group). Second, the outcomes of both THA and TKA revision and re-revision cohorts were described. The treatment outcome was defined as successful when a patient did not necessitate an additional surgical procedure for any reason after the initial revision or re-revision surgery. When the patient received an additional revision procedure for PJI or aseptic reasons, such as dislocation, instability, or aseptic loosening, the treatment was defined as failure.

Moreover, postoperative clinical variables including 30, 60, and 90-day readmission rates, mortality, and length of hospital stay were analyzed for both groups.

**Statistical analysis**

To assess the association between the clinical patient variables, periprosthetic fracture variables, as well as THA and TKA revision variables, and the risk for re-revision surgery due to treatment failure, the adjusted odds ratio (OR), controlled for confounding variables, was calculated. Variables that demonstrated a difference of $p < 0.10$ after univariate analysis were included in this final analysis. A multivariable logistic regression model of risk factors for both THA and TKA re-revision after failed revision for periprosthetic fracture was fitted using the significant parameters as covariates. The rule of a maximum of one predictor per 5–9 events was applied to reduce the risk of overfitting [21]. The OR associated with each clinical parameter was estimated and reported with the corresponding 95% confidence interval (95% CI). The OR was adjusted for confounders [22]. A chi-squared test was utilized to determine the statistical significance between the two groups. A p value of $p < 0.05$ was considered significant. All data analyses were performed using the Statistical Package for Social Sciences (SPSS®) statistics for Windows (version 26.0.0.0, Armonk, NY, USA: IBM Corp.).

## RESULTS

**Patients**

The full cohort consisted of 316 THA patients as well as 79 TKA patients who underwent revision arthroplasty for periprosthetic fracture of a primary THA and TKA (Tables 1, 2). Complications were recorded in 95 patients (24.1% of the full revision cohort), including 70 THA patients (22.2%) and 25 TKA patients (31.6%). A total of 60 THA patients (19.0%) and 23 TKA patients (29.1%) necessitated a re-revision surgery to treat the complication (re-revision group), whereas 256 THA patients (81.0%) and 56 TKA patients (70.9%) did not have a failure requiring re-revision (no re-revision group). The baseline characteristics for both the THA and TKA cohort are summarized in Tables 1 and 2. For the THA cohort, the mean age of the re-revision group was significantly lower than that of the no re-revision group (69.3 ± 11.8 vs. 74.9 ± 12.1 years, $p = 0.001$, Table 1). For the TKA cohort, the mean age of the re-revision group was also lower than that of the no re-revision group, yet not significant (66.2 ± 13.7 vs. 72.2 ± 13.0 years, $p = 0.07$, Table 2).

**Initial revision surgery**

In terms of initial revision surgery, the THA re-revision group demonstrated significantly less proximal femur fractures compared to the no re-revision group (81.7% vs. 91.0%, $p = 0.04$), with Vancouver B2 fractures in 55.0% of the THA re-revision patients and 66.8% of the no THA re-revision patients ($p = 0.08$; Table 3).

The comparisons for the fracture sites and revision types for both THA and TKA cohorts are summarized in Tables 3, 4.

**Complication rates of revision and re-revision surgery**

For the THA cohort, at an average follow up of 4.6 years (1.0–23.0), the overall complication rate after THA revision surgery was 22.2% (70 out of 316 patients), and this was higher for re-revision surgery with 35.0% (21 out of 60 patients) after an average follow up of 4.4 years (1.0–17.1). PJI was the most common indication for re-revision and third revision surgery for the THA cohorts, with 25 patients (7.9%) sustained a PJI requiring subsequent revision surgery, and this was 6 patients (10.0%) in the re-revision cohort (Tables 5, 6). The outcomes for the THA revision cohort are summarized in Tables 5, 6.

For the TKA cohort, at an average follow up of 5.1 years (1.0–25.0), the overall complication rate after TKA revision surgery was 31.6% (25 out of 79 patients), and this was higher for re-revision surgery with 39.1% (9 out of 23 patients) after an average follow up of 4.3 years (1.5–17.7). PJI was the most common indication for re-revision and third revision surgery for the TKA cohorts, with 14 out of 79 patients (17.7%) sustained a PJI requiring subsequent revision surgery, and this was 4 patients (17.4%) in the re-revision cohort (Tables 5, 6). The outcomes for the TKA revision cohort are also summarized in Tables 5, 6.

In terms of outcomes for the subgroup comparison between THA and TKA cohorts, there was a significant difference for re-revision rates (19.0% vs. 29.1%, p = 0.048) and PJI rates (7.9% vs. 17.7%, p = 0.009). No significant differences between both cohorts in terms of overall revision complication rates (22.2% vs. 31.6%, p = 0.08), 30-day readmissions (10.7% vs. 11.4%, p = 0.87), 60 day readmissions (12.3% vs. 17.7%, p = 0.21), 90 day readmissions (15.2% vs. 20.2%, p = 0.28), 1-year mortality (4.4% vs. 5.1%, p = 0.79) and length of stay (7.2 days vs. 7.6 days, p = 0.58; Table 5). Furthermore, there was no significant difference between both THA and TKA cohorts in terms of re-revision complications including overall re-revision complication rates (35.0% vs. 39.1%, p = 0.73), third revision rates (26.7% vs. 39.1%, p = 0.27), 1-year mortality (1.7% vs. 4.3%, p = 0.48) and length of stay (8.2 days vs. 7.5 days, p = 0.61; Table 7).

**Table 7.** Complications and clinical outcomes of re-revision arthroplasty.

| | Full re-revision cohort (n = 83) | THA re-revision cohort (n = 60) | TKA re-revision cohort (n = 23) | p value |
|---|---|---|---|---|
| Overall complication rate | 30 (36.1%) | 21 (35.0%) | 9 (39.1%) | 0.73 |
| Third revision | 25 (30.1%) | 16 (28.3%) | 9 (39.1%) | 0.27 |
| Periprosthetic joint infection | 10 (12.0%) | 6 (10.0%) | 4 (17.4%) | 0.45* |
| Aseptic indications | 15 (16.7%) | 10 (15.0%) | 5 (21.7%) | 0.75* |
| 30 day readmission | 15 (18.1%) | 12 (20.0%) | 3 (13.0%) | 0.54* |
| 60 day readmission | 18 (21.7%) | 13 (21.7%) | 5 (21.7%) | 1.00* |
| 90 day readmission | 20 (24.1%) | 14 (23.3%) | 6 (26.1%) | 0.79 |
| Mortality (1 year) | 2 (2.4%) | 1 (1.7%) | 1 (4.3%) | 0.48* |
| Length of stay, days (mean ± SD) | 8.0 ± 5.7 | 8.2 ± 6.0 | 7.5 ± 4.8 | 0.61 |

Bold values indicate statistical significance ($p < 0.05$); *SD* standard deviation; * Fisher's Exact Test

**Risk factors for re-revision surgery**

After univariate analyses, the parameters that demonstrated a difference of $p < 0.10$ were included in the multivariable logistic regression model. For the THA and TKA cohorts, these were periprosthetic acetabulum/pelvis fracture ($p = 0.08$), Vancouver B2 periprosthetic fracture ($p = 0.08$), revision with cerclage ($p = 0.05$; $p = 0.67$), revision with plate fixation ($p = 0.44$; $p < 0.001$), and revision with combined ORIF ($p = 0.02$; $p = 0.72$). Factors which did not predispose to the risk of failure for THA and TKA cohorts were periprosthetic acetabulum/pelvis fracture, Vancouver B2 periprosthetic fracture, and revision with cerclage. Risk factors which significantly contributed to an increased risk of failure for THA and TKA patients included revision with plate fixation [adjusted OR of 6.122 (95% CI 2.588-16.348), ($p < 0.001$)] and revision with combined ORIF [adjusted OR of 3.099 (95% CI 1.280-7.503), ($p = 0.01$)].

## DISCUSSION

The prevalence of periprosthetic fractures is projected to rise due to the growing number of primary TJAs performed [5]. Revision surgery for periprosthetic fracture is associated with high complication rates, resulting in increased patient morbidity and mortality [23]. When revision surgery for periprosthetic fracture of THA and TKA fails, substantial complications may occur in 12.0–31.0% of patients [3,8,12,13]. Subsequent re-operations have been reported in 17.1% after revision arthroplasty and 18.7% after revision with ORIF [8]. This study demonstrated that higher overall

complication rates were observed after THA and TKA re-revision (35.0%; 39.1%) compared to initial revision surgery (22.2%; 31.6%). Periprosthetic joint infection represented the most common indication for both THA and TKA re-revision (41.6%; 60.9%) and third revision surgery (37.5%; 44.4%). Risk factors for THA and TKA re-revision included revision with plate fixation and combined ORIF.

The results of our study demonstrate that the overall failure rate after initial THA and TKA revision surgery were 22.2% and 31.6%, respectively, and this increased to 35.0% and 39.1%, respectively, for patients who underwent THA and TKA re-revision surgery. Periprosthetic joint infection was the most common indication for both THA (7.9%) and TKA (17.7%) re-revision and third revision surgery (10.0%; 17.4%). Failure after initial revision surgery has been evaluated in several studies with variable complication rates. Two studies demonstrated similar failure rates for patients after revision for periprosthetic fracture when compared to our study, with Leino et al. reporting a failure rate after TKA revision in 31.0% of the patients [12], and Mortazavi et al. in 25.0% of TKA revisions [13]. Both studies reported periprosthetic joint infection as the main indication for TKA implant failure. These studies that had lower failure rates compared to our study were Springer et al. with reported failure in 18.6% of the THA cases [3], and Lindahl et al. who demonstrated failure after THA and TKA revision in 12.0% of patients [8]. The discrepancy in the complication rates may potentially be due to differences in age and comorbidity profile of the included patients' cohorts. Although the complication rates after revision for periprosthetic fracture and indications for subsequent re-revision have been reported, no studies were identified assessing the outcomes for patients who subsequently underwent re-revision surgery.

In our study, PJI was the most common indication for THA and TKA re-revision (7.9%; 17.7%) and third revision surgery (10.0%; 17.4%) after the failure of revision for periprosthetic fracture. This is in agreement with several series in the literature reporting PJI to be among the most frequent complications after THA and TKA revision for periprosthetic fracture with incidence rates of approximately 10.3% [12,24–26]. Understanding the characteristics of patients sustaining PJI after revision for periprosthetic fracture is important, as missed or not adequately treated PJI can lead to extensive consequences for the patient, such as poor functional outcome, quality of life, and potential disability [27]. Periprosthetic joint infection has been associated with significant morbidity and mortality [28,29]. The relatively large proportion of re-revisions due to PJI in the study cohort could potentially be due to disrupted vascularization prior to the initial revision surgery or peri-articular tissue damage due to the periprosthetic fracture [26,30]. Whereas the prevalence of infections after primary TJA is reported to be 0.2–0.7%, the occurrence of infection after aseptic revision surgery of the hip or knee is described to be significantly higher, ranging from 0.9 to 8.1% [31–36]. In fact, the risk is thought to increase after

re-revision surgery as every revision arthroplasty enhances the risk of infection [36]. This highlights that PJI may be a more frequently encountered complication in the future with an ageing population, expanding need for TJA, and subsequent revision surgeries [1,2].

The present study identified risk factors associated with both THA and TKA re-revision study in a cohort consisting of patients who underwent revision surgery with or without ORIF for the treatment of periprosthetic fracture. Previous studies in the literature that have reported on the risk factors for failure requiring re-operation evaluated both patients that underwent ORIF alone and patients who underwent revision with or without ORIF of revision for periprosthetic fracture. Zuurmond et al. demonstrated that the use of ORIF resulted in a significantly higher rate of re-operations when compared to THA and TKA revision with or without ORIF [7]. Similarly, Lindahl et al. showed that treatment using THA and TKA revision with or without ORIF led to a significant reduction in the risk of failure, whereas the sole use of plate fixation or cerclage wiring both significantly increased the risk of failure [8]. This may potentially be due to the influence of the ORIF on fracture healing, as fracture consolidation could be obstructed by the intramedullary TJA, tissue damage, or the impaired weight-bearing possibility leading to insufficient fracture stability. However, those studies did not assess the different types of ORIF used in addition to revision surgery. In our study, revision surgery in combination with plate fixation or combined ORIF significantly increased the risk of re-revision.

The findings of the current study should be interpreted in the context of its limitations. Firstly, due to the retrospective nature of the study, there may be a variability in the collection of parameters potentially inducing selection and misclassification bias. Secondly, the sample size of the study cohort may be of concern. However, due to the nature of re-revision arthroplasty, this study represents one of the largest series to evaluate the patient characteristics and outcomes for revision and re-revision surgery. Lastly, although the average follow-up in our study was 4.8 years, the current complication rate may be underestimated, particularly for subsequent revision surgeries for aseptic complications.

In conclusion, the overall complication rates for THA and TKA re-revision surgery following failed revision surgery for periprosthetic fracture was higher than that of THA and TKA revision surgery. The most common indication for THA and TKA re-revision and third revision surgery was periprosthetic joint infection. The risk of THA and TKA re-revision increased with the use of plate fixation or combined ORIF in addition to revision surgery. The findings of this study may assist surgeons in the management and preoperative counseling of patients undergoing THA and TKA revision surgery for a periprosthetic fracture in order to optimize the outcomes for these patients.

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# CHAPTER 10

## General discussion and future prospectives

Trauma and orthopaedic surgeons increasingly use orthopaedic implants in order to stabilize fractures and maintain the function of joints. These surgeries are highly effective in reducing pain, restoring mobility, and improving the quality of life in millions of patients annually, and this number is expected to increase in the next years [1]. However, even when pre-operative antibiotic prophylaxis is administered and sterile precautions in the operating room are taken, complications such as infections still occur. The implantation of trauma and orthopaedic implants is associated with increased susceptibility to microbial infection, which is attributed to a locally compromised host defense after fracture fixation and total joint arthroplasty [2] and to biofilm formation on the surface of the implant [3]. Although fracture-related infection (FRI) and periprosthetic joint infection (PJI) are relatively uncommon, they are important complications that often lead to higher patient morbidity, loss of function, implant failure, decreased patient-reported outcome measures (PROMs), and loss of limb in some cases [4,5]. In addition, FRI and PJI are associated with higher mortality rates compared to aseptic complications [6,7]. Trauma and orthopaedic infections generally require multiple revision surgeries and long-term antibiotic treatment. Besides the fact that FRI and PJI have a major effect on the patient, they have a considerable impact on healthcare systems due to additional treatments and extended length of stay in the hospital [8,9].

Even though FRI and PJI demonstrate similarities as they are both orthopaedic implant infections, differences exist. Both entities need stability to resolve, yet fracture stabilization can be achieved with various techniques, utilizing external (ring) fixators, plate osteosyntheses, intramedullary nails, screw fixations, K-wires, or combinations. In case of open fractures, the wounds are likely contaminated with pathogens, which is less likely in the elective arthroplasty patient. Furthermore, antibiotic suppression until bone consolidation may be an option for FRI, since fracture fixation devices can be removed after osseous healing while function and biomechanical stability remain [10,11]. Finally, for FRI, there are not only multiple anatomical localizations, but also numerous fracture patterns, degrees of soft tissue injury, and differences in mono and polytrauma [12].

The work presented in this thesis covers two major infection entities in trauma and orthopaedic surgery, namely FRIs and hip and knee PJIs. We aim to assess the diagnostic workup, describe treatment outcomes, and provide insights in the characteristics of patients sustaining those infections. The thesis is divided into two parts. The first part was performed in the Netherlands and examined the use of serum inflammatory markers and nuclear imaging as part of the diagnostic workup of FRI. It also analyzed the treatment outcome of early FRI and gained insight into the patients who suffer from this condition. The second part of this thesis was conducted in the United States of America and studied the use of serum and synovial inflammatory markers for PJI in a challenging population presenting

with a periprosthetic fracture. It also focused on the treatment and outcome of culture-negative infections, after peri-articular fracture fixation, and evaluated the outcomes of periprosthetic fracture treatment and risk factors for *re*-revision surgery.

**Infections in trauma and orthopaedic surgery**

*Use and usefulness of inflammatory markers*

The initial clinical suspicion of infection in trauma and orthopaedic surgery is usually based on a full medical history and clinical examination, yet the accuracy of these signs varies and additional investigation is generally needed to establish the diagnosis. The first and most readily available laboratory tests are serum inflammatory markers C-reactive protein (CRP), white blood cell (WBC) count, and erythrocyte sedimentation rate (ESR). CRP is considered a valid marker for the detection of bacterial infections complicating surgery [13]. It can also be used as a severity parameter for systemic inflammatory response and as a marker of tissue damage after surgery [14,15]. In trauma and orthopaedic patients without complications, levels of CRP peak at the second postoperative day and decrease rapidly between day two to 12, after which values return to normal within three weeks [16–20]. Additionally, the number of WBCs can be measured and utilized to examine and monitor infections postoperatively, however can also increase due to other causes of cell damage, such as surgery, trauma, fracture healing, systemic inflammatory diseases, and malignancies [21]. Maximum values of WBC count are observed on postoperative day one to three and decline to normal between day four to six [19,22]. Furthermore, values of ESR peak at day seven to eleven postoperatively and decrease gradually until after week six [19]. ESR has a longer half-life than CRP and is therefore more useful in the evaluation of chronic infection, while CRP is more applicable in monitoring acute infections [23,24].



For the diagnosis of FRI, some evidence regarding the usefulness of CRP, WBC count, and ESR exists, especially when a constant elevation over a longer period or when a secondary rise occurs after a decrease initially [12]. After further evaluation in our research group, however, even when optimal cut-off values and marker combinations are utilized, their diagnostic value for FRI was limited (**Chapter 2**). The reason is probably that serum inflammatory markers are not distinctive between infections and other causes of inflammatory responses, such as trauma itself, soft tissue injury, surgery, and fracture healing. Moreover, the serum inflammatory markers might show false negatives in cases of low-grade FRI. In addition, as clinicians generally base FRI suspicion on a combination of factors, clinical symptoms and patient characteristics were added in the model, although this still resulted in inadequate accuracy. Moreover, after conducting a systematic review in which only six out of 8284 potential studies could be included, the results regarding the usefulness of the

markers for diagnosing FRI were not clear-cut (**Chapter 3**). Varying sensitivities and specificities were reported, yet all average. Pooled results showed that CRP was the best marker, however not sufficiently accurate to diagnose FRI. When analyzing the literature, it appeared that heterogeneity in populations existed, as well as slightly different measuring devices, lab protocols, and utilized thresholds. Overall, serum inflammatory markers are insufficiently accurate to confirm or rule out FRI and clinicians should be cautious when interpreting the results.

For PJI, the reliability of serum inflammatory markers is considered different than for FRI. The Musculoskeletal Infection Society (MSIS) definition includes serum CRP and ESR as minor criteria [25,26] as these markers demonstrated to be discriminative screening tools for hip and knee PJI, particularly when (optimized) cut-off values are used [27–31]. Serum WBC count showed to be less useful for the diagnosis of PJI [32]. A unique possibility in the workup of PJI - which is often not available for FRI - is the assessment of inflammatory markers in synovial fluid, as PJI occurs surrounding a joint. The most commonly used markers include synovial fluid WBC count and percentage polymorphonuclear neutrophils (PMN%). The use of serum and synovial markers for PJI has been well established in literature, indicating good discriminative utility for serum CRP and ESR and very good for synovial WBC count and PMN% [33–35]. However, the diagnosis of PJI in the setting of a periprosthetic fracture is challenging. Therefore, we analyzed the diagnostic utility of the serum and synovial markers in these patients in **Chapter 6**. We demonstrated that, using MSIS thresholds, serum ESR and CRP and synovial WBC count were highly sensitive, yet not sufficiently specific. PMN% demonstrated to be the worst marker. The accuracy improved when adjusted thresholds were used and when all serum and synovial markers were combined.

Particularly CRP seems to be more useful as a diagnostic (screening) tool for PJI than for FRI. The lower sensitivity in case of FRI compared to PJI may be due to the additional impact of the trauma on marker elevation. CRP responds to both infectious and non-infectious causes and its predictive value for the presence of FRI may be altered since an elevation can be a reflection of tissue damage [36]. Furthermore, it is known that fractures cause elevation of CRP [18], likely obscuring the FRI diagnosis. In this thesis, it is suggested that fracture presence causes decreased accuracy of all inflammatory markers in both patients with FRI and PJI (**Chapter 2, 3, 6**). This indicates that the presence of a fracture in combination with an orthopaedic implant may negatively influence the markers' accuracy in all patients with trauma and orthopaedic infections. However, it remains challenging to directly compare the outcomes for the markers between FRI and PJI due to heterogeneity in study populations, with inherent differences between trauma and elective arthroplasty cohorts and study designs, with different reference tests and diagnostic criteria.

*Use and usefulness of nuclear imaging*

As part of the diagnostic workup of trauma and orthopaedic infections, clinicians may request diagnostic imaging to establish whether FRI is present, whether there are involucrae, sequestra, cloacae, sinus tracts, and intra- or subcortical abscesses, and to examine the fracture site, union rate, and integrity of the implant [37]. Several imaging techniques are available, including X-Ray, magnetic imaging resonance (MRI)-scan, and computed tomography (CT)-scan. Nuclear imaging techniques include WBC or antigranulocyte antibody (AGA) scintigraphy and fluorodeoxyglucose positron emission tomography (FDG-PET), whether or not combined with CT-scan. PET scanning is emerging since the 90s, specifically for use within orthopaedic infections and oncology [38]. The tracer $^{18}$F-FDG is created utilizing an [$^{18}$F] isotope labelled to deoxyglucose which is detected by the PET scanner as it mimics active glucose metabolism without fully undergoing glycolysis [39]. Since a locally increased metabolic uptake of glucose, and thus $^{18}$F-FDG, is expected in infection due to presence of WBCs and bacteria, higher tracer uptake can be visualized. The combination of $^{18}$F-FDG-PET scintigraphy combined with CT is gaining interest as there is no substantial compromise by tissue edema or metallic implant-associated artefacts [40]. For semiquantitative analysis, the standardized uptake values (SUVs) of $^{18}$F-FDG PET/CT can be calculated. Whereas infection demonstrates a locally increased metabolic turnover of glucose (resulting in an increased SUV), bone, bone marrow, and inactive muscles demonstrate low $^{18}$F-FDG uptake. In **Chapter 4**, we demonstrated that qualitative assessment of $^{18}$F-FDG PET/CT scans had high diagnostic accuracy and excellent negative predictive value for the diagnosis of FRI. Adding SUV measurements to qualitative assessment provided additional accuracy compared to qualitative assessment alone. However, the diagnosis of early cases of FRI is complicated by the fact that $^{18}$F-FDG PET/CT scans are not reliable during the early postoperative period (<1 month). The accuracy is negatively affected by false test results due to a locally increased turnover of glucose after surgery and during fracture healing, demonstrating a similar problem as observed in the utilization of inflammatory markers for (early) FRI.



*Treatment results and outcomes*

The clinical presentation of FRI varies widely and no distinction based on time of onset is made in its definition [12]. FRIs can be classified into early (onset <6 weeks) and late (onset ≥6 weeks) infections as the clinical presentation and management differ [41,42]. In the treatment of early FRI, the clinician faces an additional obstacle since the fracture is not fully healed within six weeks after fracture treatment. Therefore, an implant must remain in situ for stabilization. When there is a stable implant, a debridement, antibiotics, and implant retention (DAIR) procedure may be opted for. In **Chapter 5**, we found that excellent infection control was achieved for DAIR in patients with FRI onset of less than six weeks. Prior to achieving this, however, almost a fifth of patients had a recurrent infection and more than half of

our cohort needed at least one additional surgical procedure to gain control of the initial infection. This highlights the importance of a consistent follow up to monitor treatment failure [43], especially since the use of an intramedullary nail during index operation, need for additional procedures, and a decreased ISS were demonstrated to be independent predictors for FRI recurrence.

A DAIR procedure with or without modular component exchange is also frequently chosen for the treatment of early PJI with very high success rates [44]. For the treatment of chronic PJI, a two-stage revision arthroplasty remains the current gold standard, although recently, renewed interest for one-stage revision developed as it may lower morbidity and associated healthcare costs [45,46]. For the selection of the most suitable treatment, identification of the pathogen causing PJI is considered important, while culture-negative PJI still occurs in up to a third of patients. Whereas previous research has mainly focused on a selection of patients suitable to undergo one-stage surgery using pre-defined selection criteria for early PJI [47,48], similar results were found for chronic PJI in a large systematic review and meta-analysis [49,50]. Culture-negative PJI was frequently excluded from analyses. However, our study group demonstrated that one-stage revision arthroplasty had similar clinical outcomes for the treatment of chronic culture-negative PJI after TKA and THA compared to two-stage revision (**Chapter 7**). This evidence suggests that these patients may not have to be excluded and that more inclusive studies should be performed since these atypical patients should also benefit from optimal revision strategies.

Another issue overlapping both FRI and PJI is the treatment of infected fracture fixation devices surrounding the joints. First, to treat infected open reduction internal fixation of peri-articular fractures with septic arthritis of the hip [51,52] or knee [53], salvage two-stage revision arthroplasty is often performed [54–57]. To examine the influence of preceding trauma and fracture on clinical outcomes, we created a propensity-score matched control group consisting of patients who underwent two-stage revision for PJI after non-traumatic THA and TKA (**Chapter 8**). Treating a peri-articular infection associated with failed fracture fixation generated worse outcomes than the control group without associated fracture fixation. We demonstrated that the overall failure rate was twice as high for peri-articular infections. Reinfection occurred in just over a third of these patients and this was associated with mixed and resistant pathogens that are known to negatively influence treatment success. Second, in **Chapter 9**, we investigated the influence of periprosthetic fractures and the fixation after THA and TKA on clinical outcomes. We found that a quarter of patients sustained a complication, of which almost half was PJI. The PJI incidence increased from 9.9% after revision surgery to 12.0% after third revision. The results of these studies illustrate high failure and infection rates after the treatment of fractures surrounding the joints. This evidence suggests that

infection may be a more prevalent and challenging complication in the future due to an increasingly elderly, osteoporotic population and expanding need for surgical intervention [58].

**Lessons learned in this thesis**

*Fracture-related infection versus periprosthetic joint infection*
One of the most important developments in trauma and orthopaedic surgery is the introduction of patient registries containing data on large patient cohorts. There are many clinical advantages of maintaining patient registries, such as providing evidence-based data for physicians to improve patient care and aiding surgeons to reduce complications and revision rates. Moreover, the availability of these registries facilitates evaluation of essential subjects such as epidemiology, clinical findings, management strategies, benchmarking, and quality assessment [59]. Data include patient and procedure characteristics, comorbidities, complications, data on revision surgeries, and occasionally PROMs. Across the world, initiatives for trauma and orthopaedic registries have been realized, such as national registries that capture at least 90.0% of nationally collected and validated data [60]. However, these registries focus mainly on recording all patients who underwent surgery and are particularly useful to gain insight in general (patient) data, and indications and incidences of primary and revision surgeries. Specific PJI and FRI registries have been lacking until recent, interesting initiatives on the European continent evolved. In 2018, United Kingdom Bone and Joint Infection Registry (BAJIR), a national project, was established [61]. This registry aimed to collect relevant patient data such as demographics, comorbidities, microbiological culture results, and treatment strategies and their outcomes for patients with bone and joint infections. The United Kingdom-based registry is primarily aimed at including patients with PJI, yet FRI patients are also recorded. In the Netherlands, the Dutch Fracture Infection Registry (DFIR), was initiated in the University Medical Center Utrecht (UMCU) and University Medical Center Groningen (UMCG) in 2020 and is aiming to expand toward other national FRI centers in the near future.



Furthermore, until about a decade ago, the diagnosis and treatment of both PJI and FRI were hampered by lack of a clear definition. In 2011, the MSIS proposed diagnostic criteria for PJI based on expert opinion [25]. Adjustments were published after international consensus meetings in 2013 [62] and in 2018 [26]. Also in 2018, seven years after the introduction of the MSIS criteria, the characteristics of FRI were clearly defined in a consensus meeting between experts in the field of bone infection, the Arbeitsgemeinschaft für Osteosynthesefragen (AO Foundation), and the European Bone and Joint Infection Society (EBJIS) [63]. Before the implementations of these diagnostic criteria for PJI and FRI, multiple terminologies were used and this complicated the diagnosis and research due to classification bias. Initially, the

treatment of FRIs was largely adopted from PJI care and distinct research was scarce [10], which likely affected the management and outcomes for those patients. It was with the clearly defined PJI and FRI criteria that more homogenous populations were created. Research became increasingly standardized and many papers were published, finally allowing for comparison of study results leading to advancements in diagnostic and treatment concepts. However, even with the development of the criteria, the diagnosis of PJI and FRI remains difficult. None of the current standard investigations have perfect accuracy and therefore it is mandatory that research toward better tools remains ongoing and newer tests are developed in order to facilitate diagnosing these challenging conditions. For instance, recently proposed synovial biomarkers for PJI that have demonstrated encouraging results are alpha defensin (100.0% sensitivity; 96.0% specificity) [64], leukocyte esterase (81.0% sensitivity; 97.0% specificity) [64], and CRP (92.0% sensitivity; 90.0% specificity) [65]. The search to find promising serum markers continued accordingly and interestingly, these also demonstrated more useful for PJI, namely D-dimer (97.7% sensitivity; 99.5% specificity for PJI [66] and 75.0% sensitivity; 91.2% specificity for FRI) [67], and interleukin-6 (81.0% sensitivity; 94.0% specificity for PJI [68] and 57.5% sensitivity; 83.6% specificity for FRI) [69].

Since the MSIS criteria were published seven years ahead of the FRI guideline, potential lessons can be learned from evidence that was reported previously in PJI research. After years of experience with the MSIS criteria of 2011 and 2013, a modified, evidence-based guideline considering the different relative weights of diagnostic tests was proposed [26]. This resulted in an externally validated scoring system. Relative, quantitative scores are assigned to each of the individual parameters of the major and minor (preoperative) criteria, and intraoperative criteria in case of inconclusive minor criteria. Based on the sum score, the possible outcomes of the PJI scoring system are 1) infected, 2) possibly infected, 3) inconclusive, 4) or not infected. Introducing an applicable scoring system like this made it possible for clinicians to more easily diagnose patients preoperatively and deliver an accurate diagnosis for cases with uncertainty about the presence of an infection. It demonstrated excellent performance with minimal false positives [26]. For FRI, there is currently no similar scoring system.

*The United States of America versus the Netherlands*

One of the key factors for both retrospective as well as prospective studies is the number of patients that can be included in those studies. A small sample size may compromise the internal and the external validity of a study and produce inconclusive results. Therefore, a larger sample size may omit these uncertainties and lead to higher statistical power. The largest national orthopaedic registry was established in the United States. The American Joint Replacement Registry (AJRR) was created in 2009 by the American Academy of Orthopaedic Surgeons (AAOS) and

contains data of over 2.8 million arthroplasty procedures in all 50 states and the District of Columbia [70]. Helpful other large initiatives in the United States include the Centers for Medicare & Medicaid dataset [72] and the United States Department of Veterans Affairs Open Data Portal [73]. In the Netherlands, the Dutch Arthroplasty Register (LROI) was created in 2007 and contains data on nearly 650,000 primary hip and knee arthroplasties and over 75,000 revisions [71]. Several PROMs are captured to assess clinical outcomes. For trauma surgery in 2020, the AAOS and the Orthopaedic Trauma Association (OTA) created the Fracture & Trauma Registry (FTR), collecting data solely on ankle, distal femur, distal radius, hip, and proximal humerus fractures in the United States [74]. In the Netherlands, the outcomes of over 865,000 acute general and orthopaedic trauma cases have been registered in the Dutch Nationwide Trauma Registry (DNTR) since 2007, mainly focusing on the acutely admitted general trauma patient including truncal injuries and registration of the injury severity score [75,76]. Moreover, in the year 2019 alone, 15,352 hip fractures were reported to the Dutch Hip Fracture Audit (DHFA), which is over 90.0% of all annual hip fractures [77]. However, PROMs are frequently not available and it is complex to extract infection-specific data. The numbers of included patients reached by the LROI, DNTR, and DHFA are impressive. Yet it is impossible for the Dutch registries to approximate the AJRR and FTR in sample size. Therefore, it is important to join forces and register uniformly about some of the most devastating complications of implant use, namely PJI and FRI. If European countries would create an international registry, with for instance an overseeing institute such as the EBJIS as a connector between countries, high-quality PJI and FRI data would become available in the near future.

Moreover, enhancements in sample size for adequate power can be made on a smaller scale than through nationwide registries. As it is not always possible, or necessary, to utilize registries with over multiple 100,000s of patients, regional initiatives could also play a role in combining high-quality databases in order to increase patient numbers and answer research questions. For instance, a more local structure can be found with Massachusetts General Hospital (MGH) in Boston Massachusetts, in the United States. MGH works with several hospitals in the Greater Boston region to improve patient care. A few of the MGH member institutions that also offer orthopaedic surgery care include Brigham and Women's Hospital, Newton-Wellesley Hospital, and Martha's Vineyard Hospital. These institutions work together using a shared hospital information system that is accessible for each clinician and researcher. Some of the major advantages of such a shared system is that all data are in the same place, can be combined, are readily accessible for both clinical and research purposes, and that patient numbers can be increased. Although the datasets can still be biased as they are not representative for the entire population, collaborations of institutions across a country in addition to standardized, uniform data capturing are big steps forward for gaining higher

levels of evidence and statistical power. The increase in both patient numbers and hospital collaboration is a goal worth pursuing for surgeons and physicians taking care of patients with trauma and orthopaedic infections in the Netherlands. Efforts were recently initiated to establish the Dutch Trauma Research Collaboration (DTRC) which could facilitate in achieving this goal.

Another point of interest for both FRI and PJI is the referral of patients to specialized institutions as a directive referral format is not available. The fragmented system in the United States, which includes more than 1,000 insurers [78], presents significant challenges. Government programs (Medicare and Medicaid) cover less than the actual cost of care, other insurers negotiate discounts, and uninsured patients do not pay at all, causing annual shortfalls of costs that must be covered by the hospitals [79]. Consequently, the costs for patients with complications under the Medicare and Medicaid reimbursement programs are charged to hospitals, leading some to be hesitant in accepting complex cases to avoid potential financial losses. This is one of the main differences with the European healthcare system, likely influencing treatment decisions. In the Netherlands, guidelines for the level of infection care are available online. However, these guidelines are not specific and it remains dubious at what point during treatment a patient should be referred. For trauma surgeons, it is advised to use a low threshold referring FRI patients to a specialized facility, yet the timing is not specified [80]. For orthopaedic surgeons treating PJI, it is stipulated that conditions must be fulfilled, such as adequate microbiological culturing and the availability of specialists [81]. When it is not possible to comply with one of these conditions, a patient should be referred. As a rule of thumb, many regional guidelines specify that a PJI patient is referred after two DAIR surgeries. It would nonetheless be beneficial for trauma and orthopaedic infection care as a whole to make further, national agreements regarding referral instructions and to extend guidelines toward specific requirements, not only for PJI but also for FRI.

*Summary*

The preceding paragraphs highlight the need to overcome three apparent shortcomings trauma and orthopaedic infection research, namely 1) to improve the validity of research, regional, national, and international data collection initiatives should be developed with the inclusion of FRI and PJI information combined with PROMs, 2) FRI is in need of an updated diagnostic guideline to improve its definition and diagnostic pathways, and 3) the complete trauma and orthopaedic infection care system requires more directive and standardized referral and treatment guidelines.

## Future perspectives

### Diagnostic process (chapters 2, 3, 4, and 6)

*Nuclear imaging techniques*

It is important to diagnose infections in trauma and orthopaedic surgery accurately first-time to facilitate its treatment [82,83]. Current radiologic and nuclear imaging modalities provide useful data on bone and tissue abnormalities, yet are often compromised by metal artifacts on the bone-implant interface and difficulties to differentiate between infection and inflammation. Moreover, they are too expensive and scarce for routine care. Debridement is currently performed based on visual excision of pathologic tissue by the surgeon. However, multiple re-debridements are often necessary due to the challenge of discriminating infected from native tissue [84,85]. In order to more accurately diagnose and guide treatment of these complex biofilm infections, targeting probes that fluorescently label infected tissue have been proposed to facilitate (intraoperative) image-guided debridement. The 89Zr-NIR680-1D9 probe was one of the first to localize an S. aureus infection of a spinal implant in mice and to aid surgical guidance [86], followed by the 1D9-690 [87]. Recently, for the setting of FRI, the known Vanco-800CW probe provided accurate and real-time visual information [88]. These results suggest that optical imaging using probes may be useful for diagnosing and treating trauma and orthopaedic infections. However, pathogen determination is needed to direct antibiotic therapy. This may be possible by utilizing multiple tracers targeting different species. Finally, future FRI and PJI nuclear imaging research may focus on exposing the thickness and maturation of bacterial biofilm pre- or intraoperatively [89].

*Diagnostic scoring system for FRI*

In 2018, the novel PJI scoring system was published taking the relative weights of the MSIS criteria into account, resulting in four levels of certainty around the diagnosis of PJI [26]. Developing a scoring system for FRI is currently not possible. However, an increasing number of patients are included in prospective datasets across Europe and with these growing inclusions, it might in the future be feasible to prospectively validate the suggestive and confirmatory signs for the diagnosis of FRI. In order to deliver a more accurate diagnosis, the validation process would grant the possibility of constructing a weighted scoring system for the suggestive signs in the diagnosis of FRI.

### Treatment strategies (chapter 5, 7, 8, and 9)

*Trend toward one-stage surgery*

For the treatment of late FRI, a multi-stage surgical treatment (for instance Masquelet procedure) is frequently opted for when a fracture is not healed and

infection is suspected. The first surgery is performed to eradicate the infection, provide adequate soft tissue coverage and (temporarily) stabilize the fracture. The second procedure is performed to achieve fracture consolidation and restoration of function [90]. A one-stage approach utilizing antibiotic-eluting ceramic carriers demonstrated a viable option for late FRI [91–94], requiring effective dead space management, immediate eradication of infection, and direct fracture stabilization [91]. This treatment strategy may eradicate the infection and immediately stabilize the fracture without delaying union of the bone [94]. In addition, it may decrease the length of stay and total healthcare costs, and is more patient-friendly [95]. However, it remains unclear which selection criteria should be used for multi- versus one-stage procedures and studies remain scarce [91–93,95]. Future, high-quality research is necessary to assess the long-term outcomes of this approach and general validity, including the collection of PROMs.

The present gold standard treatment for the treatment of chronic hip and knee PJI is two-stage revision surgery. However, one-stage revision surgery has gained renewed interest. Not only may single surgery reduce patient morbidity, length of stay, and associated healthcare costs [48], it is also associated with improved functional outcomes [96] and higher PROMs [45,97]. It eludes a second-stage procedure with its associated morbidities, improves direct postoperative mobility, and reduces pain [98]. Generally, the decision for one- or two-stage revision is made on predefined patient and surgical criteria that have been reported previously [99–101], including absence of comorbidities and culture positivity [47,48]. However, patient selection may not yield superior outcomes [102] and the importance of preoperative identification of pathogens has been questioned [99]. In this thesis, one-stage revision for culture-negative chronic PJI showed high success rates. This suggests that patients not meeting current pre-existing criteria may benefit from one-stage revision and more inclusive research of treatment and outcome is therefore required to further adopt this treatment strategy. Our findings should be seen as a first step towards a more deliberate approach using one-stage revisions where possible.

**Recommendations for trauma and orthopaedic infection care in the (near) future**

Over the past decade, there has been an increasing interest in infections in trauma and orthopaedic surgery. Previously, the management of these infections was hampered by lack of definitions for FRI (2018) and PJI (2011). Initially, many of the FRI strategies were adopted from PJI. However, it has become increasingly evident that FRI as well as PJI are individual diseases with essential differences in soft tissue quality, wound contamination, and initial operations prior to final treatment. Another key factor contributing to the distinction between FRI and PJI is the presence of a fracture. This fracture obscures results in the diagnostic workup

of FRI and, in case of mal- or nonunion, complicates its treatment as infections with unstable fractures will not resolve. Interestingly, similar challenges in inflammatory marker accuracy occur in PJI with concomitant periprosthetic fracture. Furthermore, the treatment of septic arthritis after peri-articular and periprosthetic fractures is challenging and often results in poor clinical outcomes with high complication and recurrent PJI rates. The evidence in this thesis suggests that the presence of a fracture in combination with an orthopaedic implant may complicate the diagnostic workup and influence treatment outcomes, impacting both FRI and PJI care. For future research, it would be of interest to further elucidate the role of fractures in trauma and orthopaedic infections.

Trauma and orthopaedic infection research strives to improve holistic care for FRI and PJI patients, with PJI protocols that may fulfill an exemplary role for FRI. Herein, it is essential to keep in mind that the two conditions may be assumed to be similar, but not the same. In the future, it is important that large studies containing high-quality (prospective) data will be performed. Some perspectives to achieve this should be addressed. The first step is to improve the validity of research with the implementation of regional, national, and international data collection initiatives that lead to increased patient numbers. Particularly FRI studies are small as only a few larger series include approximately 450 patients [103,104]. Currently, combined datasets and registries comprising of just FRI and PJI patients are scarce. To better perform and understand future studies, data must be uniform, using a standardized format with inclusion of PROMs. When these datasets are initiated and continue to expand, studies can become more inclusive of condition varieties. Then, the FRI and PJI diagnostic and management strategies should be evaluated. The possibility to design an FRI scoring system based on weighted scores must be examined to facilitate easier diagnosis of patients with atypical clinical presentations of infection. As validating a scoring system would require a very large sample size due to expected heterogeneity between patients, this is still ongoing work and may be feasible in the future. In the meantime, as a single diagnostic test with absolute accuracy does not exist to date, research toward new tools for detecting, localizing, and treating some of the most devastating complications in trauma and orthopaedic care should have some priority. Last, as future registries may facilitate research toward new and personalized, patient-friendly treatment strategies, (surgical) treatment decisions must remain under review.



**Take home messages**

Based on the research presented in this thesis, we identify knowledge gaps in four distinct areas of FRI and PJI care. As the study towards better decision-making and patient management remains ongoing, several aspects of the research and guideline development within the field of trauma and orthopaedic infection care may be addressed in the near future.

**Table 1.** Take home messages.

| Area of care | Knowledge gaps |
|---|---|
| Improving the validity of research | Sample sizes should be increased by introducing specific FRI and PJI national registries and accessible regional research systems, possibly across Europe, for instance with an institute such as the EBJIS as potential overseeing institution. |
| Definition and diagnosis | There is a need for an updated FRI consensus with inclusion of adjusted details on several investigations, including the value of serum markers and nuclear imaging.<br>The possibilities for an FRI scoring system should be explored.<br>It is important to search for novel targeted imaging techniques for FRI and PJI in order to distinguish infection from inflammation. |
| Treatment strategies | The trend toward one-stage surgery in order to enable more patient-friendly and personalized treatment for FRI and PJI should be further assessed and continued. |
| Healthcare system | FRI and PJI guidelines should be stricter in defining the conditions for the referral of patients to a tertiary center, for instance after two DAIR procedures and/or in case of recurrent infection. |

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# ADDENDUM

## ENGLISH SUMMARY

The trauma and orthopaedic infection entities, fracture-related infection (FRI) and periprosthetic joint infection (PJI), are of increasing interest and receive more attention in the literature each year. They are important complications that frequently lead to major patient morbidity, loss of function, implant failure, decreased patient-reported outcome measures, and even loss of limb [1,2]. In addition, FRI and PJI are associated with substantially higher patient mortality rates compared to aseptic postoperative complications [3,4], often requiring multiple revision surgeries followed by long-term antibiotic treatment protocols. Besides the fact that both FRI and PJI have a major effect on the patient, they also have a considerable (financial) effect on healthcare systems [5,6]. Since the presentations of FRI and PJI vary widely, atypical forms of the conditions are not uncommon to trauma and orthopaedic surgeons. In order to optimize specific treatment strategies for all patients, it is important to further develop the known guidelines and perform more inclusive research, that includes these variable conditions. This thesis aims to improve the management of FRI and PJI by analyzing the diagnostic workup, describing treatment outcomes, and providing insights in patient characteristics. In this summary, an overview of the work that led to this thesis is presented.

In Chapter 1, the background and burden of the two trauma and orthopaedic infection entities FRI and PJI are introduced, their definitions and treatments are discussed, and an outline of this thesis is presented.

**Part I: Fracture-related infection**

In 2018, the definition of FRI with confirmatory and suggestive criteria was established in an international consensus meeting between experts in the field of bone and joint infections and the Arbeitsgemeinschaft für Osteosynthesefragen (AO) [7]. New studies were published utilizing a uniform definition of FRI. However, the most optimal diagnostic and treatment strategies have not been fully elucidated.

Chapter 2 evaluates the usefulness of the three most commonly used serum inflammatory markers C-reactive protein (CRP), white blood cell (WBC) count, and erythrocyte sedimentation rate (ESR) for FRI. Both the individual and combined diagnostic performance of these markers were determined in addition to clinical parameters that are known to be predictive of FRI. In this retrospective cohort study of 168 consecutive patients, CRP had 83.1% sensitivity and 34.3% specificity, for WBC this was 38.6% sensitivity and 73.5% specificity, and for ESR 45.0% sensitivity and 76.1% specificity. The diagnostic accuracy for the markers was 51.8%, 60.7%, and 79.6%, respectively. The area under the receiver operating characteristic (AUROC) curve for CRP was 0.64. The optimal threshold was 10.5 mg/L with corresponding 61.0% sensitivity and 62.9% specificity. For WBC count, the AUROC was 0.60 and the

optimal threshold 8.6 x109/L with 60.0% sensitivity and 61.2% specificity. The AUROC for ESR was 0.58 and the optimal threshold 10.0 mm/hr with 72.4% sensitivity and 50.1% specificity. Combining the markers showed an AUROC of 0.63. The AUROC of the clinical parameters was 0.62. When combining the serum inflammatory markers with the clinical parameters, an AUROC of 0.66 was computed. This study demonstrates that the diagnostic value of serum inflammatory markers and clinical parameters predictive for FRI was limited. When the inflammatory markers are within normal range, FRI can still be present. Therefore, clinicians should be cautious when interpreting the results of these tests in patients with suspected FRI.

In Chapter 3, a systematic review is performed to evaluate the literature on the diagnostic value of CRP, WBC, and ESR for the diagnosis of late FRI. A total of 8284 potential studies were identified, of which only six could be included. For CRP, the reported sensitivity ranged between 60.0% and 100.0% and specificity between 34.3% and 85.7%, with cut-off values varying between 5.0-10.0 mg/l. Sensitivity of WBC count ranged from 22.9% to 72.6% and specificity from 73.5% to 85.7%, with cut-off values ranging from 9.2-10.2 $x10^9$ cells/L. For ESR, sensitivity ranged between 37.1% and 100.0% and specificity between 59.0% and 85.0%, with cut-off values varying between 11.0–30.0 mm/h, of which two articles used different thresholds for males and females. Meta-analysis of the pooled results showed limited diagnostic value of all three markers. For CRP, sensitivity and specificity were 77.0% (95% confidence interval (95% CI) 66.5-85.0%) and 67.9% (95% CI 38.7-87.6%), for WBC count this was 51.7% (95% CI 27.2-75.5%) and 67.1% (95% CI 19.3-50.2%), and for ESR, this was 45.1% (95% CI 37.8-52.6%) and 79.3% (95% CI 71.7-85.2%), respectively. Four studies analyzed combinations of markers and reported increased diagnostic accuracy. However, due to heterogeneity these results could not be pooled. It was apparent that the quality of most of the studies is poor. Based on the available literature, the markers seem insufficiently accurate to confirm or rule out the presence of FRI and should solely be used as suggestive criteria in its diagnosis.

Chapter 4 reviews the diagnostic accuracy of $^{18}$F-FDG PET/CT for the diagnosis of FRI in a large patient cohort. The cohort consisted of 135 consecutive patients with suspected FRI who underwent 156 nuclear imaging scans were included. The scans were reassessed and a uniform reference standard was applied. Furthermore, the diagnostic performance of standardized uptake values (SUVs) was established and the impact of recent surgery evaluated. It was demonstrated that 18F-FDG PET/CT had a high sensitivity of 0.89 (95% CI 0.78–0.95) and a specificity of 0.80 (95% CI 0.70–0.87). The diagnostic accuracy was 0.83 (95% CI 0.77-0.89). SUVs on their own resulted in lower diagnostic performance, but when combined with qualitative assessments an AUC of 0.89 (95% CI 0.84-0.95) was computed. It was found that 18F-FDG PET/CT should not be performed within one month after surgery as this

was the independent variable with the highest predictive value for false test results, with an absolute risk of 46% (95% CI 27–66%).

In Chapter 5, an overview of the outcomes and risk factors for recurrence of early FRI after a debridement, antibiotics and implant retention (DAIR) is provided. The study focuses on infection control, ongoing infection, and recurrence rate. A large cohort consisting of 141 consecutive patients was retrospectively analyzed to assess the course of the condition. It was found that the FRI recurrence rate was 13% after a median of 12.0 months and 18% after a median of 23.1 months. Overall infection control was achieved in 94% of cases within the duration of the study. However prior to reaching this, 52% of patients (n = 73/141) underwent at least two surgical procedures in order to treat ongoing infection after DAIR during the first presentation of the early FRI. Univariate and multivariate analyses demonstrated that independent predictors for developing recurrent FRI were the use of an intramedullary nail during the index operation (odds ratio (OR) 4.0 (95% CI 1.1-13.8)), need for additional surgical procedures (OR 1.9 (95% CI 1.1–3.5)), and a decreased injury severity score (ISS) (inverted OR 1.1 (95% CI 1.0–1.1)). The results of this study can be used for management and preoperative counselling of early onset FRI patients.

**Part II: Periprosthetic joint infection**

Since the implementation of the PJI definition by the Musculoskeletal Infection Society (MSIS) in 2011 [8], consensus in the development of clear guidelines for both the treating medical teams and researchers was achieved. Even though many studies were published in the past 12 years utilizing this uniform definition, the study quality varies and knowledge gaps remain.

Chapter 6 evaluates the utility of the commonly used serum markers CRP and ESR and synovial markers WBC count and percentage polymorphonuclear neutrophils (PMN%) in order to improve the diagnostic workup for the diagnosis of PJI in patients presenting with a periprosthetic fracture. A large retrospective cohort of 144 consecutive patients was analyzed. Using the previously published MSIS marker thresholds, high sensitivity yet low specificity was found for CRP (93.6% sensitivity; 40.0% specificity), ESR (86.5% sensitivity; 47.6% specificity), and synovial WBC count (87.0% sensitivity; 77.9% specificity). PMN% demonstrated to be the worst marker (73.7% sensitivity; 63.2% specificity). The accuracy of the markers improved when higher thresholds were used. For the serum marker CRP, the adjusted threshold was 16.7 mg/L with associated 83.9% sensitivity and 50.8% specificity and for ESR this was 45.4 mm/hr with 75.7% sensitivity and 68.3% specificity. The altered threshold for the synovial marker WBC was 4552 cells/mL with associated 86.4% sensitivity and 85.3% specificity and for PMN%, this was 79.5% with 79.0% sensitivity and 63.2% specificity. When all serum and synovial markers were combined, 84.2% sensitivity

and 79.3% specificity were calculated. Thus, as all markers demonstrated decreased accuracy at MSIS thresholds in patients with concomitant periprosthetic fracture and PJI, clinicians should consider higher thresholds and utilizing a combination of all serum and synovial markers.

Chapter 7 assesses the treatment outcomes for one- and two-stage revision surgery for patients with chronic culture-negative PJI. Previously, predefined selection criteria have been utilized for one-stage revision and culture negativity was thought to be a contraindication. However, it was demonstrated in this chapter that one-stage revision arthroplasty had similar results compared to two-stage revision for the treatment of chronic culture-negative PJI after analyzing outcome parameters such as reinfection (16.7% vs. 20.0%, p = 0.691), re-revision (13.3% vs. 14.7%, p = 0.865), and readmission rates (30-day 10.0% vs 8.0%, p = 0.715; 60-day 16.7% vs 9.3%, p = 0.321; 90-day 26.7 vs 10.7%; p = 0.078). This suggests that culture negativity may not be a contraindication for one-stage revision arthroplasty for chronic PJI and that these patients could also benefit from this more patient-friendly treatment strategy.

In Chapter 8, the results and complications of revision total hip and knee arthroplasty as a salvage procedure to treat infection of peri-articular fracture fixation are reported. The overall failure rate was 42.5% for all internal fixation (IF) patients and 21.3% for non-IF patients (p = 0.03). For both groups, recurrent infection was the most common indication for failure, occurring in 35.0% of IF patients and 11.3% non-IF patients (p = 0.005). Aseptic failures occurred in 5.0% of IF patients compared to 8.8% of non-IF patients (p = 0.49). Subgroup analyses were performed to assess potential differences between total hip arthroplasty (THA) and total knee arthroplasty (TKA) patients. For both groups, higher failure due to reinfection was found for IF patients compared to non-IF patients, namely 29.6% vs. 9.1% (p = 0.02), respectively, for the THA group and 46.2% vs. 16.0%, respectively, for the TKA group (p = 0.04). For the IF cohort, higher polymicrobial growth (30.0% vs. 11.2%, p = 0.01)), methicillin-resistant Staphylococcus aureus (MRSA) (20.0% vs. 7.5%, p = 0.04), and other Gram-positive organisms (7.5% vs. 0.0%, p = 0.04) were encountered compared to the non- IF cohort. For patients sustaining a recurrent infection, patients in the IF group demonstrated higher rates of MRSA (21.5% vs. 11.2%, p = 0.63), Staphylococcus species (14.3% vs. 0.0%) and polymicrobial growth (21.5% vs. 0.0%, p = 0.25). The overall post-operative complications after salvage two-stage revision for infected IF of peri-articular fractures was high with over a reinfection in over a third of patients that was associated with the presence of mixed and resistant pathogens, which are notoriously difficult to treat.

Chapter 9 presents the outcomes and risk factors for re-revision surgery following failure of revision for periprosthetic fracture of the hip and knee. A large cohort

consisting of 316 THA and 79 TKA patients who underwent revision surgery for periprosthetic fracture was retrospectively assessed. Both subgroups were separately reviewed. The overall complication rate after THA revision surgery was 22.2% (70/316 patients), while this was 35.0% (21/60 patients) for re-revision surgery. PJI was the most common indication for re-revision and third revision surgery. In the revision cohort, 7.9% (25/316 patients) sustained a PJI and this was 10.0% (6/60 patients) in the re-revision cohort. After TKA revision surgery, the overall complication rate was 31.6% (25/79 patients) and after re-revision surgery, this was 39.1% (9/23 patients). PJI was the most common indication for re-revision (17.7% (14/79 patients)) and third revision surgery (17.4% (4/23 patients)). These findings may assist surgeons in the management and preoperative counseling of patients undergoing THA and TKA revision surgery for a periprosthetic fracture to optimize the outcomes for these patients.

In Chapter 10, the evidence as presented in the chapters of this thesis is summarized. The diagnostic value of serum and synovial markers for FRI and PJI, nuclear imaging for FRI, and treatment outcomes for patients with culture-negative PJI and (infected) fractures surrounding the joints are discussed. Furthermore, as this thesis was performed for both FRI and PJI in the Netherlands and United States of America, lessons that were learned while conducting the research presented in this thesis are described. Additionally, recommendations for future, inclusive research and holistic care for patients with trauma and orthopaedic infections are given. Overall, even though an increasing number of studies are performed each year, knowledge gaps still exist. It is strongly recommended collect high-quality (prospective) data while using uniform definitions to allow for validation of known diagnostic tools and treatment options, and to extend the search toward new alternatives.

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# NEDERLANDSE SAMENVATTING

De trauma- en orthopedische infecties fractuurgerelateerde infectie (*fracture-related infection*; FRI) en prothese infectie (*periprosthetic joint infection*; PJI) staan steeds meer in de belangstelling en krijgen ook in de literatuur ieder jaar meer aandacht. Het zijn belangrijke complicaties die veelal leiden tot toegenomen morbiditeit bij patiënten, functieverlies, falen van het implantaat, afgenomen patiënt-gerapporteerde uitkomstmaten (*patient-reported outcome measures*; PROMs) en zelfs amputatie van de ledemaat [1,2]. Bovendien zijn FRI en PJI geassocieerd met substantieel hogere mortaliteit ten opzichte van niet-infectieuze postoperatieve complicaties [3,4] en zijn vaak meerdere revisie-operaties noodzakelijk, gevolgd door langdurige antibiotische behandeling. Afgezien van het feit dat zowel FRI als PJI een enorm effect hebben op het leven van de patiënt, hebben zij ook een aanmerkelijk (financieel) effect op zorgstelsels [5,6]. Aangezien de presentaties van zowel FRI als PJI sterk variëren, zijn atypische varianten van de aandoeningen niet ongewoon voor de trauma- en orthopedische chirurg. Om toegespitste behandelstrategieën voor alle patiënten te optimaliseren, is het belangrijk om bekende richtlijnen verder te ontwikkelen en meer inclusief onderzoek te verrichten, ook naar de atypische varianten. Dit proefschrift heeft als doel de behandeling van FRI en PJI te verbeteren door de huidige diagnostische strategieën te analyseren, behandelresultaten te beschrijven en verdere inzichten te verschaffen in de kenmerken van patiënten. Deze samenvatting biedt een overzicht van het werk dat tot dit proefschrift heeft geleid.

In Hoofdstuk 1 wordt de achtergrond van twee de complicaties FRI en PJI geïntroduceerd, worden hun definities en behandelingen besproken en wordt een overzicht van dit proefschrift gepresenteerd.

**Deel I: Fractuur-gerelateerde infectie**
In 2018 heeft een internationale groep experts in samenwerking met de Arbeitsgemeinschaft für Osteosynthesefragen (AO) een eenduidige definitie van FRI opgesteld [7]. Hoewel er sindsdien nieuwe studies gepubliceerd zijn die door het gebruik van deze definitie van betere kwaliteit zijn, is nog niet vastgesteld wat de meest optimale diagnostische- en behandelstrategieën voor deze aandoening zijn.

Hoofdstuk 2 evalueert de diagnostische waarde van de drie meest gebruikte serum inflammatiemarkers C-reactive protein (CRP), aantal witte bloedcellen (*white blood cell count;* WBC) en bezinking (*erythrocyte sedimentation rate;* ESR) bij patiënten met FRI. Zowel de individuele als gecombineerde diagnostische waarde van deze markers werd vastgesteld naast klinische parameters die voorspellend zijn voor het hebben van een FRI werden vastgesteld. In deze retrospectieve cohortstudie van 168 opeenvolgende patiënten had CRP 83.1% sensitiviteit en 34.3% specificiteit, voor

WBC was dit 38.6% sensitiviteit en 73.5% specificiteit, en ESR 45.0% sensitiviteit en 76.1% specificiteit. De diagnostische accuratesse van de markers was respectievelijk 51.8%, 60.7% en 79.6%. De area under the receiver operating characteristic (AUROC) curve was 0.64 voor CRP. De optimale afkapwaarde was 10.5 mg/L met 61.0% sensitiviteit en 62.9% specificiteit. Voor WBC was de AUROC was 0.60 met een optimale afkapwaarde van 8.6 x109/L en 60.0% sensitiviteit en 61.2% specificiteit. De AUROC voor ESR was 0.58 met een optimale afkapwaarde van 10.0 mm/u en 72.4% sensitiviteit en 50.1% specificiteit. Wanneer alle markers gecombineerd werden, was de AUROC 0.63. De AUROC van de klinische parameters was 0.62. Een combinatie van de serum inflammatiemarkers en de klinische parameters toonde een AUROC van 0.66. De uitkomst van deze studie laat zien dat de diagnostische waarde van serum inflammatiemarkers gering is voor FRI. Zelfs als de markers binnen de normaalwaarden vallen, kan een FRI nog steeds aanwezig zijn. Daarom is het belangrijk dat clinici de resultaten van deze tests terughoudend interpreteren bij patiënten verdacht voor het hebben van een FRI.

In Hoofdstuk 3 wordt een systematische analyse van de literatuur uitgevoerd om de diagnostische waarde van CRP, WBC en ESR te onderzoeken bij patiënten met late FRI. In totaal werden 8284 potentiële studies geïdentificeerd, waarvan slechts zes studies konden worden geïncludeerd. De gerapporteerde sensitiviteit van CRP varieerde tussen 60.0% en 100.0% en specificiteit tussen 34.3% en 85.7%, met afkapwaarden tussen 5.0-10.0 mg/l. Voor WBC lag de sensitiviteit tussen 22.9% en 72.6% en specificiteit tussen 73.5% en 85.7%, met afkapwaarden tussen 9.2-10.2 $x10^9$ cellen/L. De sensitiviteit van ESR varieerde van 37.1% tot 100.0% en specificiteit van 59.0% tot 85.0%, met afkapwaarden tussen 11.0–30.0 mm/u, waarbij twee studies verschillende warden gebruikten voor mannen en vrouwen. Meta-analyse van samengevoegde resultaten liet zien dat de diagnostische waarde van alle markers gering was. CRP had een sensitiviteit van 77.0% (95% confidence interval (95% CI) 66.5-85.0%) en specificiteit van 67.9% (95%CI 38.7-87.6%). De sensitiviteit van WBC was 51.7% (95% CI 27.-75.5%) en de specificiteit 67.1% (95% CI 19.3-50.2%). ESR had een sensitiviteit van 45.1% (95% CI 37.8-52.6%) en specificiteit van 79.3% (95% CI 71.7-85.2%). Vier studies analyseerden de waarde van combinaties van serum inflammatiemarkers en rapporteerden een toename van de diagnostische accuratesse. Vanwege grote heterogeniteit konden deze studies niet worden gepoold. Het was duidelijk dat de kwaliteit van de meeste studies slecht was en dat er heterogeniteit in patiëntpopulaties bestond. Op basis van de beschikbare literatuur laat deze review concluderend zien dat de serum inflammatiemarkers onvoldoende nauwkeurig zijn om de aanwezigheid van FRI te bevestigen of uit te sluiten en daarom dienen zij slechts gebruikt te worden als suggestief criterium voor deze diagnose.

Hoofdstuk 4 onderzoekt de diagnostische accuratesse van $^{18}$F-FDG PET/CT voor de diagnose van FRI in een groot patiëntcohort. Het cohort bestond uit 135 opeenvolgende patiënten met een vermoedelijke FRI die 156 nucleaire scans ondergingen. Alle scans werden opnieuw beoordeeld waarbij een uniforme referentiestandaard werd toegepast. Tevens werd de toegevoegde waarde van standardized uptake values (SUVs) vastgesteld en werd bekeken of de scan ook kort na recente chirurgische interventie betrouwbaar is. De 18F-FDG PET/CT scan had een hoge sensitiviteit van 0.89 (95% CI 0.78–0.95) en specificiteit van 0.80 (95% CI 0.70–0.87). De diagnostische accuratesse was 0.83 (95% CI 0.77-0.89). SUVs alleen resulteerden in een lagere diagnostische prestatie, maar wanneer deze werden toegevoegd aan kwalitatieve beoordelingen nam de accuratesse toe naar 0.89 (95% CI 0.84-0.95). De 18F-FDG PET/CT dient echter niet verricht te worden binnen één maand na operatie omdat dit de betrouwbaarheid van de scan doet afnemen. Het was een onafhankelijke variabele voor valse testresultaten met een absoluut risico van 46% (95% CI 27–66%).

In Hoofdstuk 5 wordt een overzicht gegeven van de uitkomsten en risicofactoren voor een recidief van vroege FRI na een debridement, antibiotics and implant retention (DAIR) procedure. De studie richt zicht op infectiebeheersing, persisterende infectie en recidiefpercentage. Een groot retrospectief cohort bestaande uit 141 opeenvolgende patiënten was geanalyseerd om het ziekteverloop van de aandoening te beoordelen. Het FRI-recidiefpercentage bedroeg 13% na een mediaan van 12.0 maanden en 18% na een mediaan van 23.1 maanden. In 94% van de patiënten kwam de infectie binnen de studieduur onder controle, al onderging 52% van de patiënten (n = 73/141) ten minste twee aanvullende chirurgische interventies om de initiële infectie onder controle te krijgen. Univariate en multivariate analyses toonden drie verschillende onafhankelijke voorspellers voor het ontwikkelen van een recidiverende infectie aan, namelijk het gebruik van een intramedullaire nail tijdens de indexoperatie (odds ratio (OR) 4.0 (95% CI 1.1-13.8)), aanvullende chirurgische interventie (OR 1.9 (95% CI 1.1–3.5)) en een lagere injury severity score (ISS) (inverted OR 1.1 (95% CI 1.0–1.1)). De resultaten van deze studie kunnen worden gebruikt voor de behandeling en preoperatieve begeleiding van patiënten met vroege FRI.

**Deel II: Prothese infectie**

Sinds de implementatie van de PJI definitie door de Musculoskeletal Infection Society (MSIS) in 2011 [8] is er consensus bereikt over de ontwikkeling van duidelijke richtlijnen voor zowel de behandelende medische teams als onderzoekers. Hoewel er in de afgelopen 12 jaar vele studies zijn gepubliceerd met deze uniforme definitie, varieert de kwaliteit en blijven kennislacunes bestaan.

Hoofdstuk 6 beschrijft het nut van de veelgebruikte serum markers CRP en ESR en synoviale markers WBC en percentage polymorfonucleaire neutrofielen (polymorphonuclear neutrophils; PMN%) voor het diagnosticeren van PJI in patiënten met een periprothetische fractuur. Een groot retrospectief cohort van 144 patiënten werd geanalyseerd. Wanneer gebruik gemaakt wordt van de voorheen gepubliceerde MSIS afkapwaarden, werd een hoge sensitiviteit maar lage specificiteit gevonden voor CRP (93.6% sensitiviteit; 40.0% specificiteit), ESR (86.5% sensitiviteit; 47.6% specificiteit) en synoviaal WBC (87.0% sensitiviteit; 77.9% specificiteit). PMN% bleek de slechtste marker te zijn (73.7% sensitiviteit; 63.2% specificiteit). De nauwkeurigheid van de markers verbeterde wanneer hogere afkapwaarden weren gebruikt. Voor de serum marker CRP was de aangepaste afkapwaarde 16.7 mg/L met bijbehorende 83.9% sensitiviteit en 50.8% specificiteit en voor ESR was dit 45.4 mm/u met 75.7% sensitiviteit en 68.3% specificiteit. De gewijzigde afkapwaarde voor de synoviale marker WBC was 4552 cellen/mL met geassocieerde 86.4% sensitiviteit en 85.3% specificiteit en voor PMN% was dit 79.5% met 79.0% sensitiviteit en 63.2% specificiteit. Wanneer alle serum en synoviale markers werden gecombineerd, werd 84.2% sensitiviteit en 79.3% specificiteit aangetoond. Voor patiënten met gelijktijdige periprothetische fractuur en PJI vertoonden de serum en synoviale markers een verminderde nauwkeurigheid bij gebruik van de MSIS-afkapwaarden. Daarom is het belangrijk dat clinici hogere afkapwaarden overwegen en een combinatie van alle serum- en synoviale markers toepassen.

Hoofdstuk 7 beoordeelt de behandelresultaten van one- en two-stage revisiechirurgie voor patiënten met chronische kweek-negatieve PJI. Voorheen werd gebruik gemaakt van vooraf gedefinieerde selectiecriteria voor een one-stage revisieoperatie en werd aangenomen dat het uitblijven van positieve kweken een contra-indicatie voor deze chirurgische interventie was. In dit hoofdstuk wordt daarentegen aangetoond dat de resultaten van een one-stage revisieoperatie vergelijkbaar zijn met een two-stage revisieoperatie voor de behandeling van chronische kweek-negatieve PJI. Verschillende parameters werden hiertoe geanalyseerd, zoals recidiverende infectie (16.7% vs. 20.0%, p = 0.691), re-revisiechirurgie (13.3% vs. 14.7%, p = 0.865) en heropnamepercentage (30 dagen 10.0% vs 8.0%, p = 0.715; 60 dagen 16.7% vs 9.3%, p = 0.321; 90 dagen 26.7 vs 10.7%; p = 0.078). Deze resultaten suggereren dat kweeknegativiteit wellicht geen contra-indicatie is voor een one-stage revisieoperatie voor chronische PJI en dat deze patiënten ook zouden kunnen profiteren van deze meer patiëntvriendelijke behandelstrategie.

In Hoofdstuk 8 worden de resultaten en complicaties van de implantatie van een totale heup- of knieoperatie als redmiddel in de behandeling van geïnfecteerde peri-articulaire fractuurfixatie van de heup of knie geëvalueerd. Het totale mislukkingspercentage van deze operatie was 42.5% voor interne fixatie (IF)

patiënten en 21.3% voor alle niet-IF-patiënten (p = 0.03). Voor beide groepen was een FRI recidief de meest voorkomende indicatie voor falen van de operatie, namelijk in 35.0% van de IF-patiënten en 11.3% van de niet-IF-patiënten (p = 0.005). Niet-infectieuze indicaties voor falen kwamen voor in 5.0% van de IF-patiënten en 8.8% van de niet-IF-patiënten (p = 0.49). Subgroepanalyses waren uitgevoerd om mogelijke verschillen tussen patiënten met een totale heup prothese (total hip arthroplasty; THA) en totale knie prothese (total knee arthroplasty; TKA) aan te tonen. In beide groepen werd re-infectie als meest voorkomende indicatie voor falen gevonden voor IF-patiënten in vergelijking met niet-IF-patiënten, namelijk respectievelijk 29.6% vs. 9.1% (p = 0.02) voor de THA groep en 46.2% vs. 16.0% voor de TKA groep (p = 0.04). In het IF-cohort werd vaker polymicrobiële infectie (30.0% vs. 11.2%, p = 0.01)), methicilline-resistente Staphylococcus aureus (MRSA) (20.0% vs. 7.5%, p = 0.04) en andere Grampositieve pathogenen (7.5% vs. 0.0%, p = 0.04) aangetroffen in vergelijking met het niet-IF-cohort. Voor de patiënten die een recidiverende infectie vertoonden, werd in de IF-groep vaker MRSA (21.5% vs. 11.2%, p = 0.63), Staphylococcus species (14.3% vs. 0.0%) en polymicrobiële groei (21.5% vs. 0.0%, p = 0.25) gekweekt. Het totaal aantal postoperatieve complicaties na THA- of TKA-revisiechirurgie voor geïnfecteerde IF van peri-articulaire fracturen was hoog. Meer dan een derde van de patiënten kreeg een FRI recidief die geassocieerd was met gemengde en resistente pathogenen, waarvan bekend is dat zij moeilijk te behandelen zijn.

Hoofdstuk 9 geeft een overzicht van de resultaten en risicofactoren voor re-revisiechirurgie na een revisieoperatie voor periprothetische fractuur van de heup of knie. Een groot cohort van 316 THA- en 79 TKA-patiënten die een revisieoperatie voor periprothetische fractuur ondergingen werd geanalyseerd. Beide subgroepen werden afzonderlijk bekeken. Het totaal aantal complicaties na THA-revisie was 22.2% (70/316 patiënten) en dit was 35.0% (21/60 patiënten) voor TKA. PJI was de meest voorkomende complicatie voor zowel een re-revisie als derde revisieoperatie. In het revisiecohort ontwikkelde 7.9% (25/316 patiënten) een PJI en 10.0% (6/60 patiënten) in het re-revisiecohort. Na een TKA-revisie had 31.6% (25/79 patiënten) een complicatie en dit was 39.1% (9/23 patiënten) na een re-revisieoperatie. PJI was de meest voorkomende indicatie voor re-revisie (17.7% (14/79 patiënten) en derde revisieoperatie (17.4% (4/23 patiënten)). De gegevens uit deze studie kunnen worden gebruikt voor preoperatieve counseling van patiënten die een THA- of TKA-revisieoperatie ondergaan voor periprothetische fractuur.

In Hoofdstuk 10 wordt het bewijs zoals gepresenteerd in de hoofdstukken van dit proefschrift samengevat. De diagnostische waarde van serum- en synoviale markers voor FRI en PJI, nucleaire beeldvorming voor FRI en behandelingsresultaten voor patiënten met kweek-negatieve PJI en (geïnfecteerde) fracturen rond de gewrichten worden besproken. Aangezien dit proefschrift is uitgevoerd voor zowel FRI als PJI

in Nederland en de Verenigde Staten van Amerika, worden bovendien de lessen beschreven die tijdens het werk zijn geleerd. Daarnaast worden aanbevelingen gedaan voor toekomstig, meer inclusief onderzoek en holistische zorg voor patiënten met trauma en orthopedische infecties. Hoewel er elk jaar een toenemend aantal onderzoeken wordt uitgevoerd, zijn er over het algemeen nog steeds hiaten in de kennis. Het wordt ten zeerste aanbevolen om (prospectieve) data van hoge kwaliteit te blijven verzamelen en gebruik te maken van uniforme definities, zodat validatie van reeds bekende diagnostische hulpmiddelen en behandelingsopties mogelijk is, en om te blijven zoeken naar nieuwe alternatieven.

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# CURRICULUM VITAE AUCTORIS

Janna van den Kieboom was born on the 27th of April, 1992 in the city of Breda, the Netherlands. She was raised by her parents René and Tanja along with her sister Lonne in the nearby village of Terheijden. After graduating grammar school in 2011 from Stedelijk Gymnasium Breda, she studied law for a year at Utrecht University, after which she obtained a propaedeutic diploma. In the following year, she entered medical school at Utrecht University.

During the third year of her medical studies, she started her medical rotations. She left the Netherlands for Cape Town, South Africa in her fourth and fifth year to obtain experience of working in a different environment. First, she was enrolled at Stellenbosch University for a Gynaecology and Obstetrics rotation, after which she got accepted for an Emergency Medicine and Trauma elective under supervision of dr. S. Lahri. Following the completion of her rotations abroad, she realized her interest in trauma surgery and returned to the University Medical Center Utrecht to start her first research project at the Department of Surgery under supervision of prof. dr. L.P.H. Leenen, dr. G.A.M. Govaert, and dr. F.F.A IJpma.

After graduating medical school, she continued her PhD research. She received several scholarships and research grants for a combined PhD student and research fellowship at the Bioengineering Laboratory of the Department of Orthopaedic Surgery, Massachusetts General Hospital and Harvard Medical School under supervision of prof. dr. Y.-M. Kwon. She completed her research project in Boston, the United States in 2020. Her research on trauma and orthopaedic infections in both the Netherlands and the United States has ultimately culminated in the completion of this PhD thesis. Currently, she is working as a resident not in training in Occupational Medicine.

Janna is engaged to Kent H. Williams.