Towards better outcomes of revision total knee arthroplasty

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“Je moet geluk niet laten glippen als het voor je staat.”
- Daan Rieken

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Chapter 1

General introduction

General introduction

Osteoarthritis (OA) is in the top 10 of most prevalent diseases. Worldwide, OA is also one of the diseases causing the highest burden in terms of years of healthy life lost due to the disease or disability (1). Knee OA is the most prevalent form of major joint OA; the lifetime risk for developing symptomatic knee OA has been estimated to be somewhere between 14% and 45% (2-4). Knee OA is a chronic joint disease that causes severe pain and functional disability (5, 6).

Currently, there is no cure for knee OA. The focus of treatments for knee OA should be on how to reduce pain, improve knee function and enhance health-related quality of life. A stepped care approach for nonsurgical treatment of knee OA has been recommended (7). In this approach, it is suggested to start with education, lifestyle advice, and acetaminophen as pain medication, followed by treatment options such as physical therapy, dietary advise or intra-articular cortisone injections. If acetaminophen is not sufficiently effective, non-steroidal anti-inflammatory drugs are the following medical option. Surgical treatment of knee OA is only suggested for those patients where the previous steps failed to produce a satisfactory result, or when effects of the previous conservative treatment have extinguished (8). In cases with unicompartmental knee OA in combination with a varus or valgus deformity, sometimes mechanical axis correcting osteotomies can be performed to reduce the complaints (9, 10). Patients with end-stage OA who do not respond to conservative treatment, and have severe pain and loss of function, can be considered for knee replacement surgery (see box 1 for different types of knee arthroplasty) (8, 11).

Box 1. Types of knee replacement surgeries

There are four main types of knee replacement surgery (also: knee arthroplasty) (Fig. 1).

Patellofemoral arthroplasty (PFA) is a partial knee replacement that can be performed for isolated patellofemoral OA, where only the patella and corresponding articular surface on the distal femur are resurfaced. All other structures of the knee are preserved. Patellofemoral arthroplasty is a less invasive surgery with faster recovery times than in total knee arthroplasty (12). Unfortunately, the results and the survival of these patellofemoral prostheses are not very successful (13, 14). In addition, the number of patients having an isolated patellofemoral OA is limited. Hence, this prosthesis is not used very often. Also, in case of progression of OA to other knee compartments, the PFA may require a revision arthroplasty.

Unicompartmental (or partial) **knee arthroplasty** (UKA) is a suitable option for patients in whom OA has affected the articular surface of the knee unilaterally. In most cases, this comprises the medial compartment (15). In UKA, the damaged femoral condyle and the adjacent tibial plateau are replaced with an implant. UKA is also less invasive surgery than a total knee arthroplasty with a shorter recovery trajectory. A downside is that, as in the PFA prosthesis, progression of OA to other knee compartments may require conversion knee surgery to a TKA.

Total knee arthroplasty (TKA) involves replacing the entire joint surface of the tibia and femur. In some cases, the patellar surface is also replaced with a patellar button. Different prosthesis designs are available, depending on the presence and stability of cruciate and collateral ligaments, diagnosis, and available bone.

Revision total knee arthroplasty is performed when one of the previously mentioned types of prostheses needs to be replaced. Revision TKA includes the conversion to another type of prosthesis (usually PFA or UKA to TKA), a revision with the same type of implant, or the conversion to another design such as a knee prosthesis design developed especially for revisions. In revision surgery, one or more components (tibial, femoral, patellar, or insert) can be added or exchanged. This may be due to progression of OA in case of a PFA or an UKA, bone loss around the prosthesis, periprosthetic fracture, implant failure, ligament failure, stiffness, or periprosthetic joint infection. Depending on the reason and the type of prosthesis in situ, the length of the stem and the prosthetic design that are used during revision arthroplasty are chosen. Also, in case of bone defects, these need to be filled with cones or augments to ensure sufficient stability of the new prosthesis in the bone (16).

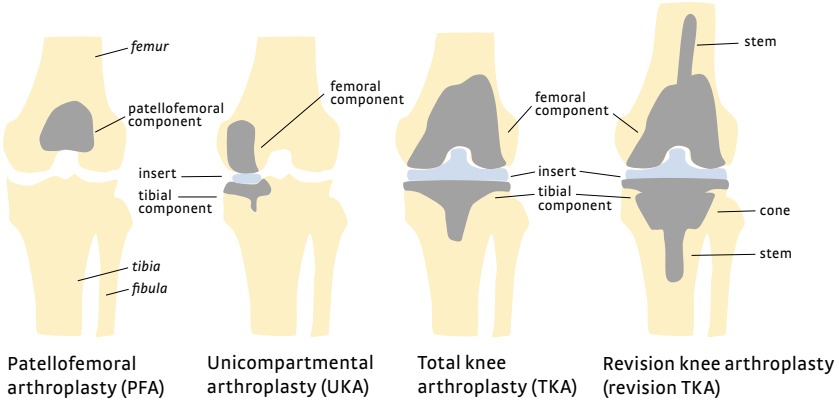

Figure 1: Components of the types of knee arthroplasty

In the Netherlands, around 30,000 primary knee arthroplasties are performed annually (17). Besides patients with primary knee OA, the procedure can also be performed in patients with severe damage to joint structures due to rheumatoid diseases or post-traumatic damage. In rare cases, these knee arthroplasties are performed for oncological reasons, however these are outside the scope of this thesis given the special patient population. In the majority of the cases, a primary knee arthroplasty is successful. Over 60% of the patients are very satisfied with the results 12 months after surgery, and up to 85% are moderately to very satisfied (17). Usually, pain during rest and activity is reduced, and physical functioning and quality of life improves (18).

Unfortunately, knee arthroplasty is not always successful. Various complications may arise following a TKA, in some cases resulting in a partial or total removal of the prosthesis and the subsequent insertion of a new implant. The estimated lifetime risk of a revision after a primary TKA is around 5% for patients aged 70 years (19). The lifetime risk increases when patients undergo primary TKA at a younger age. Women between the ages of 50 and 60 years at the moment of the knee arthroplasty have a 20% lifetime risk of revision, while men have a 35% revision risk (19). In the Netherlands, around 27,500 revision TKAs have been performed between 2013 and 2022 (17). These revisions not only impose a significant burden on patients and their families, but also result in increased healthcare costs. These often more complex revision surgeries are expensive, in addition complications are seen more frequently after revision surgery. Also re-admissions and re-operations are more frequent after revision TKA. Among patients readmitted in the hospital after a primary total knee or revision total knee in the United States, the average costs per patient ranged from $9,753 following readmission after a primary TKA to $16,186 after readmission after a revision TKA (20). The increasing number of primary TKA surgeries in aging populations poses a problem, as the number of unsuccessful surgeries may also increase and result in further expansion of healthcare expenditure (11, 21, 22).

Revision TKA

The reason to perform a revision TKA can vary widely. Usually, a patient seeks help for pain, instability, or stiffness after a TKA. The goal of revision surgery is always to reduce pain and restore function. There are multiple underlying causes for these symptoms. Revision TKA should only be considered when there is a clear diagnosis of the problem and a reasonable chance of success to resolve this problem. In the following paragraphs, the possible causes for complaints of pain, instability, and stiffness will be described. Infection is one of the leading and devastating causes of knee arthroplasty failure and therefore will be described separately.

Infection

When a patient presents with complaints after a primary TKA, the first step is ruling out an infection. A periprosthetic joint infection (PJI) is a serious complication which occurs in around 0.5-2% of the patients after a primary TKA (17, 23, 24). While the incidence of PJI is highest in the first year after primary TKA, it remains a risk throughout the patient's lifetime (25, 26). PJI is a burden for both individual patients and the healthcare system, it is associated with higher risk of morbidity and mortality and increased costs for treatment (27, 28). Symptoms of PJI include pain, stiffness, swelling and/or warmth around the joint (29, 30). Most early infections are caused by Staphylococcus aureus in the Netherlands. Microbial pathogens often form a biofilm around the prosthesis, limiting the efficacy of the antibiotics (31). Hence, treating

an PJI infection is difficult. The origin of the microbial pathogen can be various. The microbial pathogen may have been present on the patient's skin and inoculated during prosthesis placement, it can enter the wound during the surgery from the theatre environment, or it could have entered through compromised local tissues. Alternatively, bacteria may even have been introduced to the knee prosthesis via the bloodstream from another part of the body; this is especially the case for late infections more than 2 years after surgery (29).

The diagnosis of a PJI is based on the patients' history, the clinical presentation, and lab findings (e.g., c-reactive protein (CRP), erythrocyte sedimentation rate (ESR), or cultures of joint aspiration) (29, 30). Risk factors for PJI include male gender, obesity, poor glycemic control in diabetes mellitus, smoking, prior intra-articular injections and comorbidities such as cardiovascular disease and inflammatory arthritis (30, 32, 33). A prior knee surgery also increases the risk of a PJI (32). The choice of treatment depends on the timing of infection manifestation after the surgery, host factors, and the virulence of the microbial organism. The treatment options include antibiotic therapy alone, surgical debridement with antibiotics and implant retention (DAIR) or one- or two-stage revision arthroplasty with replacement of parts of the prosthesis (30). In the worst-case scenario, when the infection cannot be controlled, the situation may result in a knee arthrodesis or even an above-knee amputation.

Pain

When a PJI is ruled out, several other mechanical and soft tissue problems can cause pain, stiffness, or poor function. Knee pain alone is no indication for recurrent surgery. Pain can be associated to emotional wellbeing, such as pain catastrophizing, anxiety, and depression (34, 35). Persistent post-operative pain, matching the pre-operative levels, may also arise from issues external to the knee joint. Referred pain in the knee area may result from hip-related problems, nerve entrapment in the spine, or vascular issues (36). Of course, in these cases, knee revision arthroplasty is not a viable solution. When pain results from a clearly identified problem related to the prosthesis, a revision can be an option. Several mechanical problems can cause pain such as aseptic loosening, wear of the plastic insert, or component overhang on the tibial side (36, 37). These problems can be identified on radiographic images. Moreover, the progression of OA in partial knee prostheses or the laxity of ligaments around the knee due to abnormal stress distribution can also cause pain (36, 37). Detection of loosening of prosthesis components is often based on progressive radiolucent lines or osteolytic defects, which are frequently accompanied by stress-dependent pain. When symptomatic, mechanical problems are usually treated with a one-stage revision (38).

Pain around the patella is a common complaint after TKA surgery, both in cases in where the patella has not been resurfaced during the primary TKA, as well as in cases of a primary TKA with patella resurfacing. Patellar pain after a TKA can have different causes: patellar cartilage can be degenerated as a result of osteoarthritis in non-resurfaced patella. The patella can be painful due to mechanical problems like tracking problems. Whether a patella is resurfaced with a patella button during the primary TKA varies in clinical practice. The percentage of primary TKAs with resurfaced patellae widely differs between countries, ranging between 4 - 82% (39). The advice on patella resurfacing can also be dependent of the design of the implant. Overall, the rate of reoperations is higher in the non-resurfaced group (40). It remains unclear whether this can be attributed to the fact that secondary patella resurfacing is a surgical option for the treatment of anterior knee pain following TKA in patients with a native patella. (40). Typical problems causing patellar pain are (sub)luxation of the patella, patella button loosening or patella tracking problems. Usually, these problems can be diagnosed clinically, often supported by radiological techniques like CT imaging. A patella luxation can sometimes be solved with surgical adjustments to the soft tissue around the knee. If a patella button is loose, a revision surgery of the patella button can be performed. For tracking problems of the patella, sometimes a transposition of the tibial tuberosity can be done, in other cases a prosthesis revision is the solution (41).

Instability

If a patient experiences an unstable sensation in the knee, displays an abnormal gait, or feels pain while climbing stairs or rising from a chair, this may indicate knee instability (42). Instability can be a result of surgical or implant failure such as improper balancing of the soft tissue, implant malalignment, loosening of the implant, or wear of the insert (43). Soft tissue problems, such as (traumatic) collateral ligament failure or weakness of the quadriceps or hip abductor muscles, can also cause an unstable knee (43). Instability that coincides with tendinitis can indicate muscle overload due to compensatory muscle activity. A physical examination of the knee may not necessarily reveal objective instability. If instability is suspected or observed during a physical examination, usually X-rays and stress X-rays are taken to evaluate ligament stability and the implant positioning in the bone (42, 44). If problems are diagnosed, they may be surgically solved with a soft tissue release for equal flexion and extension gaps between the femur and tibia, a change of polyethylene insert type, or a revision to a more constrained type prosthesis (42). If the instability in the knee arises from factors unrelated to the prosthesis—such as generalized balance issues, progressive neurological disorders, or quadriceps weakness—a revision of the prosthesis is not the solution. In these situations, non-operative treatment options specifically targeted to the problem, for instance physical therapy, might be helpful (45).

Stiffness

Stiffness of the knee after a TKA is characterized by a reduced range of motion (ROM) of the knee and is a known complication of knee arthroplasty. A limited ROM can affect a patient's ability to perform activities of daily living, such as kneeling and stair climbing (46). Additionally, transportation can become problematic, as patients may be unable to drive, cycle, or use public transportation. The most frequent causes of stiffness are infection and incorrect sizing or malposition of a component (47). In these cases, revision of the component has a reasonable chance of success. Physical therapy is the primary initial treatment of stiffness (48). When stiffness presents early after primary surgery and is caused by arthrofibrosis, manipulation under anesthesia can sometimes increase ROM (49). In other cases, addressing the malfunctioning component through revision might be a solution. Stiffness of the knee can also result from an extrinsic problem such as OA of the ipsilateral hip or a hip flexion contracture (50). A revision TKA will not provide a solution for these causes of stiffness.

Outcomes of revision TKA

Generally, the outcomes of revision TKA are inferior when compared to primary TKA. The post-operative outcomes can be disappointing: complications, readmissions and reoperations occur more often after a revision compared to a primary TKA (20). While adverse events are crucial for evaluating surgical success, the absence of a revision or reoperation does not necessarily imply that the surgery was successful. Patient satisfaction or dissatisfaction after arthroplasty is typically influenced by various factors (51, 52). Patient satisfaction can be influenced by unmet pre-operative expectations, persisting limitation in activities of daily living, unmet relief of pain, inadequate restoration of function, quality of care concerns, and surgical complications (51-55). Considering these outcomes, primary TKA generally leads to more improvement and fewer complications compared to revision TKA (56-58). In revision TKA patients, relief of pain is less often achieved, patients have post-operative pain more frequently and with higher intensity compared with primary TKA (56). Furthermore, patients undergoing revision surgery often fail to reach the same levels of function observed after primary TKA and generally report a lower quality of life compared to primary surgery (56-58). Unfortunately, we cannot effectively identify which patients will likely benefit from revision arthroplasty and those who may not achieve satisfactory results. The lack of a clear definition for unsuccessful outcomes of TKA hampers both the improvement of treatment strategies and the quantification of the financial and patient burden of unsuccessful arthroplasties.

Arthroplasty registries

National arthroplasty registries have been founded to monitor primary arthroplasty implants nationwide. Arthroplasty registries generate data that can be used to

evaluate the outcome of surgical techniques and different types of joint implants used, with the aim to continuously improve the quality of arthroplasty surgery (59). To achieve this goal, data on the type of joint arthroplasty performed, as well as patient-related factors, patient and hospital identifiers are collected. The first nationwide arthroplasty registry was the Swedish Knee Arthroplasty Register, which started in 1975 (60). The Dutch Arthroplasty Register was initiated in 2007 and full coverage of all Dutch hospitals was reached in 2012. Over the years, joint registries have proven their value. For example, in the first large, long-term follow-up study of the Swedish Hip Arthroplasty Register, several underperforming implants with poor implant survival relative to the other implants were identified, resulting in change of practice (61). Given the success of registries, multiple national and regional registries exist these days. The quality of registry data depends on the coverage of the cases included and the completeness of the administration (62). Almost all patients in a national or regional population need to be recorded to avoid bias.

General aim and outline of this thesis

The number of patients requiring revision total knee arthroplasty (TKA) is likely to increase due to several factors. First, the aging population leads to an increase in knee osteoarthritis cases, resulting in higher rates of primary total knee arthroplasties (TKAs) and, consequently, more TKAs at risk for revision surgery. Secondly, the increased life expectancy of patients will lead to more wear and tear of primary knee prostheses and hence revisions. Thirdly, rising obesity rates contribute to joint problems, particularly knee OA (63). This will also increase the number of primary TKA that are at risk for a future revision. Hence, it is crucial to prevent the number of unsuccessful revisions alongside the rise in TKAs revisions. Therefore, better prediction of surgical outcome after revision TKAs is essential in tailoring the (choice for) surgery to patients who are likely to benefit, and thereby improving the outcomes. The overarching aim of this thesis is to enhance the understanding and optimization of outcomes in revision total knee arthroplasty (TKA). More specifically, our research objectives were:

1. To identify pre-operative factors that are associated with outcomes of revision TKA.
2. To investigate if bone defects before revision TKA can be objectively quantified.
3. To evaluate if registry data are helpful to better understand outcomes of revision TKA.

This thesis starts with a mapping review on factors associated with outcomes of revision TKA (**chapter 2**). This study resulted in an evidence map providing guidance on which pre-operative factors might be incorporated in new registries but can also

guide future research into research gaps that currently lack evidence. **Chapter 3** evaluates if patients undergoing revision TKA for different underlying problems (e.g., the reason for revision) have differences in outcomes. Moreover, we evaluate whether repeat revisions are performed for the same or another reason compared to the index revision TKA. **Chapter 4** focuses on another factor that can impact the outcome after revision TKA, namely severity of bone defects. A systematically and reliable evaluation of bone defects before the surgery may support the surgeon in planning the surgery, and perhaps also enables comparison between patients and evaluate the efficacy of treatment options. We develop and test the reliability of a new bone defect classification for revision arthroplasty using standard knee X-rays. In **chapter 5**, we test the validity of infection as registered in a national joint registry. We compare the number of revision knee and hip surgeries due to an infection from the Dutch Arthroplasty Registry with the number of infections registered in the Dutch National Nosocomial Infections Surveillance Network (PREZIES). In **chapter 6**, we once more use data from the Dutch Arthroplasty Registry, with the aim to test the feasibility of using registry data for external validation of previously published prediction models for outcomes of total joint arthroplasty. In the final chapters, a summary and a general discussion of the findings presented in this thesis, and directions for future research is provided (**Chapter 7**).

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Chapter 2

A mapping review on pre-operative prognostic factors and outcome measures of revision total knee arthroplasty

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Abstract

Introduction: To map literature on prognostic factors related to outcomes of revision total knee arthroplasty (revision TKA), to identify extensively studied factors and to guide future research into what domains need further exploration.

Methods: We performed a systematic literature search in: MEDLINE, Embase and Web of Science. The search string included multiple synonyms of the following keywords: "revision TKA", "outcome" and "prognostic factor". We searched for studies assessing the association between at least one prognostic factor and at least one outcome measure after revision TKA surgery. Data on sample size, study design, prognostic factors, outcomes, and the direction of the association was extracted and included in an evidence map.

Results: After screening of 5,660 articles, we included 166 studies reporting prognostic factors for outcomes after revision TKA, with a median sample size of 319 patients (range: 30-303,867). Fifty percent of the studies reported prospectively collected data, and 61 percent of the studies were performed in a single centre. In some studies, multiple associations were reported. 180 different prognostic factors were reported in these studies. The three most frequently studied prognostic factors were reason for revision (213 times), gender (125 times), and body mass index (BMI) (117 times). Studies focusing on functional scores and PROMs as prognostic factor for the outcome after surgery were limited (n=42). The studies reported 154 different outcomes. The most commonly reported outcomes after revision TKA were: re-revision (155 times), readmission (88 times), and re-infection (85 times). Only five studies included costs as outcome.

Conclusion: Outcomes and prognostic factors that are routinely registered as part of clinical practice (e.g. BMI, gender, complications) or in (inter)national registries are studied frequently. Studies on prognostic factors such as functional and sociodemographic status, and outcomes as healthcare costs, cognitive and mental function, and psychosocial impact are scarce, while they have been shown to be important for patients with osteoarthritis.

Introduction

Revision total knee arthroplasty (revision TKA) can be a complex procedure, which is illustrated by generally worse outcomes when compared to primary TKA (1-5). Ideally, a good prediction model can help to identify the patients with increased risk of unfavourable outcomes. However, no valid prediction models exist for revision TKA (6, 7). Prediction models that have been developed for primary TKA could provide a good starting point, but have generally insufficient discriminative ability, and poor external validity (8). Making clinically relevant prediction models requires data that comprehensively cover multiple domains of both patient factors and outcomes.

An evidence map can provide valuable information to guide future research into what domains need further exploration, that eventually can help better understanding and prediction of outcome following revision TKA. This map reflects which domains or topics are studied extensively, and which are understudied, thus reflecting the gaps of knowledge. Some prognostic factors and outcomes are easily accessible and acquired as they are part of routine registration (e.g. body mass index (BMI) and gender). Therefore, it is expected that the domains which are part of routine registration, in patient records or registries, are relatively well studied. On the other hand, there are likely a number of variables, identified by stakeholders as a relevant factor or outcome, that are more difficult to obtain. Relevant domains for patients with osteoarthritis (OA) have been previously identified by the International Consortium for Health Outcomes Measurement (ICHOM) and Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative and the Outcome Measures in Rheumatology (OMERACT-OARSI). They have developed standard sets of variables and outcomes that guide researchers and clinicians in the selection of variables important to patients with OA (9, 10).

In this study, we will perform a mapping review to provide an evidence map of the prognostic factors and outcome measures relevant for revision TKA. The evidence map will be used to identify gaps of knowledge and identify factors and outcomes that have been more extensively studied. These findings can guide future research with the overall goal to further our understanding of revision TKA and to improve outcome prediction.

Methods

Protocol and registration

We performed and reported a mapping review following the PRISMA guidelines for scoping reviews, as there is no alternative guideline for mapping reviews (11). The study protocol was registered at Open Science Framework: https://osf.io/je26b/ .

Eligibility criteria

We searched for studies assessing the association between at least one prognostic factor and at least one outcome measure after revision TKA surgery. We included only articles written in English. The population of interest was patients who underwent a revision TKA. We excluded reviews, case reports and studies not including humans (e.g. cadaver or animal studies). All pre-operative prognostic variables (e.g. demographical, diagnostic and psychological variables) reported in combination with any type of outcomes (e.g. clinical, patient-reported outcome measures (PROMS), or functional outcomes) were included.

Search strategy

To map the current literature, we carried out a systematic literature search from date of inception to December 2022 in MEDLINE, Embase and Web of Science. The search strategy included multiple synonyms of the terms "revision TKA" and "outcome" and "prognostic factor". The synonyms were searched in subject headings and words restricted to title and abstract, as detailed in our study protocol (see: https://osf.io/je26b/ or Appendix A).

Selection of sources of evidence

The search strategy was performed by one author (MB). Duplicates were removed from the results of the search strategy. The studies were screened in two phases. First, the titles and abstracts of all articles were screened for eligibility by two authors (MB and BR). Second, all full-text articles that were included on the basis of the abstract, were retrieved and evaluated on eligibility by the same two authors. In both steps, consensus was sought, but when no consensus could be reached, a third review author (KS) was consulted.

Data charting process and data items

Of the papers included in this review, we extracted data on publication date, journal, sample size, study design, prognostic factor(s), outcome measures, and the categories that were used for prognostic factors and/or outcome measures. Additionally, we noted the direction of the association between the prognostic factor and outcome measure. Associations that were reported as statistically significant, were defined as either a positive (e.g. more satisfied or less re-revisions) or a negative effect (e.g. more complications or worse functional scores). Non-significant associations were defined as non-significant. The direction of the effect was transformed so that the same reference category was used in all studies using that particular prognostic factor. For example, for gender, female was always used as reference group. Also, the absence of a specific comorbidity, patient or disease characteristic, and a low BMI, age, or American Society of Anaesthesiologists (ASA) score were used as a reference category. Furthermore, we extracted data about the type of analysis that was used for testing

the association, and whether it was corrected for confounding variables or not. In case of multivariable models, we also extracted how the independent variables were selected. Data was extracted by one author (MB). Next, the prognostic factors and outcomes were grouped in different categories to structure the results. Outcomes were grouped based on the OMERACT-OARSI core outcome domain set for hip and knee OA, consisting of the following domains: adverse events (including mortality), patient's global assessment of target joint, quality of life, physical function, pain, joint structure (changes in joint structure on imaging), costs, sleep, psychosocial impact, participation, effect on family/caregivers, fatigue, cognitive function (covering both cognitive and mental functioning), and clinician global assessment of target joint (10). Prognostic factor categories were: case-mix factors (such as age and gender), comorbidity, functional status, indication for surgery, lab test, medical history, medical history knee specific, and patient-reported health status (or PROMs). The prognostic factor categories were based on the ICHOM standard set for hip or knee OA (9), extended with components of the pre-operative screening, namely: indication for surgery, lab test, and medical history. An overview of all prognostic factors, outcomes, and their categories can be found in Appendix B.

Critical appraisal of individual sources of evidence

Given the nature of a mapping review, we did not assess the risk of bias of the included studies. We did extract information about the study design regarding the prospective or retrospective nature of data collection, and if the study was conducted in a single or multicentre set-up.

Synthesis of results

We used descriptive statistics to report the findings. R (version 4.1.3; R Foundation for Statistical Computing, Vienna, Austria) was used to make a graphical overview of the literature using the ggplot2 package (version 3.3.5) and an online, interactive overview with the shiny package (version 1.7.1)(12-14).

Results

The literature search resulted in 6,548 articles after removing duplicates. An overview of the identification of studies can be found in Figure 1. After the full-text screening, a total of 166 studies assessing the association between prognostic factors and outcome measures after revision TKA surgery were included in this review (Table 1). In 50% of the studies the data was collected prospectively, and the majority included patients from a single centre (61%; 101/166). The median sample size of the studies was 319 (30 to 303,867). In 59% (98/166) of the studies, a multivariable model was used

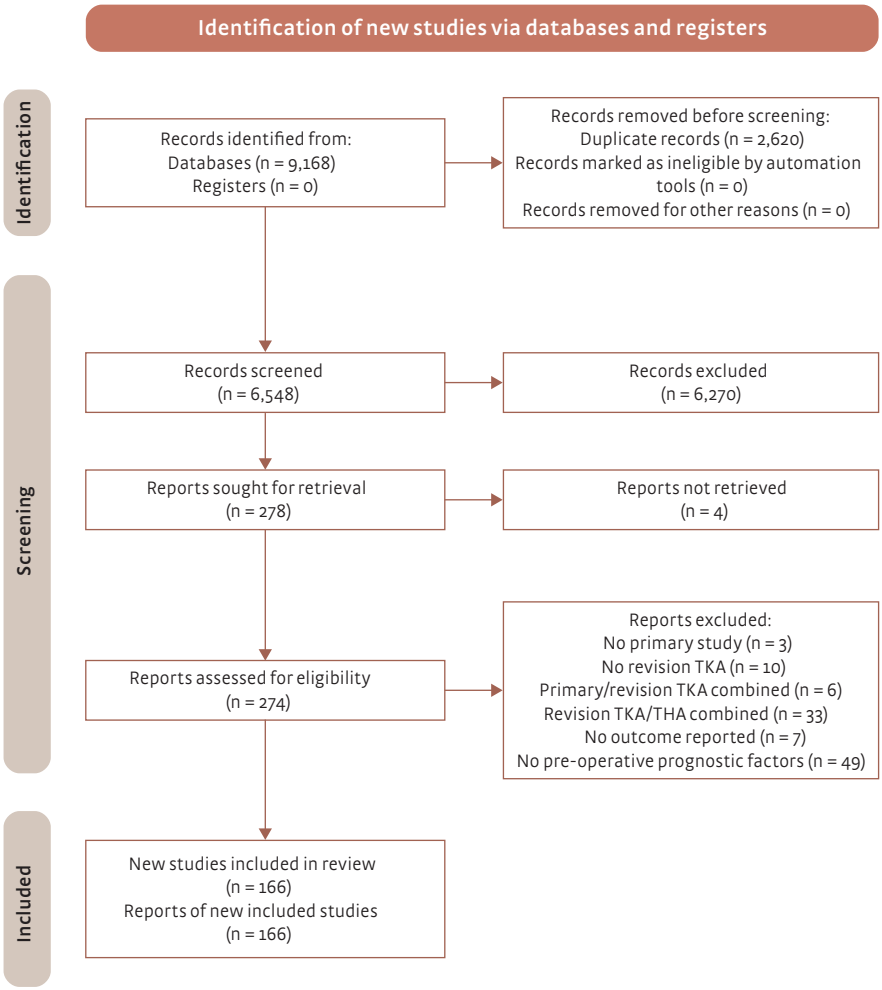

Figure 1: Flowchart of the literature search.

to study the association between the prognostic factors and the outcomes. In most studies (52%; 51/98), the covariates in the model were reported as a set of variables that the authors prespecified as confounders of the association between prognostic variable and the outcome. The other most common methods for variable selection were based on the p-value of univariable association (19%, 19/98 studies), or building the model using stepwise or backward selection based on the Akaike Information

Criterion (AIC; 12%, 12/98 studies). In the other studies, propensity score matching or machine learning methods were used to select confounders, or methods for confounder selection were not reported.

Prognostic factors of revision TKA

A total of 180 different prognostic factors were found in the included studies. The three most frequently reported prognostic factors were reason for revision, gender, and BMI. Reason for revision was described 213 times in 68/166 studies (41%), gender 125 times in 76/166 studies (46%), and BMI 117 times in 64/166 studies (38%). Studies focusing on functional scores and PROMs as prognostic factor for the outcome after surgery were limited (n=42). The prognostic factors that were most frequently reported to have a statistically significant association with the outcomes of revision TKA, either positive or negative, were reason for revision, age, gender, BMI, and opioid use. Prognostic factors that are recommended by ICHOM, but have not been described in the included literature were education level, living condition, and work status.

Outcomes of revision TKA

The studies reported 154 different outcomes. The most frequently used outcome category was adverse events, of which the majority of the studies reported re-revision, readmission, and reinfection after revision TKA. Re-revision was described 155 times in 46/166 studies (28%), readmission 88 times in 23/166 studies (14%), and re-infection 85 times in 15/166 studies (9%). Costs, psychosocial impact, and quality of life outcomes were scarce. Only five studies included costs as outcome; in four out of five studies this was limited to direct in-hospital costs of the surgery. Four studies included cognitive and mental function as outcome, measured using Patient-Reported Outcomes Measurement Information System (PROMIS) mental, score, 36-Item Short Form Survey (SF-36) mental health, and Veterans RAND 12 Item Health Survey (VR-12) Mental Component Summary (MCS. Seventeen). In all, 17 studies used the 12-Item Short Form Survey (SF-12,), SF-36, EuroQol five-dimension (EQ-5D), or Knee injury and Osteoarthritis Outcome Score quality of life subscale (KOOS-QoL) to assess quality of life after revision TKA. Outcome categories recommended in the OMERACT-OARSI set that were not described in the included studies were joint structure, sleep, psychosocial impact, effect on family/caregiver, fatigue, and clinician global assessment of target joint.

Associations between prognostic factor and outcome

A graphical overview of all studied combinations of prognostic factors and different outcome measures is presented in Figure 2. An interactive version of the plot can be found on: https://maartjebelt.shinyapps.io/review_app/ .

Table 1. Included literature

First author	Year	Sample size	Type study	Centre	Association	Covariable selection for multivariable models
Aali-Rezaie(24)	2018	1344	retrospective	single	multi	p-value univariable
Abram(25)	2021	40854	retrospective	multi	multi	set of covariables
Aggerwal(26)	2014	168	prospective	single	multi	set of covariables
Akkaya(27)	2022	66	retrospective	single	uni	
Apinyankul(28)	2022	238	retrospective	single	multi	p-value univariable
Arndt(29)	2022	3354	retrospective	multi	uni	
Bae(30)	2013	224	prospective	single	uni	
Baek(31)	2021	78	retrospective	single	uni	
Baker(32)	2012	797	prospective	multi	uni	
Barrack(33)	2002	135	prospective	multi	multi	stepwise selection
Bass(34)	2021	25441	prospective	multi	multi	set of covariables
Bedard(35)	2018	8776	prospective	multi	multi	unknown
Belmont(36)	2016	1754	prospective	multi	uni	
Belt(37)	2021	8978	prospective	multi	uni	
Bieger(38)	2013	97	prospective	single	uni	
Boddapati(39)	2018	12780	prospective	multi	multi	set of covariables
Carter(40)	2019	237	retrospective	single	uni	

Prognostic factors	Outcomes
red blood cell distribution width	complications, length of stay, mortality, readmission
age, sinus tract, BMI, Staphylococcus aureus, culture negative PJI	re-infection
age, BMI, gender, infection	re-revision
planned surgery	length of stay, consultation with health professional
reason for revision	complications, re-revision
reason for revision, age, gender, Charlson comorbidity index, opioid use	opioid use
age, gender, reason for revision	re-revision
age, gender, ethnicity, BMI, smoking, reason for revision, Charlson comorbidity index, ASA, diabetes mellitus, COPD, congestive heart failure, renal failure, metastatic cancer, bleeding disorders, wound infection	mortality
reason for revision	EQ-5D, OKS, satisfaction
prior surgery, heterotopic ossification, BMI, gender, reason for revision	heterotopic ossification, KSS, ROM
age, cancer, cerebrovascular disease, COPD, BMI, diabetes mellitus, ethnicity, heart failure, gender, history of VTE, inflammatory bowel disease, pulmonary hypertension, renal disease, rheumatoid arthritis, sleep apnoea, smoking, reason for revision, systemic lupus, thrombophilia, venous insufficiency	venous thromboembolism
smoking	complications, infection, mortality, reoperation
hypertension, cerebrovascular accident, gender	readmission
reason for revision	re-infection, re-revision
reason for revision	KSS
age, PJI, ASA, COPD, diabetes mellitus, smoking, BMI, gender	complications, blood transfusion, cardiac complications, readmission, cerebrovascular accident, deep surgical site infection, deep venous thrombosis, sepsis, length of stay, major complications, minor complications, mortality, non-home discharge, renal complications, urinary tract infection, wound dehiscence, respiratory complication, superficial surgical site infection
BMI	amputation, aseptic loosening, ICU admission, infection, manipulation under anaesthesia, mortality, wound complications

Table 1. Continued

First author	Year	Sample size	Type study	Centre	Association	Covariable selection for multivariable models
Chalmers(41)	2019	135	retrospective	single	multi	set of covariables
Chalmers(42)	2021	197	retrospective	single	multi	set of covariables
Chalmers(43)	2021	163	retrospective	single	multi	set of covariables
Chen(44)	2020	58	retrospective	single	multi	p-value univariable
Chen(45)	2021	172	retrospective	single	uni	
Choi(46)	2014	176	prospective	single	multi	set of covariables
Christiner(47)	2022	144	retrospective	single	uni	
Chung(1)	2021	13597	retrospective	multi	multi	set of covariables
Churchill(48)	2021	1676	prospective	multi	multi	unknown
Citak(49)	2019	183	retrospective	single	uni	
Cochrane(50)	2022	21610	retrospective	multi	uni	
Cochrane(51)	2022	157	retrospective	single	multi	set of covariables
Cohen(52)	2019	8559	prospective	multi	uni	

Prognostic factors	Outcomes
age, BMI, gender, prior revision, reason for revision	re-revision, re-revision for instability, re-revision for loosening
BMI, gender, prior revision, reason for revision	re-revision
reason for revision	OKS, EQ-VAS, EQ-5D, KSS, ROM
BMI, anaerobic pathogens, cirrhosis, C-reactive protein, polymicrobial infection, virulent pathogens	re-infection
chronic viral hepatitis	infection, re-revision
age, BMI, ASA, comorbidity, MRSA, gender, reason for revision	mortality
gender, anticoagulant use, prior DAIR, smoking, sinus tract, BMI, ASA	infection
coagulation	transfusion, cardiac arrest, myocardial infarction, pneumonia, reintubation, renal insufficiency
coagulation, age, ASA, bleeding disorders, blood urea nitrogen, BMI, Charlson comorbidity index, congestive heart failure, COPD, creatinine, diabetes mellitus, ethnicity, hypertension, smoking, gender	acute renal failure, length of stay, pneumonia, cerebrovascular accident, deep venous thrombosis, transfusion, sepsis, infection, unplanned intubation, wound disruption, urinary tract infection, mortality, myocardial infarction, on ventilator, pulmonary embolism, readmission, renal insufficiency, return to OR, septic shock, superficial surgical site infection, surgical site infection
age, depression, BMI, deep venous thrombosis, gender, polymicrobial infection, prior surgery, weight, Charlson comorbidity index, COPD, coronary heart disease, C-reactive protein, dementia, diabetes mellitus, haemoglobin, liver disease, prior arthroscopy, renal failure, rheumatoid arthritis, tumour history, white blood cell count	re-revision, re-infection
age, gender, ethnicity, BMI, smoking, ASA, functional status, DM insulin dep, DM non-insulin dep, COPD, heart failure, liver disease, hypertension, renal failure, dialysis, cancer, steroid use, bleeding disorders	length of stay
BMI, diabetes mellitus, anaemia, smoking	postoperative infection
Glomerular Filtration Rate	cardiac arrest, complications, death, deep venous thrombosis, deep wound infection, prolonged length of stay, fail to wean, myocardial infarction, organ infection, pneumonia, pulmonary embolism, reintubation, renal failure, wound dehiscence, urinary tract infection, renal insufficiency, return to OR, sepsis, septic shock, cerebrovascular accident, superficial surgical site infection

Table 1. Continued

First author	Year	Sample size	Type study	Centre	Association	Covariable selection for multivariable models
Courtney(53)	2018	10848	prospective	multi	multi	set of covariables
Dahlgren(54)	2018	171	retrospective	single	uni	
Dai(55)	2021	32349	prospective	multi	multi	propensity score matched
de Carvalho(56)	2015	30	retrospective	single	uni	
Deehan(57)	2006	94	prospective	single	uni	
Deere(58)	2021	33292	prospective	multi	uni	
DeMik(59)	2022	22262	retrospective	multi	multi	p-value univariable
Dieterich(60)	2014	3421	prospective	multi	multi	p-value univariable
Dowdle(61)	2018	5414	prospective	multi	multi	set of covariables
Drain(62)	2022	222	retrospective	multi	uni	

Prognostic factors	Outcomes
reason for revision	cardiac arrest, complications, cerebrovascular accident, deep venous thrombosis, fail to wean, infection, mortality, myocardial infarction, pneumonia, pulmonary embolism, readmission, reintubation, renal failure, renal insufficiency, reoperation, sepsis, septic shock
age, BMI, albumin, ASA, bleeding disorders, COPD, diabetes mellitus, dialysis, dyspnoea on exertion, ethnicity, haematocrit, hypertension, International Normalized Ratio, platelet count, serum creatinine, smoking, steroid use, white blood cell count, gender	readmission
reason for revision	anaemia, blood transfusion, cardiac complications, central nervous system, complications, costs, deep venous thrombosis, gastrointestinal complication, hematoma, length of stay, mortality, postoperative infection, pulmonary embolism, respiratory complication, urinary system complication, vascular complication, wound dehiscence
BMI, reason for revision	WOMAC
prior revision	KSS
age, gender, prior revision	re-revision
transfusion pre-op, haematocrit, bleeding disorders, COPD	blood transfusion
age, ASA, dialysis, emergency operation, pulmonary disease, gender	complications
age, anxiety, depression, BMI, diabetes mellitus, smoking, gender, opioid use	manipulation under anaesthesia
reason for revision	mortality, Charlson comorbidity index, mortality related to infection, mortality related to comorbidities, mortality due to myocardial infarction, mortality due to cerebrovascular event, mortality due to congestive heart failure, mortality due to pulmonary embolism, mortality due to liver failure, mortality due to respiratory failure, mortality due to renal failure, mortality due to cancer, mortality due to sepsis, mortality due to systemic inflammatory response syndrome, mortality due to multiple causes

Table 1. Continued

First author	Year	Sample size	Type study	Centre	Association	Covariable selection for multivariable models
Edmiston(2)	2019	14486	retrospective	multi	multi	set of covariables
Faschingbauer(63)	2020	96	retrospective	single	uni	
Fassihi(64)	2020	10973	retrospective	multi	multi	p-value univariable
Fleischman(65)	2017	223	prospective	single	multi	backward selection
Fury(66)	2021	213	retrospective	single	uni	
Gao(67)	2019	260	retrospective	single	multi	set of covariables
Geary(68)	2020	1632	retrospective	single	multi	unknown
Ghanem(69)	2007	93	prospective	single	multi	set of covariables
Ghomrawi(70)	2009	308	prospective	multi	multi	set of covariables
Goh(71)	2021	245	prospective	single	multi	set of covariables
Grayson(72)	2016	177	prospective	single	uni	
Gu(73)	2018	9921	prospective	multi	multi	p-value univariable
Gu(74)	2020	13246	prospective	multi	uni	
Gu(75)	2021	13313	prospective	multi	multi	p-value univariable
Gu(76)	2019	6849	prospective	multi	multi	p-value univariable

Prognostic factors	Outcomes
BMI, gender, AIDS, alcohol abuse, anaemia, cardiac arrhythmia, chronic pulmonary disease, bleeding disorders, congestive heart failure, connective tissue disorder, dementia, diabetes mellitus, fluid electrolyte disorder, lymphoma, metastatic cancer, peripheral vascular disease, renal failure, weight loss	surgical site infection
alcohol abuse, COPD, diabetes mellitus, heart failure, hypertension, renal failure, malignancies, rheumatoid arthritis, smoking	re-infection
steroid use	length of stay, mortality, septic shock
age, BMI, gender, reason for revision	re-revision
reason for revision	re-revision
surgical history	re-revision
age, gender, reason for revision	re-revision
reason for revision	pain, SF-36 mental health, SF-36 physical, WOMAC function
age, BMI, comorbidity, extension contracture, gender, flexion contracture, reason for revision	pain, SF-36, Lower-Extremity Activity Scale (LEAS), WOMAC function
age, BMI, Charlson comorbidity index, gender, reason for revision, SF-36 MCS	expectations, satisfaction
reason for revision	KSS clinical, KSS function, satisfaction, UCLA
age, COPD, BMI, ASA, diabetes mellitus, gender	length of stay, complications, reoperation, mortality
DM insulin dep, DM non-insulin dep	cardiac arrest, death, deep surgical site infection, deep venous thrombosis, fail to wean, length of stay, myocardial infarction, organ infection, pneumonia, wound dehiscence, pulmonary embolism, urinary tract infection, transfusion, reintubation, renal failure, renal insufficiency, return to OR, sepsis, septic shock, cerebrovascular accident, superficial surgical site infection
anaemia	bleeding, cardiac complications, complications, wound complications, urinary tract infection, length of stay, mortality, pulmonary complications, renal complications, return to OR, septic shock, thromboembolic event
blood transfusion	deep venous thrombosis, unplanned intubation, transfusion, fail to wean, myocardial infarction, organ infection, pneumonia, readmission, sepsis, septic shock

Table 1. Continued

First author	Year	Sample size	Type study	Centre	Association	Covariable selection for multivariable models
Gu(77)	2020	9914	prospective	multi	multi	
Hagerty(78)	2021	615	retrospective	single	multi	set of covariables
Halder(79)	2020	23664	prospective	multi	multi	set of covariables
Hamaway(80)	2022	106534	retrospective	multi	uni	
Hannon(81)	2022	60	retrospective	single	uni	
Hardcastle(82)	2016	228	retrospective	single	uni	
Hardeman(83)	2012	146	prospective	single	uni	
Heesterbeek(84)	2016	40	prospective	single	uni	
Hernigou(85)	2017	72	retrospective	single	multi	set of covariables
Hoell(86)	2016	59	retrospective	single	uni	
Ingall(87)	2021	330	prospective	single	uni	propensity score matched
Jannelli(88)	2022	105	retrospective	single	uni	
Jeschke(89)	2022	34643	retrospective	multi	multi	set of covariables

Prognostic factors	Outcomes
age, ASA, bleeding disorders, blood transfusion, diabetes mellitus, dyspnoea, ethnicity, functional status, renal failure, BMI, gender, COPD	prolonged length of stay, return to OR, cardiac arrest, complications, deep venous thrombosis, deep wound infection, fail to wean, mortality, myocardial infarction, organ surgical site infection, pneumonia, pulmonary embolism, reintubation, renal failure, renal insufficiency, sepsis, septic shock, cerebrovascular accident, superficial surgical site infection, urinary tract infection, wound dehiscence
type of infection	re-infection
hospital volume	adverse events, mortality, re-revision
age, Charlson comorbidity index, BMI, ASA, reason for revision, renal disease, anaemia, diabetes mellitus, gender, smoking	prolonged length of stay
age, gender, BMI	re-revision
elevated C-reactive protein / erythrocyte sedimentation rate	aseptic loosening, instability, infection, fracture, re-revision
age, tibial tuberositas osteotomy, time to revision, reason for revision	KSS clinical, KSS function, pain, re-revision
ROM	KSS function, pain, satisfaction
primary diagnosis, reason for revision	KSS clinical, KSS function, re-revision, ROM, satisfaction
BMI, blood transfusion, diabetes mellitus, periprosthetic fracture, smoking, tumour	re-infection
opioid use	KOOS-PS, PROMIS physical, PROMIS mental, Physical Function SF10A
iron deficiency	length of stay, costs, acute renal injury, pneumonia, respiratory failure, ileus episode, urinary tract infection, myocardial infarction, cerebrovascular accident, deep venous thrombosis, surgical site infection, venous thromboembolism, pulmonary embolism, complications
age, gender, BMI, fluid electrolyte disorder, cardiac arrhythmia, renal failure, congestive heart failure, valvular disease, bleeding disorders, neurological disease, alcohol abuse, drug abuse, psychoses, pulmonary circulation disorder, prior revision, anticoagulant use	blood transfusion

Table 1. Continued

First author	Year	Sample size	Type study	Centre	Association	Covariable selection for multivariable models
Kamath(90)	2017	4551	prospective	multi	multi	
Kasmire(91)	2014	175	prospective	single	multi	set of covariables
Keswani(92)	2016	4977	prospective	multi	multi	p-value univariable
Kienzle(93)	2020	100	retrospective	single	uni	
Kildow(94)	2022	178	retrospective	multi	uni	
Kim(95)	2010	807	prospective	single	multi	set of covariables
Kim(96)	2019	77	prospective	single	multi	backward selection
Kingsbury(97)	2022	263	prospective	multi	multi	propensity score matched
Kirschbaum(98)	2022	63	retrospective	single	uni	
Klasan(99)	2020	1720	prospective	multi	multi	p-value univariable
Klasan(100)	2021	633	retrospective	single	multi	set of covariables
Klemt(101)	2022	2228	retrospective	single	multi	recursive feature elimination through random forest algorithms
Klemt(102)	2022	2512	retrospective	single	multi	artificial intelligence, best predictors
Kubista(103)	2011	368	retrospective	single	multi	backward selection
Kurd(104)	2010	102	prospective	single	uni	

Prognostic factors	Outcomes
albumin	acute renal failure, cardiac arrest, cardiac pulmonary complication, complications, wound disruption, unplanned intubation, urinary tract infection, transfusion, wound infection, cerebrovascular accident, deep surgical site infection, deep venous thrombosis, mortality, myocardial infarction, on ventilator, organ surgical site infection, pneumonia, pulmonary embolism, renal insufficiency, sepsis, septic shock, superficial surgical site infection, systemic infection
BMI, gender, comorbidity, KSS function, KSS clinical, pain, stiffness	stiffness, WOMAC function, KSS function, pain
age, BMI, ASA, cardiac disease, diabetes mellitus, ethnicity, hypertension, renal disease, pulmonary disease, smoking, cerebrovascular accident, gender, reason for revision	readmission
prior revision, ASA, gender	aseptic loosening, complications, infection
polymicrobial infection, antibiotic resistant organism, gender, prior two-stage revision, diabetes mellitus, chronic renal disease, coronary vascular disease, myocardial infarction, congestive heart failure, deep venous thrombosis, smoking, former smoking, systemic disease, chronic lung disease	re-infection
age, BMI, gender, ROM, time to revision, reason for revision	stiffness
central sensitization	satisfaction, pain, stiffness, WOMAC function
age, gender, primary diagnosis, index of multiple deprivation, reason for revision, elixhauser comorbidity index	mortality
reason for revision, BMI, gender, age	re-revision
age, gender, ASA, time to revision	re-revision, OKS
obesity, smoking, diabetes mellitus	reoperation, re-revision, amputation above knee, infection, extensor mechanism failure, ligamentous laxity, malposition, stiffness
diabetes mellitus, opioid use, gender, age, social status, ethnicity, reason for revision, insurance status, ASA	non-home discharge
age, BMI, gender, comorbidity, diabetes mellitus, type of infection, rheumatoid arthritis	re-infection
age, BMI, ASA, gender, DAIR, diabetes mellitus, type of infection, smoking, steroid use	re-infection

Table 1. Continued

First author	Year	Sample size	Type study	Centre	Association	Covariable selection for multivariable models
Labaran(105)	2020	18359	prospective	multi	multi	set of covariables
Labaran(106)	2020	7459	retrospective	multi	multi	
Larson(107)	2021	110	retrospective	single	multi	set of covariables
Laudermilch(108)	2010	103	retrospective	single	uni	
Lee(109)	2017	206	retrospective	single	uni	
Lee(110)	2020	16428	prospective	multi	multi	p-value univariable
Lee(111)	2020	5204	prospective	multi	multi	
Leta(112)	2015	145	prospective	multi	multi	set of covariables
Liang(113)	2018	224	retrospective	single	uni	
Lindberg-Larsen(114)	2022	3118	retrospective	single	multi	set of covariables
Liodakis(115)	2015	2425	prospective	multi	multi	AIC

Prognostic factors	Outcomes
haemodialysis-dependent	complications, infection, length of stay, mortality, readmission, costs, septicaemia
renal transplant	infection, length of stay, major complications, mortality, readmission, septicaemia
reason for revision, gender, age, Charlson comorbidity index, obesity, index of multiple deprivation, geographical rurality, ethnicity	mortality
MRSA	activity of daily living limitation, SF-36, KSS clinical, KSS function, WOMAC
reason for revision	Hospital for Special Surgery score (HSS), KSS, ROM, WOMAC
DM insulin dep, DM non-insulin dep	blood transfusion, cerebrovascular accident, death, deep surgical site infection, deep venous thrombosis, prolonged length of stay, myocardial infarction, pneumonia, unplanned intubation, urinary tract infection, pulmonary embolism, readmission, renal failure, renal insufficiency, return to OR, sepsis, superficial surgical site infection
chronic renal disease	acute renal failure, blood transfusion, cardiac arrest, cerebrovascular accident, deep surgical site infection, deep venous thrombosis, prolonged length of stay, wound disruption, unplanned intubation, ventilator dependence, urinary tract infection, length of stay, mortality, myocardial infarction, organ surgical site infection, pneumonia, pulmonary embolism, renal insufficiency, return to OR, septic shock, superficial surgical site infection, non-home discharge, systemic sepsis
age, gender, patella resurfacing	re-revision
age, gender, primary diagnosis	re-revision
prior revision, walking aid, BMI, haemoglobin, cardiac disease, pulmonary disease, psychiatric disorder pharmacologically treated, DM insulin dep, age, gender, elixhauser comorbidity index, hospital volume	length of stay, readmission, mortality
age, BMI, ASA, bleeding disorders, COPD, diabetes mellitus, heart failure, haematocrit, hypertension, smoking, gender	major complications, prolonged length of stay

Table 1. Continued

First author	Year	Sample size	Type study	Centre	Association	Covariable selection for multivariable models
Lopez-de-Andres(116)	2017	1390	prospective	multi	uni	
Lu(117)	2017	6830	prospective	multi	multi	p-value univariable
Luque(118)	2014	125	retrospective	single	multi	p-value univariable
Ma(119)	2018	108	retrospective	single	multi	p-value univariable
Mahomed(120)	2005	11726	prospective	multi	uni	
Malviya(121)	2012	120	prospective	single	multi	set of covariables
Malviya(122)	2012	120	prospective	single	multi	set of covariables
Massin(123)	2016	285	retrospective	multi	multi	p-value univariable
Matar(124)	2021	1298	retrospective	single	multi	set of covariables
Matar(125)	2021	292	prospective	single	multi	forward selection
Meyer(126)	2021	235	retrospective	multi	uni	
Mortazavi(127)	2011	499	prospective	single	uni	
Mulhall(128)	2007	291	prospective	multi	multi	set of covariables
Nikolaus(129)	2016	1802	retrospective	single	uni	
Novicoff(130)	2009	308	retrospective	multi	uni	
Oganesyan(131)	2021	1689	retrospective	single	uni	

Prognostic factors	Outcomes
diabetes mellitus, hypertension, smoking, BMI, reason for revision	anaemia, cardiac complications, central nervous system, complications, deep venous thrombosis, gastrointestinal complication, genitourinary complications, hematoma, infection, length of stay, mortality, peripheral vascular disease, wound dehiscence, urinary tract infection, pulmonary embolism, renal failure, respiratory complication, septic shock
anaemia	complications, length of stay, mortality, readmission
age, renal failure, rheumatoid arthritis, tibial tuberositas osteotomy, reason for revision	re-revision
ASA, age, BMI, gender, gout	treatment success
age, comorbidity, ethnicity, gender, Medicaid	complications, mortality, reoperation
age, BMI, reason for revision	WOMAC, satisfaction, SF-36
age, BMI, gender, comorbidity, reason for revision	SF-36 bodily pain, SF-36 physical, WOMAC function, WOMAC pain
age, BMI, gender, diabetes mellitus, pathogen, prior infection	re-infection
reason for revision	mortality
age, gender, haemoglobin, ASA, arterial hypertension, anticoagulant use, myocardial infarction, chronic heart disease, diabetes mellitus, chronic renal disease, COPD, BMI	blood loss
age, gender, reason for revision	re-revision
age, BMI, bilateral, cancer, comorbidity, diabetes mellitus, gastrointestinal disease, cardiac disease, inflammatory arthritis, liver disease, renal disease, cerebrovascular accident, thyroid disease, vascular arterial disease, vascular venous disease, gender, reason for revision	infection, re-revision
BMI	Lower-Extremity Activity Scale (LEAS), KSS, re-revision, WOMAC function, WOMAC pain
age, BMI, ASA, comorbidity, liver disease, smoking, gender	infection
low back pain	Lower-Extremity Activity Scale (LEAS), SF-36, KSS, WOMAC clinical, WOMAC function
prior arthroscopy	mortality, readmission, re-revision, re-revision for aseptic loosening, re-revision for infection, re-revision for instability, re-revision for pain, re-revision for stiffness

Table 1. Continued

First author	Year	Sample size	Type study	Centre	Association	Covariable selection for multivariable models
Patil(132)	2009	56	prospective	single	multi	set of covariables
Piuzzi(133)	2020	246	prospective	single	multi	
Pun(134)	2008	67	retrospective	single	uni	
Quinn(135)	2022	202	retrospective	single	uni	
Rajgopal(136)	2018	184	retrospective	single	uni	
Rajgopal(137)	2013	142	retrospective	single	uni	
Reeves(138)	2018	46836	prospective	multi	uni	
Ritter(139)	2004	355	prospective	single	uni	
Ro(140)	2018	144	retrospective	single	multi	stepwise selection
Ross(141)	2022	51548	retrospective	multi	multi	unknown
Rossmann(142)	2021	40	retrospective	single	uni	
Roth(143)	2019	9773	prospective	multi	multi	set of covariables
Russo(144)	2022	108	retrospective	single	multi	set of covariables
Sabah(145)s	2021	10329	prospective	multi	multi	backward selection
Sabry(146)	2014	3809	retrospective	single	multi	p-value univariable
Sakellariou(147)	2015	110	prospective	single	multi	backward selection
Samuel(148)	2020	3531	retrospective	multi	multi	unknown
Schairer(149)	2014	1408	retrospective	single	multi	stepwise selection
Schwarze(150)	2022	157	retrospective	single	uni	
Shen(151)	2022	414	retrospective	multi	uni	
Sheng(152)	2006	2637	prospective	multi	multi	p-value univariable

Prognostic factors	Outcomes
reason for revision	KSS, satisfaction, SF-36 mental health, SF-36 physical
age, BMI, ethnicity, gender, pain, prior surgery, reason for revision, ROM, smoking	pain, KOOS quality of life, KOOS-PS, VR-12 MCS, VR-12 PCS
gender, reason for revision	KSS, pain
gender, age, weight, BMI, reason for revision, prior revision, ROM	OKS, ROM
failed DAIR	KSS, time to re-revision, re-revision, ROM, re-revision for infection
reason for revision	re-revision, ROM
reason for revision	length of stay, mortality, readmission
age, pre-operative alignment, preoperative flexion, gender	flexion, extension
age, primary diagnosis, ROM, BMI, gender, reason for revision	Hospital for Special Surgery score (HSS), KSS clinical, KSS function, ROM
hepatitis C, reason for revision	any medical complication, deep venous thrombosis, pulmonary embolism, acute renal injury, urinary tract infection, transfusion, readmission, complications, manipulation under anaesthesia, re-revision, periprosthetic joint infection, aseptic loosening, periprosthetic fracture
age, gender	re-infection
BMI	adverse events, major complications, minor complications, readmission, reoperation
reason for revision, organ transplant	length of stay, readmission, re-revision, mortality
age, disability, EQ-5D 3L anxiety/depression, EQ-5D 3L self-care, OKS	OKS change
ASA, diabetes mellitus, pre-operative antibiotics, prior infection, gender, prior surgery	infection, re-infection
age, BMI, ASA, gender, comorbidity, MRSA	re-infection
age, gender, BMI, smoking, ASA, prior surgery, C-reactive protein, type of infection	re-revision
reason for revision	readmission
positive cultures	re-revision
KSS function, ROM, coronal deviation, tibial malrotation, age, pain	KSS function
age, gender, primary diagnosis, time to revision, reason for revision	re-revision

Table 1. Continued

First author	Year	Sample size	Type study	Centre	Association	Covariable selection for multivariable models
Sinclair(153)	2021	32354	retrospective	multi	uni	
Singh(154)	2014	1533	prospective	single	multi	set of covariables
Singh(155)	2013	4090	prospective	single	multi	set of covariables
Singh(156)	2011	2695	prospective	single	multi	
Singh(157)	2013	725	prospective	single	multi	set of covariables
Singh(158)	2013	1533	prospective	single	multi	set of covariables
Singh(159)	2010	1533	prospective	single	multi	set of covariables
Singh(160)	2014	1533	prospective	single	multi	set of covariables
Singh(161)	2014	1533	prospective	single	multi	set of covariables
Siqueira(162)	2017	438	retrospective	single	uni	
Sisko(163)	2019	174	prospective	single	uni	
Sloan(164)	2019	15286	prospective	multi	multi	set of covariables
Sodhi(165)	2020	28779	prospective	multi	multi	set of covariables
Staats(166)	2017	98	retrospective	single	uni	
Sternheim(167)s	2012	102	retrospective	single	uni	
Suarez(168)	2008	566	retrospective	single	uni	
Theil(169)	2022	119	retrospective	single	uni	
Traven(170)	2019	16304	prospective	multi	multi	set of covariables
Turnbull(171)	2019	112	retrospective	single	multi	p-value univariable
Upfill-Brown(172)	2022	303867	retrospective	multi	uni	
van den Kieboom(173)	2021	79	retrospective	single	uni	

Prognostic factors	Outcomes
age, gender, BMI, vascular disease, hypertension, diabetes mellitus, malignancy, renal failure, C-reactive protein, causative pathogen	readmission
comorbidity, anxiety, depression	knee function
age, ASA, BMI, comorbidity, gender, reason for revision	periprosthetic fracture
age, BMI, comorbidity, gender	pain
ipsilateral hip involvement	activity of daily living limitation, pain
connective tissue disorder, COPD, diabetes mellitus, cardiac disease, peripheral vascular disease, anxiety, renal disease, depression	pain
age, comorbidity, BMI, gender	walking aids, activity of daily living limitation
comorbidity, age, BMI, anxiety, depression, gender	narcotic pain medication, NSAIDs
reason for revision	activity of daily living limitation, pain
reason for revision	re-revision
BMI	deep infection, KSS, reoperation, re-revision, SF-12, WOMAC
BMI	deep venous thrombosis, pulmonary embolism
depression, BMI, gender, opioid use, alcohol abuse, cannabis abuse, bleeding disorders, congestive heart failure, diabetes mellitus, electrolyte imbalance, hypertension, hypothyroidism, iron deficiency, peptic ulcer, renal failure, rheumatoid arthritis, sleep apnoea	surgical site infection
positive minor criteria for PJI	re-revision
reason for revision	KSS clinical, KSS function, narcotic pain medication, pain, ROM
age, reason for revision	re-revision
reason for revision, prior revision	re-revision
frailty	complications, mortality, readmission, non-home discharge
age, gender, OKS, prior revision, social deprivation Scottish index of multiple deprivation, reason for revision, UCLA activity	OKS, UCLA
age, gender	pain
age, BMI, ASA, gender, smoking, alcohol use, drug use, renal disease, cardiovascular disease, hypertension, diabetes mellitus, malignant tumour, inflammatory disease, depression, haematological disease, neurological disease, pulmonary disease	re-revision

Table 1. Continued

First author	Year	Sample size	Type study	Centre	Association	Covariable selection for multivariable models
van Kempen(174)	2013	150	prospective	single	uni	
van Laarhoven(175)	2022	100	prospective	single	multi	backward selection
van Rensch(176)	2020	129	prospective	single	uni	mixed model
Verbeek(177)	2019	295	retrospective	single	multi	backward selection
Wang(178)	2004	48	prospective	single	uni	
Watts(179)	2014	111	prospective	single	multi	one confounder
Watts(180)	2015	186	prospective	single	multi	one confounder
Wilson(181)	2020	13973	retrospective	multi	multi	set of covariables
Wilson(182)	2020	11786	retrospective	multi	multi	set of covariables
Winther(183)	2022	178	prospective	single	uni	
Xiong(184)	2021	197	retrospective	single	uni	
Xu(185)	2019	1224	prospective	single	multi	set of covariables
Yapp(186)	2021	8894	prospective	multi	multi	set of covariables
Yapp(187)	2022	8343	retrospective	multi	multi	set of covariables

ASA, American Society of Anaesthesiologists; COPD, chronic obstructive pulmonary disease; DAIR, debridement, antibiotics, and implant retention; DM, diabetes mellitus; EQ-5D, EuroQol five-dimension; EQ-5D EQ-5D-3L, EuroQol five-imension three-level; EQ-VAS, EuroQol visual analogue scale; ICU, intensive care unit; KOOS-PS, Knee Injury and Osteoarthritis Outcome Score – Physical Function Short Form; KSS, Knee Society Score; VR-12 MCS, Veterans rand 12 item mental health component summary; MRSA, methicillin-resistant

Prognostic factors	Outcomes
reason for revision	complications, KSS clinical, KSS function, pain, ROM, satisfaction
age, gender, BMI, reason for revision	reoperation
reason for revision	KSS clinical, KSS function, pain, ROM, satisfaction
age, gender, KSS function, reason for revision	KSS function
reason for revision	KSS, pain, ROM, SF-12
age, BMI, gender, DAIR, diabetes mellitus, negative culture, rheumatoid arthritis, smoking	re-infection, reoperation, re-revision
BMI	KSS function, pain, periprosthetic joint infection, reoperation, re-revision
depression	emergency department visit, prolonged length of stay, infection, wound complications, pain related ED visit, periprosthetic joint infection, readmission, re-revision, sepsis, thromboembolic event, costs, opioid use, non-home discharge
opioid use	emergency department visit, prolonged length of stay, opioid overdose, infection, pain related ED visit, periprosthetic joint infection, readmission, wound complications, re-revision, sepsis, thromboembolic event, non-home discharge
reason for revision	pain during mobilisation, pain at rest, KOOS-PS, KSS, EQ-5D
reason for revision	extension deficit, flexion, pain, ROM, stiffness
sinus tract	mortality, treatment failure
age, gender, comorbidity, hospital volume, reason for revision	re-revision
reason for revision	mortality, KSS clinical, KSS function, Koval grade

Staphylococcus aureus; NSAID, non-steroidal anti-inflammatory drug; OKS, Oxford Knee Score; OR, operating room; VR-12 PCS, Veterans Rand 12 item physical health component summary; PJI, periprosthetic joint infection; PROMIS, Patient-Reported Outcomes Measurement Information System; ROM, range of motion; SF-36, 36-Item Short Form Survey; UCLA, University of California at Los Angeles; VTE, venous thromboembolism; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

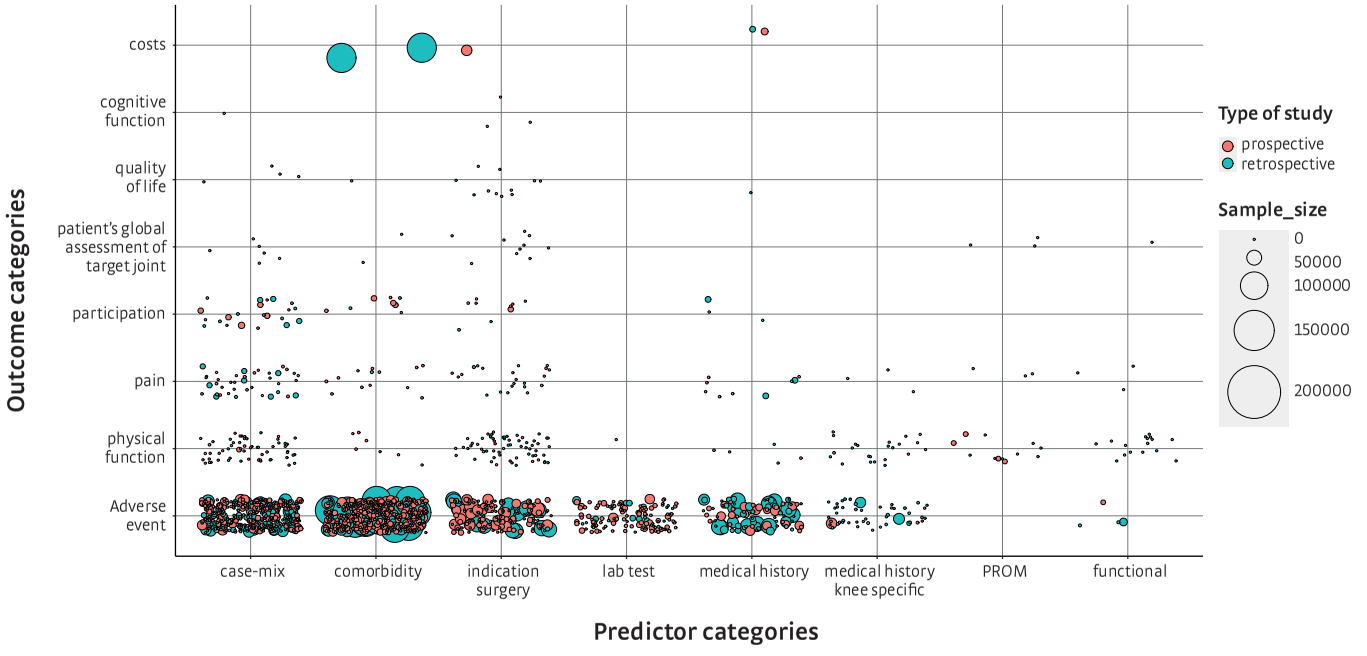

Figure 2: Bubble plot of associations reported in the included studies.

The combinations of prognostic factor and outcome categories that were studied most often were comorbidities with adverse events (402 times reported in 54 studies), case-mix factors with adverse events (368 times reported in 79 studies), and indication of surgery with adverse events (160 times reported in 62 studies; Table 2). The association between prognostic factors measuring functional status or PROMs with any type of outcomes after revision TKA were the least frequently studied combination. Associations that were most frequently reported as statistically significant, either a positive or negative effect, were: age and re-revision (12 times reported positive, one time reported negative, and eight times reported non-significant), reason for revision and re-revision (13 times reported negative, eight times reported non-significant), and reason for revision and mortality (nine times reported negative, one time reported non-significant).

Table 2. Number of times a combination of prognostic factor and outcome is reported (number of unique studies)

Prognostic factor categories	Outcome categories								
	Adverse event	Physical function	Pain	Participation	Patients asses. target joint	Quality of life	Cognitive function	Costs	Total
Case-mix	368 (79)	60 (20)	39 (11)	22 (7)	6 (1)	4 (2)	1 (1)	0 (0)	500 (102)
Comorbidities	402 (54)	7 (6)	13 (6)	8 (5)	2 (1)	1 (1)	0 (0)	2 (1)	435 (66)
Indication surgery	160 (62)	63 (30)	22 (14)	9 (6)	10 (8)	11 (8)	3 (3)	1 (1)	279 (92)
Lab test	126 (21)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	127 (21)
Medical history	101 (30)	5 (2)	9 (4)	3 (3)	0 (0)	1 (1)	0 (0)	2 (2)	121 (35)
Medical history, knee specific	50 (28)	23 (11)	3 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	76 (35)
PROMs	0 (0)	12 (4)	3 (3)	0 (0)	3 (2)	0 (0)	0 (0)	0 (0)	18 (7)
Functional	4 (3)	16 (8)	3 (3)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	24 (12)
Total	1211 (122)	187 (47)	92 (26)	42 (14)	22 (10)	17 (10)	4 (4)	5 (4)	1580 (166)

Discussion

The goal of the study was to provide an evidence map of studies on prognostic factors and outcomes of revision TKA. Adverse events were the most frequently reported outcomes. The most frequently used prognostic factors were reason for revision, gender, and BMI. These factors were also most frequently associated with the outcome of revision. Both the most used prognostic factors and clinical outcomes are usually part of routine registration in (electronic) patient records or as part of (national) registries.

This mapping review also identified some gaps of knowledge. Factors such as education level, living condition, and work status were not reported in the included literature at all. Also, PROMs (measuring for instance quality of life, functional status or pain) and functional tests were not often evaluated as prognostic factors. Whereas in primary TKA, prediction models have showed that a low pre-operative OKS (assessing pain and function), patient-reported anxiety or depression, and higher pre-operative pain ratings are associated with worse outcomes (15-17). The predictive value of these factors in revision TKA patients remains to be investigated. Moreover, these domains also matter to patients with OA according to ICHOM (9). Together, this highlights the importance of investigating these domains in revision TKA.

In the current healthcare environment, it might be useful to evaluate whether subgroups can be identified where revision TKA is more cost-effective. Studies where both quality of life and costs are studied simultaneous, cost-effectiveness studies, were lacking in this evidence map. The direct costs of the surgery were only included as outcome in four studies. However, none of these four studies included the net costs; all surgical costs minus medical costs from averted adverse events and treatments. In addition, studies reporting quality of life and psychosocial impact are scarce, while improving these are important for the patient (9, 10, 18). During the development of the ICHOM standard set, all patients and experts of OA agreed that quality of life should be included as an outcome in the set (9). In a study of patients' perspectives after arthroplasty, the patients prioritized pain relief, improved function, and restored quality of life as most important outcomes after hip and knee arthroplasty (18). Previous studies showed that revision hip and knee arthroplasty increased the quality-adjusted life year (QALY), although the gain in QALY was lower compared to primary arthroplasty (19, 20). Also, there seems to be a considerable variation in patient outcomes across the procedures, hinting at the need to identify patients at risk for poor outcome (20).

Considering pre-operative psychological factors when looking at pain and functional outcomes might be of importance (21). The evidence map shows that anxiety and depression is mainly studied in association with adverse events, one study looked into the association between anxiety/depression with physical function. Although

patient-reported physical functioning and pain seems to be linked with self-reported anxiety and depression in older adults and patients with knee arthroplasty, this association is lacking in this evidence map (21, 22).
Although over 100 different prognostic factors and outcomes were described in the included literature, they were not all completely unique. Some factors represented the same construct, but had different operationalizations. For instance, the outcomes re-revision for infection, postoperative infection, reinfection, periprosthetic joint infection, and (superficial/deep) surgical site infection all described an adverse event related to infection, in a specific location or in general. Overlap in variables was also observed in the prognostic factors; some studies reported the presence of comorbidities in general, others reported multiple specific comorbidities such as diabetes mellitus, renal failure and chronic obstructive pulmonary disease. Thus, the variety in variables found in literature is slightly lower than the evidence map suggests.

Limitations

The main limitation of the evidence map is that it only reflects the factors and outcomes that are most commonly studied, which are not necessarily the most important ones. Limitations of the individual studies might also affect the quality of the evidence map. Not all studies corrected the association between the prognostic factor and outcome for potentially confounding variables. In a minority of studies, only univariable associations were reported. The other studies did correct for confounding variables, but it is not unlikely that the models were wrongly specified and also included colliders or mediators in the multivariable models (23). The heterogeneity in model specification combined with differences between populations could partly explain the variation in associations (i.e. negative, non-significant, or positive) between a single prognostic factor and outcome that were found in the current review. As a result, the direction of the association found could deviate from the actual association.

In conclusion, the evidence map can be used to guide future research. As expected, the most frequently reported variables in revision TKA studies were those that are typically registered in electronic patient files or as part of registries. While these measures are of importance in clinical settings, to further our understanding of outcomes of revision TKA, it might be valuable to focus on the factors and outcomes that are studied to a lesser extent. Important gaps in literature include functional measures, psychological factors, and sociodemographic variables as prognostic factor, costs, and psychosocial impact as outcomes. Research focused on these gaps could provide a more comprehensive perspective on outcomes after revision TKA and contribute to better prediction.

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Appendix

A. Search strategy per database

Pubmed:

((((((“Arthroplasty, Replacement, Knee”[Mesh] OR total knee arthroplasty [title] OR total knee replacement [title]))) AND ((“Reoperation”[Mesh] OR revision [tiab] OR re-operation [tiab]))))) AND (predict* [tiab] OR “Risk Factors”[Mesh] OR risk factor* [tiab] OR “Prognosis”[Mesh] OR prognos* [tiab] OR factor [tiab] OR “Association”[Mesh] OR associate* [tiab] OR correlate* [tiab] OR effect [tiab] OR influence* [tiab] OR cause [tiab])) AND (“Outcome Assessment (Health Care)”[Mesh] OR Outcome [tiab] OR result [tiab] OR “Patient Reported Outcome Measures”[Mesh] OR patient reported [tiab] OR outcome score [tiab] OR PROM [tiab] OR clinical [tiab] OR function* [tiab] OR “Patient Satisfaction”[Mesh] OR satisfaction [tiab] OR “Survival”[Mesh] OR survival [tiab] OR “Prosthesis Failure”[Mesh] OR failure [tiab] OR re-revision [tiab] OR repeat revision [tiab] OR “Reoperation”[Mesh] OR re-operation [tiab] OR “Pain”[Mesh] OR pain [tiab] OR “Postoperative Complications”[Mesh] OR complication* [tiab] OR “Postoperative Period”[Mesh] OR post-operative [tiab] OR “Long Term Adverse Effects”[Mesh] OR long-term [tiab])

Embase:

(exp knee arthroplasty/ or total knee arthroplasty.m_titl. or total knee replacement.m_titl.) and (reoperation.mp. or exp reoperation/ or exp revision arthroplasty/ or revision.mp.) and (exp predictive value/ or predictive value.mp. or risk factor.mp. or exp risk factor/ or exp prognosis/ or prognosis.mp. or factor.mp. or exp association/ or association.mp. or exp correlation analysis/ or correlation.mp. or correlate*.ti,ab. or effect.ti,ab. or influence*.ti,ab. or cause.ti,ab.) and (exp outcome assessment/ or Outcome.ti,ab. or result.ti,ab. or exp patient-reported outcome/ or “patient reported”.ti,ab. or “outcome score”.ti,ab. or PROM.ti,ab. or clinical.ti,ab. or function*.ti,ab. or exp patient satisfaction/ or satisfaction.ti,ab. or exp survival prediction/ or exp survival/ or exp survival rate/ or exp survival analysis/ or survival.ti,ab. or exp prosthesis complication/co, di, ep, pc or failure.ti,ab. or re-revision.ti,ab. or “repeat revision”.ti,ab. or exp reoperation/ or re-operation.ti,ab. or exp knee pain/ or exp pain/ or exp postoperative pain/ or exp bone pain/ or pain.ti,ab. or exp postoperative complication/ or complication*.ti,ab. or exp postoperative period/ or post-operative.ti,ab. or exp adverse event/co, si, su or long-term.ti,ab.)

Web of science:

Ti=(total knee arthroplasty OR total knee replacement) AND TS=(“Reoperation” OR reoperation OR revision)
AND

TS=(predict* OR “Risk Factors” OR “risk factor*” OR Prognosis OR prognos* OR factor OR Association OR associate* OR correlate* OR effect OR influence* OR cause)
AND
TS=(“Outcome Assessment (Health Care)” OR Outcome OR result OR “Patient Reported Outcome Measures” OR “patient reported” OR “outcome score” OR PROM OR clinical OR function* OR “Patient Satisfaction” OR satisfaction OR Survival OR survival OR “Prosthesis Failure” OR failure OR re-revision OR “repeat revision” OR Reoperation OR re-operation OR Pain OR pain OR “Postoperative Complications” OR complication* OR “Postoperative Period” OR post-operative OR “Long Term Adverse Effects” OR long-term)

B. Variables in prognostic factor and outcome categories

Prognostic factor category	Prognostic factor
case-mix	age
case-mix	alcohol abuse
case-mix	alcohol use
case-mix	BMI
case-mix	cannabis abuse
case-mix	drug abuse
case-mix	drug use
case-mix	ethnicity
case-mix	former smoking
case-mix	frailty
case-mix	gender
case-mix	geographical rurality
case-mix	hospital volume
case-mix	index of multiple deprivation
case-mix	insurance status
case-mix	Medicaid
case-mix	obesity
case-mix	opioid use
case-mix	smoking
case-mix	social status
case-mix	weight
case-mix	weight loss
comorbidity	AIDS
comorbidity	arterial hypertension
comorbidity	ASA
comorbidity	bleeding disorders
comorbidity	cardiac arrhythmia
comorbidity	cardiac disease
comorbidity	cardiovascular disease
comorbidity	cerebrovascular disease
comorbidity	Charlson comorbidity index
comorbidity	chronic heart disease
comorbidity	chronic kidney disease
comorbidity	chronic lung disease
comorbidity	chronic pulmonary disease
comorbidity	chronic viral hepatitis

Prognostic factor category	Prognostic factor
comorbidity	comorbidity
comorbidity	congestive heart failure
comorbidity	connective tissue disorder
comorbidity	COPD
comorbidity	coronary heart disease
comorbidity	coronary vascular disease
comorbidity	diabetes mellitus
comorbidity	dialysis
comorbidity	DM insulin dep
comorbidity	DM insulin dep
comorbidity	DM non-insulin dep
comorbidity	elixhauser comorbidity index
comorbidity	fluid electrolyte disorder
comorbidity	gastrointestinal disease
comorbidity	gout
comorbidity	heart failure
comorbidity	haematological disease
comorbidity	hypertension
comorbidity	hypothyroidism
comorbidity	inflammatory arthritis
comorbidity	inflammatory disease
comorbidity	iron deficiency
comorbidity	kidney disease
comorbidity	kidney failure
comorbidity	liver disease
comorbidity	lymphoma
comorbidity	malignancies
comorbidity	malignancy
comorbidity	neurological disease
comorbidity	peptic ulcer
comorbidity	peripheral vascular disease
comorbidity	pulmonary circulation disorder
comorbidity	pulmonary disease
comorbidity	pulmonary hypertension
comorbidity	renal disease
comorbidity	renal failure
comorbidity	rheumatoid arthritis

Prognostic factor category	Prognostic factor
comorbidity	sleep apnoea
comorbidity	stroke
comorbidity	systemic disease
comorbidity	thyroid disease
comorbidity	valvular disease
comorbidity	vascular arterial disease
comorbidity	vascular disease
comorbidity	vascular venous disease
functional	functional status
functional	KSS clinical
functional	KSS function
functional	preoperative flexion
functional	ROM
functional	stiffness
functional	walking aid
indication surgery	anaerobic pathogens
indication surgery	antibiotic resistant organism
indication surgery	causative pathogen
indication surgery	culture negative PJI
indication surgery	diagnosis
indication surgery	emergency operation
indication surgery	extension contracture
indication surgery	flexion contracture
indication surgery	infection
indication surgery	MRSA
indication surgery	negative culture
indication surgery	pathogen
indication surgery	periprosthetic fracture
indication surgery	PJI
indication surgery	planned surgery
indication surgery	polymicrobial infection
indication surgery	positive cultures
indication surgery	positive minor criteria for PJI
indication surgery	pre-operative alignment
indication surgery	pre-operative antibiotics
indication surgery	reason for revision
indication surgery	sinus tract

Prognostic factor category	Prognostic factor
indication surgery	Staphylococcus aureus
indication surgery	type of infection
indication surgery	virulent pathogens
lab test	albumin
lab test	anaemia
lab test	blood urea nitrogen
lab test	coagulation
lab test	C-reactive protein
lab test	creatinine
lab test	electrolyte imbalance
lab test	elevated CRP/ESR
lab test	Glomerular Filtration Rate
lab test	haematocrit
lab test	haemoglobin
lab test	International Normalized Ratio
lab test	platelet count
lab test	red blood cell distribution width
lab test	serum creatinine
lab test	white blood cell count
medical history	anticoagulant use
medical history	anxiety
medical history	bilateral
medical history	blood transfusion
medical history	tumour
medical history	cirrhosis
medical history	deep venous thrombosis
medical history	dementia
medical history	depression
medical history	dialysis
medical history	dyspnoea
medical history	dyspnoea on exertion
medical history	haemodialysis-dependent
medical history	hepatitis C
medical history	history of VTE
medical history	inflammatory bowel disease
medical history	ipsilateral hip involvement
medical history	low back pain

Prognostic factor category	Prognostic factor
medical history	malignant tumour
medical history	myocardial infarction
medical history	organ transplant
medical history	psychiatric disorder pharmacologically treated
medical history	psychoses
medical history	renal transplant
medical history	steroid use
medical history	systemic lupus
medical history	thrombophilia
medical history	TIA/CVA
medical history	transfusion pre-op
medical history	tumour history
medical history	venous insufficiency
medical history knee specific	coronal deviation
medical history knee specific	DAIR
medical history knee specific	failed DAIR
medical history knee specific	heterotopic ossification
medical history knee specific	patella resurfacing
medical history knee specific	previous arthroscopy
medical history knee specific	previous revision TKA
medical history knee specific	previous two-stage
medical history knee specific	primary diagnosis
medical history knee specific	prior arthroplasty
medical history knee specific	prior DAIR
medical history knee specific	prior infection
medical history knee specific	prior revision
medical history knee specific	prior surgery
medical history knee specific	surgical history
medical history knee specific	tibial malrotation
medical history knee specific	tibial tuberositas osteotomy
medical history knee specific	time to revision
medical history knee specific	wound infection
pain	pain
PROM	central sensitization
PROM	disability
PROM	EQ-5D 3L anxiety/depression
PROM	EQ-5D 3L self-care

Prognostic factor category	Prognostic factor
PROM	KSS function
PROM	OKS
PROM	pain
PROM	SF-36 MCS
PROM	social deprivation SIMD
PROM	UCLA activity

Outcome category	Outcome
adverse event	acute kidney injury
adverse event	acute renal failure
adverse event	adverse events
adverse event	amputation
adverse event	amputation above knee
adverse event	anaemia
adverse event	any medical complication
adverse event	aseptic loosening
adverse event	bleeding
adverse event	blood loss
adverse event	blood transfusion
adverse event	cardiac arrest
adverse event	cardiac complications
adverse event	cardiac pulmonary complication
adverse event	central nervous system
adverse event	cerebrovascular accident
adverse event	Charlson comorbidity index
adverse event	complications
adverse event	consultation with health professional
adverse event	death
adverse event	deep infection
adverse event	deep surgical site infection
adverse event	deep venous thrombosis
adverse event	deep wound infection
adverse event	emergency department visit
adverse event	extended length of stay
adverse event	extensor mechanism failure

Outcome category	Outcome
adverse event	fail to wean
adverse event	fracture
adverse event	gastrointestinal complication
adverse event	genitourinary complications
adverse event	hematoma
adverse event	heterotopic ossification
adverse event	ICU admission
adverse event	ileus episode
adverse event	infection
adverse event	length of stay
adverse event	ligamentous laxity
adverse event	major complications
adverse event	malposition
adverse event	manipulation under anaesthesia
adverse event	minor complications
adverse event	mortality
adverse event	mortality due to cancer
adverse event	mortality due to cerebrovascular event
adverse event	mortality due to congestive heart failure
adverse event	mortality due to liver failure
adverse event	mortality due to multiple causes
adverse event	mortality due to myocardial infarction
adverse event	mortality due to pulmonary embolism
adverse event	mortality due to renal failure
adverse event	mortality due to respiratory failure
adverse event	mortality due to sepsis
adverse event	mortality due to systemic inflammatory response syndrome
adverse event	mortality related to comorbidities
adverse event	mortality related to infection
adverse event	myocardial infarction
adverse event	on ventilator
adverse event	organ infection
adverse event	organ surgical site infection
adverse event	peripheral vascular disease
adverse event	periprosthetic fracture

Outcome category	Outcome
adverse event	periprosthetic joint infection
adverse event	pneumonia
adverse event	postoperative infection
adverse event	prolonged length of stay
adverse event	pulmonary complications
adverse event	pulmonary embolism
adverse event	readmission
adverse event	re-infection
adverse event	reintubation
adverse event	renal complications
adverse event	renal failure
adverse event	renal insufficiency
adverse event	reoperation
adverse event	re-revision
adverse event	re-revision for aseptic loosening
adverse event	re-revision for infection
adverse event	re-revision for instability
adverse event	re-revision for loosening
adverse event	re-revision for pain
adverse event	re-revision for stiffness
adverse event	respiratory complication
adverse event	respiratory failure
adverse event	return to OR
adverse event	sepsis
adverse event	septic shock
adverse event	septicaemia
adverse event	stiffness
adverse event	stroke
adverse event	superficial surgical site infection
adverse event	surgical site infection
adverse event	systemic infection
adverse event	systemic sepsis
adverse event	thromboembolic complication
adverse event	thromboembolic event
adverse event	time to re-revision

Outcome category	Outcome
adverse event	transfusion
adverse event	treatment failure
adverse event	treatment success
adverse event	unplanned intubation
adverse event	urinary system complication
adverse event	urinary tract infection
adverse event	vascular complication
adverse event	venous thromboembolism
adverse event	ventilator dependence
adverse event	wound complications
adverse event	wound dehiscence
adverse event	wound disruption
adverse event	wound infection
cognitive function	PROMIS mental
cognitive function	SF-36 mental health
cognitive function	VR-12 MCS
costs	costs
pain	narcotic pain medication
pain	NSAIDs
pain	opioid overdose
pain	opioid use
pain	pain
pain	pain at rest
pain	pain during mobilisation
pain	pain related ED visit
pain	SF-36 bodily pain
pain	WOMAC pain
participation	activity of daily living limitation
participation	Koval grade
participation	Lower-Extremity Activity Scale (LEAS)
participation	non-home discharge
patient's global assessment of target joint	expectations
patient's global assessment of target joint	satisfaction
physical function	extension

Outcome category	Outcome
physical function	extension deficit
physical function	flexion
physical function	Hospital for Special Surgery score (HSS)
physical function	instability
physical function	knee function
physical function	KOOS-PS
physical function	KSS
physical function	KSS clinical
physical function	KSS function
physical function	OKS
physical function	OKS change
physical function	Physical Function SF10A
physical function	PROMIS physical
physical function	ROM
physical function	SF-36 physical
physical function	stiffness
physical function	UCLA
physical function	VR-12 PCS
physical function	walking aids
physical function	WOMAC
physical function	WOMAC clinical
physical function	WOMAC function
quality of life	EQ-5D
quality of life	EQ-VAS
quality of life	KOOS quality of life
quality of life	SF-12
quality of life	SF-36

Chapter 3

Reasons for revision are associated with the outcome of revised total knee arthroplasties: an analysis of 8,978 index revisions in the Dutch Arthroplasty Register

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Abstract

Introduction: From previous studies, we know that clinical outcomes of revision total knee arthroplasty (revision TKA) differ between reasons for revision. Whether the prevalence of repeat revision TKAs is different between reason for index revision TKA is unclear. Therefore, the aims of this study were 1) to compare the repeat revision rates between the different reasons for index revision TKA, and 2) to evaluate whether the reason for repeat revision TKA was the same as the reason for the index revision.

Methods: Patients (n=8,978) who underwent an index revision TKA between 2010-2018 as registered in the Dutch Arthroplasty Register were included. Reasons for revision, as reported by the surgeon, were categorized as: infection, loosening, malposition, instability, stiffness, patellar problems, and other. Competing risk analyses were performed to determine the cumulative repeat revision rates after an index revision TKA for each reason for revision.

Results: Overall, the cumulative repeat revision rate was 18% within 8 years after index revision TKA. Patients revised for infection had the highest cumulative repeat revision rate (28%, 95% CI: 25%-32%) within 8 years after index revision TKA. The recurrence of the reason was more common than other reasons after index revision TKA for infection (18%), instability (8%), stiffness (7%), and loosening (5%).

Conclusion: Poorest outcomes were found for revision TKA for infection: over 1 out of 4 infection revision TKAs required another surgical intervention, mostly due to infection. Recurrence of other reasons for revision (instability, stiffness, and loosening) was also considerable. Our findings also emphasize the importance of a clear diagnosis before doing revision TKA to avert second revision surgeries.

Introduction

The number of revision total knee arthroplasties (revision TKA) has increased over the past years, and projections predict further increases in the coming decades (1-3). The outcome of these revision TKAs are in general inferior compared with the outcome of the primary total knee arthroplasty (4-6). Evidence suggests that one of the determinants for outcome of revision TKA is the indication for the revision. To illustrate, several studies have shown a relatively poor prognosis when the revision TKA is performed for infection or stiffness compared with revisions for aseptic loosening (5, 7-10). Poor results were reported in terms of complication rates, patient satisfaction, and survival of the prosthesis. However, the majority of these studies based their findings on small samples, and single-center cohorts.

A repeat revision indicates that either the initial problem was not resolved despite the index revision, or that another problem occurred. Several reasons for a failed index revision TKA can be: inaccurate diagnosis, the decision to choose for operative versus nonoperative treatment, surgical failure, the occurrence of complications, or insufficient rehabilitation protocols. Insight into whether the reason for index revision TKA is related to the same reason for the repeat revision TKA might provide a base for improvement of treatment choices in these revision surgeries.

Therefore, we 1) compared the repeat revision rates among the different reasons for index revision TKA, and 2) evaluated how often the reason for repeat revision TKA was the same as the reason for the index revision.

Methods

Data was obtained from the Dutch Arthroplasty Register (LROI), which is a nationwide register on all arthroplasties performed in the Netherlands that started in 2007. The data completeness for revision TKAs is 97% up to 2018 (3). The completeness was first assessed in 2012, yielding 86% coverage. Thus, there is no complete coverage of all revision TKAs performed in the Netherlands between 2010 and2018. All hospitals in the Netherlands report patient characteristics, surgical specifications of each knee arthroplasty procedure, and patient reported outcomes to the LROI (3). To ensure all revision cases were first revisions after primary TKA, we retrieved data of all patients who had a primary TKA in the Netherlands between 2007 and 2018. Next, we excluded all cases without revision TKA or with an revision TKA registration before 2010 due to limited completeness of revision TKA before 2010. The first revision after primary TKA was defined as the index revision TKA. The second revision after primary TKA was defined as the repeat revision TKA. Patients who had received a hinged-type prosthesis as primary implant, or who had a primary TKA performed because of a tumor were excluded.

Reasons for revision were registered in the LROI as infection, patellar dislocation, patellar pain, wear of the insert, periprosthetic fracture, malalignment, instability, loosening of the femoral component, loosening of the tibial component, loosening of the patellar button, revision after removal of prosthesis, arthrofibrosis, and other reason for revision. Multiple reasons could be reported for one revision procedure by the surgeon. When multiple reasons for revision were registered for one patient, we used a hierarchy tree to define the main reason for the revision. This hierarchy is based on the Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) (11). The hierarchy was: infection, malposition, loosening (component loosening of femur and/or tibia), patellar problems, instability, stiffness (arthrofibrosis), and other (fracture, wear insert, other non-specified).
An revision TKA was defined as a report of any change (insertion, replacement and/or removal) of one or more components of the prosthesis in the register. Time to event was defined as the time between the index revision surgery and repeat revision TKA or death. In case of a two-stage revision (n=367), we used the re-implantation date as index revision. The study was conducted and reported according to STROBE guidelines.

Statistical analysis

The median follow-up time was calculated using reverse Kaplan Meier. Competing risk analysis was performed to determine the cumulative incidence of repeat revision rates after index revision TKA, with death considered as competing event, stratified for the reason of index revision. Log-rank tests were used to test differences in repeat revision rate between the reasons for index revision. To evaluate the probability of having a repeat revision TKA for the same reason as the index revision, we conducted a competing risk analysis. In this analysis competing events were a repeat revision TKA for any reason other than the reasons for index revision and death. Differences in repeat revision rate were tested with a log-rank test. 95% confidence intervals (CI) were calculated for the cumulative incidences. All analyses were performed using R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) using the packages 'rms' and 'survival' (12, 13).

Ethics, funding, data sharing, and potential conflict of interest

Ethical approval for the current study was not applicable according to the Dutch Medical Research Involving Human Subjects Act. Data are available from the LROI (Dutch Arthroplasty Register). This study received no funding, and the authors declare that they have no competing interests.

Results

Characteristics of index revisions

Between January 2010 and December 2018, a total of 8,868 patients underwent 8,978 index revision TKAs as registered in the LROI (110 bilateral revision TKA cases). 432 (4%) patients died during the follow-up period. The mean age at the time of the index revision surgery was 67 years (SD 9.6), and 65% were females (Table 1). A patellar problem (n = 2,058, 23%) was the most common reason for index revision, 93% of the index revisions for patellar problems were isolated patellar resurfacings. In 700 revision TKAs (8%) the reason for index revision was classified as 'other', and in 354 revision TKAs (4%) the reason for revision was not reported.

Repeat revision TKA (Table 2)

1,123 repeat revision TKAs following the index revision TKA were registered. The most common reasons for repeat revision TKA were infection (n=366, 33%), instability (n=208, 18%), and loosening (n=195, 17%).

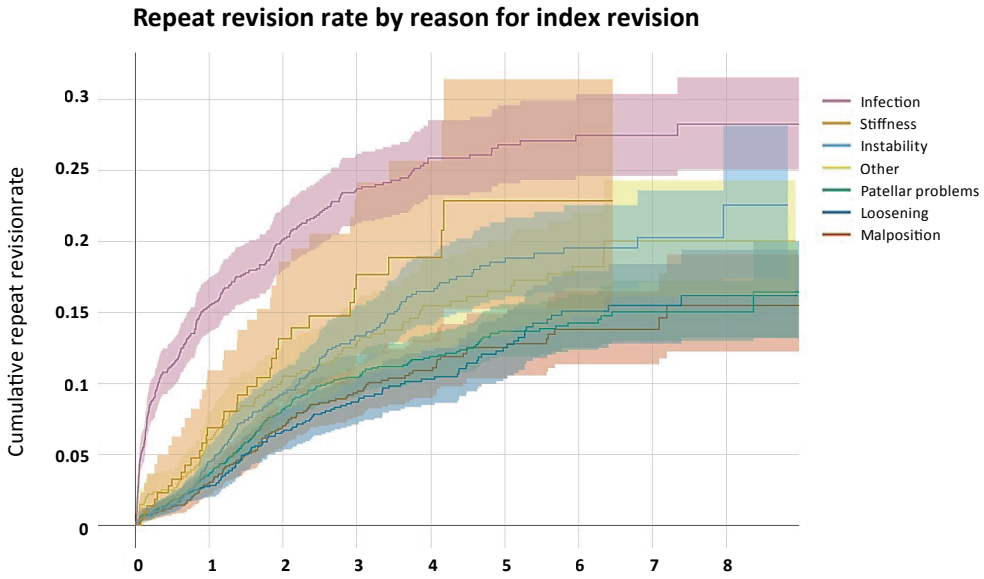
The cumulative repeat revision rate of all index revision TKA was 6% (CI: 5-6) within one year after surgery, and 19% (CI: 18-20) within eight years. A log-rank test showed a significant difference in repeat revision rate between reasons for index revision. The highest cumulative repeat revision rate within eight years was observed for index revision for infection (28%; CI: 25-32) (Fig.1). Patients revised for instability and stiffness had lower repeat revision rates compared to the infection group. The cumulative repeat revision rate for an index revision TKA for instability was 23% (CI: 18-28) at eight years. In revision TKAs revised for stiffness the cumulative repeat revision rate was 23% (CI: 16-32) at, the maximum observed follow-up for this group, six years after index revision TKA. revision TKAs revised for loosening, malposition, or patellar problems had the lowest rate of repeat revision surgeries. The cumulative repeat revision rate within 8 years for loosening was 17% (CI: 14-20), and for malposition and patellar problems 15% (CI: 11-19).

Table 1. Patient characteristics by reason for index revision TKA.

Factor	Reason for revision[1]			
	Infection (n=1538)	Loosening (n=1422)	Malposition (n=1241)	Patellar problems (n=2043)
Age (mean (SD)) in years	69 (9.6)	67 (8.9)	66 (9.4)	68 (9.5)
Gender				
Female	787 (51.2%)	955 (67.2%)	871 (70.1%)	1390 (68.0%)
Missing	2 (0.1%)	1 (0.1%)	2 (0.1%)	4 (0.2%)
ASA				
I	157 (10.2%)	158 (11.1%)	176 (14.2%)	224 (11.0%)
II	853 (55.5%)	972 (68.4%)	837 (67.4%)	1439(70.4%)
III- IV	504 (32.8%)	273 (19.2%)	205 (16.5%)	341 (16.7%)
Missing	24 (1.6%)	19 (1.3%)	23 (1.9%)	39 (1.9%)
Diagnosis of primary TKA				
Osteoarthrosis	1435 (93.3%)	1344 (94.5%)	1169 (94.2%)	1950 (95.4%)
Osteonecrosis	6 (0.4%)	8 (0.6%)	2 (0.2%)	4 (0.2%)
Posttraumatic	37 (2.4%)	27 (1.9%)	25 (2.0%)	32 (1.6%)
Rheumatoid arthritis	33 (2.1%)	19 (1.3%)	16 (1.3%)	33 (1.6%)
Inflammatory arthritis	3 (0.2%)	0 (0%)	0 (0%)	0 (0%)
Other	10 (0.7%)	5 (0.4%)	8 (0.6%)	6 (0.3%)
Missing	14 (0.9%)	19 (1.3%)	21 (1.7%)	18 (0.9%)
Follow-up time (median (IQR)) in years	3.01 (1.46;5.15)	3.21 (1.55;5.63)	3.46 (1.79;5.53)	3.67 (1.87;5.75)

1: The reasons for revision in the table are the ones from the hierarchy.

	Reason for revision[1]			
	Instability (n=1452)	Stiffness (n=228)	Other (n=700)	Overall (n=8978)
Age (mean (SD)) in years	65 (9.5)	64 (9.2)	68 (10.4)	67 (9.6)
Gender				
Female	964 (66.4%)	135 (59.2%)	451 (64.4%)	5787 (64.5%)
Missing	3 (0.2%)	2 (0.9%)	2 (0.3%)	17 (0.2%)
ASA				
I	204 (14.0%)	38 (16.7%)	95 (13.6%)	1081 (12.0%)
II	989 (68.1%)	154 (67.5%)	445 (63.6%)	5807 (64.7%)
III- IV	233 (16.0%)	30 (13.2%)	138 19.7%)	1780 (19.8%)
Missing	26 (1.8%)	6 (2.6%)	22 (3.1%)	310 (3.5%)
Diagnosis of primary TKA				
Osteoarthrosis	1350 (93.0%)	212 (93.0%)	655 (93.6%)	8446 (94.1%)
Osteonecrosis	3 (0.2%)	0 (0%)	2 (0.3%)	26 (0.3%)
Posttraumatic	45 (3.1%)	10 (4.4%)	11 (1.6%)	191 (2.1%)
Rheumatoid arthritis	27 (1.9%)	4 (1.8%)	17 (2.4%)	151 (1.7%)
Inflammatory arthritis	2 (0.1%)	1 (.4%)	1 (0.1%)	7 (0.1%)
Other	8 (0.6%)	1 (0.4%)	4 (0.6%)	49 (0.5%)
Missing	17 (1.2%)	0 (0%)	10 (1.4%)	108 (1.2%)
Follow-up time (median (IQR)) in years	2.90 (1.37;4.90)	2.67 (1.47;4.06)	3.74 (1.80;6.27)	3.35 (1.66;5.54)



Numbers at risk	Follow-up (in years) from index revision TKA								
Infection	1464	991	744	513	355	250	156	93	45
Stiffness	227	172	118	82	47	16	1	0	0
Instability	1452	1142	835	594	391	267	160	82	28
Other	699	568	444	346	263	200	144	75	23
Patellar problems	2040	1690	1348	1053	757	521	348	201	86
Loosening	1422	1153	877	663	501	358	232	141	57
Malposition	1238	1037	812	612	447	311	191	104	32

Figure 1: Cumulative repeat revision rate of index revision TKA by reason for revision.

Reason for repeat revision by reason for index revision

In cases index revised for infection who needed repeat revision TKA within 8 years, the most common reason for the repeat revision TKA was infection (18%; CI: 15-21; Fig. 2). Similar results were observed when an index revision was performed for instability, stiffness, or loosening. The cumulative incidence of a repeat revision for the same reason as the index revision was 7% (CI: 5-9) for instability, 7% (CI: 3-14) for stiffness, and 5% (CI: 3-6) for loosening.

Table 2. Cumulative repeat revision rate after revision TKA by reason for revision.

	Repeat revision rate (95% CI)		
	at 1 year	at 8 years	at 8 years for the same reason as the index revision
Overall	0.06 (0.05-0.06)	0.19 (0.18-0.20)	-
Infection	0.16 (0.14-0.18)	0.28 (0.25-0.32)	0.18 (0.15-0.21)
Loosening	0.03 (0.02-0.04)	0.16 (0.13-0.19)	0.05 (0.03-0.06)
Malposition	0.03 (0.02-0.04)	0.15 (0.12-0.19)	0.02 (0.01–0.03)
Patellar problems	0.04 (0.03-0.05)	0.15 (0.13-0.17)	0.02 (0.02–0.03)
Instability	0.04 (0.03-0.06)	0.23 (0.17-0.28)	0.07 (0.05–0.09)
Stiffness	0.07 (0.04-0.11)	0.23 (0.15-0.31) *	0.07 (0.03–0.14) *
Other	0.06 (0.04-0.08)	0.20 (0.16-0.24)	0.01 (0.00–0.04)

*at 6 year follow-up

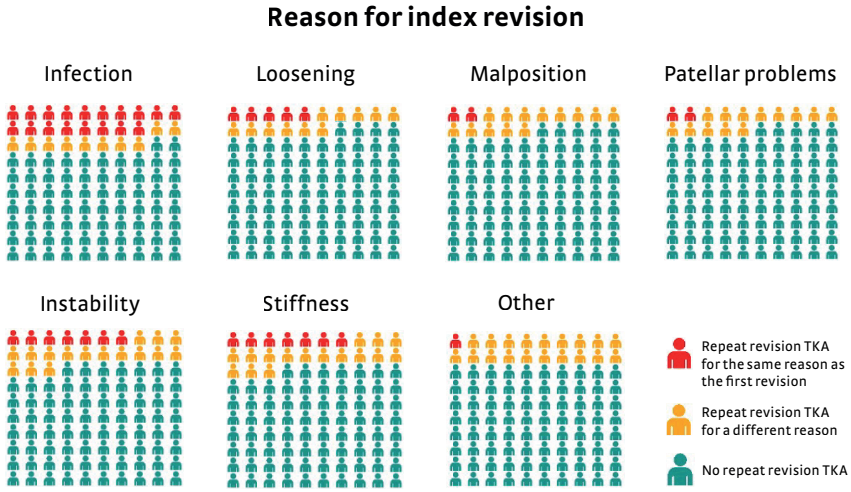


Figure 2: Cumulative repeat revision rate 8 years* after revision TKA per 100 men, by reason for revision. For every reason for first revision, the cumulative incidence of repeat revision TKA for the same reason as the first revision (red), the repeat revision TKAs for a different reason than the first revision (orange), and the patients with the revision TKA in situ (green). See Appendix A for the cumulative repeat revision rates and reason for repeat revision TKA specified.

Note: The follow-up period for stiffness is limited to 6 years.

Discussion

The aims of this study were to compare the repeat revision rates between the different reasons for index revision TKA, and to evaluate whether the reason for repeat revision TKA was the same as the reason for the index revision. Poorest outcomes in terms of a repeat revision TKA were observed in patients who had had an revision TKA for infection. More than 1 in 4 cases revised for infection, needed repeat revision TKA for any reason, almost 1 in 5 had a repeat revision TKA due to a new or recurrent infection, within eight years after index surgery. The lowest repeat revision rates were observed in index revision TKAs for aseptic loosening, malposition or patellar problems. However, repeat revision rates in these groups were still substantial, with a cumulative repeat revision rate between 15% and 23%. Consistent with infection, in index revision TKAs revised for loosening, instability, or stiffness the most prevalent reason for the repeat revision was the same as the index revision.

The most common reason for index revision TKA was patellar problems (23%), while in other registries infection and loosening are reported as most common reasons for revision (14). An explanation for this finding may stem from the relatively low percentage of primary TKAs with resurfaced patellae in Dutch clinical practice (18%) compared with most other registries (4-82%) (15). This increases the likelihood that in the case of poor outcomes in non-resurfaced primary TKAs, a first step is to resurface the patella in a reoperation (16). Indeed, in our dataset the large majority of index revision TKAs in patients with patellar problems were isolated resurfacings (>92%).

A large body of literature has consistently shown that periprosthetic joint infections are difficult to treat (17-19). Our findings of the repeat revision rate after revision for infection are comparable to the Norwegian Arthroplasty Registry (NAR). Five years after revision TKA for infection, 21% (1-Kaplan Meier estimate) of the patients had a repeat revision TKA (19). The majority of these patients underwent a repeat revision TKA due to infection (85 of the 104 repeat revision cases). The large number of infections in index and repeat revision TKAs shows that we should keep focusing on the treatment and the prevention of joint infections.

It is worth mentioning that more patients revised for infection were classified as ASA class 3+4 compared to the other reasons for revision (32.8% vs 19.8% overall). Whether patients with high ASA class are more susceptible for infection, patients with an infection are more likely to receive revision surgery even if they are ASA 3+, or patients with a high ASA class are more likely to need repeat revision TKA cannot be concluded from our data.

We observed a higher repeat revision rate after index revision TKA for instability and stiffness compared with the NJR (NJR number of subsequent repeat revision TKA: 10.4% after instability, 11.5% after stiffness) (14). These differences might be explained by the method of reporting the incidence (cumulative incidence versus percentage

by the NJR), due to different definitions of the indications, or due to the willingness to re-operate. Nonetheless, the NJR reported that instability, infection, and stiffness are more common indications for repeat revision TKA than for index revision TKA, which corresponds to the results of our study. The NJR hypothesizes that repeat revision TKA for instability, infection and stiffness reflects the complexity and soft tissue element that contribute to the outcome of revision TKA (14). The latter is consistent with the generally poor results that are reported after revision TKA for stiffness and instability (20-22).

Lowest repeat revision rates were found in patients revised for loosening, malposition and patellar problems. They were least likely to undergo a repeat revision surgery. This is in line with multiple previous studies (5, 7, 10). However, the majority of the index revisions for patellar problems, were isolated patella resurfacings (93%). In 10% of the cases this isolated patellar resurfacing was followed by a subsequent repeat revision for amongst other causes infection, malposition, and instability. This suggests that the initial patella resurfacing did not address the original failure diagnosis or induced a new one.

Limitations

Our findings should be regarded in the context of a number of strengths and limitations. The use of nationwide registry data has benefits, including the large sample size and high generalizability. Another strength is we accounted for death as competing event in the survival analysis of revision TKA, which potentially provides a more accurate estimate of the repeat revision rate than Kaplan-Meyer analysis. Also, we did not limit the inclusion of revision TKAs to patients who had a primary TKA for osteoarthritis (OA), to make the results generalizable to all revision TKA patients. We performed an additional analysis where we included only patients with OA. This additional analysis showed cumulative repeat revision rates similar to those reported in the current manuscript.

A limitation of our analysis method is that a subject can only have one reason for revision in the analysis, while multiple reasons were reported in some cases. Therefore, we used a hierarchy in the reasons for revision to rank cases with more than one reason for revision. A sensitivity analysis showed this resulted in slightly different cumulative repeat revision rate estimates (see appendix B). Second, to ensure that all cases in our study were the first revision after primary TKA, we included only cases with the primary TKA registered. As a consequence, the follow-up time of the patients was limited. Complications that often present shortly after surgery, such as infection, are therefore better represented in the data compared with long-term complications such as loosening. Resulting in higher repeat revision TKA estimates for the short-term reasons for revision compared to the reasons that present at long-term. Thus, the repeat revision surgeries were mostly

due to short- to mid-term complications. Third, the reason for revision was registered by orthopedic surgeons who may use different interpretations of the definitions for the reasons. Another limitation related to the registry data is that the registry forms are filled in once, directly following the surgery. A (suspected) infection might not be proven at that point, thus cases of infection might still be underreported despite the already high proportion of revision due to infection (23, 24). Also, the registry does not have a complete coverage of all primary and revision TKA procedures performed in the Netherlands between 2007 and 2018. Fourth, we did not correct for correlated bilateral cases in the analysis, while the methods of our statistical analysis do assume independent observations. Although, previous studies have shown bilateral surgeries do not introduce significant dependency problems in register studies (25, 26). Finally, we acknowledge the ongoing discussion of survival analysis in arthroplasty registers considering ease of interpretation versus accuracy of survival. Both Kaplan-Meier and competing risk analysis each have their advantages and disadvantages. However, we decided to report cumulative incidences of repeat revision TKA

In conclusion, the reason for index revision seems associated with the incidence of repeat revision TKA at 8 years follow-up. Poorest outcomes were found for revision TKA for infection: more than 1 in 4 infection revision TKAs required another surgical intervention, often due to a new or persistent infection. Recurrence of other reasons for revision (instability, stiffness, and loosening) was also considerable. This study confirms the complex treatment to manage periprosthetic infections. Our findings also emphasize the importance of a clear diagnosis before doing revision TKA to avert second revision surgeries

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A. Reason for repeat revision TKA

Cumulative repeat revision rate after index? rTKA by reason for revision, specified by reason for repeat revision.

Reason for index rTKA	Repeat revision (95% CI) rate at 8 years due to:						
	Infection	Loosening	Malposition	Patellar problems	Instability	Stiffness	Other
Infection	0.18 (0.15-0.21)	0.03 (0.02-0.05)	0.02 (0.01-0.03)	0.02 (0.01-0.03)	0.02 (0.01-0.04)	0.00 (0.00-0.01)	0.01 (0.00-0.01)
Loosening	0.03 (0.02-0.05)	0.05 (0.03-0.06)	0.02 (0.01-0.04)	0.02 (0.01-0.03)	0.02 (0.01-0.04)	0.01 (0.00-0.01)	0.01 (0.00-0.04)
Malposition	0.02 (0.01-0.04)	0.03 (0.02-0.04)	0.02 (0.01-0.03)	0.03 0.02-0.06)	0.03 (0.02-0.06)	0.01 0.00-0.02)	0.01 (0.01-0.03)
Patellar problems	0.02 (0.01-0.03)	0.03 (0.02-0.04)	0.03 (0.02-0.05)	0.02 (0.02-0.03)	0.03 (0.02-0.05)	0.01 (0.00-0.01)	0.01 (0.00-0.01)
Instability	0.05 (0.02-0.12)	0.03 (0.02-0.05)	0.02 (0.01-0.04)	0.04 (0.03-0.06)	0.07 (0.05-0.09)	0.00 (0.00-0.01)	0.01 (0.00-0.02)
Stiffness*	0.04 (0.02-0.07)	0.02 (0.01-0.08)	0.05 (0.02-0.10)	0.03 (0.01-0.13)	0.01 (0.00-0.05)	0.07 (0.03-0.14)	0.01 (0.00-0.05)
Other	0.04 (0.03-0.06)	0.03 (0.02-0.06)	0.03 (0.02-0.05)	0.03 (0.01-0.05)	0.04 (0.02-0.06)	0.01 (0.00-0.04)	0.01 (0.00-0.04)

* at 6 year follow-up

B. Sensitivity analysis hierarchy

A limitation of our main analysis method is that a subject can only have one reason for revision in the analysis, while multiple reasons were reported in some cases. Therefore, we used a hierarchy in the reasons for revision to rank cases with more than one reason for revision. To test the effect of that hierarchy, we performed this sensitivity analysis. The first column is the cumulative repeat revision rate by reason for index rTKA, as reported in the manuscript. In the second column, we did not use a hierarchy in the reasons for revision, but instead conducted a separate competing risk analysis for each of the different reasons for index rTKA. As a result, patients with multiple reported reasons for revision are represented more than once.

Factor	Repeat revision rate at 8 years (95% CI)	Repeat revision rate without hierarchy at 8 years (95% CI)
Overall	0.19 (0.18-0.20)	-
Infection	0.28 (0.25-0.32)	0.28 (0.25-0.32)
Malposition	0.15 (0.12-0.19)	0.16 (0.12-0.19)
Loosening	0.16 (0.13-0.19)	0.19 (0.16-0.21)
Patellar problems	0.15 (0.13-0.17)	0.16 (0.14-0.18)
Instability	0.23 (0.17-0.28)	0.22 (0.18-0.26)
Stiffness*	0.23 (0.15-0.31)	0.22 (0.16-0.29)
Other	0.20 (0.16-0.24)	0.20 (0.17-0.23)

*at 6 year follow-up

Chapter 4

What is the Reliability of a New Classification for Bone Defects in Revision TKA Based on Preoperative Radiographs?

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Abstract

Introduction: Accurate quantification of bone loss facilitates preoperative planning and standardization for research purposes in patients who undergo revision TKA. The most commonly used classification to rate bone defects in this setting, the Anderson Orthopaedic Research Institute classification, does not quantify diaphyseal bone loss and reliability is not well studied. We developed a new classification scheme to rate bone defects in patients undergoing revision TKA and tested (1) the intraobserver and interobserver reliability of this classification for revision TKA based on preoperative radiographs, and (2) whether additional CT images might improve interobserver reliability.

Methods: This was a preregistered observational study. Interobserver reliability was analyzed using preoperative radiographs of 61 patients who underwent (repeat) revision TKA, and their bone defects were rated by five experienced orthopaedic surgeons. For intraobserver reliability, ratings were repeated at least 2 weeks after the first rating (Timepoints 1 and 2). Directly after the radiographic assessments of Timepoint 2, the observers were provided with CT images of each patient and asked to rate the bone defects for a third time (Timepoint 3), to assess the additional value of CT. Intraobserver and interobserver reliability were tested using Gwet's agreement coefficient 2, which is a measure of agreement between observers in categorical data. Substantial agreement was defined as coefficients between 0.61 to 0.8 and almost perfect agreement as > 0.8.

Results: The intraobserver reliability varied between 0.55 (95% CI 0.40 to 0.71) and 0.87 (95% CI 0.78 to 0.96) in the epiphysis, between 0.69 (95% CI 0.58 to 0.80) and 0.98 (95% CI 0.95 to 1) in the metaphysis, and between 0.95 (95% CI 0.90 to 0.99) and 0.99 (95% CI 0.98 to 1) in the diaphysis. The interobserver reliability varied between 0.48 (95% CI 0.39 to 0.57) and 0.49 (95% CI 0.42 to 0.56) in the epiphysis and between 0.81 (95% CI 0.75 to 0.87) and 0.88 (95% CI 0.83 to 0.93) in the metaphysis, and was 0.96 (95% CI 0.93 to 0.99) in the diaphysis at Timepoint 1. The interobserver reliability at Timepoint 2 was similar to that of Timepoint 1. The addition of CT images did not improve reliability (Timepoint 3).

Conclusion: The bone defect classification was less reliable in the epiphyseal area, compared with the metaphysis and diaphysis. This finding may be explained by prosthetic components obscuring this region or the more severe bone defects in this region. The addition of CT scans did not improve reliability. Further testing of reliability with observers from other institutions is necessary, as well as validity testing, by testing the classification in relation to intraoperative findings.

Introduction

The frequency of revision TKA is increasing, with the incidence of revision TKA in the Netherlands doubling from 9.8 to 17.8 per 100,000 persons between 2010 and 2017 (1). Patients are younger at the time of their primary TKA and have a longer life expectancy, increasing the likelihood of revision TKA (2-4). Revision TKA is generally more challenging than primary TKA, and orthopaedic surgeons often must treat bone defects (5-10). The management of bone defects predominantly depends on their size and location (9, 11). Surgical options include the use of newly developed cones and sleeves for larger epiphyseal or metaphyseal bone defects, and variations in stem length and type of fixation for diaphyseal defects. Such options seem to be successful in creating a stable implant in most patients with a metaphyseal bone defect. However, clear indications for which option is the best available solution are absent and outcomes of different surgical options are rarely studied. A reproducible and accurate classification of the bone defects is required to aid such research. Moreover, standard classification of bone defects facilitates comparisons of patients between cohorts or registries.

The Anderson Orthopaedic Research Institute (AORI) classification is the most commonly used classification for bone defects in the femur and tibia (11, 12). However, AORI only partially quantifies the metaphyseal area and does not quantify diaphyseal bone loss, and might be less suited for detailed assessment in revision TKA patients. It should also be noted that obtaining implant fixation in two of three anatomic zones (epiphysis, metaphysis, diaphysis), as recommended to ensure sufficient stability of the revision implant, might be aided by preoperative planning, allowing for a more detailed assessment of bone defects (9).

In clinical practice, the primary assessment of bone loss is performed with radiographs. However, additional CT images may theoretically result in better estimates of bone loss and location of bone defects because of the 3-D nature of CT scans (13). The modality used for evaluating bone defects may thus influence reliability. In this study, we developed a new three-zone bone defect classification to evaluate bone defects in patients undergoing revision TKA, which includes a separate evaluation of the size and severity of the defect in the epiphysis, metaphysis, and diaphysis.

We tested (1) the intraobserver and interobserver reliability of this classification for revision TKA based on preoperative radiographs, and (2) whether additional CT images might improve interobserver reliability.

Methods

Study Design and Setting

This study was registered on the Open Science Framework before data were collected. The study protocol, raw data, and analytical code are deposited and accessible via: https://osf.io/mdcz2.

Design of the Bone Defect Classification

First, a concept classification was designed, and the diaphyseal, metaphyseal, and epiphyseal zones of the femur and tibia were described using anatomic landmarks (Fig. 1). The concept classification was tested in a pilot study by four orthopaedic surgeons (three experienced (VB, GvH, JS) and one resident in training (AvH)) from our center. The orthopaedic surgeons independently rated the bone defects of 15 patients on de-identified radiographs using the new classification. AP and lateral radiographs of the knee were available. A researcher was present to take notes for further discussion about necessary adjustments. After the first pilot test, two changes were made to the classification. First, the definition of epiphysis defects was altered from the percentage of bone loss (cutoff of 50%) to the size of bone loss (cutoffs of 5 mm and 10 mm) to remain consistent with the AORI classification [4]. Second, in the definition of diaphyseal defects, the state of the cortex was also incorporated. A distinction was made between an intact cortex, partial intrusion into the cortex, and discontinuation of the cortex. The adjusted classification was subsequently tested in a new pilot test by three other orthopaedic surgeons (all residents in training [SvG, AvH, BN]) (Fig. 2). The difference in ratings among these observers was described and used in a consensus meeting with all orthopaedic staff who specialized in knee arthroplasty. No changes were deemed necessary during this consensus meeting. An instructional video (Supplemental Videos 1-5; supplemental materials are available with the online version of *CORR*®) was made to illustrate the definition of the zones to be rated and where to measure the bone defects. This is accessible via website Sint Maartenskliniek.

Bone Defect Classification

The bone defect classification consisted of four rating options for bone defects (none, mild, moderate, severe), which are rated separately per zone (epiphysis, metaphysis, and diaphysis) for the femur and tibia (Fig. 2). The zones were defined using anatomic landmarks (Fig. 1). The epiphysis is defined from the original saw cut to the epicondyle (femur) or until the tip of the fibular head (tibia). The bone defect of metaphysis is rated at the adductor tubercle (femur) or at the widest part of the fibular head (tibia). The diaphysis is measured at the worst part of the bone defect, which is usually, but not necessarily, at the tip of the stem. A bone defect was defined as the volume when the normal bone is absent. This included volumes with the implant, cement, osteolytic lesions, and radiolucent lines, as no bone is present in these areas. Bone quality is not incorporated in the classification because an additional DEXA scan is needed for an adequate and consistent evaluation of the bone quality, and bone quality is not part of standard preoperative radiologic examinations. For the epiphysis, the AORI classification was maintained. For the metaphysis, the bone defect was classified as mild when the defect covered less than 50% of the AP or mediolateral distance of the

metaphyseal zone. When the defect covered more than 50% of the AP or mediolateral distance of the metaphyseal zone, a contained defect was classified as moderate, and when there was discontinuation of the cortex, it was classified as severe. The description of the diaphyseal bone defect was also based on 50% as a cutoff of the AP or mediolateral diameter, but less than 50% was classified as none. When the defect was more than 50%, a distinction was made between an intact cortex (mild), partial intrusion of the defect into the cortex (moderate), and discontinuation of the cortex (severe). To illustrate the new bone defect classification, we have collected example radiographs for every type of bone defect (fig. 4).

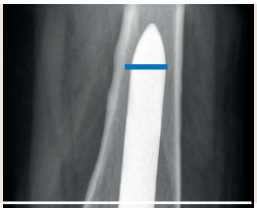
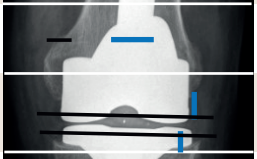
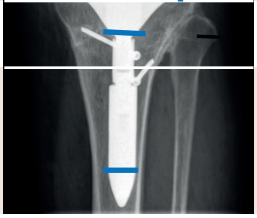
Zone		Location of measurement
Diaphysis		Worst part of the bone defect
Metaphysis		At the adductor tubercle
Epiphysis		Original saw cut to the epicondyle Original saw cut to the tip of the fibular head
Metaphysis		At the widest part of the fibular head
Diaphysis		At the worst part of the bone defect

Figure 1: This shows the definition of femoral and tibial zones used for rating bone defects. The blue lines indicate the cutoff points for the zones. The dotted lines (blue) indicate where the measurements of the bone defects for the specific zones should be taken. The anatomic landmarks for the measurements per zone are described on the right and indicated in the picture (black lines).

Femur	Epiphysis	Metaphysis	Diaphysis
None	No visual bone loss, stability of component not compromised	Intact, no stem in situ	Intact or <50% trabecular bone loss
Mild	<5 mm bone loss in one condyle	<50% trabecular bone loss, stem in situ	>50% trabecular bone loss and normal cortical bone thickness
Moderate	5-10 mm bone loss in one condyle or bone loss in both condyle	>50% trabecular bone loss and sclerosis, contained defect	>50% trabecular bone loss and partial intrusion of stem in cortical bone
Severe **A**	>10 mm bone loss in both condyle or epiphysis absent.	>50% trabecular bone loss, non-supportive, discontinuation cortex	>50% trabecular bone loss and discontinuation of original cortex

Tibia	Epiphysis	Metaphysis	Diaphysis
None	No visual bone loss, stability of component not compromised	Intact, no stem in situ	Intact or <50% trabecular bone loss
Mild	<5 mm bone loss in one condyle	<50% trabecular bone loss, stem in situ	>50% trabecular bone loss and normal cortical bone thickness
Moderate	5-10 mm bone loss in one condyle or bone loss in both condyle	>50% trabecular bone loss and sclerosis, contained defect	>50% trabecular bone loss and partial intrusion of stem in cortical bone
Severe **B**	>10 mm bone loss in both condyle or bone defects below the fibular head	>50% trabecular bone loss, non-supportive, discontinuation cortex	>50% trabecular bone loss and discontinuation of original cortex

Figure 2: The bone defect classification for the (A) femur and (B) tibia.

Reliability

The sample size calculation was based on the agreement probability and chance agreement probability of the ratings done during the design phase of the classification. The chance agreement reflects the agreement between observers based on random rating, not on true agreement, and is used to adjust the agreement to avoid over-estimation of the agreement probability. The sample size was powered at 80%, with an expected overall agreement probability of 0.8, a chance agreement probability of 0.4 , and assuming the sample was drawn from a population of n = 100. This resulted in a required sample size of 61 (14). Preoperative clinical images of all patients who underwent revision TKA or a repeat revision TKA in our hospital in 2018 were collected. Patients were excluded when 1) no CT image was available, 2) more than 6 months elapsed between the radiograph and CT, 3) radiograph and CT image taken more than 6 months before surgery, and 4) fracture of the tibia or femur evident on the radiographs. This resulted in 61 patients to be included in the study.

Table 1. Number of patients per type of bone defect, specified by the six zones

Bone	Zone	None	Mild	Moderate	Severe
Femur	Epiphysis	23	22	9	7
	Metaphysis	48	6	4	3
	Diaphysis	50	8	2	1
Tibia	Epiphysis	5	17	20	19
	Metaphysis	0	46	13	2
	Diaphysis	48	9	4	0

Ratings of bone defects as rated by the majority (three or more) of the observers.

All images were de-identified. Five orthopaedic surgeons (KD, RdJ, GvH, JL, JS) independently rated the severity of bone defects on the images of all patients. All five observers were members of the clinical knee reconstruction unit of our clinic and were experienced in revision TKA, with between 5 and 23 years of experience. No observers had participated in the pilot study during the design phase. All observers scored all defects twice on radiographs, with a minimum of 2 weeks between the two timepoints (Timepoint 1 [T1] and Timepoint 2 [T2]) (Fig. 3). The order of the radiographs was identical at T1 and T2. After the second rating, the observer was provided with the CT image of each patient and was asked to adjust their bone defect rating if they deemed it necessary (Timepoint 3 [T3]).

Typically, the grading of bone defects, classified according to the rating of most of the observers, were none or mild (Table 1). Moderate to severe bone defects were most frequently observed in the epiphysis of the tibia. The duration of the T1 measurements on radiographs ranged between 1:10 minutes and 2:15 minutes per radiograph (median: 1:50 minutes per radiograph).

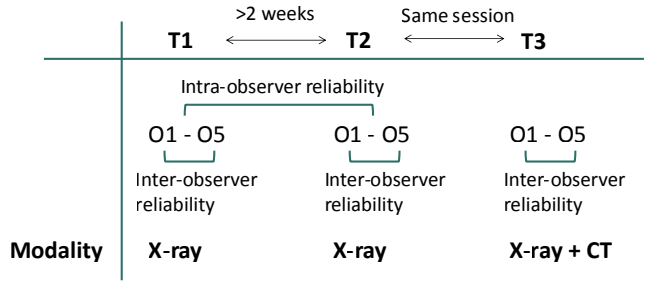


Figure 3: This figure shows the measurement schedule and comparisons for the reliability testing. T1 = Timepoint 1; T2 = Timepoint 2 (minimum of 2 weeks after T1); T3 = Timepoint 3 (directly after T2); O1-O5 = Observer 1 to Observer 5.

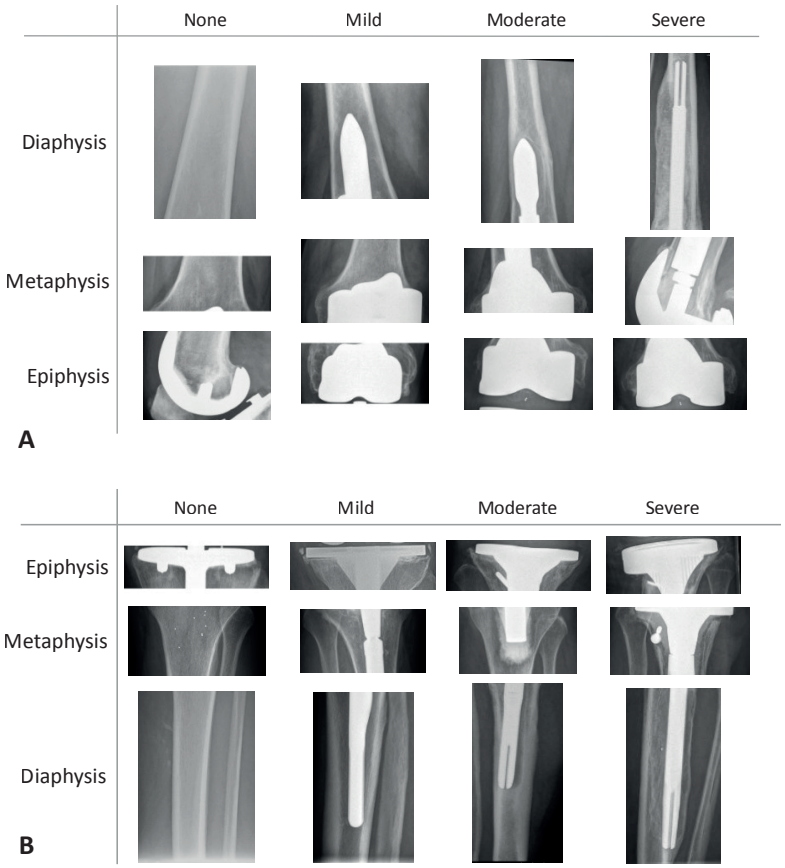


Figure 4: Example radiographs for every type of bone defect, for both femur (A) and tibia (B).

Radiographs and CT Images

All clinical images were collected retrospectively. Preoperatively, AP and lateral knee radiographs, made in supine position with the knee in extension (Philips Healthcare, Best, the Netherlands). The distance from the beam was adjusted to make sure the entire knee prosthesis was visible on the radiograph. Preoperative CT scanning of the knee was performed with the patient in the supine position. The patients underwent scanning in the axial plane. CT images were collected using the Toshiba Aquillion 32 (Otawara, Japan) with metal artefact reduction (135 kV/250 mAs; slice thickness: 1.0 mm) or the Philips Ingenuity (Philips Healthcare, Best, the Netherlands), 128 slice, with metal artefact reduction for large orthopaedic implants (140 kV; slice thickness: 1.0 mm).

Statistical Analysis

Given the categorical nature of the classification, we used Gwet's agreement coefficient (AC) to test reliability. This is considered a better alternative to Cohen's kappa because Gwet's AC is less affected by prevalence (15). Also, Gwet's AC is often close to the percentage agreement between observers, and thereby easily interpretable. We analyzed the intraobserver reliability by comparing the ratings on radiographs at T1 and T2, using Gwet's AC with second-order chance correction (AC2) with linear weights (16). We analyzed interobserver reliability at T1 by comparing ratings between observers using Gwet's AC2 with linear weights. Interobserver reliability was also tested at the ratings on radiographs at T2, and at the CT ratings on T3 All statistical tests were performed using R version 3.5.3 (The R Foundation for Statistical Computing, Vienna, Austria). The agreement coefficient function was used for calculating Gwet's AC (17). The agreement coefficient was interpreted using the Landis and Koch scale for Kappa statistics because there is no equivalent scale for Gwet's AC (18). In the Landis and Koch scale for kappa statistics, k < 0 reflects poor agreement, 0 to 0.20 is slight, 0.21 to 0.4 is fair, 0.41 to 0.60 is moderate, 0.61 to 0.8 is substantial, and above 0.8 is almost perfect.

Results

Intraobserver Reliability

The intraobserver reliability (Table 2) of the radiography ratings at T1 and T2 varied between 0.55 and 0.99. The lowest agreement was observed in the epiphysis of the tibia, with reliability ranging between 0.55 (95% CI 0.40 to 0.71) and 0.78 (95% CI 0.69 to 0.88). Agreement in the metaphysis was substantial to almost perfect for both the tibia and femur, ranging between 0.69 (95% CI 0.58 to 0.80) and 0.98 (95% CI 0.95 to 1). For the diaphysis, the reliability ranged between 0.95 (95% CI 0.90 to 0.99) and 0.99 (95% CI 0.97 to 1). The reliability was similar for the femur and tibia.

Interobserver Reliability

The interobserver reliability (Table 3) using radiographs varied from 0.48 (95% CI 0.39 to 0.57) to 0.97 (95% CI 0.95 to 0.99). The lowest reliability was observed in the epiphysis (between 0.48 (95% CI 0.39 to 0.57) and 0.55 (95% CI 0.46 to 0.64), for both the femur and tibia. The metaphysis and diaphysis had almost perfect reliability (between 0.81 [95% CI 0.75 to 0.87] and 0.97 [95% CI 0.95 to 0.99]), according to the Landis and Koch scale. The interobserver reliability on CT (T3) ranged between 0.44 (95% CI 0.38 to 0.51) and 0.96 (95% CI 0.93 to 0.99), and thus did not substantially differ from reliability using only radiographs. Similar to the intraobserver agreement, the lowest reliability coefficients were observed for the ratings of the epiphysis.

Table 2. Intraobserver reliability per zone on radiographs

Observer	Femur epiphysis	Femur metaphysis	Femur diaphysis	Tibia epiphysis	Tibia metaphysis	Tibia diaphysis
Observer 1	0.73 (0.63-0.83)	0.86 (0.79-0.94)	0.97 (0.94-1)	0.78 (0.69-0.88)	0.91 (0.86-0.96)	0.95 (0.90-0.99)
Observer 2	0.64 (0.53-0.75)	0.69 (0.58-0.80)	0.96 (0.93-0.99)	0.64 (0.53-0.75)	0.89 (0.82-0.95)	0.98 (0.96-1)
Observer 3	0.87 (0.78-0.96)	0.98 (0.95-1)	0.99 (0.97-1)	0.72 (0.60-0.84)	0.98 (0.96-1)	0.98 (0.96-1)
Observer 4	0.62 (0.49-0.75)	0.96 (0.92-0.99)	0.99 (0.98-1)	0.66 (0.54-0.77)	0.96 (0.92-0.99)	0.96 (0.92-1)
Observer 5	0.67 (0.52-0.81)	0.83 (0.75-0.91)	0.99 (0.97-1)	0.55 (0.40-0.71)	0.94 (0.90-0.99)	0.96 (0.93-0.99)

Reliability is expressed using Gwet's AC2 with linear weights (95% confidence interval). AC = agreement coefficient. Red = fair to moderate reliability; orange = substantial reliability; green = almost perfect reliability.

Table 3. Interobserver reliability per zone, separately for timepoint of the rating and modality

Timepoint	Femur epiphysis	Femur metaphysis	Femur diaphysis	Tibia epiphysis	Tibia metaphysis	Tibia diaphysis
T1 radiograph	0.49 (0.42-0.56)	0.81 (0.75-0.87)	0.96 (0.93-0.99)	0.48 (0.39-0.57)	0.88 (0.83-0.93)	0.96 (0.93-0.99)
T2 radiograph	0.5 (0.42-0.58)	0.87 (0.82-0.92)	0.97 (0.95-0.99)	0.55 (0.46-0.64)	0.9 (0.86-0.94)	0.96 (0.93-0.99)
T3 CT + radiograph	0.44 (0.38-0.51)	0.86 (0.81-0.91)	0.96 (0.92-0.99)	0.54 (0.45-0.63)	0.89 (0.84-0.93)	0.96 (0.93-0.99)

Reliability is expressed using Gwet's AC2 with linear weights (95% confidence interval). AC = agreement coefficient; T1 = Timepoint 1; T2 = Timepoint 2. Red = fair to moderate reliability; orange = substantial reliability; green = almost perfect reliability.

Discussion

For revision TKA, a reproducible and extensive classification for bone defects in all anatomic zones of the tibia and femur is needed to compare the outcome of surgical options for revision TKA and for comparisons of patients between cohorts and registries. We developed and described here a new bone defect classification, including the diaphysis, which is not part of the most commonly used AORI system for bone defects. We found that this bone defect classification had high intra- and inter-rater agreement for bone defects in the metaphysis and diaphysis, but performed worse for bone defects in the epiphysis.

Limitations

This study has several limitations that merit attention. First, our study only tested reliability of the bone defect classification. Evaluation of the validity of the classification by comparing it to intraoperative findings, and its clinical value for decision making, is required before implementation for research or clinical purposes. Future studies of a prospective nature, and thus an independent data set, are necessary. Second, all observers in this study work in the same high-volume clinic. Therefore, they are all familiar with evaluating radiographs of a prosthesis in situ and discussing patients based on radiographs, which may improve agreement between raters and thus limit generalizability. Future evaluation with observers from other centers is warranted to substantiate our findings. Third, the order of the radiographs was not randomized due to practical issues involving a software limitation. We attempted to reduce recall bias by having a minimum of 2 weeks between the radiographic ratings.

We also extensively described the classification to the observers to minimize the confounding effect of learning on reliability (19). We provided standardized verbal instructions that were supplemented by instructional videos (Supplemental Videos 1-5; supplemental materials are available with the online version of *CORR*®) describing the bone defects of five patients using the new classification. We consider this instruction part of the bone defect classification and have made it publicly available (website Sint Maartenskliniek).

Intra- and Interobserver Reliability of the Epiphysis

Overall, the reliability was substantially lower for the epiphysis than for the other two zones. This might be because the prosthesis is in situ, obscuring bony defects and complicating an evaluation of them. In particular, the visibility of epiphyseal defects in the femur was influenced to a great extent by the component type. TKAs with a posterior-stabilized design resulted in poorer visibility of the epiphysis than did a cruciate-retaining design. Lower agreement between raters may also be due to larger bone defects existing in the epiphysis, due to the presence of the prosthesis. It should be noted that a difference between the scoring of the epiphysis and other zones

existed in the new bone defect classification: where the epiphysis is scored based on size of defect in mm (according to AORI), and the diaphysis and metaphysis are scored as percentage bone loss. This may be an alternative explanation for the difference in reliability between the zones. We are aware of only one study that has assessed agreement between observers using the AORI classification (20). The authors reported a moderate agreement between observers, with the outcome of the study reported as the percentage of physicians scoring the same way. To enable a direct comparison, we re-calculated the interobserver reliability based on that study's results using the same statistical test. This resulted in a interobserver reliability of 0.39 (95% CI 0.27 to 0.51) for the tibia and 0.57 (95% CI 0.45 to 0.69) for the femur, and that previous study had slightly lower agreement than we did.

Use of CT Did Not Improve Reliability of Classification

The interobserver reliability when both CT and radiographic images were used to rate bone defects at T2 was similar to the rating reliability using radiograph only. This suggests that, in most cases, CT images did not add value to agreement among and between raters. In particular, the metal of the prosthesis resulted in artefacts in the epiphysis that obscured the images, even with metal subtraction software, decreasing the visibility of small defects. This was contrary to our expectations because CT generally provides more detailed images, and a previous study on the reliability of a classification on ossifications found that the reliability improved when CT-images were added (13, 21). However, in some cases, CT was decisive on the size or severity of the defect. For example, discontinuation of the cortex caused by intrusion of the stem tip was sometimes missed on radiographs but was visible on CT.

This study was a first step to standardize bone defects in all zones relevant for revision TKA. In addition to this single-center reliability study, further studies testing reliability of use of the bone defect classification by raters outside our clinic and validity testing are necessary. Such studies should clarify if the new bone defect classification can be used for research purposes, such as development of treatment algorithms and the evaluation of the outcomes of different treatment options for large bone defects. Such a classification scheme could also enable comparisons of revision TKA patients across different registries.

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Chapter 5

Validation of the incidence of reported periprosthetic joint infections in total hip and knee arthroplasty in the Dutch Arthroplasty Register

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Abstract

Introduction: Arthroplasty registers underreport the incidence of periprosthetic joint infections (PJIs). However, the magnitude of underreporting in the Dutch Arthroplasty Register (LROI) is not well known. We validated the incidence of reported PJIs in total hip and knee arthroplasties (THAs/TKAs) in the LROI using data from the Dutch National Nosocomial Surveillance Network (PREZIES).

Methods: All primary THAs and TKAs performed between 2012 and 2018 from the LROI and all primary THAs and TKAs performed between 2012 and 2018 in consenting hospitals from PREZIES were matched on date of birth, date of surgery, sex, hospital and type of procedure (n=171,512). Of the 171,512 matches, 53% were THAs and 47% TKAs. For the LROI, PJI was defined as revision for infection or resection arthroplasty within one year. The PJI definition of PREZIES was based on that of the European Center of Disease Control and Prevention. The sensitivity, specificity, positive predicted value (PPV), and negative predicted value (NPV) were calculated for PJIs registered in the LROI, using PREZIES as reference.

Results: The incidence of registered PJIs in THAs was 1.2% in PREZIES and 0.5% in the LROI. For TKAs, this was 0.7% and 0.4% respectively. The PJIs in THAs in the LROI had a sensitivity of 0.32 (Confidence interval (CI): 0.29-0.35), a specificity of 1.00 (CI: 1.00-1.00), a PPV of 0.74 (CI: 0.70-0.78), and a NPV of 0.99 (CI: 0.99-0.99). In TKAs, the sensitivity, specificity, PPV, and the NPV were 0.38 (CI: 0.34-0.42), 1.00 (CI: 1.00-1.00), 0.65 (CI: 0.59-0.70), and 1.00 (CI: 1.00-1.00), respectively.

Conclusion: The LROI captures approximately one-third of the PJIs as revision within one year for infection or resection arthroplasty. The capture rate of PJIs can be improved by including all reoperations without component exchange and non-surgical treatments with antibiotics only.

Introduction

Revisions due to periprosthetic joint infections (PJIs) remain a major problem in both total hip and knee arthroplasty (THA/TKA) and are associated with high morbidity, poor postoperative outcomes such as higher re-revision rates, and even higher mortality rates (1, 2). Population-based registry studies have shown that approximately 1% of all total joint arthroplasties are revised due to PJIs (3-5). However, concerns have been raised regarding the validity of reported PJIs in national arthroplasty registers (6-9). Multiple population-based registry studies have found an underreporting of PJIs of up to 40% (6-9). Several reasons have been suggested for the underreporting of PJIs in these registers. Most national arthroplasty registers record revisions, which are defined as a replacement, removal or addition of one or more components of the prosthesis. However, a PJI can also be treated with a Debridement, Antibiotics, and Implant Retention (DAIR) procedure without component exchange or non-operatively with antibiotics, and these PJIs are therefore not included in those registers. Also, the reason for revision is usually reported immediately after surgery, whereas diagnosing a PJI based on cultures usually takes several days. It is unlikely that a reason for revision other than a PJI reported at the time of surgery will be updated after a proven PJI (6-9).

Since 2007, the Dutch Arthroplasty Register (LROI) has been registering THAs and TKAs on a nationwide basis. A recent study found that only 47% of the PJIs were captured in the LROI (10). However, in that study the LROI data was benchmarked against a Regional Infection Cohort, including only 8 hospitals located in the South-East of the Netherlands.

Based on the previous registry studies, the LROI is expected to underreport the incidence of PJIs in the Netherlands. It is important to quantify the possible under-reporting of PJIs in the LROI to obtain reliable data of PJIs that can guide future optimalization steps in the Netherlands. The Dutch National Nosocomial Surveillance Network (PREZIES) is a healthcare associated infection (HAI) surveillance network. One of the PREZIES modules focuses on the surveillance of surgical site infections (SSIs), such as PJIs in THAs and TKAs. The PREZIES collects these surveillance data in a national registration system for infectious diseases (11, 12). Therefore, this study aims to validate the incidence of reported PJIs in THAs and TKAs in the LROI using data from PREZIES.

Methods

Data were obtained from the LROI and PREZIES. The LROI is the national population-based arthroplasty register of the Netherlands, established by the Netherlands Orthopaedic Association (NOV) in 2007. In 2012, 100% coverage of Dutch hospitals was achieved with a completeness of more than 95% of primary THAs and TKAs (13). Nowadays, completeness of primary and revision hip and knee arthroplasties is reported to be higher than 97%, and validity is higher than 94% for hip arthroplasties, 3 and 97% for knee arthroplasties (14). The LROI contains data on patient, prosthesis, and procedure characteristics of primary and revision arthroplasties.

The PREZIES is the national surveillance system for the incidence of HAIs in the Netherlands, founded in 1996 and coordinated by the National Institute for Public Health and the Environment (RIVM). The goal of this network is to gain insight into the incidence and prevalence of HAIs using standardized surveillance methods, which result in national reference values. Participation is voluntary and almost all Dutch hospitals take part in one or more modules of the PREZIES program. In the SSI module, hospitals can choose each year to send their data on several surgical procedures, including THAs and TKAs, towards PREZIES to keep track of their infections (11, 12). The PREZIES data are owned by the hospital where the procedure was performed. Therefore, approval to use their data was needed from all hospitals delivering data to PREZIES. In total, 52 hospitals (52% of all Dutch hospitals) gave approval to use their data in this study. Of these 52 hospitals, 85% were general hospitals, 13% were private clinics, and 2% were university medical centers.

In this study, we included all primary THAs (n=197,924) and TKAs (n=168,712) performed between 2012 and 2018 from the LROI and all primary THAs (n=105,006) and TKAs (n=95,264) performed between 2012 to 2018 in consenting hospitals from PREZIES. Data from the LROI and PREZIES were matched on case-level using a pseudonym created by a Trusted Third Party (ZorgTTP, Houten, the Netherlands) on the variables: date of birth, date of surgery, sex, hospital of primary procedure and type of procedure (THA or TKA). Sensitivity analyses were performed to determine the number of variables required for the matching procedure, showing that those 5 variables were needed to achieve the optimal number of matched cases with a limited number of multiples cases with the same pseudonyms. Our matched dataset did not include the variables date of birth, date of surgery, and hospital of primary procedure. Therefore, patient privacy was ensured in this study. Patients in the LROI were excluded before matching if they were diagnosed with a tumor (THA n=402, TKA n=98) or had a missing date of birth (THA n=155, TKA n=134). After matching, several cases had the same pseudonyms based on the 5 matching variables; these cases (THA n=682, TKA n=488) were excluded (Figure 1).

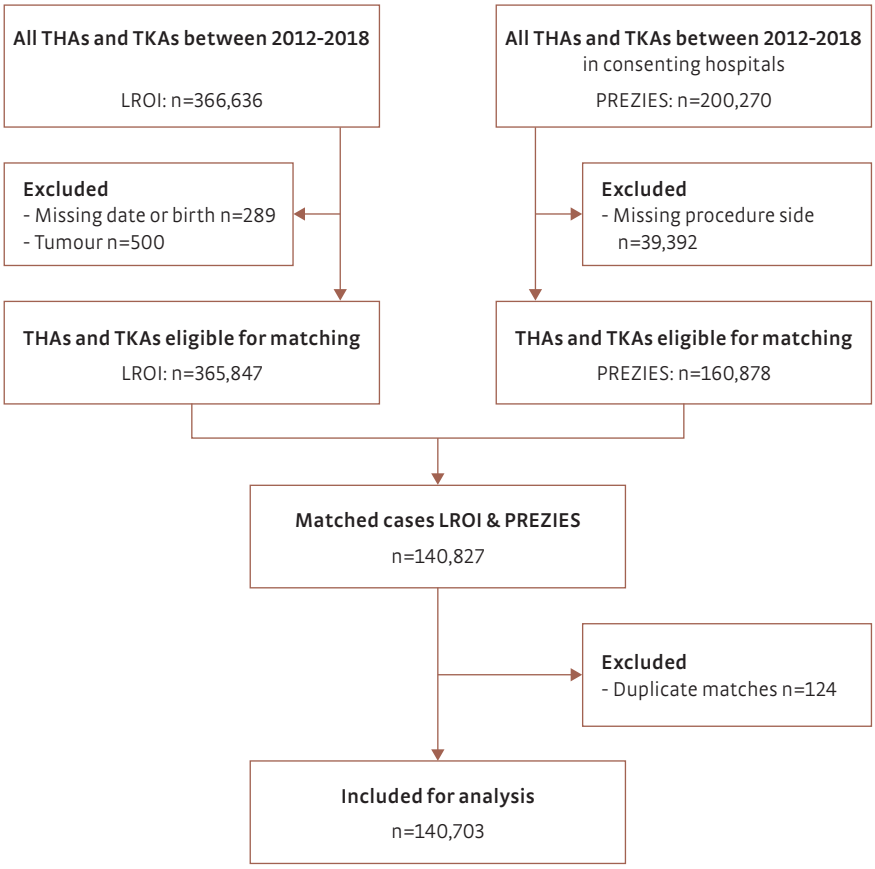

Figure 1: Flow chart.

In total, 171,512 matches could be made between the LROI and PREZIES, of which 91,208 (53%) THAs and 80,304 (47%) TKAs (Table 1). Most THA and TKA patients were women (THA 66%; TKA 65%), were diagnosed with osteoarthritis (THA 90%; TKA 97%), and had an American Society of Anesthesiologists (ASA) II score (THA 65%; TKA 68%). Most THA patients were pre-obese (36%) or had a normal (26%) Body Mass Index (BMI). In TKA patients, pre-obese (34%) and obese class 1 (24%) were the most common BMI classes. The most commonly used type of fixation in THAs was cementless (62%), whereas TKAs were more often cemented (94%).

Table 1. Characteristics of matched total hip arthroplasties (THAs) and total knee arthroplasties (TKAs) between the Dutch Arthroplasty Register (LROI) and the Dutch National Nosocomial Surveillance Network (PREZIES).

	Total n=140,703	THAs n=74,761	TKAs n=65,942
Gender			
Female (%)	91,410 (65)	49,039 (66)	42,371 (64)
Diagnosis (%)			
Osteoarthritis	131,211 (93)	67,267 (90)	63,944 (97)
Fracture	2,675 (1.9)	2,675 (3.6)	n.a.
Osteonecrosis	1,981 (1.4)	1,685 (2.3)	296 (0.4)
Late post-traumatic	1,508 (1.1)	816 (1.1)	692 (1.0)
Dysplasia	1,406 (1.0)	1,406 (1.9)	n.a.
Inflammatory arthritis	1,297 (0.9)	509 (0.7)	788 (1.2)
Other	238 (0.2)	174 (0.2)	64 (0.1)
Missing	387 (0.3)	229 (0.3)	158 (0.2)
ASA score (%)			
ASA I	21,878 (16)	13,048 (18)	8,830 (13)
ASA II	93,436 (66)	48,602 (65)	44,834 (68)
ASA III-IV	25,090 (18)	12,931 (17)	12,159 (18)
Missing	299 (0.2)	180 (0.2)	119 (0.2)
BMI (kg/m2) (%)			
Underweight (<18.5)	677 (0.5)	573 (0.8)	104 (0.2)
Normal (18.5-24.9)	32,952 (23)	22,675 (30)	10,277 (16)
Pre-obese (25.0-29.9)	56,340 (40)	30,419 (41)	25,921 (39)
Obese Class 1 (30.0-34.9)	31,016 (22)	13,097 (18)	17,919 (27)
Obese Class 2 (35.0-39.9)	10,102 (7.2)	3,507 (4.7)	6,595 (10)
Obese Class 3 (≥40.0)	3,368 (2.4)	953 (1.3)	2,415 (3.7)
Missing	6,248 (4.4)	3,537 (4.7)	2,711 (4.1)
Type of fixation (%)			
Cemented	81,833 (58)	19,585 (26)	62,248 (94)
Cementless	48,114 (34)	45,988 (62)	2,126 (3.2)
Hybrid	10,553 (7.5)	9,074 (12)	1,479 (2.2)
Missing	203 (0.1)	114 (0.2)	89 (0.1)

Both the definition of a PJI and the follow-up of THAs and TKAs differed between the LROI and PREZIES. Participation in PREZIES required a mandatory follow-up of one year in 2012 to 2014, and of 90 days in 2015 to 2018. In the LROI, follow-up for primary THAs and TKAs ends at the time of first revision, death of the patient or end of follow-up (January 1, 2022). A PJI is defined as a revision with reason 'infection' within the LROI. In this study, revisions with reason 'Girdlestone' were also considered a PJI. A Girdlestone is defined as a hip revision procedure in which the prosthesis is removed and no new prosthesis is implanted (i.e., resection arthroplasty), often due to a bacterial infection (14). Therefore, in the LROI data, we defined a PJI as a revision within one year with reason 'infection' or 'Girdlestone'. The definition of a PJI in PREZIES is based on that of the European Center of Disease Prevention and Control (ECDC) and has been described elsewhere (15, 16). This ECDC definition includes both superficial and deep SSIs. In this study, only deep SSIs in the PREZIES data were considered a PJI, as superficial SSIs are more likely to be wound complications than PJIs. These PJIs cover PJIs treated with revision surgery, treated with reoperation without component exchange or non-surgical treatment. This study was reported in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines.

Statistics

Descriptive statistics were used to summarize the patient and procedure characteristics as well as the incidence of PJIs in the LROI and the PREZIES databases. BMI was classified as underweight (<18.5), normal (18.5 to 24.9), pre-obese (25.0 to 29.9), obese class 1 (30.0 to 34.9), obese class 2 (35.0 to 39.9), or obese class 3 (≥40.0). Sensitivity, specificity, positive predicted value (PPV), and negative predicted value (NPV) including 95% confidence intervals (CI) were calculated for PJIs registered in the LROI, using PREZIES as reference standard. Only PJIs that have been treated with a revision procedure can be captured by the LROI. Therefore, patient status (i.e., alive without revision, deceased or revision) was described for PJIs with no revision for infection or resection arthroplasty within one year in the LROI to assess the proportion of PJIs that were rightly not reported to the LROI. Results were stratified by type of procedure. R (version 4.2.0, R Foundation for Statistical Computing, Vienna, Austria) was used to perform all analyses.

Results

Among THAs, 1,101 (1.2%) PJIs were registered in PREZIES and 476 (0.5%) in the LROI, of which 353 PJIs were reported in both the LROI and PREZIES (Table 2). For TKAs, there were 547 (0.7%) PJIs registered in PREZIES and 332 (0.4%) in the LROI, of which 209 PJIs were reported in both the LROI and PREZIES. The PJI in THAs in the LROI had a sensitivity of 0.32 (CI: 0.29-0.35), a specificity of 1.00 (CI: 1.00-1.00), a PPV of 0.74 (CI: 0.70-0.78) and an NPV of 0.99 (CI: 0.99-0.99). In TKAs, the sensitivity, 5 specificity, PPV and the NPV were 0.38 (CI: 0.34-0.42), 1.00 (CI: 1.00-1.00), 0.65 (CI: 0.59-0.70) and 1.00 (CI: 1.00-1.00), respectively.

A total of 748 (68%) THA patients and 338 (62%) TKA patients with a PJI in PREZIES were not captured by the LROI as revision for infection or resection arthroplasty within one year. Of these, 87% of the THA patients and 89% of the TKA patients were alive without a revision one year after primary THA or TKA, 9% of the THA patients and 7% of the TKA patients had a revision procedure within one year that was registered for reasons other than infection or resection arthroplasty, and 4% of the THA and TKA patients were deceased within one year (Table 3).

Table 2. Sensitivity, specificity, positive predictive value (PPV) and negative predicted value (NPV) of periprosthetic joint infections (PJIs) registered in the Dutch Arthroplasty Register (LROI) and the Dutch National Nosocomial Surveillance Network (PREZIES) according to type of procedure.

		Total n=171,512			THAs n=91,208			TKAs n=80,304		
		PREZIES: PJI								
		Yes	No	Total	Yes	No	Total	Yes	No	Total
LROI: PJI	**Yes**	562	236	798	353	123	476	209	113	322
	No	1,086	169,628	170,714	748	89,984	90,732	338	79,644	79,982
	Total	1,648	169,864	171,512	1,101	90,107	91,208	547	79,757	80,304
Sensitivity		0.34 (CI: 0.32 - 0.36)			0.32 (CI: 0.29 - 0.35)			0.38 (CI: 0.34 - 0.42)		
Specificity		1.00 (CI: 1.00 - 1.00)			1.00 (CI: 1.00 - 1.00)			1.00 (CI: 1.00 - 1.00)		
PPV		0.70 (CI: 0.67 - 0.74)			0.74 (CI: 0.70 - 0.78)			0.65 (CI: 0.59 - 0.70)		
NPV		0.99 (CI: 0.99 - 0.99)			0.99 (CI: 0.99 - 0.99)			1.00 (CI: 1.00 - 1.00)		

LROI: Dutch Arthroplasty Register; PREZIES: Dutch National Nosocomial Surveillance Network; THA: total hip arthroplasty; TKA: total knee arthroplasty; CI: 95% confidence interval.

Table 3. Status within one year of patients with non-registered periprosthetic joint infections (PJIs) in the Dutch Arthroplasty Register (LROI) according to the Dutch National Nosocomial Surveillance Network (PREZIES) by type of procedure.

	Total n=1,086	THAs n=748	TKAs n=338
Alive without revision within one year	953 (88)	653 (87)	300 (89)
Revision within one year	92 (8)	68 (9)	24 (7)
Deceased within one year	41 (4)	27 (4)	14 (4)

THA: total hip arthroplasty; TKA: total knee arthroplasty. Number (percentage).

Discussion

This study shows that only approximately one-third of the PJIs in THAs and TKAs, according to the international definition used by PREZIES, are registered in the LROI as revision for infection or resection arthroplasty within one year. The proportion of PJIs registered in the LROI that were correctly classified compared to the PREZIES database was 74% in THAs and 65% in TKAs.

The capture rate of PJIs reported in the LROI in this study is substantially lower than in other national arthroplasty registers, which report a minimum of 60% of the PJIs as revision or re-operation for infection (6-9). This can partly be explained by the limitations in the documentation system of the LROI. After the primary procedures, the LROI registers only revisions where at least one of the components has been replaced, removed, or added. The Finnish and Swedish arthroplasty registers include these revisions as well as re-operations without component exchange (6, 7). In the Danish arthroplasty register, debridement without component exchange is also considered a revision procedure, whereas in the LROI only a DAIR procedure with exchange of the femoral head and/or inlay is considered a revision (8). These factors likely contribute to a higher capture rate of PJIs.

A previous study showed that the LROI captured 47% of the PJIs, which is higher than in the current study (10). However, this previous study only included revision surgeries and DAIR procedures from the Regional Infection Cohort, which was used as a benchmark, while PREZIES also includes PJIs treated non-operatively. A study using data from the Swedish arthroplasty registers has shown that 9% of the deep PJIs in THAs were treated non-operatively with antibiotics (17). Moreover, the definition of a PJI was stricter in the Regional Infection Cohort than in PREZIES. In the Regional Infection Cohort, a PJI was diagnosed when there were at least 2 phenotypically identical pathogens, isolated in cultures from at least 2 separate tissues obtained from the affected prosthesis (10). In PREZIES, the presence of microorganisms is

not required, as other evidence of infection, such as an abscess, is sufficient to diagnose a PJI (15).

The majority of patients who have a non-registered PJI in the LROI were alive without a revision procedure one year after the primary THA or TKA. These patients likely underwent reoperation without 6 component exchange, non-surgical treatment with antibiotics or no treatment was required, suggesting that they were rightly not reported in the LROI. This stresses the importance of a more extensive registration system. The LROI, in collaboration with the Netherlands Orthopaedic Association (NOV), has recently started a complication registration system to improve orthopaedic care and patient safety in which complications related to a joint arthroplasty are reported (18). This complication registration system could make it possible to capture PJIs in the LROI that do not require revision arthroplasty. Unfortunately, LROI data on complications without revision procedures are not yet available for research purposes, as registration has started in 2022.

A total of 68 (9%) and 24 (7%) of the non-registered PJIs in THAs and TKAs in the LROI, respectively, involved patients undergoing revision procedures. These revision procedures are likely registered as revision due to, for example, aseptic loosening, dislocation, wear, or peri-prosthetic fractures in THAs, and instability, aseptic loosening, patellar pain, or malalignment in TKAs (14). Registration of the revision procedure, including the reason for revision, will usually take place during or immediately after surgery. However, an assessment of any microorganism present from cultures taken during the procedure will probably become available after the revision procedure is reported in the LROI. An already reported, reason for revision is unlikely to be modified when pathogens are found to be present in those cultures. However, delaying reporting of the revision procedure to improve the capture rate of PJIs is likely to negatively impact the completeness of revision arthroplasties (8). A small proportion of the patients who have a non-registered PJI had died within one year after the primary THA or TKA. It is unclear if these deaths were related to the PJIs.

More than 25% of the PJIs in THAs and TKAs in the LROI could not be confirmed by PREZIES. This may include revisions for infection or resection arthroplasty between 90 days and one year after primary procedures performed in 2015 to 2018, as PREZIES changed the mandatory follow-up from one year to 90 days in 2015. Therefore, the PJIs registered in PREZIES between 2015 to 2018 reflect only the acute PJIs rather than the acute and delayed PJIs (19). It was not possible to differentiate between primary procedures performed in 2012 to 2014 and 2015 to 2018, as the matched dataset did not contain information on procedure year. Another explanation may be that the orthopaedic surgeon suspects a PJI as the indication for revision, but this suspicion is ultimately not confirmed by the PREZIES criteria for deep SSIs.

Limitations

A strength of this study is the large number of matched cases between the LROI and PREZIES, showing that combining the LROI and PREZIES databases is feasible. This offers new possibilities for future registry studies on PJIs in the Netherlands, as the LROI collects data on patient, prosthesis, and procedure characteristics as well as the survival of prostheses, whereas PREZIES collects data on associated microorganisms. Microorganisms that cause PJIs can be identified per patient, prosthesis, 7 or procedure characteristic to investigate whether the most common antibiotic treatments for PJIs are still suitable for these microorganisms.

The findings of the study should be interpreted carefully. Participation in the PREZIES program is voluntary and not all Dutch hospitals gave approval to use their data in this study. Consequently, PREZIES data were missing in a minority of hospitals. However, we assume that the participating hospitals in this study are representative of the Netherlands. Another potential limitation may be the different definitions of a PJI in the LROI and PREZIES. The PREZIES uses the ECDC criteria for SSIs instead of the Musculoskeletal Infection Society (MSIS) criteria for diagnosing a PJI, where we considered the deep SSIs as PJIs (15, 16, 20). Within the LROI, it is unclear whether orthopaedic surgeons use criteria to diagnose a PJI. This may result in false positive or false negative PJIs in the LROI or PREZIES data, leading to an over- or underestimation of the capture rate of PJIs in the LROI. Also, due to privacy regulations, it was impossible to validate the LROI database to the PREZIES database on hospital-level. The Swedish arthroplasty register has shown that the capture rate of PJIs varies between hospitals (6).

In conclusion, the LROI captures approximately one-third of the PJIs in THAs and TKAs, according to PREZIES, as revision for infection or resection arthroplasty within one year. The capture rate of PJIs can be improved by including reoperations without component exchange, such as DAIR procedures, and non-surgical treatments with antibiotics. Combining the LROI and PREZIES databases is feasible, enabling new research opportunities to improve outcomes of PJIs in primary THAs and TKAs in the Netherlands.

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Chapter 6

Clinical prediction models for patients undergoing total hip arthroplasty. An external validation of based on a systematic review and the Dutch Arthroplasty Register

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Abstract

Introduction: External validation is a crucial step after prediction model development. Despite increasing interest in prediction models, external validation is frequently overlooked. We aimed to evaluate if joint registries can be utilized for external validation of prediction models, and whether published prediction models are valid for the Dutch population with a THA.

Methods: We identified prediction models developed in patients undergoing arthroplasty through a systematic literature search. Model variables were evaluated for availability in the Dutch Arthroplasty Registry (LROI). We assessed the model performance in terms of calibration and discrimination (area under the curve [AUC]). Furthermore, the models were updated and evaluated through intercept recalibration and logistic recalibration.

Results: After assessing 54 papers, 19 were excluded for not describing a prediction model (n = 16) or focusing on non-TJA populations (n = 3), leaving 35 papers describing 44 prediction models. 90% (40/44) of the prediction models used outcomes or predictors missing in the LROI, such as diabetes, opioid use, and depression. 4 models could be externally validated on LROI data. The models' discrimination ranged between poor and acceptable, and was similar to that in the development cohort. The calibration of the models was insufficient. The model performance improved slightly after updating.

Conclusion: Registry data can be used for external validation of prediction models, although it is heavily reliant on the availability of predictors and outcomes in the registry. External validation of the 4 models resulted in suboptimal predictive performance in the Dutch population, highlighting the importance of external validation studies.

Introduction

Several prediction models have been developed for hip and knee arthroplasty, aiming to predict the probability of an outcome after surgery (1-6). These predicted probabilities can provide valuable information to patients and clinicians and aid in clinical decision-making and expectation management. However, existing prediction models for joint arthroplasty are often not suitable for use in clinical practice, due to either poor predictive performance or lack of external validation (7, 8).
External validation plays a vital role in assessing the generalizability and performance of these models in a different set of patients (9). Ideally, data for external validation purposes are collected specifically for the purpose of external validation, but this approach can be time-consuming and resource-intensive. Another, more common option, is to use previously collected data for external validation, although absence of variables or different variable definitions may complicate the use of existing databases.
Large data sets, such as (inter)national registries, are a potentially rich source for external validation. Registry data is relatively easy accessible and often includes large patient cohorts. However, one drawback is that registry data is not collected specifically for the purpose of external validation of prediction models. As a result, the definitions of predictor variables may differ from those required for external validation, or certain predictor variables may not be collected in the registry at all (10). Nonetheless, it is worthwhile to explore whether joint registries, such as the Dutch Arthroplasty Registry (LROI), can be utilized for external validation of clinical prediction models. The objective of this study was 1) to assess if joint registries can be utilized for external validation of prediction models, and 2) to evaluate whether published prediction models are valid for the Dutch total hip arthroplasty (THA) population.

Methods

Study design

The study was designed as a systematic literature search performed in PubMed from the date of inception to April 2023 for studies describing prediction models that predict the risk of revision or mortality after total joint arthroplasty (TJA).

The study is reported according to TRIPOD reporting guideline.

Use of joint registries for external validation

The search string was based on the keywords arthroplasty, prediction models, revision, and mortality as the latter 2 are outcomes available in the LROI (see Appendix A

for the detailed search strategy). Literature was screened by 1 author (MB). Papers were excluded if no prediction model was described, or the model was not developed for TJA patients. To assess if joint registries can be utilized for external validation of prediction models, we used the Dutch Arthroplasty Registry (LROI), as an example. We evaluated the utility of using joint registries for this purpose by evaluating the frequency of the predictors of the models that were found by the literature search and whether they are available in the LROI. Next, we evaluated the quality of the registry data by assessing the percentage of missing data per predictor variable, and whether the definitions of the variables used are standard or could be harmonized (10).

External validity of published prediction models

Next, we selected prediction models from the literature search that could be externally validated on data from the LROI to test their validity in Dutch clinical practice. Models were included if a prediction model was developed for patients who underwent total joint arthroplasty, and when the outcome and all predictors in the model were available in the LROI. This resulted in two papers describing four prediction models (Table 1).

The four selected prediction models were all developed in patients undergoing primary total hip arthroplasty (THA). As a result, the study population was narrowed down from TJA to THA. Three out of four identified models (model 1 to 3) were originally developed in a Finnish population (3). Data of all primary THAs (N =25,919) performed in Finland between May 2014 and January 2018 was collected in the Finnish Arthroplasty Register and used for model development. The first model (model 1) predicts the risk of short term (<6 months after primary THA) revision for dislocation. The second model (model 2) was developed to predict the risk for short term (<6 months after primary THA) revision for periprosthetic fracture. The third model (model 3) was developed to assess the risk of short term (<6 months) mortality after primary THA. The last model (model 4) aimed to predict the risk of revision within 5 years after primary THA (N= 20,592) (2). It was developed on data from the Kaiser Permanente's Total Joint Replacement Registry. The cohort included all patients who had primary procedures performed between April 2001 and July 2008.

LROI dataset for external validation

Data for external validation was obtained from the LROI, a nationwide population-based register on TJAs performed in the Netherlands since 2007. All Dutch hospitals report patient characteristics, surgical techniques, prosthesis characteristics, and patient-reported outcomes of total joint arthroplasties to the LROI. The data completeness for primary total hip arthroplasties (THA) was 97% in 2013 and up to 99% since 2016 (11).

Table 1. Four prediction models that were included from the literature.

	Paper	Model	Model coefficients*
1	Venäläinen et al. (2021) (3)	Logistic regression model predicting short term revision (within six months) for dislocation	Linear predictor = -6.801 + 0.459*ASA class + 0.861*preoperative fracture + 0.675*previous contributing operations + 0.606*posterior surgical approach + 0.355*32 mm head diameter
2	Venäläinen et al. (2021) (3)	Logistic regression model predicting short term revision (within six months) for periprosthetic fracture	Linear predictor = -9.138 + 0.404*ASA class + 0.244*Age (per 10 years) + 1.479*cementless fixation
3	Venäläinen et al. (2021) (3)	Logistic regression model predicting short term mortality (within six months)	Linear predictor = -7.017 + 0.491*ASA class + 0.104*age (per 10 years) + 0.878*preoperative fracture
4	Paxton et al. (2015) (2)	Logistic regression model predicting the risk of a revision surgery within five years after total hip arthroplasty	Linear predictor = -2.66834 + -0.01742*age + 0.215285*female gender + 0.067322*√BMI + -0.16622*osteoarthritis

*The predicted probability of the outcome is calculated as: $\frac{1}{1+e^{-(linear\ predictior)}}$

External validation cohorts

Cohort 1. For the validation of the first three models, the outcomes of interest were revision (models 1 and 2) or mortality (model 3) within 6 months after THA. Data of all registered primary THA performed between January 2007 and December 2020 in the Netherlands were provided by the LROI. All surgeries before 2014 were excluded to match patient sampling time between the development and external validation cohort. Patients operated after December 2019 were excluded to ensure sufficient follow-up time. Thus, we included all patients with a primary THA performed between January 2014 and December 2019 for the external validation.

Cohort 2. For the validation of the fourth model, a different group of patients was selected from the LROI dataset. As BMI was a predictor in the model, and BMI has only been registered in the LROI since 2014, all surgeries before 2014 were excluded. To ensure a minimal follow-up of 5 years, all arthroplasties performed after December 2015 were excluded. Hence, we included all patients who received a primary THA between January 2014 and December 2015.

Predictor definitions LROI

The four models used a subset of the following predictors: gender, age, BMI (in kg/m^2), ASA classification, osteoarthritis or fracture as diagnosis for primary THA, the presence of one or more previous contributing surgeries, surgical approach (anterolateral or posterior), type of fixation (cemented or cementless) and head diameter (Table 1). All were reported to the LROI at the time of primary surgery. Osteoarthritis was defined as all types of osteoarthritis (including secondary arthritis and coxarthrosis). Fracture as diagnosis for primary THA was defined as the implantation of primary THA within 5 days after hip fracture (including medial/lateral collum fracture, femoral neck fracture, trochanter femur fracture). Previous surgeries of the hip include: osteosynthesis, osteotomy, arthrodesis, Girdlestone procedure, arthroscopy, and/or other. Surgical approach was categorized as: straight lateral, posterolateral, anterolateral, anterior, straight superior, or other. An overview of the variable definitions of both the LROI and the model development papers can be found in Table 2. Two predictors had different definitions in the development paper compared to the LROI. In the development paper, surgical approach was categorized as posterior or anterolateral, where the LROI uses six categories. In the external validation, we used the posterolateral versus all other categories to calculate the predicted risk. Also, the predictor previous surgeries was defined slightly different between the development paper and the LROI. Girdlestone procedure, and arthroscopy are not explicitly mentioned as previous contributing surgery in the development paper, but were included in the LROI data. Also, both included 'other' as category. In either case, it is not explicitly stated which operations are included, thus it is

unclear whether the same previous surgeries are included in the predictor. In the external validation, we used the predictors as described above, according to the LROI definition.

Outcome definitions LROI

A revision surgery was defined as the removal or exchange of the inlay, femoral head, acetabulum, and/or femur component, and was registered in the LROI. In models 1 and 2, only revisions within 6 months for dislocation or for periprosthetic fracture were analyzed. Dislocation was defined as recurring dislocation of the hip prosthesis. Periprosthetic fracture was defined as a fracture around the hip prosthesis causing an interruption of the fixation or stability and therefore needing a revision surgery. The reason for revision was reported by the surgeon directly after surgery to the LROI. In the fourth model, all revision surgeries within five years after primary THA were included as event. Model 4 and the LROI use the same definition for a revision surgery. In the paper of model 1 to 3, the exact definition of the outcome was not described, and therefore the authors may have used another definition.
For model 3, the outcome of interest was mortality within 6 months after primary THA. Mortality is obtained from the Dutch national insurance database (Vektis), and linked to the LROI. Vektis contains records of all deaths of all Dutch citizens.

Sample size

No formal sample size calculation was performed. All patients in the LROI who were eligible for the study were included. This resulted in validation cohorts that exceeded the development cohort and recommendations for sample size (12, 13).

Statistical analysis methods

In cohort 1 (model 1 to 3), ASA was missing in 285 patients and age in 71 patients. In cohort 2, BMI was missing in 2,580 patients and age in 45 patients. Due to the low number of missing data points in LROI data (cohort 1: <1%; cohort 2: <5%), and assuming missing completely at random, we decided to do a complete case analysis. Patient age values were excluded if the age was above 105 years (n=17) or below 10 years (n=25). BMI values were excluded if BMI exceeded 70 (n=29) or was below 10 (n=2). These cut-off thresholds were applied according to LROI recommendations (14). The baseline characteristics were described as means and standard deviation (SD) or median and interquartile range (IQR) for continuous variables (as appropriate), and number and percent (%) of total for categorical variables.
To evaluate model performance on LROI data, we assessed discrimination and calibration. Discrimination of the models was assessed by calculating the area under the receiver-operating characteristic curve (AUC). The discrimination reflects the ability of a model to discriminate between those with and those without the outcome.

Table 2. Overview of variable definitions in the development and validation cohorts.

Variable	Definition LROI	Definition Model 1-3	Definition Model 4
Mortality	Retrieved from national insurance database	Dates of death are retrieved from the Population Information System maintained by the Population Register Centre, Finland	-
Revision	Removal or exchange of the inlay, femoral head, acetabulum, and/or femur component	A change or removal of at least one prosthetic component	Removal or exchange of at least one prosthetic component.
Reason for revision	Infection; Wear of cup/liner; periprosthetic fracture; malposition or malalignment; luxation; peri articular ossification; loosening of acetabular component; loosening of femur component; symptomatic metal on metal articulation; Girdlestone; other	Dislocation or periprosthetic fracture of femur or acetabulum reported as main reasons for revision	-
ASA	I / II / III / IV	I / II / III / IV	-
Pre-operative fracture	Primary THA within 5 days after hip fracture (including medial/lateral collum fracture, femoral neck fracture, trochanter femur fracture)	Primary THA for fracture	-
Previous surgeries	Includes: Osteosynthesis, Osteotomy, Arthrodesis, Girdlestone procedure, Arthroscopy, and/or Other	Includes: Osteotomy of acetabulum or femur, Osteosynthesis of tibia or femur, or Other (e.g. arthrodesis)	-
Approach	Straight lateral Posterolateral Anterolateral Anterior Straight superior Other	Posterior Anterolateral (modified Hardinge)	-
Head diameter	22-28 mm 32 mm 36 mm >= 38 mm	28 mm 32 mm 36 mm >36 mm	-

Age	In years	In years	
Type of fixation	Cemented Cementless Hybrid: acetabulum and femur cemented Hybrid: acetabulum and femur cementless Hybrid: acetabulum cemented Hybrid: femur cemented Hybrid: missing which component cemented	Cemented Cementless Hybrid Reverse hybrid	-
Gender	Male Female Non specified Unknown	Male Female	Male Female
BMI	in kg/m^2	in kg/m^2	in kg/m^2
Osteoarthritis	All types of osteoarthritis (including secondary arthritis and coxarthrosis) as primary diagnosis	-	Osteoarthritis as primary diagnosis

For interpretation of AUC values, cut off values <0.7 (poor), 0.7-0.8 (acceptable), 0.8-0.9 (excellent) and >0.9 (outstanding) were used (15). Calibration was evaluated by plotting the observed probabilities against the predicted probabilities of the outcome, and calculating the calibration slope and the intercept (or calibration-in-the-large) (16). Calibration reflects the agreement between the predicted probability of developing the outcome as estimated by the model and the observed outcome. A perfect calibration-in-the-large (or mean calibration) has a slope of 1 and an intercept of 0. A calibration curve close to the diagonal indicates that the predicted probability corresponds well to the observed probability.

After the validation of the models on LROI data, models were updated in two steps (17). First, the intercepts were recalibrated to improve calibration-in-the large by aligning observed outcome rates and mean predicted probability. Second, logistic recalibration was performed to correct miscalibration of the predicted probabilities, to prevent general over- or underestimation of risks. In this step, the model intercepts as well as the predictor coefficients were updated (17). These updated models were re-evaluated by analyzing their discrimination and calibration performance.

All analyses were performed using R software (version 4.2.1; R Foundation for Statistical Computing, Vienna, Austria) with packages rms (v6.3.0) and CalibrationCurves (v1.0.0) (18-20). The study protocol was published before analysis at: https://osf.io/tqu6d/. The study was reported according to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement for prediction model studies (21).

Results

Use of joint registries for external validation

Our literature search resulted in 54 hits, of which 16 papers did not describe a prediction model, and 3 papers described a non-TJA population, and were therefore excluded (Figure 1). This resulted in 35 papers describing one or more prediction models developed for a TJA population. A total of 44 unique prediction models were described in the 35 papers. While the literature search was aimed at outcomes that are available in the LROI, the prediction models also predicted outcomes other than revision or mortality. Complications, or specifically infection, was commonly used as outcome. A total of 193 unique predictors were used in the prediction models, only 31 occurred in more than one model (appendix B). The most prevalent predictors that are not available in the LROI are: diabetes mellitus (used in 9 prediction models), depression (used in 6 prediction models), insurance type (used in 6 prediction models), and opioid use (used in 6 prediction models). Most predictors that are available in the LROI have less than 1% missing data and are either measured in a standardized way

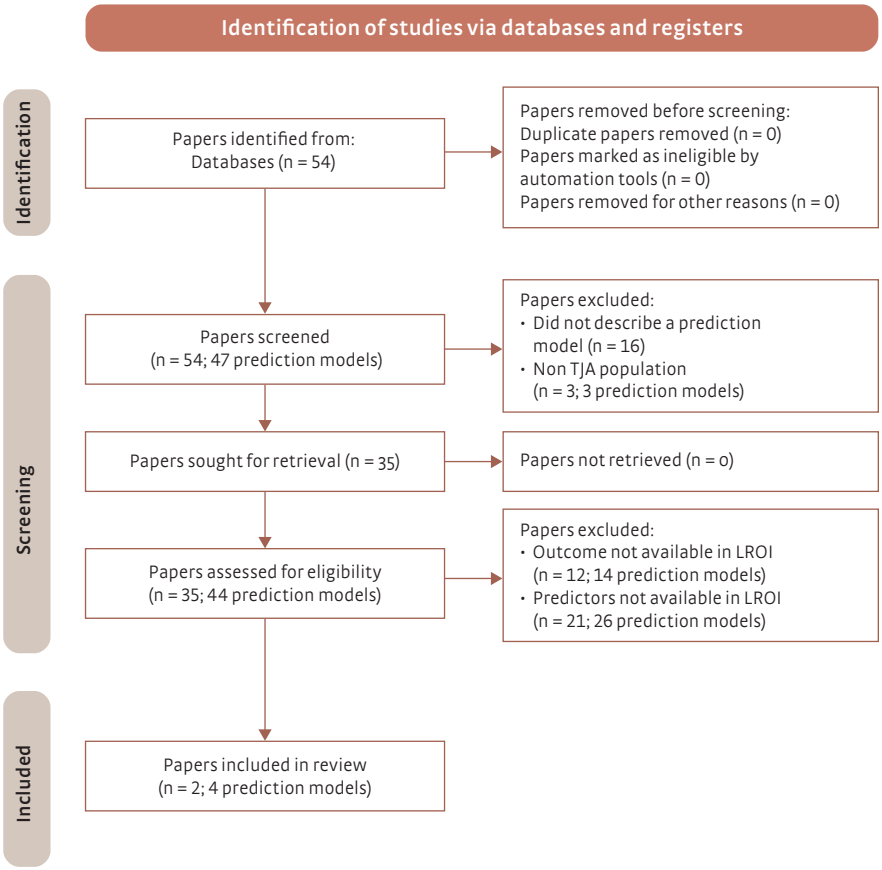

Figure 1: Flow chart of literature search.

or can be harmonized. BMI, which has been recorded since 2014, has a maximum of 4.6% missing data. This may limit the follow-up period for patients when BMI is used as a predictor, potentially impacting the validity of the results.

External validity of published prediction models

Of the 35 papers from the literature search that described 44 prediction models, fourteen models were excluded because the outcome of the model was not available in the LROI, and 26 models were excluded because the prediction models included predictors that were not available in the LROI (Figure 1; see appendix C for prediction model papers and reasons for exclusion). After excluding 40/44 models, four prediction models described in two papers were left (2, 3). Thus, 4 out of 44 models (9%) on a TJA population could be externally validated using LROI data.

Table 3. Baseline characteristics.

	External validation cohort 1 (LROI) (n=178,422)	External validation cohort 2 (LROI) (n=56,675)	Development study model 1-3 (3) (n = 8,640)
Gender			
Female	116,198 (65.1%)	37,132 (65.5%)	4,967 (57.5%)
Age mean (SD)	68.9 (10.5)	68.8 (10.6)	67.6 (10.8)
BMI mean (SD)	27.3 (4.57)	27.3 (4.57)	28.1 (4.8)
missing	3,135 (1.8%)	2,580 (4.6%)	-
ASA			
1	30,832 (17.3%)	11,183 (19.7%)	1,014 (12.0%)
2	114,124 (64.0%)	36,832 (65.0%)	4,065 (48.2%)
3-4	33,181 (18.6%)	8,401 (14.8%)	3,357 (39.8%)
missing	285 (0.2%)	259 (0.5%)	-
Diagnosis			
Osteoarthritis	154,597 (86.6%)	48,942 (86.4%)	7,138 (85.8%)
Fracture	7,918 (4.4%)	1,128 (2.0%)	527 (6.4%)
Inflammatory arthritis	195 (0.1%)	66 (0.1%)	144 (1.7%)
missing	482 (0.3%)	377 (0.7%)	-
Previous surgeries			
Yes	8,421 (4.7%)	2,710 (4.8%)	167 (1.9%)
Approach			
Posterolateral	102,677 (57.5%)	34,605 (61.1%)	6,731 (80%)
Anterior	44,044 (24.7%)	8,261 (14.6%)	-
Anterolateral	8,330 (4.7%)	2,948 (5.2%)	1,688 (20%)
Straight lateral	21,626 (12.1%)	10,477 (18.5%)	-
Other	1,437 (0.8%)	154 (0.2%)	-
missing	308 (0.2%)	230 (0.4%)	-
Head diameter			
22-28 mm	32,736 (18.3%)	14,204 (25.1%)	105 (1.2%)
32 mm	106,498 (59.7%)	30,547 (53.9%)	2,076 (24,7%)
36 mm	36,775 (20.6%)	11,406 (20.1%)	6,130 (73%)
>= 38 mm	513 (0.3%)	143 (0.3%)	89 (1.1%)
missing	1,905 (1,1%)	115 (0.2%)	-
Type of fixation			
Cementless	115,017 (64.5%)	35,387 (62.4%)	5,448 (65.4%)
Cemented	44,727 (25.1%)	15,172 (26.8%)	676 (8.1%)
Hybrid	18,527 (10,3%)	6,005 (10,6%)	2,205 (26.5%)
missing	151 (0.1%)	111 (0.2%)	-
Revision for dislocation <6 months	0.4%	-	0.7%
Revision for fracture <6 months	0.3 %	-	0.5%
Mortality < 6 months	0.6%	-	0.7%
Revision <5 years	-	3.1%	-

NB. The baseline characteristics of the test cohort of model 4 were not described in the article, and thus not included in this table.

External validation cohort

Cohort 1. A total of 178,422 patients received a primary THA between 2014 and 2020 in the Netherlands (Table 3). Mean age of the cohort was 69 years (SD 10.5), and 65% was female. Most patients received a THA due to osteoarthritis (87%). The baseline characteristics of the LROI validation cohort were comparable to the development cohort of model 1 to 3, only ASA and head diameter were differently distributed. The majority of the patients had ASA 2, while in the development cohort ASA 3-4 was more common. In the LROI, in 60% of the surgeries the head diameter was 32 mm, compared to 73% had 36mm in the development cohort. Comparing the outcome prevalence between the cohort on which the models were developed and the LROI validation cohort, revealed a prevalence of revision within 6 months due to dislocation of 0.4% in the LROI, and 0.7% in the development cohort (Table 3). A revision due to fracture within 6 months occurred in 0.3% of the patients in the LROI, and 0.5% in the development cohort. The prevalence of mortality <6 months was 0.6% in the LROI, and 0.7% in the development cohort.

Cohort 2. A total of 56,675 patients received a primary THA between 2014 and 2015. The baseline characteristics were comparable to the patients operated between 2014 and 2020. The baseline characteristics of the development cohort of model 4 were not described in the development paper, and thus could not be included Table 3. The prevalence of revision <5 years was 3.1% in the LROI, and 3.1% in the development cohort.

External validation

Model 1, predicting the risk of revision for dislocation <6 months, had a poor discriminative ability, the AUC was 0.64 (95% CI: 0.59-0.68) in the external validation cohort (Table 4). The AUC of model 2 that predicts risk of revision for fracture <6 months, was 0.67 (0.65-0.70). Model 3 that predicts the risk for mortality <6 months had the best discriminative ability of the four models; with an AUC of 0.79 (0.77-0.80) the discrimination was acceptable. The lowest discrimination was that of model 4, predicting risk of all cause revision within 5 years, with an AUC of 0.53 (0.51-0.54). Discriminative ability of the models in the external validation cohort was similar to the discriminative ability in the development cohorts (Table 4).

All models had far from optimal calibrated risk predictions (Fig. 2a-5a). Model 3, largely underestimated the risk of mortality within 6 months. Predicted probabilities between 1% and 2.5% were lower than observed proportions. The other three models generally overestimated the risk of revision. The intercept and slope are included in the calibration plot. Calibration plots were not presented in the development papers, and therefore could not be compared.

Table 4: Area under the curve (AUC; (95%CI)) for the development cohort and in the LROI dataset.

Model	AUC external validation cohort	AUC test cohort development study
1. Revision for dislocation <6 months	0.64 (0.59-0.68)	0.64 (0.56-0.72)
2. Revision for fracture <6 months	0.67 (0.65-0.70)	0.65 (0.58-0.72)
3. Mortality <6 months	0.79 (0.77-0.80)	0.84 (0.78-0.90)
4. Revision <5 years	0.53 (0.51-0.54)	0.56 -*

* The AUC of model 4 was not described in the paper, and requested from the authors.

Model updating

Calibration of all four models improved slightly by recalibrating the intercept. Logistic recalibration improved the calibration of all models (Fig. 2c-5c). In model 3, the underestimation of probabilities improved to a slight overestimation of the predicted risks above 2%. The calibration of the other models improved to a lesser extent, although the predicted risks were overall more accurate. In model 1, the logistic recalibrated model accurately predicted risks below 2%. In model 2, the logistic recalibrated model accurately predicted risks below 1%. The logistic recalibrated model 4 accurately predicted risks between 3% and 4%. The discrimination of the models did not improve after updating.

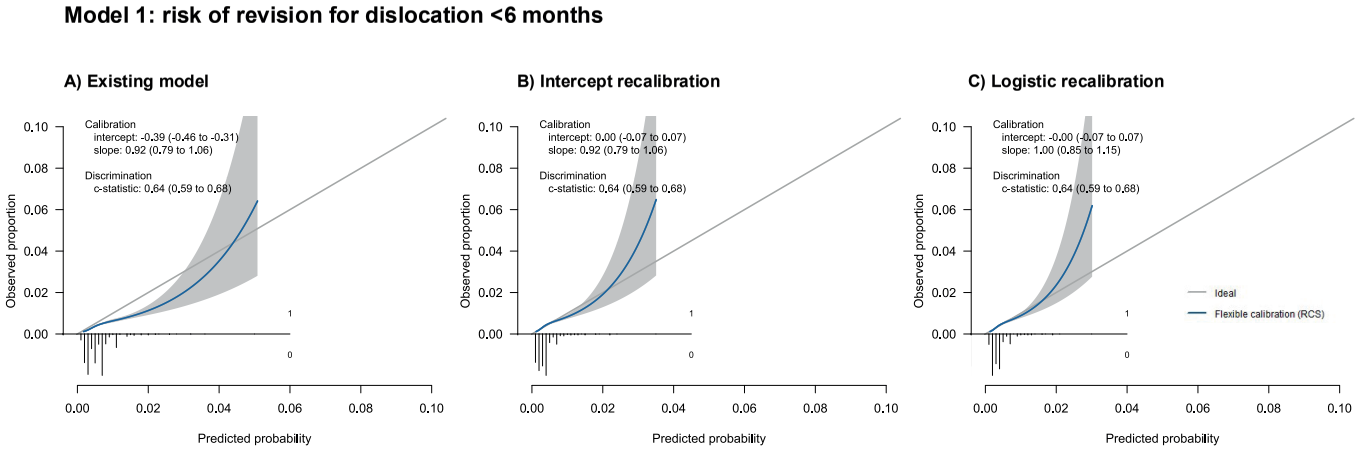

Figure 2: Calibration plots external validation of model 1. A. Calibration plot for predicted risk of revision for dislocation within 6 months after THA based on the existing model, externally validated on LROI data. The calibration curve allows examination of calibration across a range of predicted values. A curve close to the diagonal line (i.e. perfect calibration) indicates that predicted (x-axis) and observed probabilities (y-axis) correspond well. The linear bar chart shows the distribution of patients with (= 1) or without (= 0) an observed outcome. B. Calibration plot for predicted risk of revision for dislocation within 6 months after THA after intercept recalibration. C. Calibration plot for predicted risk of revision for dislocation within 6 months after THA after logistic recalibration.

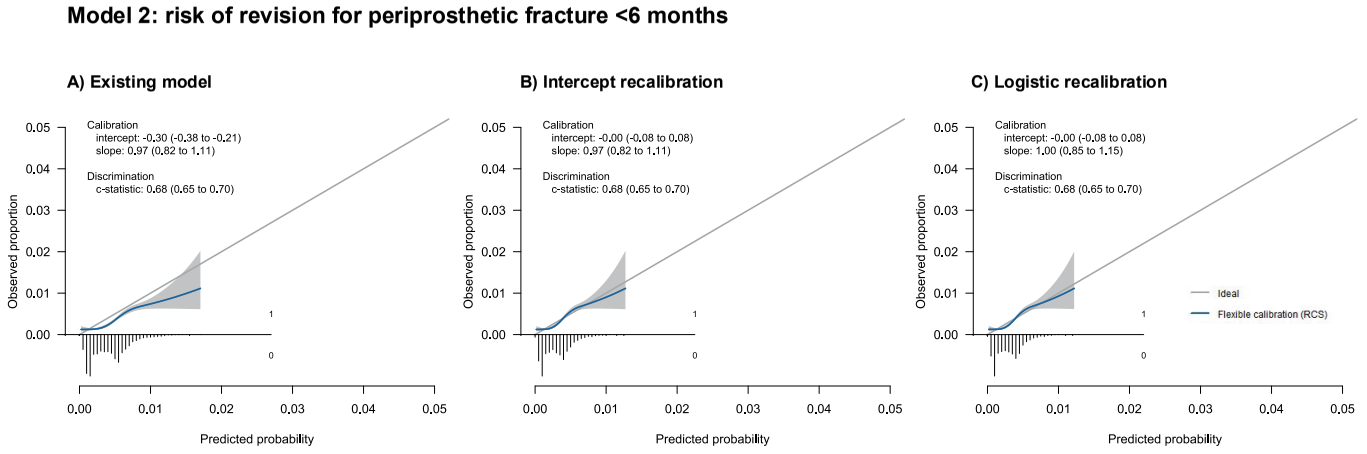

Figure 3: Calibration plots external validation of model 2. A. Calibration plot for predicted risk of revision for periprosthetic fracture within 6 months after THA based on the existing model, externally validated on LROI data. The calibration curve allows examination of calibration across a range of predicted values. A curve close to the diagonal line (i.e. perfect calibration) indicates that predicted (x-axis) and observed probabilities (y-axis) correspond well. The linear bar chart shows the distribution of patients with (= 1) or without (= 0) an observed outcome. B. Calibration plot for predicted risk of revision for periprosthetic fracture within 6 months after THA after intercept recalibration. C. Calibration plot for predicted risk of revision for periprosthetic fracture within 6 months after THA after logistic recalibration.

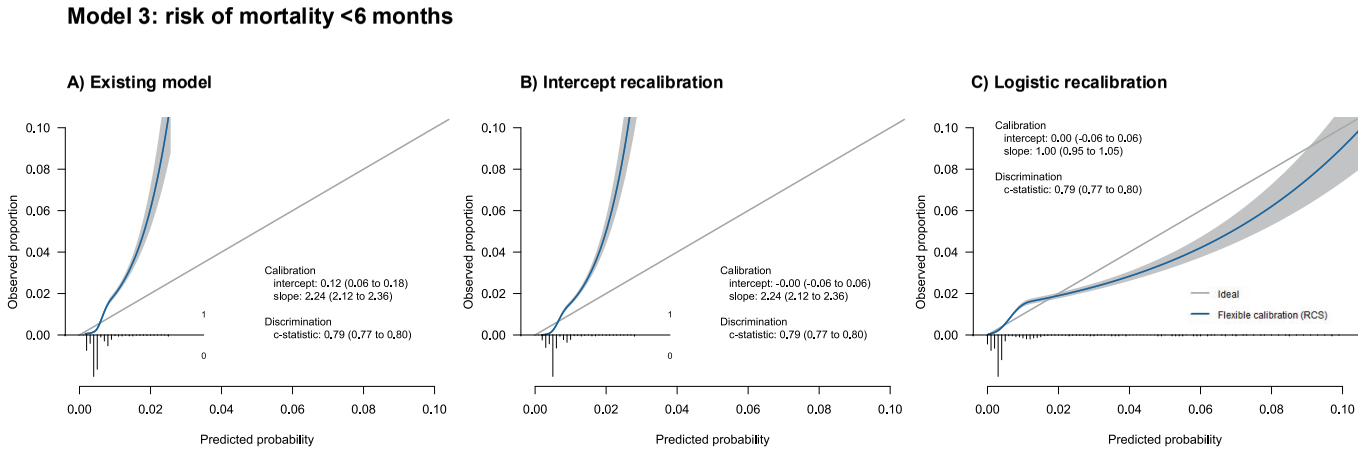

Figure 4: Calibration plots external validation of model 3. A. Calibration plot for predicted risk of mortality within 6 months after THA based on the existing model, externally validated on LROI data. The calibration curve allows examination of calibration across a range of predicted values. A curve close to the diagonal line (i.e. perfect calibration) indicates that predicted (x-axis) and observed probabilities (y-axis) correspond well. The linear bar chart shows the distribution of patients with (= 1) or without (= 0) an observed outcome. B. Calibration plot for predicted risk of mortality within 6 months after THA after intercept recalibration. C. Calibration plot for predicted risk of mortality within 6 months after THA after logistic recalibration.

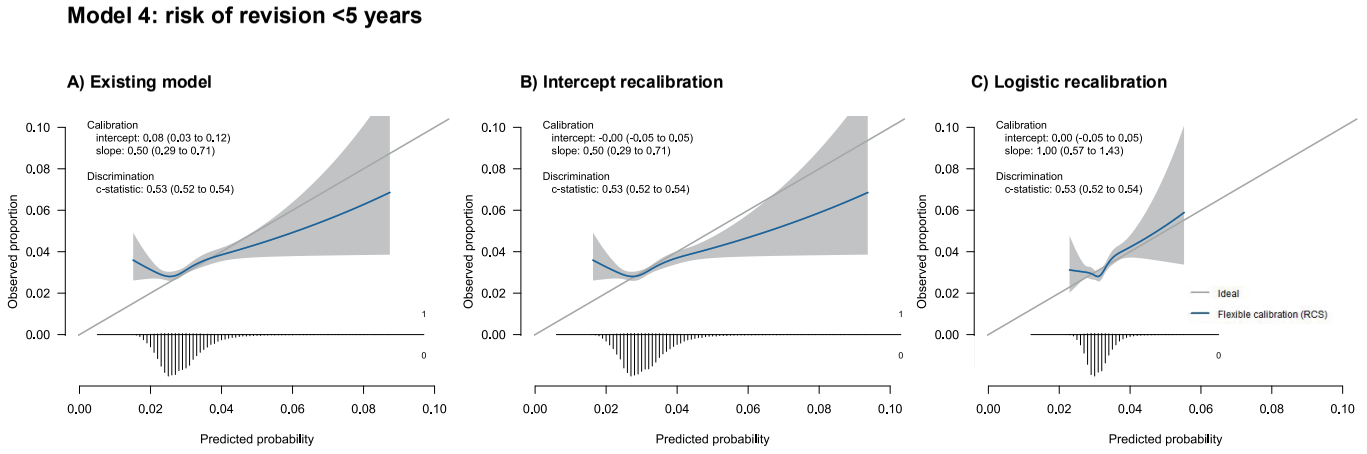

Figure 5: Calibration plots external validation of model 4. A. Calibration plot for predicted risk of revision within 5 years after THA based on the existing model, externally validated on LROI data. The calibration curve allows examination of calibration across a range of predicted values. A curve close to the diagonal line (i.e. perfect calibration) indicates that predicted (x-axis) and observed probabilities (y-axis) correspond well. The linear bar chart shows the distribution of patients with (=1) or without (=0) an observed outcome. B. Calibration plot for predicted risk of revision within 5 years after THA after intercept recalibration. C. Calibration plot for predicted risk of revision within 5 years after THA after logistic recalibration.

Discussion

In this study, we assessed if joint registries can be utilized for external validation of prediction models, and we evaluated the performance of four published prediction models in Dutch clinical practice using data from the LROI. We showed that registry data can be used for external validation, however, the use of registry data for external validation is heavily reliant on the availability of predictors and outcomes in the registry. The predictors that are available in the LROI seem to have sufficient completeness to be used for external validation. The discrimination in the validation cohorts was similar to the discrimination in the development cohorts. Although the models tended to over- or underestimate risks at higher predicted probabilities, they demonstrated good calibration and outperformed individual risk factors at lower predicted probabilities, which cover the majority of the data. However, due to unavailability of calibration plots of the models on development cohort, a comparison between development and validation cohorts could not be made.

Our results support the feasibility of use of registry data for external validation of prediction models. A systematic review by Groot et al. showed that only 10/59 of the available machine learning prediction models for orthopedic surgical outcome were externally validated (22). These 10 models were externally validated in 18 different studies. However, only two studies used registry data for external validation. The other studies did use existing data sets, which were collected in a single institution in the majority of the studies (14/18 studies). Furthermore, another study in arthroplasty patients also used registry data for prediction model development. Garland et al. used data of two nationwide registries to develop and externally validate a prediction model for 90-day mortality after THA (1). These results, together with the current study, show that for future external validation studies, the use of national registries is possible and worth considering.

The critical factor for the use of registry data for external validation is the availability of variables in registries. Out of the 35 papers describing prediction models in our literature search, only two papers described models that could be validated using LROI data. This was due to the unavailability of predictors (e.g. diabetes mellitus or other comorbidities) or the unavailability of the outcome (e.g. infection rate, adverse events). Previous studies aiming to externally validate models using a specific registry also reported limitations as result of variable unavailability (23-25). Slieker et al. (2021) aimed to externally validate models for nephropathy in patient with diabetes mellitus type 2 (23). In this study, only 25% prediction models were excluded due to unavailability of prediction or outcome variables. Hueting et al. (2023) aimed to validate models for breast cancer patients on the Netherlands Cancer Registry (NCR) (24). More in line with our results, 78% of the models were excluded due to variable unavailability. The limited availability of variables can be explained by the aim of

registries to monitor and compare prostheses, and the need to limit the administrative burden. On the contrary, these results can also indicate that important variables are lacking in a registry when the variables show strong predictive value in multiple prediction models. In addition, all models in this study were also developed on registry data, and thus were presumably also based on a limited number of available variables. Because registries are designed to monitor prosthesis designs, the available variables do not necessarily have the strongest association possible with the outcome of interest, which may have affected the predictive performance of the models.

The included prediction models performed suboptimally in the Dutch THA population. The discriminative ability was insufficient in three out of four models. In addition, the calibration plots provide a visual interpretation of how well predicted probabilities align with observed probabilities across the range of predictions. The models provided well calibrated probabilities within a narrow range of predicted probabilities. For example, the model predicting revision for dislocation within 6 months accurately predicted risks below 2%. However, within the lower well calibrated range, it is unlikely that a patient and surgeon jointly would decide to refrain from surgery based on this prediction. A good calibration in higher ranges of probabilities is therefore important as these may affect decision-making. Therefore, understanding model performance in practice is crucial, as poorly calibrated prediction models can result in incorrect and potentially harmful clinical decisions (16). Even if a model appears to be well calibrated and shows good discrimination, this does not necessarily imply it will have added benefit in clinical practice (26).

Models with poor performance are not easily improved. One factor affecting a model's predictive ability is a different prevalence of the outcome in development and validation cohorts. To minimize this effect, the model can be recalibrated by adjusting the intercept or through logistic recalibration. Logistic recalibration refers to the updating of the original regression coefficients with new data to adjust the equation to local and contemporary circumstances (27, 28). Recalibration can be particularly useful to correct miscalibration of the predicted probabilities, when there is general over- or underestimation of risks.

In this study, ASA score was distributed differently in the LROI data set compared to the development cohort. This discrepancy may be explained by differences in background morbidity, variations in access to surgery, and scoring differences (29). The difference in ASA distribution may have prevented perfect calibration on LROI data, even after applying recalibration. Besides intercept updating and logistic recalibration, other updating methods are available to improve existing prediction models to better suit other populations. These methods include adding more predictors and/or re-estimating predictor coefficients (17). Opinions on whether model updating is appropriate in external validation differ among researchers (9). Some argue that changing or adding predictors is essentially constructing a new prediction model,

which in turn requires internal and external validation. Furthermore, it can also be questioned whether extending an existing model to improve poor performance is favorable over developing an entirely new model. Nonetheless, even if models' performance would have been good, clinical utility is not guaranteed and remains to be investigated in clinical impact evaluation (27).

Limitations

Some limitations need to be discussed. The definitions of some predictors differed between the data sets underlying the development and external validation models. The definition of type of fixation and approach were not identical, which may have affected the model performance (30). Harmonization of variables and definitions across joint registries is currently an important topic (31, 32), which will positively influence the feasibility of registry data for validation of models in different countries. Other factors that may affect predictive performance and may limit generalizability of prediction models to other settings are differences in healthcare systems, time period in which patients were treated, and treatment strategies between countries, for example, differences in approach of THA or in the preferred type of fixation (33).

In conclusion, registry data can be used for external validation of prediction models, although it is heavily reliant on the availability of predictors and outcomes in the registry. External validation of the 4 models resulted in suboptimal predictive performance in the Dutch population. In perspective, prediction models should be externally validated to assess their performance in new settings before they are implemented in clinical practice, in order to prevent incorrect predictions. To strengthen the utility of registry data for future prediction models, efforts could focus on incorporating additional relevant predictors and outcomes within registries. This will improve both model development and external validation efforts and help refine predictive accuracy.

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Appendix

A. Literature search

PubMed search (last search April 12th 2023) strategy:

(prediction [title] OR prognostic model [title] OR risk calculator* [title] OR risk model [title] OR nomogram [title] OR risk score [title])
AND arthroplast* [tiab] AND (hip [tiab] OR knee [tiab])
AND (revision [tiab] OR failure [tiab] OR reoperation [tiab] OR mortality [tiab])

B. Frequency of predictors

Predictor	Frequency	LROI	% missing*	Variable definition
Age	29	Yes	0.01%	Standard / harmonized
Gender	21	Yes	0.01%	Standard
ASA	13	Yes	0.4%	Standard
BMI	11	Yes	4.6%	Standard / harmonized
Diabetes mellitus	9	No	-	-
Depression	6	No	-	-
Insurance type	6	No	-	-
Opioid use	6	No	-	-
Charlson comorbidity index	5	Yes	4%	Standard
Fracture	4	Yes	1.3%	Standard
Obesity	4	Yes	4.6%	Harmonized
Osteoarthritis	4	Yes	1.3%	Standard
Previous surgery	4	Yes	unknown	Depends on what surgeries are included in model
Smoking	4	Yes	3%	Standard, though smoking history is absent in LROI
Cancer	3	No	-	-
COPD	3	No	-	-
Drug abuse	3	No	-	-
Fixation	3	Yes	0.6%	Standard / harmonized
Head diameter	3	Yes	0.3%	Standard / harmonized
Operative time	3	No	-	-
Rheumatoid arthritis	3	Yes	1.3%	Standard
Approach	2	Yes	0.7%	Standard / harmonized

Predictor	Frequency	LROI	% missing*	Variable definition
Comorbidities	2	No	-	-
C-reactive protein	2	No	-	-
Dementia	2	No	-	-
Electrolyte disorder	2	No	-	-
Hemoglobin	2	No	-	-
Hypertension	2	No	-	-
Morbid obesity	2	Yes	4.6%	Harmonized
Peripheral vascular disease	2	No	-	-
Preoperative anemia	2	No	-	-

* Based on yearly LROI reports, data available since 2017. Lowest validity percentage reported.
NB: only predictors that occurred in more than one model are included in this table.

C. Literature search results

Our literature search resulted in 54 hits, of which 15 papers did not include a prediction model, and 4 papers described a different population. These papers were therefore excluded from this overview. The remaining papers are listed below. The papers highlighted in blue are included in our proposal and can be externally validated using Dutch Arthroplasty Register data.

First author	Year	Cohort	Outcome	Predictors
Buddhiraju	2023	revision TKA	nonhome discharge	age, BMI, revision for infection, perioperative transfusion, ASA
Klemt	2023	revision TKA	PJI	smoking, age, gender, Medicare insurance, revision indication, depression, diabetes, extremity condition, obesity, drug abuse, >1 open procedure prior to revision TKA
Cuthbert	2022	THA and TKA	time to revision	THA: femoral cement, patient depression, use of pain medication (opioids), gastro-esophageal reflux disease, gender, age and steroid responsive diseases TKA: age, use of pain medication (opioids), use of patella resurfacing, prosthesis stability, prosthesis bearing surface, and patient depression
Klemt	2022	THA	revision within 2 years	Charlson comorbidity index, obesity, depression, nonprivate insurance, diabetes, age, gender
Lu	2022	THA	1 year mortality	age, Charlson Comorbidity Index, ASA, urea, serum Ca2+, postoperative hemoglobin
Onishchenko	2022	THA and TKA	Postoperative major adverse cardiac events	comorbidities: respiratory, cardiovascular, ophthalmological, hypertensive, immune, hematologic, reproductive, central nervous system, all infections, injuries, respiratory infections, musculoskeletal, frailty, integumentary, metabolic, endocrine, digestive, psychiatric, bacterial infections, peripheral nervous system, fungal & infections, neoplasms, otic, allergies, developmental.
Pakarinen	2022	THA	revision for dislocation	mean corpuscular volume, age, gender, Charlson comorbidity index, use of anti-Parkinson drugs, psychiatric or neurological disease, femoral head size, serum creatinine level, ASA, BMI, acetabular fixation, primary reason for surgery, use of antiepileptic drugs, femoral fixation

Sample size	DOI	Reason
52,533	10.1016/j.arth.2023.02.054	Outcome + predictors not available in LROI
1,432	10.1055/s-0043-1761259	not all predictors available in LROI
321,945 + 151,113	10.1186/s12874-022-01644-3	not all predictors available in LROI
7,397	10.5435/JAAOS-D-21-01039	not all predictors available in LROI
246	10.3389/fsurg.2022.926745	not all predictors available in LROI
445,391	10.1161/JAHA.121.023745	not all predictors available in LROI
16,454	10.1371/journal.pone.0274384	not all predictors available in LROI

First author	Year	Cohort	Outcome	Predictors
Sancho	2022	DAIR	failed DAIR	serum CRP levels, positive blood cultures, indication for index arthroplasty other than osteoarthritis, not exchanging the modular components, use of immunosuppressive medication, late acute (hematogenous) infections, methicillin-resistant Staphylococcus aureus infection, overlying skin infection, polymicrobial infection, and age
Wyles	2022	THA	dislocation	age, gender, BMI, neurologic disease, spine disease, spine procedure, THA indication, approach/liner/headsize
Xie	2022	TKA	90 day local complications	reoperation (including implant revision or removal for any reason and manipulation under anesthesia), infection, bleeding requiring ≥4 unit transfusion of red blood cells within 72 hours of surgery, and peripheral nerve injury
Andersen	2021	TKA	2 year revision	gender, BMI, age, pain rest, pain activity, diabetes mellitus, previous surgery in the knee, OKS, EQ-5D, length of stay, duration of surgery, number of comorbidities
Fassihi	2021	THA	30 day mortality	preoperative international normalized ratio, age, body mass index, operative time, and preoperative hematocrit
Garland	2021	THA	90 day mortality	Age, sex, ASA, cancer, CNS disease, kidney disease, obesity
Klemt	2021	revision TJA for PJI	reinfection	previous DAIR, previous surgeries, obesity, drug abuse, depression, smoking, presence of Enterococcus species
Meyer	2021	THA and TKA	adverse events	hospital frailty score, operative time, gender, age, ASA
Shah	2021	THA	complications	Malnutrition, dementia, cancer, COPD, Medicare, chronic arthrosclerosis, renal failure, other insurance, osteoarthritis, workers' compensation, skeletal disorders, Medi-Cal, rheumatoid arthritis, diabetes, morbid obesity, hospital volume, age
Venäläinen	2021	THA	Short-term revision for infection, revision for dislocation, revision for fracture, death	Infection: ASA, gender, BMI, anesthesia Dislocation: ASA, pre-op diagnosis, previous op, surgical approach, head diameter Fracture: ASA, age, fixation Death: ASA, age, preop diagnosis

Sample size	DOI	Reason
64	10.3390/diagnostics12092097	Outcome + predictors not available in LROI
29,349	10.2106/JBJS.21.01171	not all predictors available in LROI
410	10.1177/23259671211073331	Outcome + predictors not available in LROI
538	10.1016/j.jor.2021.03.001	not all predictors available in LROI
77,145	10.1016/j.jor.2021.11.013	not all predictors available in LROI
53,099	10.1302/0301-620X.103B3.BJJ-2020-1249.R1	not all predictors available in LROI
1081	10.1016/j.arth.2020.08.004	Outcome + predictors not available in LROI
565	10.1007/s00264-021-05038-w	Outcome + predictors not available in LROI
545	10.1016/j.arth.2020.12.040	Outcome + predictors not available in LROI
25,919	10.2106/JBJS.OA.20.00091	included

First author	Year	Cohort	Outcome	Predictors
Williams	2021	TKA	90 day mortality	age, gender, cancer, COPD, gout, heart failure, hypertension, kidney disease, osteoarthritis, diabetes mellitus type 2, opioid use, psycholeptics use
Dibra	2020	THA and TKA	discharge destination	age, gender, ambulation, walking aids, use of community support, postoperative caregiver,
Meyer	2020	THA and TKA	adverse events	Hospital Frailty Risk Score, age, sex, ASA
Zhang	2020	TKA	Mega prosthetic failure	motion mode (fixed/hinged), BMI, type of surgery (primary/revision), type of prosthesis, length of bone resection, operative time
Harris	2019	TKA and THA	30 day mortality	Age, ASA, functional health status, bleeding disorders, dialysis, disseminated cancer, sepsis, >10% loss body weight
Jain	2019	THA, TKA, and posterior lumbar fusions	90 day complications, 90 day readmission, and 1 year revision surgery	pre-operative opioid use
Klausing	2019	TKA	postoperative medical complications	Charlson Comorbidity Index, Index of Coexistent Disease, age, hemoglobin, hematocrit, creatinine, leukocytes, c-reactive protein, international normalized ratio, partial thromboplastin time.
Verbeek	2019	TKA	5 year functional outcome	Age, gender, functional KSS, reason for revision, type of bone defect
Harris	2018	TKA and THA in veterans	30 day mortality	Age, CVA, PTCA, dyspnea-minimal exertion, dyspnea rest, albumin, thromboplastin time, wound infection, dementia, ulcers, malignancy, hemiplegia, angina, PVD, ASA
Starr	2018	TKA	revision TKA	Chronic opioid use, age, gender, BMI, diabetes, chronic kidney disease, nonchronic opioid use
Tan	2018	THA and TKA	Periprosthetic joint infection	BMI, gender, government insurance, THA/TKA/revision, prior procedures, comorbidities, smoking, drug abuse
Everhart	2016	TKA, revision TKA, THA, revision THA	30 day infection, 1 year infection	Procedure, COPD, Diabetes mellitus, rheumatoid arthritis, smoking, osteomyelitis, fracture, morbid obesity, bone cancer, reaction to implant, staphylococcal septicemia,

Sample size	DOI	Reason
193,615	10.1007/s00167-021-06799-y	not all predictors available in LROI
716	10.1016/j.arth.2020.05.057	Outcome + predictors not available in LROI
8250	10.1016/j.arth.2020.06.087	Outcome + predictors not available in LROI
214	10.1016/j.arth.2020.05.016	not all predictors available in LROI
107,792	10.1097/CORR.0000000000000601	not all predictors available in LROI
14,734 + 32,667 + 10,681	10.2106/JBJS.18.00502	Outcome + predictors not available in LROI
649	doi: 10.1016/j.arth.2018.12.034	Outcome + predictors not available in LROI
295	10.1007/s00167-019-05365-x	Outcome + predictors not available in LROI
70,569	10.1016/j.arth.2017.12.003	not all predictors available in LROI
32,297	10.1097/AJP.0000000000000544	not all predictors available in LROI
27,717	10.2106/JBJS.16.01435	not all predictors available in LROI
6,789	10.2106/JBJS.15.00988	not all predictors available in LROI

First author	Year	Cohort	Outcome	Predictors
Hussey	2016	Metal-on-metal THA	Revision risk	Harris hip score, blood metal ion levels
Inacio	2015	THA and TKA	Revision surgery	Age, gender, diagnosis (ICD-10), Charlson, ATC code comorbidities, Elixhauser
Paxton	2015	THA and TKA	Revision risk	TKA: Age, sex, BMI, Diabetes mellitus, osteoarthritis, post traumatic arthritis, osteonecrosis THA: sex, age, BMI, osteoarthritis
Sabry	2014	TKA	infection after two-stage revision	BMI, time from index surgery, duration of symptoms, number of previous surgeries, hemoglobin, soft tissue coverage required, previous infection same joint, previous two-stage revision, type of organism, diabetes, immunocompromised, heart disease
Wuerz	2014	THA and TKA	major postoperative complications	Lowest heart rate, estimated blood loss, blood urea nitrogen, type of arthroplasty (primary/partial/revision), ethnicity, ASA, comorbidities, fracture
Bozic	2013	THA	2 year PJI and 90 day mortality	PJI: Gender, age, alcohol abuse, depression, electrolyte disorder, peptic ulcer disease, urinary tract infection, rheumatologic disease, preoperative anemia, cardiopulmonary (cardiac arrhythmia, congestive heart failure, ischemic heart disease, chronic pulmonary disease) comorbidities, and peripheral vascular disease. Mortality: gender, age, electrolyte disorder, hemiplegia/paraplegia, hypertension, hypothyroidism, metastatic tumor, preoperative anemia, coagulopathy, cardiopulmonary (congestive heart failure, chronic pulmonary disease) and psychiatric (psychoses, depression) comorbidities, malignancies, and peripheral vascular disease

Sample size	DOI	Reason
1,709	10.2106/JBJS.15.00685	not all predictors available in LROI
11,848 + 18,972	10.1016/j.arth.2015.06.009	not all predictors available in LROI
22,721 + 41,750	10.1007/s11999-015-4506-4	included
314	10.1016/j.arth.2013.04.016	not all predictors available in LROI
3511	10.1016/j.arth.2013.09.007	outcome not available in LROI
53,252	10.1007/s11999-012-2605-z	not all predictors available in LROI

Chapter 7

Summary and general discussion

The overall objective of this thesis was to enhance the understanding and optimization of outcomes in revision total knee arthroplasty (TKA). To achieve this goal, the following research objectives were formulated:

1. To identify pre-operative factors that are associated with outcomes of revision TKA.
2. To investigate if bone defects before revision TKA can be objectively quantified.
3. To evaluate if registry data are helpful to better understand outcomes of revision TKA.

Summary

The first objective was addressed in the studies outlined in **chapter 2** and **3**. **Chapter 2** was a mapping review that was performed to create an overview of what already is known in literature about prognostic factors associated with outcomes of revision TKA. Using a systematic literature search, we identified 166 eligible studies. Outcomes and prognostic factors that are routinely registered as part of clinical practice or in national registries are studied frequently. Reason for revision, gender, and BMI were the most often reported prognostic factors. The most commonly observed outcomes were re-revision, readmission, and reinfection. However, the mapping review also pinpointed substantial gaps in literature. The important gaps in literature include measurements of physical functioning of the knee, psychological factors (such as anxiety and depression) and sociodemographic variables (such as education level and work status) as prognostic factors. Outcome domains that are important for patients with osteoarthritis, such as quality of life and psychosocial impact, were underrepresented in the existing revision TKA literature. In addition, the costs of revision knee arthroplasty surgery have seldom been studied. It might be useful to evaluate the cost-effectiveness of revision TKA procedures within specific patient subgroups in the current healthcare environment. The evidence map provides a basis for variables that can be considered for new registries, but also to guide future research into what domains require further exploration.

In **chapter 3**, we investigated whether the number of repeat revisions varies depending on the reasons for revision. Secondary, we evaluated how often the reason for repeat revision was the same as the reason for index revision. Data of all index revision surgeries were retrieved from the Dutch Arthroplasty Register (LROI) and included in the study. In the Netherlands, the most common reason for index revision TKA was patellar problems (23%), while in other registries infection and loosening are reported as most common reasons for revision. Reason for revision seemed to be associated with the incidence of subsequent repeat revision TKA. The lowest repeat revision rates were found in patients revised for loosening, malposition, and patellar problems. The worst outcomes were found for revision TKA performed due to

infection: over 1 out of 4 revisions for infection required another surgical intervention. The most common reason for repeat revision after infection was a new or persistent infection, indicating that periprosthetic joint infections (PJIs) are challenging to treat. In other reasons for revision, the pre-existing problem also recurred, although to a lesser extent. After an index revision for instability, stiffness, or loosening, around 30% of the repeat revisions were conducted for the same underlying problem. The data, however, does not allow us to infer whether the same problem recurred, or if the problem remained unresolved after the index surgery. This study confirms the complexity of the treatment required to manage periprosthetic infections. The results also emphasize the importance of a clear diagnosis of the problem before doing a revision TKA, to avert repeat revision surgeries.

This thesis continued with the second research objective, aiming to investigate if we can reliably estimate the severity of bone defects before a revision TKA procedure. Adequate management of bone defects during revision surgery is important for implant fixation and creating a stable knee, and depends on the size and location of the defect. The most commonly used bone defect classification is the Anderson Orthopaedic Research Institute (AORI) classification. This classification is not suitable for revision surgery, because not all anatomic zones are evaluated. Therefore, in **chapter 4** we developed and tested a new bone defect classification for revision arthroplasty. The AORI classification was amended with bone loss evaluation in the metaphyseal and diaphyseal area. We tested the intra- and interobserver reliability of the new classification, and evaluated whether additional CT images improved interobserver reliability. The classification demonstrated a good to almost perfect intra- and interobserver reliability in the metaphyseal and diaphyseal areas. Lower reliability was observed in the epiphyseal area compared to the metaphyseal and diaphyseal areas, likely due to prosthetic components obscuring this region. Evaluating bone defects on both radiographs and CT scans did not improve the reliability. These findings suggest the newly developed classification could be used as a tool for standardized bone defect evaluation in revision TKA patients. However, further testing with observers from other institutions and validation against intraoperative findings is necessary.

Chapters 5 and 6 aim to answer the third objective: to evaluate whether registry data are helpful in better understanding the outcomes of revision TKA. As confirmed in chapter 2 and 3, infection after TKA is one of the most difficult to treat and among the most commonly studied complications (chapter 3). Thus, to ensure unbiased results when studying infection within joint registry data, it is essential to evaluate the validity of infections reported in the registry. In **chapter 5**, we compared the number of revision knee arthroplasties due to an early infection in the LROI with the number of PJIs registered in the National Institute for Public Health and the Environment (RIVM) PREZIES-network. Within one year after TKA the incidence of

PJIs was 0.7% in PREZIES and 0.4% in the LROI. Only 38% of the knee infections registered in PREZIES, were also registered in the LROI. Besides, 35% of the knee revisions for infection in the LROI were not registered in PREZIES. These results show substantial underreporting for the indication infection in the LROI, which may partly be explained by the difference in PJI definition. First, a simple washout surgery of an early infected total knee prosthesis is not registered within the LROI, for registration in the LROI it is required that at least one part of the prosthesis (in knee infection most of the time the polyethylene insert) is exchanged. In addition, the LROI only includes surgically treated infections that were reported as infection by the surgeon based on the clinical suspicion at the moment of surgery, so if after surgery cultures become positive unexpectedly proving that the prosthesis was infected, unfortunately this is often not corrected by the surgeon in the LROI data. This is in contrast to PREZIES that includes all infections regardless of the type of treatment. The underreporting raises major concerns about the validity of registration of infections in the LROI. To improve the capture rate of infections, reoperations without component exchange and non-surgical treatments with antibiotics should be included.

If registry data has been validated and sufficient data is available, it could be used to develop a prediction model. Knowing the predictive factors for poor outcomes in revision TKA may be helpful for better understanding how to improve these outcomes. In **chapter 6**, we illustrated the feasibility of using registry data for the purpose of external validation of existing prediction models. We systematically searched the literature for prediction models developed in patients undergoing TJA. Four prediction models were eligible for external validation based on the availability of the models' predictors in the LROI. All four models were developed for patients undergoing primary total hip arthroplasty (THA), and since none were available for TKA, we had to shift our research focus to models in THA. For the external validation, we included all primary THAs that were performed between 2014-2019 and registered in the LROI. We demonstrated that registry data can be utilized for the external validation of prediction models, although the feasibility heavily depends on the availability of relevant variables within the registry. The models exhibited poor to moderate discriminative ability and poor calibration in the Dutch population. Consequently, given the predictive performance of these models, they do not provide added value in Dutch clinical practice. These findings also highlight the importance of conducting external validation studies.

Discussion and future prospects

Pre – operative factors and choice of outcomes

The first aim of this thesis was to identify pre-operative factors that are associated with outcomes of revision total knee arthroplasty (TKA). The mapping review in chapter 2 presents an overview of what is already studied regarding pre-operative factors associated with revision TKA outcomes. From this mapping review, it could be concluded that the main focus in the literature has been on variables that are routinely collected in patient files or registries, such as comorbidities and BMI. Complications are also often reported in the literature. This is unsurprising, as assessing complications is an important first step in evaluating a surgical intervention.

However, chapter 2 also highlighted a lack of studies focusing on the prognostic value of factors related to mental health status and socio-economic conditions in revision patients. In patients with osteoarthritis (OA), there is strong evidence of a positive correlation between pain severity and symptoms of depression and anxiety (1). It is still unclear whether chronic pain leads to mental health issues or if it results from anxiety or depression (1). These psychological factors are often underrecognized and undertreated, contributing to a further decline in quality of life (QoL) (2). The socioeconomic status (SES) of the patient is another factor that is rarely studied in the revision TKA literature, despite its strong association with higher rates of postoperative complications, poorer health status, and worse preoperative function in patients undergoing primary TKA (3-8). Furthermore, patients with lower SES may be at greater risk of receiving inadequate social support, potentially exacerbating health inequalities (9). According to the Social Determinants of Health (SDH) framework, socioeconomic position affects health equity and well-being through intermediary determinants, including psychosocial factors, behavioral or biological factors (such as nutrition, physical activity, and genetic factors) (10). While it has been demonstrated that mental health and socio-economic conditions have a significantly impact on overall health, their effects remain a gap of knowledge in revision TKA research.

Most studies on outcome of revision TKA have primarily focused on prosthesis survival and occurrence of complications (chapter 2). However, patient satisfaction encompasses more than just the absence of complication (11, 12). For people with OA, the guidelines of OARSI recommend evaluating outcomes across various domains, including physical function, QoL, and pain (11-13). Although physical function and pain have been studied in revision TKA literature, quality of life has rarely been assessed (chapter 2). It is also important to recognize that the definition of a successful surgery can vary from patient to patient. The reasons for undergoing a revision TKA differ among patients, leading to diverse expectations regarding the results. For example, while some patients prioritize pain relief, others may also aim to return to sport. Thus, healthcare providers must acknowledge and manage these expectations to

help patients set realistic goals for revision surgery, ultimately enhancing patient satisfaction (14-18). Tools such as the Canadian Occupational Performance Measure (COPM) or the Patient Specific Functional Scale (PSFS) can assist in defining specific outcome objectives for individual patients, facilitating goal setting and outcome evaluation (19-25).
Future research in revision TKA should focus on addressing existing knowledge gaps. To understand why the 'unhappy patient' is dissatisfied, studies should prioritize outcome domains that matter most to patients, such as quality of life. Using patient-specific outcome assessment such as PSFS can help set realistic goals. Additionally, addressing knowledge gaps requires studying social determinants of health, such as depression, anxiety, and SES, as preoperative factors. Understanding both the direct and indirect effects of these factors on outcomes such as pain, quality of life, and physical functioning can help identify the root causes for dissatisfaction. If these studies confirm the importance of mental health and SES, preoperative mental health assessments could identify those patients who may benefit from additional support to enhance their quality of life. Moreover, discussing the potential impact of SES on revision TKA outcomes with patients could help align expectations and improve satisfaction (7).

Reasons for revision TKA

The severity of periprosthetic bone defects is a crucial factor to be considered before surgery, as these bone defects influence the difficulty of the surgery, the choice of prosthesis and the need for additional fixation options, such as cones or augments (29). To study the effectiveness of various prosthetic options for specific bone defects, a systematic and reproducible evaluation of bone defects, preferrable pre-operative, is necessary. In Chapter 4, we developed a scoring system to classify bone defects for revision TKA, assessed using pre-operative radiographic images. While the reproducibility within and between observers was good in our center, external validation by orthopedic surgeons from other institutions is required to establish its reproducibility. Ideally, the preoperative classification should be validated against intraoperative findings to assess its accuracy. However, since additional bone loss may occur during the removal of the prosthesis, intraoperative evaluation of bone defects is probably not a perfect gold standard for a preoperative classification. However, if a high correlation between preoperative and intraoperative bone defects is established, this classification could be used to compare the effectiveness of treatment options for different bone defect variations.
The reason for revision is one of the pre-operative factors that is often studied in literature (chapter 2). Previous studies have shown differences in outcomes between reasons for revision (chapter 3). Postoperative complications after revision TKA, measures of physical function, and, in some studies, post-surgical pain scores, are

associated with the specific reason for a revision TKA (26-28). The difference in outcomes between reasons for revision are unsurprising, given the range of symptoms and pathologies that are addressed by revision surgery. This underlines the importance of evaluating subgroups of revision TKAs based on the underlying etiology, rather than combining all patients together solely based on the fact that they underwent a second or subsequent TKA. Additionally, many knee revision surgeries are performed for multiple reasons, yet most studies report only the primary reason for revision. Therefore, in the future, all reasons for performing the revision should be reported (e.g. malposition of the implant and stiffness) rather than just the main indication.

Evaluating the effectiveness of revision TKA to resolve the initial problem, requires adequate diagnosis and measurement of the underlying etiology. The results from chapter 3 raise the question whether subsequent re-revisions, driven by the same reason as the initial revision, implicate a persistent problem that was inadequately addressed during the initial surgery or whether a similar problem reappeared despite a successful surgery? Unfortunately, the Dutch arthroplasty register only records etiology as a single variable. More detailed diagnostic information and supportive measurements are needed to answer this question. For instance, in infections, the causal mechanisms are apparent (i.e., the presence of a specific microorganism). Thus, post-operatively, the presence of that microorganism can be assessed again to evaluate whether the surgery successfully eradicated the infection. However, when instability or stiffness is the reason for revision, multiple factors can contribute to these issues, making the underlying cause less clear. This complexity also makes objective diagnostic tests for identifying these causes less evident. Hence, prospective studies focusing on specific reasons for revision are necessary, utilizing accurate diagnostic tests to pinpoint the underlying etiology.

To further explore the different problems leading to a revision, ideally, we need a longitudinal study to assess pain and physical function starting before the primary TKA, as these are the main symptoms to consider a TKA. A longitudinal study allows us to assess patient trajectories over a longer follow-up period. These trajectories can then be compared between patients who underwent subsequent revisions and those who had a successful primary TKA. Hereby, early signs indicative of patients experiencing poor outcomes might be identified. Other factors that can be addressed before or during surgery could also be of interest in the study. For example, patient expectations, conservative treatments that were followed, and HbA1c levels in blood as a reflection on well managed diabetes mellitus. In addition, comparing long-term follow-up data of patients who have had a revision TKA with data of conservatively treated OA and primary TKA patients without reoperation can provide valuable information. Hereby, we can compare the impact of revision surgery in OA patients on physical function against natural age-related decline.

Use of registry data for revision TKA evaluation

The main advantages of using registry data are the size of the datasets and a long follow-up time of patients (30). Also, patients can be followed over time, even if they undergo implant revisions in hospitals other than where the original surgery was performed. Thorough evaluation of arthroplasty surgery typically requires long-term follow-up to assess its success, as key outcomes like implant failure are rare. Achieving this in prospective studies is difficult because lengthy follow-ups of 10 years or more can be costly and may lead to issues with patient compliance. Data in regional or national registries is mainly gathered from medical records and is therefore less burdensome for the patient. Overall, using registry data helps to efficiently use resources by limiting research time and costs compared to performing a new prospective study.

One of the main limitations of registry data is the limited number of variables collected, both in the pre-operative and outcome variables sets. The mapping review in chapter 2 revealed many studies that relied on national or institutional registers, not surprisingly because of the large sample sizes and relatively easy accessibility of the data. Consequently, the research focus tends to be on commonly collected registry outcomes like complications and re-revisions. However, as previously discussed, these outcomes alone do not reflect the success of a surgery. Outcomes in registries that rely on patient-reported data, such as PROMs that have been introduced in the last decade, require time investment from both patients and hospital organizations, and therefore often have low response rates so far.

The limited number of variables available in registries also hampers our attempt to externally validate prediction models using registry data. Unfortunately, there were no suitable models available for revision TKA to validate using registry data, which led to a shift towards studies on total hip arthroplasty (THA). The validation of THA models was also constrained by the limited preoperative variables available in the Dutch Arthroplasty Register (LROI), with nearly 85% of prediction models excluded due to missing relevant variables. This limitation underscores that registry data may not address all research questions and highlights the risk of residual confounding when necessary variables are absent from the registry (31).

The validity of registry data can also pose limitations. In addition to the importance of completeness and coverage, ensuring the validity of all variables in the registry is important to prevent misclassification (31). The problem of misclassification was best illustrated for infections after TKA (chapter 5). Since the results of per-operative cultures are available between two and 14 days after surgery, there is a risk of missing infections if the registry forms are not updated when culture results, received days later, indicate an infection. Unfortunately, it is not common practice for surgeons to correct the reason for revision to periprosthetic infection in the registry once culture data are available. On the other hand, if a surgeon performs a revision for the

diagnosis infection and report this to the LROI, the indication for the surgery can change if no positive cultures are obtained later on. Both situations can lead to misclassification bias if a patient is categorized under the wrong reason for revision (32). In chapter 3 we showed that infections are a serious and difficult to treat complication in knee arthroplasty, with over one in four revision TKAs for infection requiring additional surgery. However, chapter 5 revealed that only 40% of all surgical site infections are registered as such in the LROI. This suggests that the prevalence of a recurrent intervention after an infection, likely exceeds the one in four patients mentioned in chapter 3. To improve the validity of infections in the LROI, it would be beneficial to include preoperative culture results and report all infections, regardless of treatment method, to minimize bias in periprosthetic joint infection (PJI) research based on registry data.

The effectiveness of (surgical) interventions cannot be evaluated with registry data alone. Registries exclusively record data on patients who receive surgical treatment, and many registries include these surgeries only if one or more of the implant components are revised. While it is possible to conduct pre- and post-surgery comparisons using registry data, assessing effectiveness requires a randomized clinical trial (RCT) with a control group (33). Alternatively, registry-based nested randomized trial designs can be useful for phase 4 trials or situations where identifying and recruiting eligible patients is challenging (34). Within the LROI, a registry-nested RCT has been conducted to examine the impact of a quality improvement intervention on patient outcomes following TKA and THA, compared to standard care within orthopedic departments (35). In this study, LROI data was linked and supplemented with hospital data on readmission, complications, and length of stay to limit administrative burden and minimize interference with routine care (36).

Linking databases offers opportunities to improve data quality and utility, but also presents practical challenges related to data quality, data harmonization, and storage of data (39). As mentioned in chapter 5, it is not always possible to match all records when linking datasets based on a set of variables (38). While unique identifiers can facilitate linking multiple datasets, the privacy of patients may be compromised.

Future recommendations

The goal of this thesis was to enhance the understanding and optimization of outcomes in revision TKA. Several factors, including the reason for revision and gender, are known to be associated with revision TKA outcomes. However, additional factors, such as mental health, require further investigation. There is also a need to document well-established predictive factors in greater detail to better understand their impact on outcomes or to tailor the surgical approach accordingly. For example, we have made progress in classifying bone defects, but it is essential to assess the reliability and validity of this new classification system before it can be widely

adopted. Additionally, more precise documentation of reasons for revision could provide insights into why some patients need repeated revision TKA for the same issue. Registry data can be used to create or validate predictive models, which can offer valuable information on the success rates of upcoming surgeries. To achieve this, I recommend exploring the following areas further:

1. Investigate the impact of depression on pain and quality of life before and after revision TKA through observational studies comparing patients with and without depression. Alternatively, integrate a screening instrument such as Hospital Anxiety and Depression Score (HADS) in joint registry PROMs to examine the association between depressive symptoms and pain severity pre- and post-surgery. HADS could then also be included as a case-mix factor in future studies.
2. Explore SES as a potential factor influencing revision TKA outcomes via registry-based or cohort studies. SES is typically measured through education, income, and occupation, or approximated using patients postal code (3). Health outcomes like complications, physical function, and quality of life could be analyzed in relation to SES, and interventions targeting physical activity, nutrition, or social support may help improve outcomes if SES is found to be associated.
3. Enhance registry data by incorporating measures that accurately reflect the etiology underlying the reason for revision, such as peri-operative cultures for infections. Evaluate instruments to accurately assess reasons for revision, like instability and stiffness. Functional measurements as range of motion and stress X-rays could be assessed, however, other tests may also be appropriate. If reliable measures are found, incorporate them into registries to evaluate whether the initial issue was resolved after revision TKA.
4. Registry data can be expanded with temporary additional data collection to efficiently utilize research resources. Long-term outcomes such as physical function and quality of life can be compared between successful primary TKA patients and those who underwent revisions to assess the effects of a revision. Additionally, it would be interesting to explore whether early signs can be identified that indicate poor outcomes in patients.

In conclusion, this thesis highlights the importance of examining under-explored pre-operative factors that influence outcomes in revision total knee arthroplasty (TKA). Future research should aim to fill these knowledge gaps and improve data collection to better address the specific needs of patients. By taking these steps, we can significantly enhance patient satisfaction and overall surgical success.

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Chapter 8

Nederlandse samenvatting

Het hoofddoel van mijn proefschrift was inzicht krijgen in welke gegevens belangrijk zijn om te begrijpen welke factoren van invloed zijn op de resultaten van revisie van een totale knieprothese (TKP). De volgende subdoelstellingen zijn geformuleerd:

1. Het identificeren van preoperatieve factoren die geassocieerd zijn met de uitkomsten van revisie TKP.
2. Het onderzoeken of we botdefecten objectief kunnen kwantificeren vóór revisie TKP.
3. Het evalueren van het gebruik van register data voor onderzoek dat tot een beter begrip van de uitkomsten van revisie TKP moet leiden.

Het eerste doel werd behandeld in de studies beschreven in **hoofdstukken 2 en 3**. In **hoofdstuk 2** hebben we door middel van een mapping review een overzicht gemaakt van de huidige literatuur over prognostische factoren die van invloed zijn op de uitkomsten van revisie van een totale knieprothese (TKP). We doorzochten systematisch de literatuur en identificeerden 166 relevante studies. Op dit moment zijn de meest onderzochte prognostische factoren en uitkomsten de factoren die routinematig worden geregistreerd in de klinische praktijk of nationale registers. Reden voor revisie, geslacht en BMI werden het vaakst gerapporteerd als prognostische factoren, terwijl her-revisie, opname en her-infectie de meest beschreven uitkomsten waren. De mapping review identificeerde echter ook enkele hiaten in de literatuur. Uitkomstdomeinen zoals fysiek functioneren, pijn en kwaliteit van leven worden v eel minder vaak onderzocht. Bovendien worden socio-demografische variabelen (zoals opleidingsniveau en werkstatus) en het mentale welzijn van de patiënt zelden onderzocht, terwijl deze factoren belangrijk zijn gebleken voor patiënten met osteoartritis. Dit literatuuroverzicht biedt een basis voor het overwegen van deze variabelen in nieuwe registraties en kan toekomstig onderzoek richting geven aan de domeinen die verdere verkenning vereisen.
In **hoofdstuk 3** onderzochten we of het aantal re-revisies (tweede revisies) varieerde voor de verschillende redenen voor de initiële revisie. We evalueerden ook hoe vaak de reden voor de re-revisie overeenkwam met de reden voor de oorspronkelijke revisie. Voor deze studie maakten we gebruik van gegevens van alle eerste revisie-operaties uit het Landelijke Registratie Orthopedische Interventies (LROI). In Nederland was een patella probleem (23%) de meest voorkomende reden voor initiële revisie TKP, terwijl in registers van andere landen infectie en loslating als meest voorkomende redenen voor revisie worden gerapporteerd. Er werd een associatie gevonden tussen de reden voor de initiële revisie en de incidentie van re-revisies. Patiënten die een revisie ondergingen vanwege loslating, malpositie of patella-problemen hadden de laagste incidentie van een re-revisie. De hoogste incidentie werd echter gezien bij revisies voor infectie: meer dan een op de vier revisies voor infectie vereiste een vervolgoperatie. Re-revisies na infectie werden meestal veroorzaakt door een nieuwe

of aanhoudende infectie. Hoewel ook andere revisie-redenen vaak weer opdoken, was dit in mindere mate het geval. Na een initiële revisie voor instabiliteit, stijfheid of loslating werd ongeveer 30% van de re-revisies uitgevoerd voor hetzelfde probleem. Uit de data kunnen we echter niet concluderen of hetzelfde probleem zich opnieuw voordeed, of dat het probleem onopgelost bleef na de initiële chirurgie. Deze studie bevestigt de complexiteit van de behandeling van peri-prothetische infecties en onderstreept het belang van een duidelijke diagnose van het probleem voordat een revisie TKP wordt uitgevoerd, om het risico op re-revisies te verminderen.

Het tweede onderzoeksdoel van het proefschrift richtte zich op het onderzoeken of we de ernst van botdefecten bij revisie TKP betrouwbaar kunnen inschatten. Een adequate behandeling van botdefecten tijdens revisiechirurgie is cruciaal voor een goede fixatie van het implantaat en het creëren van een stabiele knie, waarbij de grootte en locatie van het defect bepalend zijn. De meest gebruikte classificatie voor botdefecten is de Anderson Orthopaedic Research Institute (AORI) classificatie, maar deze is niet optimaal voor revisiechirurgie omdat niet alle anatomische zones worden beoordeeld. In **hoofdstuk 4** hebben we een nieuwe classificatie voor botdefecten bij revisie-artroplastiek ontwikkeld en getest. Deze nieuwe classificatie breidt de AORI-classificatie uit met de evaluatie van botverlies in de metafyse en diafyse. We hebben de intra- en inter-beoordelaarsbetrouwbaarheid van deze classificatie getest en onderzocht of aanvullende CT-beelden de betrouwbaarheid verbeterden. Over het algemeen bleek de betrouwbaarheid goed tot bijna perfect, hoewel deze lager was in de epifyse vergeleken met de metafyse en diafyse, waarschijnlijk door de interferentie van het implantaatmetaal in dat gebied. Het combineren van röntgenfoto's en CT-scans verbeterde de betrouwbaarheid niet. De resultaten van **hoofdstuk 4** suggereren dat de nieuwe classificatie kan worden gebruikt voor een gestandaardiseerde evaluatie van botdefecten bij revisie TKP patiënten. Verdere studie met beoordelaars uit andere instellingen en validatie tegen intra-operatieve bevindingen is echter noodzakelijk om de classificatie verder te onderbouwen.

De volgende twee hoofdstukken droegen bij aan het behalen van het derde subdoel, het evalueren van het gebruik van registratiedata om de uitkomsten van revisie TKP beter te begrijpen. Zoals beschreven in **hoofdstuk 2 en 3**, is infectie na TKP een van de moeilijkst te behandelen en meest bestudeerde complicaties (**hoofdstuk 3**). Het is daarom essentieel om de validiteit van infecties te evalueren om betrouwbare onderzoeksresultaten te waarborgen bij studies naar infecties die gebruikmaken van registerdata.

In **hoofdstuk 5** vergeleken we het aantal revisies van TKA en totale heupprothesen (THP), als gevolg van een infectie, in de LROI met het aantal periprosthetische infecties (PJIs) geregistreerd in het PREZIES-netwerk van het Rijksinstituut voor Volksgezondheid en Milieu (RIVM). Binnen één jaar na TKP was de incidentie van PJIs 0.7% in PREZIES en 0.4% in de LROI. Slechts 38% van de knie-infecties geregistreerd

in PREZIES werden ook geregistreerd in het LROI. Omgekeerd werd 35% van de knie-revisies wegens infectie in de LROI niet geregistreerd in PREZIES. Deze resultaten wijzen op aanzienlijke onderrapportage van infecties in de LROI, deels door verschillen in de definitie van PJI. In de LROI worden alleen infecties geregistreerd waarbij ten minste één onderdeel van de prothese (meestal het polyethyleen bij infectie) wordt vervangen. Bovendien rapporteert de chirurg een infectie in de LROI op basis van klinische verdenking tijdens de operatie, maar worden positieve kweekresultaten na de operatie vaak niet gecorrigeerd in de LROI-gegevens. PREZIES omvat daarentegen alle infecties, ongeacht de behandeling. De onderrapportage roept vragen op over de validiteit van de registratie van infecties in het LROI. Om de registratie van infecties te verbeteren, zouden ook heroperaties zonder componentwissel en antibiotica behandelingen moeten worden opgenomen.

Het ontwikkelen van een predictiemodel om de kans op succes van een revisiechirurgie te voorspellen kan alleen wanneer er voldoende en gevalideerde data beschikbaar is, bijvoorbeeld verzameld in een register of cohort. In **hoofdstuk 6** onderzochten we de haalbaarheid van het gebruik van registratiedata voor de externe validatie van bestaande predictiemodellen. We hebben in de literatuur gezocht naar predictiemodellen die zijn ontwikkeld bij patiënten die een TKP of THP operatie ondergingen. Met de beschikbare data in de LROI konden we vier predictiemodellen valideren die voor primaire THP-patiënten waren ontwikkeld. Voor de externe validatie hebben we alle THA's die zijn uitgevoerd tussen 2014-2019 en geregistreerd zijn in de LROI geïncludeerd. Het onderzoek toonde aan dat het mogelijk is om registerdata te gebruiken voor externe validatie van predictiemodellen, hoewel de beschikbaarheid van variabelen in het register een kritieke factor is voor de haalbaarheid. De modellen vertoonden een slechte tot matige discriminerende waarde in de Nederlandse populatie en een slechte kalibratie. Op basis van de voorspellende waarde hebben de gebruikte modellen geen toegevoegde waarde in de Nederlandse klinische praktijk. Deze bevindingen onderstrepen ook het belang van het uitvoeren van externe validatiestudies.

Appendices

Dankwoord
Curriculum Vitae
List of publications
Research data management
PhD portfolio
Theses Sint Maartenskliniek

Curriculum Vitae

Maartje Belt werd op 15 september 1992 geboren te Millingen aan de Rijn. Na het behalen van haar VWO diploma begon zij in 2011 aan de studie Biomedische Wetenschappen aan de Radboud Universiteit Nijmegen. Na het behalen van haar bachelorsdiploma vervolgde ze in 2015 haar studie met de master Biomedical Sciences met hoofdvakken Epidemiologie en Bewegingswetenschappen. Tijdens de master deed ze onderzoekservaring op tijdens een stage bij de afdeling Kinderfysiotherapie van het Radboudumc. De master sloot ze af met een stage bij de afdeling orthopedie van het Copenhagen University Hospital Hvidovre onder begeleiding van Prof. Dr. Anders Troelsen.

Na afronding van de studie is Maartje in 2018 gestart als junior onderzoeker bij de Sint Maartenskliniek. In 2019 mondde dit uit tot een promotietraject rondom het voorspellen van uitkomsten van een revisie knieoperatie. Dit traject werd begeleid door Dr. Katrijn Smulders, Dr. Gerjon Hannink en Prof. Dr. Wim Schreurs, en heeft geleid tot het huidige proefschrift. Momenteel werkt Maartje als epidemioloog bij Bergman Clinics.

List of publications

This thesis

Belt M, Smulders K, Schreurs BW, Hannink G. (2024). Clinical prediction models for patients undergoing total hip arthroplasty: an external validation based on a systematic review and the Dutch Arthroplasty Register. Acta Orthopaedica, 95, 685.

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Belt M, Gliese B, Muharemovic O, Malchau H, Husted H, Troelsen A, Gromov K. (2019). Sensitivity and specificity of post-operative interference gap assessment on plain radiographs after cementless primary THA. Clinical Imaging, 54, 103-107.

Conference abstracts

Belt M, Smulders K, Schreurs BW, Hannink G. External validation of clinical prediction models for patients undergoing total hip arthroplasty using data from the Dutch Arthroplasty Register. ISAR congress, 2022 (oral presentation).

Belt M, te Molder M, Heesterbeek PJ. RSA in revision TKA: difficulties and recommendations. IRSA meeting, 2021 (oral presentation).

Belt M, Hannink G, Smolders JM, Spekenbrink-Spooren A., Schreurs BW, Smulders K. Reasons for revision are associated with rerevised total knee arthroplasties: an analysis of 8,978 index revisions in the Dutch Arthroplasty Register. WAC congress, 2021 (oral presentation).

Belt M, Smulders K, van Houten A, Wymenga A, Heesterbeek PJ, van Hellemondt GG. What is the reliability of a new classification for bone defects in revision TKA based on preoperative Radiographs? EKS congress, 2019 (oral presentation).

Belt M, Gliese B, Muharemovic O, Malchau H, Husted H, Troelsen A, Gromov K. Sensitivity and specificity of post-operative interference gap assessment on plain radiographs after cementless primary THA. DOS congressen, 2017 (oral presentation).

Belt M, Muharemovic O, Gliese B, Gromov K, Husted H, Troelsen A. Intra- and inter-observer variability in computed tomography assessment of gaps after cementless total hip arthroplasty. DOS congressen, 2017 (oral presentation).

Research data management

Ethics and privacy

This thesis is based on the results of research involving human participants (or existing data from published papers), which were conducted in accordance with relevant national and international legislation and regulations, guidelines, codes of conduct and Radboudumc policy. Research Data Management was conducted according to the FAIR principles. For the studies in this thesis ethical approval was not applicable according to the Dutch Medical Research Involving Human Subjects Act. The studies described in chapter 3, 5, and 6 were based on data registered by the Landelijke Registratie Orthopedische Implantaten (LROI). Data from the LROI was received completely anonymous, to ensure the privacy of all patients and hospitals. Data from the LROI was send using via a secured environment used by the LROI, and stored on a server of the Research department of the Sint Maartenskliniek or in the Azure Digital Research Environment (DRE) portal from the Radboudumc. At the end of each project, datasets were returned to and stored at a secured environment of the LROI. When the datasets were sent back to the LROI everything was deleted from the server of the hospital. The data collected for this thesis will be available at the LROI for further analyses for at least 10 years.

Availability of data

All studies are published open access. Preregistrations of the studies can be found on osf.io/ae4g2 . Data of Chapter 2 and 4 are stored on the server of the research department at the Sint Maartenskliniek. The data will be archived for 15 years after termination of the study. Data of Chapter 2 is available on https://maartjebelt.shinyapps.io/review_app/ and is also stored at the Radboud Data Repository in a Data Sharing Collection (https://doi.org/10.34973/axb6-bx55). The Radboud Data Repository is only accessible by project members working at the RUMC. Requests for access will be checked, by a data access committee. Data of Chapter 4 can be found on Open Science Framework (OSF). The datasets of the other chapters are available upon request by the LROI.

PhD portfolio of Maartje Belt

Department: R**esearch, Sint Maartenskliniek**
PhD period: **01/05/2019 – 16/04/2025**
PhD Supervisor(s): **Prof. B.W. Schreurs**
PhD Co-supervisor(s): **Dr K. Smulders, Dr. G.J. Hannink**

Training activities	Hours
Courses	
- EBROK (2018)	42.00
- Analytic Storytelling (2019)	28.00
- Prediction models in health science (2019)	84.00
- Science Journalism and Communication (2020)	84.00
- RIHS - Introduction course for PhD candidates (2020)	15.00
- RIHS PhD introduction course (2020)	21.00
- Mixed models winter course - EpidM (2021)	84.00
- Scientific Integrity for PhD candidates (2021)	28.00
- Effective Writing Strategies (2021)	84.00
- Causal Inference - EpidM ((2022)	24.00
- RU - Achieving your Goals and performing more successfully in your PhD (2022)	28.00
- Introduction to machine learning with R and R studio Radboud Summer School (2023)	56.00
Conferences	
- European Knee Society arthroplasty conference 2019 (2019) (oral presentation)	21.00
- EFORT congress 2020 (2020)	21.00
- World Arthroplasty Congress 2021 (2021) (oral presentation)	28.00
- International RSA meeting 2021 (2021) (oral presentation)	28.00
- WEON conference (2022)	16.00
- International Congress of Arthroplasty Registries (ISAR) 2022 (2022) (oral presentation)	30.00
Other	
- Research lunch Sint Maartenskliniek (journal club) (2018-2022)	28.00
- Junior refereren epidemiologie – Klinische predictiemodellen (2020)	42.00
- Junior refereren epidemiologie – Risk assessment (2020)	28.00
- Junior refereren epidemiologie – Innovative study designs (2021)	42.00
- Junior refereren epidemiologie - Genetische epidemiologie (2021)	42.00
- Junior refereren epidemiologie - Pharmacoepidemiology (2022)	42.00
Teaching activities	
Lecturing	
- Workshop Data Visualisation (2022)	10.00
- BMW jaar 1 onderwijs (2022)	28.00
- Journal Club (2022)	20.00
Total	**1004.00**

Theses Sint Maartenskliniek

Ensink, C. (2025) Sensing the path to mobility - advancing gait rehabilitation with sensor technology. Radboud University Nijmegen, Nijmegen. The Netherlands.

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Verhoef, L. (2019). Effective and efficient use of bDMARDs in rheumatoid arthritis. Radboud University Nijmegen, Nijmegen. The Netherlands.
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Bikker, I.(2018). Organizing timely treatment in multi-disciplinary care. University of Twente, The Netherlands.
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