# Introduction

Periprosthetic joint infection (PJI) is the most devastating of early complications after total hip arthroplasty (THA), mainly due to its association with increased mortality, re-operation risk, long-term antibiotic treatment, and often persistently impaired quality of life1. Many risk factors for the development of PJI are identified, with anaemia, diabetes, and obesity being important, to some extent modifiable risk factors, whereas advanced age and male sex are examples of non-modifiable risk factors2–6. Individualized PJI risk stratification would be a highly relevant tool in the pre-operative assessment of patients scheduled for THA. Both the American Society for Anesthesiologists’ (ASA) classification or considerably more complex comorbidity indices can be used for risk profiling, but their use is rather challenging. Although high ASA class is a risk factor for worse clinical outcomes, it was never developed for the purpose of predicting PJI7. The Charlson and Elixhauser comorbidity indices are based on 17 or 31 conditions according to the International Classification of Diseases (ICD), respectively, but they are cumbersome to use in a clinical setting, and they were also not designed for prediction of specific adverse events after THA. The same is true for the Rx Risk V-classification with 46 conditions codified along the Anatomical Therapeutic Chemical (ATC) Classification8. Several attempts have been made at developing prognostic individualized risk prediction models for clinical usage, with the Universal American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) Surgical Risk Calculator being one of the first9,10. Additional models have since been derived on US or Australian cohorts, but none has gained general acceptance10–12. This is mainly due to often limited, sometimes single-center based samples, low discriminating ability or sub-optimal calibration of the prediction models, or the absence of external model validation. We therefore aimed to develop a prognostic prediction model of PJI within 90 days after THA that is based on easily accessible data that are available in the setting of clinical decision-making. Furthermore, we aimed to validate the model both internally in Sweden, as well as externally on a Danish national cohort.

# Patients and Methods

We used data from the Swedish Hip Arthroplasty Register (SHAR) for model derivation and internal validation of discrimination and calibration. The best model was then validated externally on a cohort from the Danish Hip Arthroplasty Register (DHR). We followed the TRIPOD checklist for the reporting of the study.

## Derivation cohort (Sweden)

The derivation cohort was obtained from SHAR 2008-2015, with the choice of 2008 as the starting year because registration of ASA class and body mass index (BMI) was initiated then. Deterministic data linkage was achieved by using personal identity numbers that are assigned to all Swedish residents at birth or immigration13,14. The diagnosis underlying the index THA procedure (categorized into primary osteoarthritis, secondary osteoarthritis, sequelae after childhood hip disease, avascular necrosis of the femoral head [AVN] and inflammatory joint disease), type of THA fixation (cemented or uncemented stem and cup respectively), age at index surgery, sex, BMI prior to surgery, ASA class at the time of surgery, type of hospital, and year of surgery, were obtained from the SHAR. Data on comorbidities recognized during one year prior to index surgery, were obtained from the National Patient Register (NPR) where diagnoses based on in- and outpatient episodes in all private and public hospitals are coded according to ICD-10 together with admission and discharge dates. Data on marital status and the educational level of patients were obtained from the longitudinal integration database for health insurance and labour market studies (LISA) from Statistics Sweden. The SHAR has completeness of 96-98 % and 100 % coverage (82 hospitals in 2020)15, the LISA has coverage of 98 % with 85 % accuracy, and completeness for the NPR is above 99 % and the positive predictive value is 85-95 %. Death dates were linked from the national population register. Only the last operated hip was considered for patients with bilateral THA16. Patients with missing information on ASA class, or an ASA class of IV and above, were excluded, as were patients with missing information on BMI or a measurement above 50. Patients with missing information on educational levels or the type of hospital performing index surgery were also excluded, as were children under the age of 18.

## External validation cohort (Denmark)

Danish THA patients were operated from 2016 until the last of September 2018. This period was chosen due to availability of ASA and BMI data and possibility for all patients to have 90 days of follow up.

All surgery related variables, ASA and BMI were obtained from the DHR. The DHR is a clinical quality database established in 1995 on all primary and revision THA surgeries, with registration completeness of more than 95 % during the last decade for both primary and revision THAs17. All hospitals performing THA in Denmark (40 in 2019) are included in the register. The Danish National Patient Register holds data on ICD-10 codes as well as all procedures codes for hospitalizations and outpatient visits at Danish public and private hospitals18. Data on education and civil status were obtained from Statistics Denmark19.

Similar exclusion criteria were applied for diagnosis, ASA class, BMI and bilateral prosthesis. Education and type of hospital were not used in the final model and therefore not required for the Danish patients. Most people in the Swedish cohort were of age 35 to 99. We therefore chose to validate the model for this age group only.

## Definitions of covariates and outcomes

The Charlson and Elixhauser comorbidity indices are based on the presence of ICD-10 codes grouped into 17 and 31 categories each20. Such codes were identified from reported in- and outpatient hospital visits recorded in the national patient registers during one year prior to surgery. Diagnostic categories from those indices were combined to define 21 categories of comorbidity that were chosen in order to be easily identifiable in a clinical setting (Supplementary Tab. 3).

Some of the combined comorbidities were observed for less than 10 patients with or without PJI, and these diagnoses were not considered as potential predictors to reduce the risk of overfitting the model to spurious events.

PJI was defined by the occurrence of relevant ICD-10 or procedural Nordic Medico-Procedural Committee (NOMESCO)-codes recorded in the national patient registers for hospital visits within 90 days of THA (Supplementary Tab. 4), or if the patient was reported to SHAR or DHR as re-operated due to infection within the same time frame.

## Model development

Model development was performed by bootstrap ranking and a logistic least absolute shrinkage and selection operator (LASSO)21–23. Age was normalized prior to modelling, and the estimated coefficients thus indicated variable importance on the same scale as categorical variables. BMI was divided into four categories based on the six intervals proposed by the World Health Organization (WHO; BMI : under- or normal weight, : overweight, : class I obesity, and BMI : class II-III obesity).

Ten-fold cross validation was performed with a range of potential penalty values (:s) in the LASSO model, keeping the that minimized the mean cross-validated deviance. 100 bootstrap samples were then drawn from the observed data set.

Logistic LASSO regression was performed for each sample using the chosen as penalty term. Regression coefficients were ranked based on their absolute values as a measure of variable importance. We then used Bayesian methods to estimate a posterior distribution and to identify two change points in a linear segmented piecewise regression model. The second change point was then used as a break-point. Influential predictors with absolute coefficients value above this point scored a point and the entire process was repeated 100 times, yielding 10,000 bootstrap samples in total. Potential predictors that were selected at least 10 out of 100 times were then used in a main effects multivariable logistic regression model without penalty and without pre-normalization of age. An even more parsimonious “reduced” model with potential predictors chosen at least 80 out of 100 times was evaluated for comparison. Odds ratios for the final models were estimated with 95 % confidence intervals based on the whole derivation cohort.

## Reference models

Univariable prediction models based on either ASA class, the Charlson, Elixhauser, or the Rx Risk V comorbidity indices were fitted for comparison, as well as multivariable models combining those measures with age, sex and BMI (10 models in total). The Rx Risk V index is a comorbidity index based on medical prescriptions coded by the Anatomical Therapeutic Chemical (ATC) classification system during one year prior to surgery. This data was retrieved from the Swedish and Danish24 national prescription registers and classified according to Pratt et al8.

## Model validation

The main, reduced and the 10 reference models were used to predict the probability of PJI within 90 days for patients derived from the SHAR (internal validation). Receiver operating characteristic (ROC) curves and their corresponding areas under the curve (AUC) were used to describe discrimination with 95 % confidence intervals. The bias-corrected Somers’ rank correlation based on 100 resamples was used to adjust for optimism, but the correction for optimism only affected the third decimals in the presented results, and will therefore not be further discussed. Predicted probabilities and observed proportions were plotted with 95 % confidence intervals to graphically assess model calibration25. Coefficients of determination were estimated by Nagelkerke’s for each model. The baseline model with the lowest () was compared to the other models, by . This is the fraction of new information, or the proportion of added explainable variation for model compared to baseline26.

The derived model was then externally validated on the Danish cohort, both with the coefficient estimates from the Swedish cohort and with new estimates based on the Danish cohort. The 10 reference models, with adopted coefficient estimates, were also applied to the Danish cohort for comparison. Finally, the new coefficient estimates for the derived model, re-estimated with Danish data, were empirically compared to analogues estimates derived from subsamples of the Swedish data with sample sizes to match the Danish cohort (supplementary, Tab 7 and Fig. 7).

## Statistical tools

We used R version 4.1.0 (2021-05-18) (R Foundation for Statistical Computing, Vienna, Austria) with significant packages coder27, decoder, furrr, pROC, rms, tidymodels and tidyverse. We build a shiny-based web calculator to aid clinical usage (<https://erikbulow.shinyapps.io/thamortpred/>).

## Patient and Public Involvement

Patient representatives are elected as ordinary members of the steering committees for SHAR and DHR, where the development of shared decision making has been discussed. Our web calculator will be available for (potential) patients and the public.

## Ethical approval

Ethical approval for this study was obtained from the Regional Ethical Review Board in Gothenburg (360-13). The study was approved by the Danish Data Protection Agency (journal number 2015-57-0002) and recorded at Aarhus University (journal number 2016-051-000001).

# Results

## Study participants

We included 88,830 patients (44 % males) with a mean age of 68 (SD = 11) years in the derivation cohort from the SHAR (Fig. 1). 2.45 % (n = 2,173) of these developed a PJI within 90 days (Tab. 1). The proportion of patients with ASA class III was 17 % (n = 14,945); 24 % (n = 21,393) had at least one comorbidity according to the Charlson comorbidity index, 43 % (n = 38,617) according to Elixhauser index, and 71 % (n = 62,874) had medications classified according to Rx Risk V.

In addition, 18,854 patients (42.1 % males) with a mean age of 70 (SD = 11) years were included in the external validation cohort (Fig. 2). 2.2 % (n = 410) of these developed a PJI within 90 days (Tab. 1). The proportion of patients with ASA class III was 18 % (n = 3,334); 14 % (n = 2,722) had at least one comorbidity according to the Charlson comorbidity index, 22 % (n = 4,101) according to Elixhauser index, and 56 % (n = 10,625) had medications classified according to Rx Risk V.

## Model development and internal validation

Patients with AIDS/HIV, coagulopathy and weight loss were uncommon, why these comorbidities were excluded as potential predictors prior to further modelling.

Results from the 100 bootstrap replicates for variable selection were mostly coherent. Diagnosis, BMI and some comorbidities where selected each time. Age was selected 82 out of 100 times, but some factors, such as civil status and type of hospital, were only sporadically selected (Supplementary Tab. 5).

The reduced model (variables with in Tab. 5) included the underlying diagnosis for THA, BMI, ASA class, sex, age, and the presence of arrhythmia, CNS disease, fluid electrolyte disorders, liver disease or lung and airways disease with estimated coefficient values in Tab. 2.

ROC-curves and AUC-values for the main and reduced models were very similar, and for simplicity, we therefore focused on the reduced model.

The reduced model had an AUC = 0.68 (95 % CI: 0.66 to 0.69), whereas univariable models with ASA class (AUC = 0.59, 95 % CI: 0.58 to 0.60), the Charlson comorbidity index (AUC = 0.56, 95 % CI: 0.55 to 0.57), the Elixhauser comorbidity index (AUC = 0.58, 95 % CI: 0.57 to 0.60), and Rx Risk V (AUC = 0.58, 95 % CI: 0.57 to 0.59) had less discriminatory abilities (Fig. 3 left panel and 4 left panel). The univariable model with the Charlson comorbidity index had the lowest AUC and Nagelkerke’s 0.73, and compared to this model, the fraction of new information for the reduced model was 84 % (Tab. 6).

The reduced model had good internal calibration for predictions up to 10 % (Fig. 6). Estimated probability density curves for patients with and without PJI were partially overlapping, but patients with PJI had on average higher predicted probabilities for this outcome (Fig. 5).

## External validation

The reduced model derived from the Swedish cohort produced a very similar ROC curve when applied to the Danish cohort (Fig. 3 right panel), and its AUC value was 0.66 (95% CI: 0.64 to 0.69). This did not change for the model with re-estimated coefficient values based on the Danish cohort (0.67, 95 % CI: 0.65 to 0.7). AUC values for some of the reference models, estimated on the Danish cohort, did differ from the Swedish cohort, but all those models were less accurate (had broader 95 % CIs) than the reduced model (Fig. 4 right panel). The re-estimated model coefficients of the reduced model were coherent with the estimates based on the Swedish data (supplementary Tab. 7).

Calibration was good for predictions up to 3 %, with some tendency to over-estimating higher probabilities, which improved after initial re-calibration of the model intercept to the Danish PJI incidence (Fig. 6).

# Discussion

## Principal findings

A model based on the underlying diagnosis for THA, BMI, ASA class, sex, age, and the presence of arrhythmia, CNS disease, fluid electrolyte disorders, liver disease or lung and airways disease was better at predicting PJI within 90 days after THA than models based on either ASA class or the Charlson, Elixhauser or Rx Risk V comorbidity indices, with or without adjustments for age and sex, in terms of AUC, Nagelkerke’s and calibration.

## Strengths and weaknesses

Our external validation is a strength, which showed that the model works equally well in Denmark, despite some perceived differences between the countries, partially explained by different coding routines in each country (Tab. 1).

Both Sweden and Denmark have strived for mass higher education28. This is, to a higher degree achieved via the university sector in Sweden, while the educational system is more diverse in Denmark.29 National comparisons of educational levels are therefore difficult, since the Danish student register does not include adult- or continuing education30. Patient distribution among ASA classes were similar in both countries, but the comorbidity burden seems to differ. ICD-10 and NOMESCO codes are recorded for both in- and outpatient hospital visits in the national patient registries in both countries, but the recording of (optional) secondary diagnoses is 23 % in Denmark18, compared to 47 % in the Swedish cohort. Serious comorbidities such as cancer, are therefore reported equally in both countries, while for example arterial hypertension, is less documented in Denmark. Also, patients with chronic conditions, such as diabetes, are more commonly treated in primary care settings in Denmark, and are therefore less reported to their national patient register18. The RxRisk V index is a weighted index, which is difficult to compare without further analysis. Prescription patterns might differ by indications based on different national guidelines, different subsidization, and different medications sold over-the-counter. Also, the Danish, but not the Swedish, national prescription register, includes prescriptions from nursery homes and other long-term care facilities. Taken together, the similarities between the countries might be more pronounced than indicated by Tab. 1.

However, the difference in the mode of THA fixation, with a dominance of cemented components in Sweden and much more widespread usage of uncemented components in Denmark is tangible and has been described elsewhere31.

## Strengths and weaknesses in relation to other studies

Cancer seems to confer an increased risk of PJI in several observational studies3,10,32,33, but this comorbidity was not included in our model. It nevertheless appeared in 57 of the 100 bootstrap replicates (Tab. 5), and could have been included in a less parsimonious model. Neither diabetes was included in our model, but has been in previous risk calculators10,34,35. On the other hand, diabetes is not consistently found to be associated with the risk of surgical site infection or PJI after THA surgery36.

Information on peri-operative hyperglycaemia, morning blood glucose, HBA1c37,38, or low preoperative haemoglobin,5 could have improved our model. But although we had access to the ICD codes defining the presence of anaemia, we had no information on actual laboratory findings. Use of subcutaneously applied Tumour Necrosis Factor-alpha blockers39,40, intra-articular steroid application41 or operating time6,7,42, are also associated with the risk of PJI after THA. However, we chose to only consider factors available before surgery and are thus able to use the model as a tool for shared decision making using the implemented web calculator. This is a strength of our model.

We also confirmed that, although mentioned as risk factors for surgical site infections after joint arthroplasty5,12, prediction models based on the comorbidity indices developed by Charlson or Elixhauser and the RxRisk V index, resulted in poor predictive power. This agrees with previous findings describing that these measures of comorbidity rather poorly predict mortality and patient reported outcomes after THA43,44. However, when used in conjunction with information on age and sex, the AUC for these comorbidity indices increased, although never quite reaching the AUC of our model (Fig. 4 and Supplementary Tab. 6).

## Meaning of the study

Our model can be presented in a simple formula where is the estimated probability, and are the estimated intercept and coefficients (Tab. 2) and are corresponding patient characteristics. For example, a 60-year-old female with normal BMI and primary osteoarthritis without comorbidities would have a probability of 0.7 % of suffering from a PJI within 90 days, whereas an 85-year-old male with overweight, secondary osteoarthritis, psoriasis, dementia and ASA class III would have a probability of 15.1 %. Note, however, that observed proportions above 10 % were rare, and predicted probabilities above this limit are subject to extrapolation.

It should be noted that the aim of prediction is different from statistical inference. As such, confidence intervals presented for the model coefficients (Table 2) were based solely on the final logistic regression model. Additional uncertainty introduced by the variable selection process was not incorporated. Hence, those intervals should not be interpreted in support of any implicit hypothesis testing concerning the relevance of any individual variable. Also, the individual odds ratios should not be interpreted as effect measures of individual relations since some variables are correlated.

The selected variables are nevertheless coherent with previous studies. Patients with primary osteoarthritis seem less prone to developing PJI than patients receiving THA for other reasons3,12,45,46. Obesity is associated with an increased risk of reoperations or adverse events after THA47 and with an increased risk of developing surgical site infections or PJI after total hip or knee arthroplasty4,6,32,34,48. CNS disease (cerebrovascular disease, dementia, hemiplegia, and Parkinson’s disease) has also been previously associated with PJI3, as have male sex10,34,46, liver disease49 and ASA class7,36,50.

THA fixation using cement without antibiotics confers an increased risk of PJI46, but such cement brands were not in clinical use in Sweden during the studied period. We found no indication that the type of fixation was associated with the risk of PJI, and the mode of THA fixation was also not selected as a potential predictor variable in any of the iterations during model development.

## Unanswered questions and future research

The proportion of explained variation (Nagelkerke’s = 4.72 %) was low. The question of what other variables might be needed to further refine prediction models remains open, but information that is notoriously difficult to obtain within the setting of large register studies, such as smoking status, might be of value. In addition, a potential underlying susceptibility to PJI -— as has been described for patients with osteomyelitis -— could be a factor of considerable influence on the outcome, but information on single nucleotide polymorphisms in genes that have been associated with musculoskeletal infections was unavailable to us. Such shortcomings could be addressed by future genome-wide association studies.

## Conclusion

Our results indicate that the risk of early PJI after THA can be pre-operatively assessed by a parsimonious prediction model. We hope that this model, with its accompanying web calculator, will facilitate shared decision-making between physicians and their patients in need of THA.

##### Page break

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# Author contributions

NPH initiated the study. OR managed the ethical review board application in Sweden and ABP in Denmark. EB developed the statistical model. UH and ITA performed the external validation. NPH and EB drafted, and all authors edited and finalized the manuscript.

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# Conflict of interest

All authors have completed the ICMJE uniform disclosure form at <http://icmje.org/downloads/coi_disclosure.docx> and declare: no support from any organisation for the submitted work; OR is principal investigator for research partly founded by Pfizer; OR is register director of the Swedish Arthroplasty Register (SAR) and board member of the International Society of Arthroplasty Registries; NPH has received institutional support from Waldemar Link GmbH, and Zimmer Biomet; NPH is president of the Nordic Arthroplasty Register Association, member of the steering committee of SAR, and Co-Editor of Acta Orthopaedica; no other relationships or activities that could appear to have influenced the submitted work.

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# Figure legends

**Figure 1:** Flowchart with inclusion criteria and number of patients. Data from the Swedish Hip Arthroplasty Register were used for model derivation and internal validation

**Figure 2:** Flowchart with inclusion criteria and number of patients. Data from the Danish Hip Arthroplasty Register were used for external model validation.PAGE BREAK

**Figure 3**: Receiver Operation Characteristics (ROC) curves combines sensitivity and specificity to illustrate discriminative abilities of the different models. The main and reduced models performed almost identical for prediction of PJI within 90 days after surgery. They both performed better than all other models (left panel). The reduced model performed as well when applied to the Danish validation cohort (right panel).PAGE BREAK

**Figure 4:** Area Under the Receiver Operation Characteristics Curve (AUC) as a measure of predictive discriminative ability with 95 % confidence intervals (De-Long). The reduced model performed no different than the main model on the Swedish data, and both of these models performed better than all other models (left panel). Similar models were fitted to the Danish cohort (right panel). Coefficient values based on the Swedish data, Reduced model (SE), performed almost as good as the reduced model (DK) with coefficient values refitted to the Danish cohort.

**Figure 5:** Separation between patients with and without PJI within 90 days versus their predicted probabilities of this event. Most patients did not have PJI, wherefore the pink bars dominate the histogram (left panel; note the scales). A normalized density plot reveals, however, that patients with PJI had, on average, higher predicted probabilities for this adverse event (right panel).

**Figure 6:** Calibration for the reduced model. Proportions of PJI above 10 % were rarely observed and therefore omitted. Internal calibration (green 95 % confidence band) is good; predicted probabilities are similar to observed proportions, as indicated by close proximity to the diagonal line. External calibration with the same model (pink) indicates some over-estimation and less accuracy. This is expected due to smaller sample size in the Danish cohort, and due to national differences. Calibration improves after re-calibration of the model intercept to better resamble the Danish base incidence (blue).