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Patient specific prediction models for complications after total hip- and knee arthroplasty.

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Title Page

(1) Title

Patient specific prediction models for complications after total hip- and knee arthroplasty.

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Abstract

Objective. The aim of the study was to develop prediction models for patients with THA and TKA to predict the risk for surgical complications based on personal factors, comorbidities, and medication use.

Setting. Tertiary Care in outpatient clinic of university medical center.

Participants. 3,776 patients with a primary THA or TKA between 2004 and 2018.

Primary and secondary outcome measures. Multivariable logistic regression models were developed for primary outcome surgical site infection, and secondary outcomes venous thromboembolism, postoperative bleeding, luxation, delirium, and nerve damage.

Results. For surgical site infection, age, smoking status, BMI, presence of immunological disorder, diabetes mellitus, liver disease, and use of NSAID's were included. Liver disease showed to be the strongest predictor with an odds ratio of 10.7 (95%-CI=2.4-46.6). An area under the curve (AUC) of 71.9% (95%-CI=69.4-74.4) was found. Postoperative bleeding and nerve damage showed an AUC of 73.0% and 76.6% respectively. For delirium an AUC of 85.9% was found, and for the predictive algorithms for luxation and venous thromboembolism we found least favorable results (AUC= 58.4% and 66.3%).

Conclusions. Discriminative ability was reasonable for surgical site infection and predicted probabilities ranged between 0.01%-51.0%. We expect this to enhance shared decision making in considering THA or TKA since current counseling is predicated on population-based probability of risk, rather than using personalized prediction. We consider our models for surgical site infection, delirium and nerve damage appropriate for clinical use when taking under- and overestimation of predicted risk into account. For venous thromboembolism and postoperative bleeding caution concerning overestimation should be taken into account.

Keywords. total hip arthroplasty; total knee arthroplasty; surgical complications; prediction; prognosis; comorbidities; medication use

Strengths and limitations of this study.

- The predictors are easily to assess and thereby easily to implement in care
- No additional patient information is needed since data is collected in usual care

- Used data was not primarily registered for research purposes and therefore their detail and accuracy could be less than optimal
- External validity and clinical impact of the models is not determined yet

Introduction

Joint replacement is a recommended intervention for people with end stage hip or knee osteoarthritis.[1] Whether surgery is the best solution depends on many individual factors such as severity of the disease, level of experienced pain and discomfort, medication use, personal circumstances, comorbid diseases, and intended type of surgery.[2-4] Because the decision to have surgery or not is complex, a shared decision making (SDM) process is warranted. This process allows patients and clinicians to discuss treatment options consistent with the patient's values and preferences.[5]

Information on most likely prognosis is central in this dialogue as the clinician provides guidance and information about expected outcomes, including the risk on surgical complications, when facing the decision to pursue or forgo surgery. However, providing personalized information about the risk on surgical complications, based on personal characteristics of the patient, is challenging. Available evidence often consists of average outcomes and current guidelines on prediction of outcome still recommend counselling predicated on population-based probability of risk, rather than using personalized prediction.[6]

To overcome this problem, the development of prediction models is emerging. It has been shown that useful prediction on postoperative outcome can be made predicated on preoperative data like demographic factors, pain scores, and physical functioning measured with Patient Reported Outcome Measures (PROMs), to identify patients at risk of not benefitting from total knee arthroplasty (TKA) in general.[7-9] Another study developed a preoperative prediction model to predict residual complaints on pain, functional outcome and treatment success for individual patients after TKA.[10] To our knowledge, none of the currently available prediction models predict the risk for surgical complications, such as surgical site infections. This is remarkable, as discussing potential risks is an important aspect of SDM.[11 12]

It is known that personal factors including demographic characteristics and comorbidities have an impact on surgical complications,[3] and might therefore serve as basis for a risk prediction model. Therefore, the aim of this study is to develop a prediction model for clinicians and patients with hip- or knee osteoarthritis considering surgery, by predicting risk for surgical complications based on personal factors, comorbidities and medication use.

Methods

Study design and setting

For this retrospective cohort study, we established a cohort of patients who underwent primary total hip- (THA) or TKA between 2004 and 2018 at the Orthopedic department of Radboud university medical center Nijmegen, the Netherlands. Datasets were merged into one centralized database based on patient-number, birthdate and date of surgery.

This study was performed and reported in line with transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD)-guidelines (eTable 1, TRIPOD-checklist).[13]

Data collection

Data used for this study were extracted from (electronic) medical records of Radboudumc, Dutch Arthroplasty Register (LROI), and Radboudumc registry of complications. We primarily extracted comorbidities and medication use from medical records. These data were extracted based on coding and were obtained by three researchers (LS, TW and AT) by use of a standardized operating procedure, and stored in a centralized platform (Castor Electronic Data Capture (EDC)).[14] Data about patient characteristics like age, sex, BMI, smoking status, American Society of Anesthesiologists (ASA)-classification and diagnosis for surgery were extracted from LROI. Furthermore, date of surgery, type of surgery (primary or revision), surgery side, and type of implant were extracted.[15] From the register of complications we extracted all surgeries and complications which occurred within one year after THA or TKA.[16] In this registry, surgery related orthopedic complications were registered as well as other medical complications.[17] All complications were registered by location code combined with a code for the nature of the complication.[16] Some registrations were unclear and could refer to one of predefined complications and were therefore checked in medical records by LS. For all included location- and nature of complication codes per surgical complication, see eTable 2.

Inclusion and exclusion criteria

Patients were eligible for inclusion in the cohort if the surgery concerned primary THA or TKA. We defined primary THA or TKA as the first time a total prosthesis is placed. Revision arthroplasty was defined as any change (replacement, removal, or addition) of one or several components of the joint

prosthesis.[15] We expected revision arthroplasty to influence risk for complications negatively, therefore revision arthroplasty was excluded for this study.

Outcome (dependent variables)

Prediction models were developed over the pooled THA and TKA data for six predefined surgical complications. Primary outcome was surgical site infection (SSI), and secondary outcomes included venous thromboembolism (VTE), postoperative bleeding (POB), luxation, delirium, and nerve damage (NER). All prediction models were developed based on primary THA and TKA data, except for the models for luxation and NER which were developed based on primary THA data. These surgical complications are uncommon in TKA.

Predictors (independent variables)

In total sixteen predictor candidates were selected based on evidence from previous reports and clinical reasoning in relation to the outcomes. These included patient characteristics, comorbidities, and medication use (as specified in eTable 3 and 4). Note that we made a purposive selection from the sixteen predictors candidates to serve as predictors for the different surgical complications.

Comorbidities extracted from medical records were categorized according to the English National Health Service (NHS). The NHS considered these categories relevant comorbid categories in terms of outcome prediction.[3] Medication use was reduced to the active substance of the drug and was categorized to drug groups according the Dutch pharmacotherapeutic compass.[18]

Sample size

It is recommended that at least five events are collected for each predictor that is evaluated in multivariable regression analysis.[19 20] An event was defined as the least frequent outcome status, which in our case was the presence of surgical complication. In the Netherlands, the estimated risk of a complication like SSI is 3%[21]; therefore, in order to develop a model with six predictors, at least 30 events were required, and so a sample size of at least 1000 patients was required.

Missing data

Data were checked for completeness by investigating patterns of missingness to assess presence of a nonrandom element. Incomplete data were double-checked. Missing data were imputed using multiple imputation, as the omission of patients who have one or more predictor variables missing from analysis can cause considerable loss of precision and might bias the results.[22 23] The number of imputations was set to ten. The imputation was checked for accuracy by visual inspection and frequencies.

Statistical analysis methods

Model development

Evidence from literature, clinical reasoning and eyeballing guided selection of predictors to be included in the models. Eyeballing was done by evaluation of potential higher frequencies of predictors in relation to the outcome.[24] All selected predictors were entered into a multivariable logistic regression model, using the occurrence of a surgical complication as outcome variable. The prediction model was pooled over the imputed datasets.[25]

Internal validation

To reduce risk of over-fitting, we internally validated the model using bootstrapping. In this step, B-bootstrap samples of B=1000 were drawn with replacement from original data, which reflects drawing samples from underlying population. This was performed to estimate the performance in future patients, and to adjust the model by the calculated shrinkage factor so that future predictions will be less extreme.[19]

Performance of the model

We quantified measures of performance, discrimination and calibration. Overall model performance is the distance between predicted- and actual outcome.[23] To quantify overall model performance, we assessed Brier, $Brier_{scaled}$ and Nagelkerke's R^2. For Brier, squared differences between actual outcome and predictions were calculated. Brier can range from 0 for a perfect model to 0.25 for a non-informative model with 50% incidence of the outcome. $Brier_{scaled}$ is scaled by its maximum under a non-informative model and range between 0-100%. Nagelkerke's R^2 is a measure of explained variation.[26] The ability of the model to discriminate between those with and without the outcome was quantified as the area under the curve (AUC). This can range from 50% (no discriminative capacity) to 100% (perfect discriminative

capacity). The discriminative capacity was interpreted as reasonable when AUC was >0.70 and good when AUC was >0.80.[27] Calibration of the model is the agreement between predicted probabilities (probability of an event calculated with the model) and observed frequencies of outcome (accuracy) and was assessed by visually inspecting the calibration plot.[23] Furthermore, we computed Hosmer and Lemeshow (H-L) goodness-of-fit as a quantitative measure of calibration. A high H-L statistic is related to a low P-value, and indicates a poor fit.[19]

All statistical analyses were performed using R 3.5.3. Packages vim, mice, rms, pROC, and generalhoslem were used.

Patient and Public Involvement

Patients were involved in the design of the study. Furthermore, patients were involved in the process of incorporating the prediction models in a patient decision aid.

Results

Participants

In total 3,776 patients with primary THA or TKA were identified as eligible for the present study. Of these patients, 2,494 patients underwent THA and 1,282 patients underwent TKA. See Figure 1 for participant flow. Baseline characteristics of the final cohort are presented in Table 1.

Model development

The number of missing values per predictor are shown in Table 1. For the majority of potential predictors, there was only a small quantity of missing data; however, smoking status was missing in 24.7%. After imputation, all patients were available for multivariable modelling. There were no missing values in surgical complications.

Model specification

According to our selection of predictor candidates per outcome (depicted in eTable 5), we entered all selected predictors in the model. For SSI, these predictors were: age, smoking status, BMI, presence of an immunological disorder, diabetes mellitus, liver disease, and use of Non-Steroidal Anti-Inflammatory Drugs (NSAID's). We found a significant influence of age, immunological disorder, diabetes mellitus and liver disease of which the presence of liver disease showed to be the strongest predictor with an odds ratio of 10.7 (95%-CI=2.4–46.6). The bootstrap yielded a shrinkage factor of 0.984, which was used to adjust the regression coefficients. Table 2 shows the adjusted prediction models and odds ratios that estimates the risk for SSI and secondary outcomes. For original prediction models and adjusted coefficients, see eTable 6.

Model performance

Brier, $Brier_{scaled}$ and Nagelkerke's R^2, to assess overall performance of the model for SSI, were 0.010, 0.026 and 0.081 respectively.

The discriminative performance of the model for SSI is shown in Figure 2. The AUC was 71.9 (95%-CI=69.4–74.4%), which indicates reasonable discriminative ability. Predicted probabilities ranged between 0.01%-51.0%, with a mean of 1.0% (SD=1.5%). Calibration was poor, indicated by significant H-L statistic ($p<0.001$). The corresponding calibration plot that represents the accuracy of the model is

shown in Figure 3. The calibration plot showed quite accurate prediction, especially when the risk is low. The model underestimates the risk with a predicted probability >0.10.

The performance, discrimination and calibration of SSI and secondary outcomes are presented in Table 3. The predictive algorithms for POB and NER showed reasonable discriminative values (AUC=73.0 and 76.6) and explained fraction of variance by a Nagelkerke's R^2 of 0.072 and 0.086 respectively. The prediction model for delirium showed good discriminative value (AUC=85.9) and explained fraction of variance of 0.193. The models for luxation and VTE showed least favorable results on discrimination (AUC=58.4 and 66.3 respectively) and explained fraction of variance of 0.010 and 0.047 respectively. The ROC curves and calibration plots for secondary outcomes are presented in eFigure 1.

Table 1. Patient characteristics

Patient characteristics	Missing values	Total population (n=3776)	Total hip replacement (n=2494)	Total knee replacement (n=1282)
Age, mean (SD), years	0.1%	60.2 (15.8)	57.7 (17.0)	65.1 (11.7)
Gender: female No. (%)	0.1%	2298 (60.9%)	1468 (58.9%)	829 (64.7%)
BMI, mean (SD), kg/m^2	2.6%	27.5 (5.2)	26.6 (4.7)	29.3 (5.6)
Smoking: yes No. (%)	24.7%	498 (13.2)	341 (13.7)	157 (12.2)
ASA classification No. (%)	0.4%			
I		839 (22.2)	669 (26.8)	170 (13.3)
II		2091 (55.4)	1314 (52.7)	777 (60.6)
III		829 (22.0)	500 (20.0)	329 (25.7)
Diagnosis hip No. (%)	0.4%			
arthrosis			1599 (64.1)	
rheumatoid arthritis			68 (2.7)	
dysplasia			241 (9.7)	
osteonecrosis			228 (9.1)	
other			349 (14.0)	
Diagnosis knee No. (%)	0.9%			
arthrosis				1037 (80.9)
rheumatoid arthritis				123 (9.6)
other				111 (8.7)
Side affected: right No. (%)	0.3%	1915 (50.9)	1257 (50.4)	658 (51.3)
Surgical complications No. (%)	0%			
surgical site infection		38 (1.0)	25 (1.0)	13 (1.0)
venous thromboembolism		26 (0.7)	17 (0.7)	9 (0.7)
postoperative bleeding		47 (1.2)	28 (1.1)	19 (1.5)
luxation		32 (0.8)	31 (1.2)	1 (0.1)

delirium nerve damage		24 (0.6) 24 (0.6)	20 (0.8) 21 (0.8)	4 (0.3) 3 (0.2)

Table 2. Models including the coefficient per predictor per surgical outcome

	Surgical site infection		Venous thromboembolism		Postoperative bleeding		Luxation		Delirium		Nerve damage	
Variable	Coefficient *	Odds Ratio (95% CI)	Coefficient *	Odds Ratio (95% CI)	Coefficient *	Odds Ratio (95% CI)	Coefficient *	Odds Ratio (95% CI)	Coefficient *	Odds Ratio (95% CI)	Coefficient *	Odds Ratio (95% CI)
Intercept	-7.272	-	-4.790	-	-7.172	-	-5.864	-	-14.307	-	-2.250	-
Age (years)	0.031	1.032 (1.005-1.059)	-0.008	0.991 (0.966-1.018)	0.033	1.034 (1.006-1.062)	0.013	1.014 (0.991-1.038)	0.127	1.137 (1.067-1.212)	-0.051	0.949 (0.926-0.974)
Gender (male/female)	-	-	-0.168	0.844 (0.377-1.888)	-	-	-	-	-	-	-0.254	0.772 (0.319-1.868)
BMI (kg/m^2)	-0.002	0.998 (0.937-1.063)	-	-	0.012	1.012 (0.954-1.073)	0.021	1.023 (0.951-1.099)	-	-	-	-
Obesity (yes/no)	-	-	1.376	4.040 (1.462-11.159)	-	-	-	-	-	-	-	-
Smoking status (yes/no)	0.757	2.145 (0.883-5.213)	-	-	-0.023	0.952 (0.336-2.701)	0.491	1.667 (0.651-4.268)	-	-	0.572	1.754 (0.510-6.029)
Lung disease (yes/no)	-	-	-	-	-	-	-	-	-	-	-	-
Immunological disorder (yes/no)	0.891	2.474 (1.186-5.158)	-	-	-	-	-	-	-	-	-	-
Rheumatoid arthritis (yes/no)	-	-	-	-	-	-	0.538	1.752 (0.408-7.530)	-	-	-	-
Diabetes mellitus (yes/no)	0.904	2.494 (1.125 - 5.529)	0.829	2.317 (0.870-6.173)	-	-	-	-	-	-	-	-
Liver disease (yes/no)	2.345	10.659 (2.441-46.555)	-	-	-	-	-	-	-	-	-	-
Heart disease (yes/no)	-	-	-	-	0.729	2.086 (1.040-4.183)	-	-	0.348	1.422 (0.590-3.428)	-	-
Disease of central nervous system (yes/no)	-	-	-	-	-	-	0.106	1.113 (0.324-3.822)	0.898	2.465 (0.936-6.490)	-	-
Thromboembolic event (yes/no)	-	-	1.501	4.586 (1.521-13.826)	-	-	-	-	-	-	-	-
Dysplasia (yes/no)	-	-	-	-	-	-	-	-	-	-	-0.009	0.993

												(0.217-4.552)
Vitamin K antagonist use (yes/no)	-	-	-	-	0.787	2.220 (1.022-4.821)	-	-	-	-	-	-
NSAID's (yes/no)	0.619	1.877 (0.946-3.725)	-	-	-	-	-	-	-	-	-	-
To calculate the absolute risk for the surgical complications: $P_{(surgical\ complication)}$= 1/(1+exp- linear part) x 100%. Linear part = intercept + (coefficients * variables). *adjustment for over-fitting by shrinkage factor (SF); the intercept was re-estimated. BMI: Body Mass Index, NSAID's: Non-Steroidal Anti-Inflammatory Drugs												

Table 3. Model performance

	Surgical site infection	Venous Thrombo-embolism	Post-operative bleeding	Luxation	Delirium	Nerve damage
Brier score	0.010	0.007	0.012	0.012	0.006	0.008
$Brier_{scaled}$	0.026	0.007	0.010	0.003	0.027	0.012
Nagelkerke's R^2	0.081	0.047	0.072	0.010	0.193	0.086
AUC (95%CI)	71.9 (69.4-74.4)	66.3 (62.7-69.9)	73.0 (70.7-75.4)	58.4 (55.0-61.8)	85.9 (83.8-87.9)	76.6 (73.2-80.0)
H-L statistic (p-value)	p < 0.001	p < 0.001	p < 0.001	p < 0.001	p < 0.001	p < 0.001
Predicted possibilities						
Mean	0.010	0.007	0.012	0.012	<0.001	0.008
SD	0.015	0.007	0.012	0.004	0.012	0.010
Range	0.001-0.510	0.003-0.147	0.001-0.090	0.005-0.045	<0.001-0.147	0.001-0.072
Shrinkage factor	0.984	0.986	0.989	0.941	0.993	0.987

Discussion

The prediction models developed in this study are aimed for personalized counselling and SDM in orthopedic outpatient clinics. With our models, risk for surgical site infection (SSI), venous thromboembolism (VTE), postoperative bleeding (POB), luxation, delirium, and nerve damage (NER) can be predicted by patient characteristics, comorbidities and medication use. For SSI, predicted probabilities range between 0.01%-51.0%, which makes the model useful in adding relevant personalized information for adequate SDM compared to the previously used population-based probability of risk of 3%.[21] However, it is important to state that the model showed moderately accurate prediction, especially when the risk is low. The model underestimates the risk with a predicted probability >10%. Therefore, predicted probabilities exceeding 10% should be interpreted with caution. Furthermore, other performance measures were moderate to reasonable, indicating moderate overall performance of the model for SSI. We found similar results for other outcomes, except for the model for luxation; this model seriously underestimates the risk for luxation and could therefore not be used for personalized counselling.

Our results are comparable with the results of a recent meta-analysis on impact of comorbidities on SSI in THA or TKA. The authors stated diabetes and liver disease to contribute to a higher risk for SSI.[3] Another study with similar discriminative capacity found BMI, use of immunosuppression, ASA-score, procedure duration, and prior surgeries as risk factors for SSI.[28] Some of these predictors did not contribute to a higher performance in our model and were therefore not included. We additionally found age to be a significant predictor for SSI.

Based on literature we expected use of thromboprophylaxis, such as platelet aggregation inhibitors, direct oral anticoagulants, low-molecular-weight heparin, and/or vitamin K antagonists to be important predictors for POB. However, we could not demonstrate this finding in our model.[29] This is perhaps due to low frequencies of these predictors in our participants with POB and due to improved preoperative care regarding anticoagulant therapy. Our model for delirium included comparable predictors as other studies; they showed that age and pre-existing cognitive impairment are important for delirium.[30 31] Our model confirms this finding. Kalisvaart et al., 2006 developed a comparable model based on acute- and elective hip-surgery patients and found comparable predictors. The authors additionally found acute admission as predictor for delirium.[30] We cannot confirm this in our model since we focused on primary

THA and TKA and these interventions are not primarily preferred in acute admissions due to hip fracture. The AUC indicates that our model is more accurate in estimating the risk for delirium (85.9 vs. 73).[30] For VTE we only found obesity and thromboembolic event as significant risk factors.[3 32] This can be explained by the fact that the recurrence rate is high after earlier thromboembolic events.[33] Since we aimed our models to support preoperative SDM, we only used patient-related variables as these variables are considered modifiable.[34 35]

Strengths and limitations

A strong point is that we thoroughly created a big dataset and we used state-of-the-art statistics for our analyses. Furthermore, the simplicity of our models is a strength because we used predictors collected in usual care. The predictors are easily to assess and thereby easily to implement in care. Several limitations in this study should be noted. We retrospectively analyzed prospectively collected data. These data were not primarily registered for research purposes and therefore their detail and accuracy could be less than optimal. Moreover, changes in reporting systems took place during the studied period, for instance the introduction of electronic medical records. It is known that changes in coding practice may change completeness of data.[36 37] Although researchers performed data collection thoroughly, data about comorbidities and medication use could be missed because it was reported elsewhere. Moreover, we expect a small quantity of underreporting regarding comorbidities since physicians and anesthesiologists perchance make a selection of important comorbidities in their report. We tried to correct for this limitation by including medication use since all drugs are registered in preoperative anesthesia-report. Also, data from 2004 until 2018 were used. In this period preoperative care has been changed. To evaluate the effect of this change on our outcome, we checked our patterns of complications and found no differences in this period. Furthermore, due to a low estimated event rate (1-3%) we needed a large population to have enough events to include predictors into our models. However, since not all predictors were significant in our final models, we expect that inclusion of more predictors would not lead to a considerably different model. Another limitation is that we were not yet able to determine external validity and clinical impact of the models.

Conclusion

Clinical prediction models were developed to contribute to more unbiased and accurate counselling in considering THA or TKA and are expected to be useful for identifying patients at risk for surgical complications. For SSI, the discriminative ability was reasonable and predicted risk varied between 0.01%-51.0%. We expect the individual predicted risk to enhance SDM and support a well-founded choice. We consider our models for SSI, delirium, and NER appropriate for clinical use when taking under- and overestimation of predicted risk into account. For clinical use of the models VTE and POB, caution concerning overestimation exceeding predicted probability of 0.08 and 0.05 (data presented in calibration plots in eFigure 1), respectively, should be taken into account. Future studies should evaluate whether our models are feasible in an external population.

Supplementary information

In the supplementary file, an excel file with the prediction models calculator is provided. The decision aid including the prediction models is published in Dutch at the website of the Radboud university medical center.

Ethics Statement

Approval for this study was obtained at the Medical Ethical Committee of Radboudumc (2018-4880).

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Competing interests

P. Van der Wees participates in the Scientific Advisory Panel of the American Physical Therapy Association (APTA)

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Data sharing statement

Raw data will not be shared by Dryad data repository. Data will be available upon request via the Data repository from Radboudumc.

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Abbreviations used in manuscript

ASA: American Society of Anesthesiologists

AUC: Area under the receiver operating characteristic curve

H-L: Hosmer and Lemeshow

LROI: Dutch Arthroplasty Register

NER: Nerve damage

NHS: National Health Service

NOV: Dutch Orthopaedic Association

NSAID's: Non-Steroidal Anti-Inflammatory Drugs

POB: Postoperative bleeding

PROMs: Patient Reported Outcome Measures

SDM: Shared decision making

SSI: Surgical site infection

THA: Total hip arthroplasty

TKA: Total knee arthroplasty

VTE: Venous Thromboembolism

Figure 1. Flow chart for inclusion and exclusion of patients. Variables indicated with an asterisk* were primarily extracted from the LROI database. When these data were missing, the data were extracted from the (electronic) medical record. Castor EDC is indicated by Castor

Figure 2. Receiver Operating Characteristic curve of the prediction model for surgical site infection AUC=71.9 (95%-CI = 69.4–74.4%)

Figure 3. Calibration plot with the actual probability against the predicted probability for the model for surgical site infection. The triangles indicate quantiles (g=10) of patients with a similar predicted probability of success. The grey diagonal line represents perfect agreement between predicted and actual probability

Figure 1. Flow chart for inclusion and exclusion of patients. Variables indicated with an asterisk* were primarily extracted from the LROI database. When these data were missing, the data were extracted from the (electronic) medical record. Castor EDC is indicated by Castor

236x110mm (150 x 150 DPI)

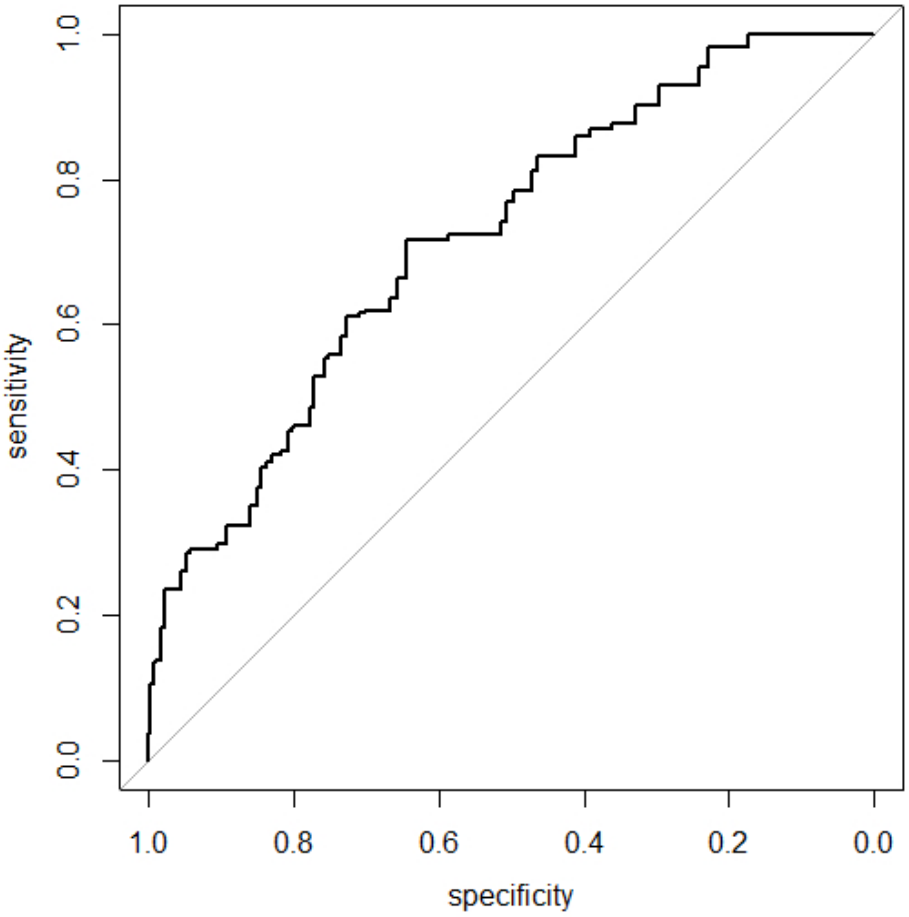


Figure 2. Receiver Operating Characteristic curve of the prediction model for surgical site infection
AUC=71.9 (95%-CI = 69.4–74.4%)

145x145mm (96 x 96 DPI)

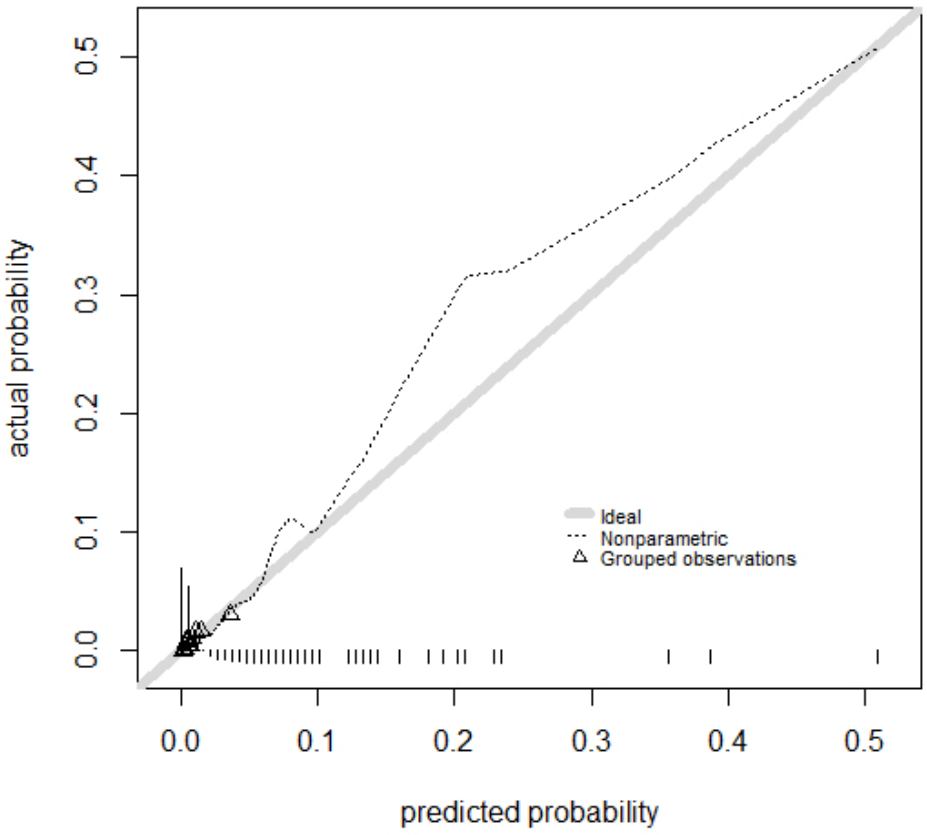


Figure 3. Calibration plot with the actual probability against the predicted probability for the model for surgical site infection. The triangles indicate quantiles (g=10) of patients with a similar predicted probability of success. The grey diagonal line represents perfect agreement between predicted and actual probability

145x145mm (96 x 96 DPI)

Supplemental Material

eTable 1. TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	3
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	5
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	5
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	6
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	6
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	6
	5b	D;V	Describe eligibility criteria for participants.	6-7
	5c	D;V	Give details of treatments received, if relevant.	6-7
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	7
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	N/A
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	7
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	N/A
Sample size	8	D;V	Explain how the study size was arrived at.	7
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	7-8

Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	8-9
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	8-9
	10c	V	For validation, describe how the predictions were calculated.	8-9
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	8-9
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	N/A
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	N/A
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	N/A
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	10, Figure 1
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	10, Table 1
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	N/A
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	10, Table 1
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	eTable 6
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	Table 2, eTable 6
	15b	D	Explain how to the use the prediction model.	Table 2, eTable 6, 11
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	Table 2, eTable 6
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	N/A
Discussion				

Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	17-19
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	17-19
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	17-19
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	17-19
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	19-20
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	19

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

eTable 2. Categorization of surgical complications

Location code**	Location**	Code nature of complication**	Nature of complication**
Surgical site infection*			
24	Pelvis	012	Prosthesis infection
40	Hip	083	Deep infection
42	Knee	134	Infected organ
Venous thromboembolism			
24	Pelvis	104	Thrombosis
40	Hip	105	Embolus
41	Femur/upper leg		
42	Knee		
43	Lower leg		
50	Lung		
56	Venous system		
Luxation			
40	Hip	041	Luxation
		086	Disconnection prosthesis
Delirium			
54	Central nervous system	141	Psychological decompensation
58	Total		
Nerve damage			
40	Hip	094	Nerve lesion
41	Femur/upper leg		
43	Lower leg		
57	Arterial system		
Postoperative bleeding			
40	Hip	014	Wound leakage
41	Femur/upper leg	022	Bleeding

42 56	Knee Venous system	100 136	Secondary bleeding/hematoma Bleeding organ

* the records registered with the nature of complication 010 (infection around sutures), 011 (superficial infection), 013 (local wound necrosis) and 014 (wound leakage) are checked for occurrence of surgical site infection and added to the outcome surgical site infection when this was the case.

** only depicted when location code or code of the nature of complication occurred in the register.

Furthermore records registered with nature of complication 125 (interruption of sterility) were checked for occurrence of a surgical complication.

eTable 3. Predictors per outcome

	OR*/RR** (95% CI)	Study
Surgical site infection		
Age		
THA (>70years)	0.7** (0.3-1.5)	Almustafa et al (2018) (1)
TKA (>70years)	1.7** (0.9-3.3)	Almustafa et al (2018) (1)
Smoking status	0.16** (0.05-0.52)	Møller et al (2002) (2)
BMI	6.7* (NR)	Namba et al (2005) (3)
	4.8** (1.9-12.0)	Almustafa et al (2018) (1)
	2.53* (1.25-5.13)	Chen et al (2013) (4)
Immunological disorder	-	*Clinical reasoning*
NSAID's	-	*Clinical reasoning*
Diabetes mellitus	1.90* (1.32-2.74)	Podmore et al (2018) (5)
Liver disease	2.46* (1.46-4.12)	Podmore et al (2018) (5)
Venous thromboembolism		
Age		
THA(≥75years)	1.82* (1.15-2.87)	Migita et al (2014) (6)
TKA(≥75years)	1.30* (0.99-1.71)	Migita et al (2014) (6)
Sex		
THA(female>risk)	2.31* (1.03-5.18)	Migita et al (2014) (6)
TKA(female>risk)	1.58* (1.08-2.31)	Migita et al (2014) (6)
Diabetes mellitus	1.26* (0.92-1.72)	Podmore et al (2018) (5)
(TKA)	1.36* (1.07-1.72)	Yang et al (2015) (7)
Thromboembolic event *(TKA)*	1.11* (0.36-3.46)	Migita et al (2014) (6)
Obesity		
THA(BMI>30)	0.89* (0.36-2.20)	Migita et al (2014) (6)
TKA(BMI>30)	0.90* (0.58-1.38)	Migita et al (2014) (6)
Postoperative bleeding		
Age		
THA(>70 years)	2.61** (1.50-4.53)	Quintero et al (2016) (8)

TKA(>70years)	2.25** (1.03-4.94)	Quintero et al (2016) (8)
BMI	-	*Clinical reasoning*
Heart disease	-	*Univariate analysis*
Vitamin K antagonists	-	*Clinical reasoning*
Smoking status	-	*Univariate analysis*
Luxation		
Age	1.27* (1.02-1.57)	Kunutsor et al (2019) (9)
Smoking status	1.08* (0.96-1.21)	Kunutsor et al (2019) (9)
BMI	1.38* (1.03-1.85)	Kunutsor et al (2019) (9)
Rheumatoid arthritis	1.50* (1.05-2.15)	Kunutsor et al (2019) (9)
Disease of the central nervous system	2.54* (1.86-3.48)	Kunutsor et al (2019) (9)
Delirium		
Age	2.20* (1.80-2.71)	Huang et al (2019) (10)
Disease of the central nervous system *(dementia)*	7.44* (3.54-14.60)	Huang et al (2019) (10)
Heart disease *(congestive)*	0.83* (0.39-1.61)	Huang et al (2019) (10)
Nerve damage		
Age *(<45 (vs 65-74)*	7.17* (1.17-44.00)	Shetty et al (2016) (11)
BMI *(<BMI >risk)*	0.96* (0.77-1.21)	Kawano et al (2018) (12)
Sex *(female > risk)*	Not reported	Shetty et al (2016) (11)
Smoking status	1.90* (1.06-3.38)	Shetty et al (2016) (11)
Dysplasia	3.69* (1.65-8.28)	Farrell et al (2005) (13)
*results reported as odds ratio (OR); ** results reported as risk ratio (RR).		

eTable 4. Categorization of comorbidities

Categorization of comorbidities	
Comorbid category*	**Included comorbid conditions****
Bleeding diseases	Hemophilia
Blood quality	Anemia
Cancer	Prostate cancer Leukemia Breast cancer Lymph node cancer Bowen's disease
Central nervous system	Parkinson's disease Dementia TIA CVA
Cognitive impairment	Down syndrome
Diabetes mellitus	Diabetes mellitus
Heart disease	Ischemia of the heart Valve damage blood regurgitation Valve damage reduced blood flow Valve replacement Cardiomyopathy decreased contraction Cardiomyopathy decreased relaxation Heart decompensation Heart attack Angina pectoris Atrial fibrillation
High blood pressure	Hypertension
Hyper hormonal	Hyper hormonal
Hypo hormonal	Hypo hormonal

Immunological disorder	Scleroderma Rheumatoid arthritis Gout Psoriasis Artritides Dermal barrier disease General immune disorder Organ transplantation
Inflammation	Chronic bladder infection
Kidney disease	Kidney insufficiency
Liver disease	Liver cirrhosis
Lung disease	Chronic bronchitis Asthma COPD Emphysema Dyspnea
Mood sickness	Depression Psychosis
Obesity	Obesity
Peripheral nervous system	Nerve compression Lumbar vertebral stenosis
Poor peripheral blood flow	Atherosclerosis Claudication intermittent
Thromboembolic event	Deep venous thromboembolism Pulmonary embolism

* the comorbid categories are used for analysis.

** comorbid conditions are depicted when the frequency was ≥ 10 or when the comorbid condition was considered as a relevant comorbid condition in terms of outcome prediction.

eTable 5. Categorization of drug groups

Categorization of medication use	
Drug category	**Drugs groups according to the Dutch pharmacotherapeutic compass** (14)
Acenocoumarol	Acenocoumarol*
Antifibrinolytica	Antifibrinolytica
Antimycotics	Antimycotic antibiotics Others
Antiretroviral agents	Antiretroviral agents
Bisfosfonates	Bisfosfonates
Colchinine group	Colchinine group
Directly working oral anticoagulants	Directly working oral anticoagulants
DMARD's biologicals	Immunosuppresives selective Immunosuppresives others
Factors in blood coagulance	Factors in blood coagulance
Fenprocoumon	Fenprocoumon*
Imidazoles	Cutane imidazoles Others
Immunosuppressives	Interferons Interleukin antagonists Monoclonal antibodies
Local antibacterial agents	Cutaneous antibacterial agents Ocular antibacterial agents
Local corticosteroids	Cutane corticosteroids Nasal corticosteroids Corticosteroides for inhalation
Low molecular weight heparins	Low molecular weight heparins
Methotrexate	Methotrexate

NSAID's**	Coxib's Others
Oncology related detoxificants	Oncology related detoxificants
Salicylates	Analgetic salicylates Trombocytic salicylates
Statins	Statins
Systemic antibacterial agents	Cephalosporins Macrolides Penicillin's Tetracyclines Carbapenems Ceftriaxone Glycopeptides Aminoglycosides Rifamycins tuberculose Sulfonamides and trimethroprimides Triazoles Fluoroquinolones Others
Thrombocyte-aggregationblockers	P2y12 blockers Others
Xanthineoxidase inhibitor	Xanthineoxidase inhibitor

* according the Dutch pharmacotherapeutic compass, acenocoumarol and fenprocoumon belong to the drug group 'vitamin k antagonists'. Based on expert opinion, acenocoumarol and fenprocoumon were included separately in the analysis because of the differences in half-life.

** Non-Steroidal Anti-Inflammatory Drugs

eTable 6. Original prediction models and adjusted coefficients

Prediction model for estimation of risk for surgical site infection

Variable	Regression coefficient	Regression coefficient (adjusted with SF)*	Odds Ratio (95% CI)
Intercept	-7.305	-7.272	-
Age (years)	0.031	0.031	1.032 (1.005-1.059)
BMI (kg/m²)	-0.002	-0.002	0.998 (0.937-1.063)
Smoking status (yes/no)	0.769	0.757	2.145 (0.883-5.213)
Immunological disorder (yes/no)	0.905	0.891	2.474 (1.186-5.158)
Diabetes mellitus (yes/no)	0.918	0.904	2.494 (1.125-5.529)
Liver disease (yes/no)	2.382	2.345	10.659 (2.441-46.555)
NSAID's (yes/no)	0.629	0.619	1.877 (0.946-3.725)
To calculate the absolute risk of surgical site infection: $P_{(\text{surgical site infection})} = 1/(1+e^{-\text{linear part}}) \times 100\%$; Linear part = -7.272 + (0.031 x age – 0.002 x BMI + 0.757 x smoking status + 0.891 x immunological disorder + 0.904 x diabetes mellitus + 2.345 x liver disease + 0.619 x NSAID's). *adjustment for over-fitting by shrinkage factor (SF) (SF = 0.984); the intercept was re-estimated.			

Prediction model for estimation of risk for venous thromboembolism

Variable	Regression coefficient	Regression coefficient (adjusted with SF)*	Odds Ratio (95% CI)
Intercept	-4.764	-4.790	-
Age (years)	-0.009	-0.008	0.991

			(0.966-1.018)
Gender (male/female)	-0.170	-0.168	0.844 (0.377-1.888)
Obesity (yes/no)	1.396	1.376	4.040 (1.462-11.159)
Diabetes mellitus (yes/no)	0.841	0.829	2.317 (0.870-6.173)
Thromboembolic event (yes/no)	1.523	1.501	4.586 (1.521-13.826)
To calculate the absolute risk of venous thromboembolism: $P_{(\text{venous thromboembolism})} = 1/(1+e^{-\text{linear part}}) \times 100\%$; Linear part = -4.790 + (-0.008 x age – 0.168 x gender + 1.376 x obesity + 0.829 x diabetes mellitus + 1.501 x thromboembolic event). *adjustment for over-fitting by shrinkage factor (SF) (SF = 0.986); the intercept was re-estimated.			

Prediction model for estimation of risk for postoperative bleeding.

Variable	Regression coefficient	Regression coefficient (adjusted with SF)*	Odds Ratio (95% CI)
Intercept	-7.182	-7.172	-
Age (years)	0.033	0.033	1.034 (1.006-1.062)
BMI (kg/m²)	0.012	0.012	1.012 (0.954-1.073)
Smoking status (yes/no)	-0.023	-0.023	0.952 (0.336-2.701)
Heart disease (yes/no)	0.737	0.729	2.086 (1.040-4.183)
Vitamin K antagonist use (yes/no)	0.796	0.787	2.220 (1.022-4.821)
To calculate the absolute risk of postoperative bleeding: $P_{(\text{postoperative bleeding})} = 1/(1+e^{-\text{linear part}}) \times 100\%$;			

Linear part = -7.172 + (0.033 x age + 0.012 x BMI – 0.023 x smoking status + 0.729 x heart disease + 0.787 x vitamin K antagonist use). *adjustment for over-fitting by shrinkage factor (SF) (SF = 0.989); the intercept was re-estimated.

Prediction model for estimation of risk for luxation.

Variable	Regression coefficient	Regression coefficient (adjusted with SF)*	Odds Ratio (95% CI)
Intercept	-5.976	-5.800	-
Age (years)	0.014	0.013	1.014 (0.991-1.038)
BMI (kg/m²)	0.022	0.021	1.023 (0.951-1.099)
Smoking status (yes/no)	0.521	0.491	1.667 (0.651-4.268)
Rheumatoid arthritis (yes/no)	0.572	0.538	1.752 (0.408-7.530)
Disease of central nervous system (yes/no)	0.113	0.106	1.113 (0.324-3.822)
To calculate the absolute risk of luxation: $P_{(luxation)} = 1/(1+e^{-\text{linear part}}) \times 100\%$; Linear part = -5.800 + (0.013 x age + 0.021 x BMI + 0.491 x smoking status + 0.538 x rheumatoid arthritis + 0.106 x disease of central nervous system). *adjustment for over-fitting by shrinkage factor (SF) (SF = 0.941); the intercept was re-estimated.			

Prediction model for estimation of risk for delirium.

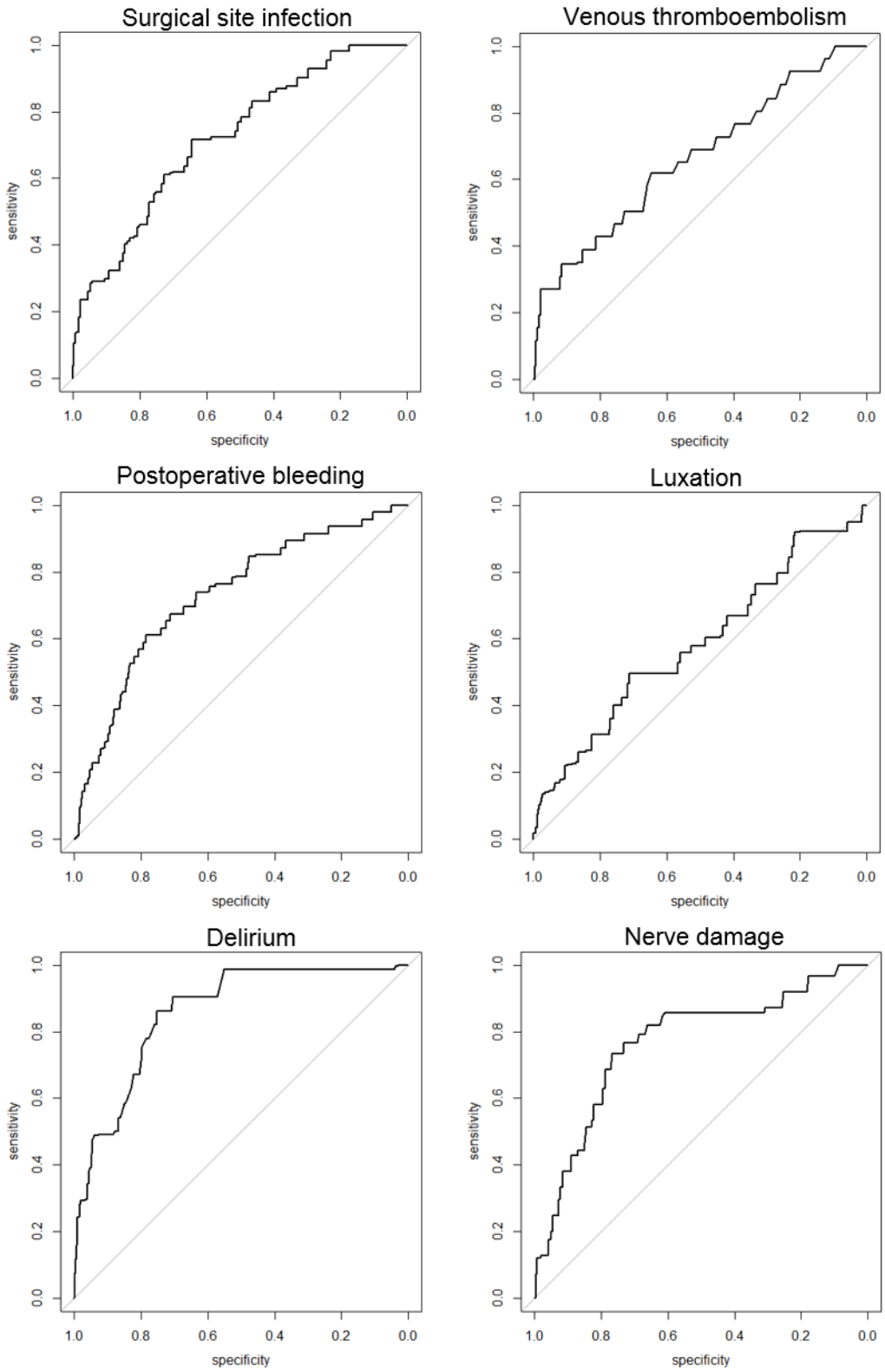
Variable	Regression coefficient	Regression coefficient (adjusted with SF)*	Odds Ratio (95% CI)
Intercept	-14.368	-14.307	-
Age (years)	0.129	0.127	1.137 (1.067-1.212)
Heart disease (yes/no)	0.351	0.348	1.422

			(0.590-3.428)
Disease of central nervous system (yes/no)	0.904	0.898	2.465 (0.936-6.490)
To calculate the absolute risk of delirium: $P_{(delirium)}$= 1/(1+$e^{-\text{linear part}}$) x 100%; Linear part = -14.307 + (0.127 x age + 0.348 x heart disease + 0.898 x disease of central nervous system). *adjustment for over-fitting by shrinkage factor (SF) (SF = 0.993); the intercept was re-estimated.			

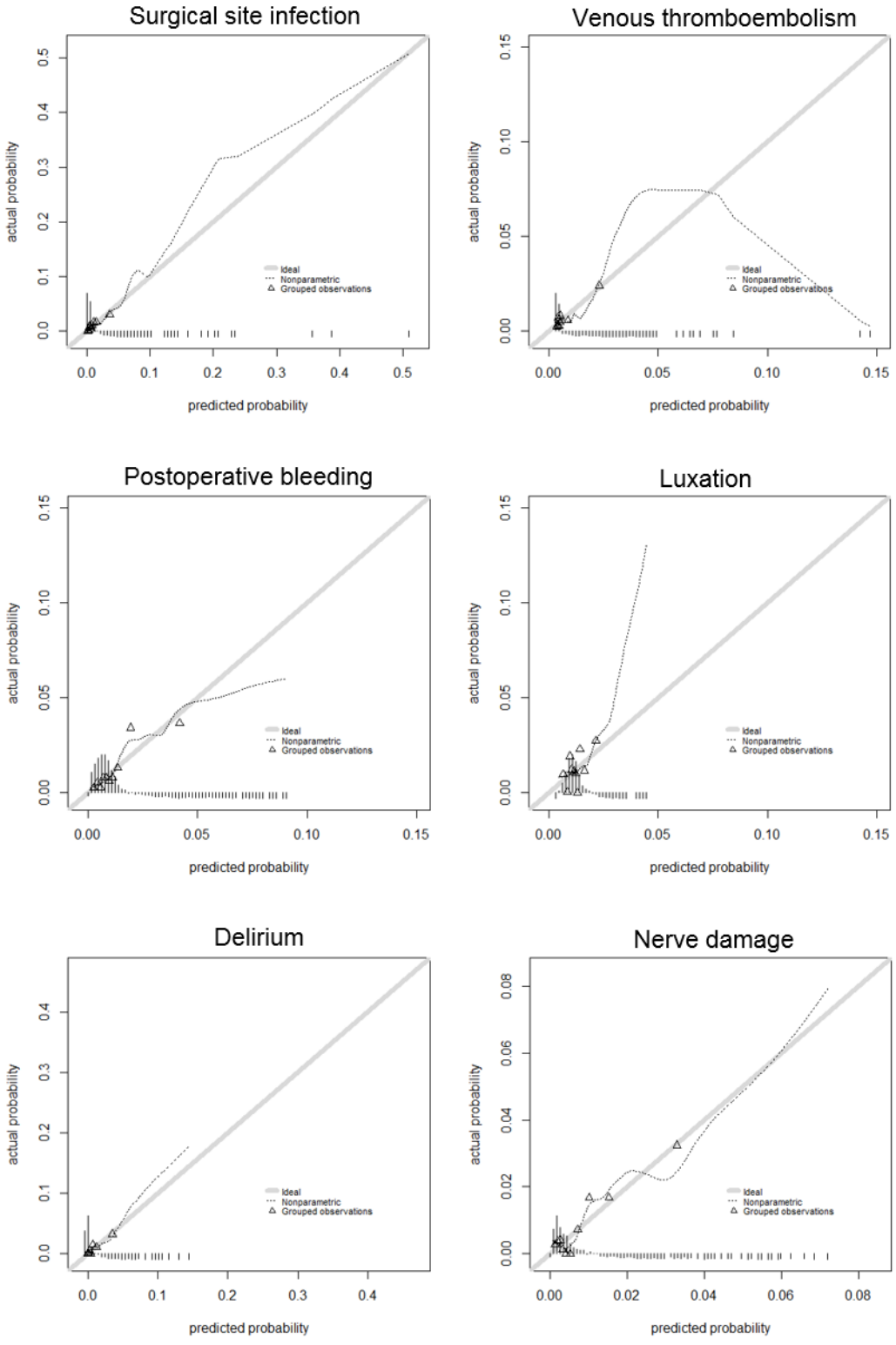
Prediction model for estimation of risk for nerve damage.

Variable	Regression coefficient	Regression coefficient (adjusted with SF)*	Odds Ratio (95% CI)
Intercept	-2.209	-2.250	-
Age (years)	-0.052	-0.051	0.949 (0.926-0.974)
Gender (man/woman)	-0.258	-0.254	0.772 (0.319-1.868)
Smoking status (yes/no)	0.580	0.572	1.754 (0.510-6.029)
Dysplasia (yes/no)	-0.009	-0.009	0.993 (0.217-4.552)
To calculate the absolute risk of nerve damage: $P_{(nerve\ damage)}$= 1/(1+$e^{-\text{linear part}}$) x 100%; Linear part = -2.250 + (-0.051 x age – 0.254 x gender + 0.572 x smoking status – 0.009 x dysplasia). *adjustment for over-fitting by shrinkage factor (SF) (SF = 0.987); the intercept was re-estimated.			

eFigure 1. ROC curves and Calibration plots



eFigure 1.1. Receiver Operating Characteristic curves of the prediction models for surgical site infection, venous thromboembolism, postoperative bleeding, luxation, delirium and nerve damage



eFigure 1.2. Calibration plots with actual probability against the predicted probability for the models for surgical site infection, venous thromboembolism, postoperative bleeding, luxation, delirium and nerve damage. The triangles indicate quantiles (g=10) of patients with a similar predicted probability of success. The grey diagonal line represents perfect agreement between predicted and actual probability

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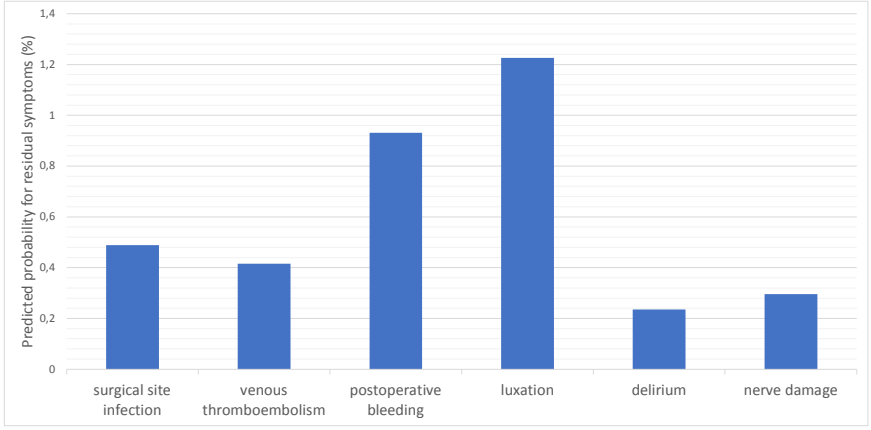
Input variables*		Surgical site infection		Venous thromboembolism		Postoperative bleeding		Luxation		Delirium		Nerve damage	
Age (years)	65	0,031	2,015	-0,008	-0,52	0,033	2,145	0,013	0,845	0,127	8,255	-0,051	-3,315
Gender (male/female)	1		0	-0,168	-0,168		0		0		0	-0,254	-0,254
BMI (kg/m2)	30	-0,002	-0,06		0	0,012	0,36	0,021	0,63		0		0
Obesity (yes/no)	0		0	1,376	0		0		0		0		0
Smoking status (yes/no)	0	0,757	0		0	-0,023	0	0,491	0		0	0,572	0
Lung disease (yes/no)	0		0		0		0		0		0		0
Immunological disorder (yes/no)	0	0,891	0		0		0		0		0		0
Rheumatoid arthritis (yes/no)	0		0		0		0	0,538	0		0		0
Diabetes mellitus (yes/no)	0	0,904	0	0,829	0		0		0		0		0
Liver disease (yes/no)	0	2,345	0		0		0		0		0		0
Heart disease (yes/no)	0		0		0	0,729	0		0	0,348	0		0
Disease of central nervous system (yes/no)	0		0		0		0	0,106	0	0,898	0		0
Thromboembolic event (yes/no)	0		0	1,501	0		0		0		0		0
Dysplasia (yes/no)	0		0		0		0		0		0	-0,009	0
Vitamin K antagonist use (yes/no)	0		0		0	0,787	0		0		0		0
NSAID use (yes/no)	0	0,619	0		0		0		0		0		0
		-7,272	1,955	-4,79	-0,688	-7,172	2,505	-5,864	1,475	-14,307	8,255	-2,25	-3,569
			-5,317		-5,478		-4,667		-4,389		-6,052		-5,819
Predicted probability for residual symptoms (%)		**0,48834885**		**0,41602963**		**0,93128835**		**1,22609394**		**0,23476267**		**0,29617761**	
		surgical site infection		venous thromboembolism		postoperative bleeding		luxation		delirium		nerve damage	

* Age: in years, Gender: male scored as 1 and female scored as 2, BMI: in kg/m2, Obesity: no scored as 0 and yes as 1, Smoking status: no scored as 0 and yes as 1, Lung disease: no scored as 0 and yes as 1, Immunological disorder: no scored as 0 and yes as 1



embolic event: no scored as 0 and yes as 1, Dysplasia: no scored as 0 and yes as 1, Vitamin K antagonists use: no scored as 0 and yes as 1, NSAID's: no scored as 0 and yes as 1

TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	3
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	5
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	5
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	6
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	6
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	6
	5b	D;V	Describe eligibility criteria for participants.	6-7
	5c	D;V	Give details of treatments received, if relevant.	6-7
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	7
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	N/A
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	7
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	N/A
Sample size	8	D;V	Explain how the study size was arrived at.	7
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	7-8
Statistical	10a	D	Describe how predictors were handled in the analyses.	8-9

analysis methods				
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	8-9
	10c	V	For validation, describe how the predictions were calculated.	8-9
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	8-9
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	N/A
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	N/A
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	N/A
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	10, Figure 1
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	10, Table 1
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	N/A
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	10, Table 1
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	eTable 6
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	Table 2, eTable 6
	15b	D	Explain how to the use the prediction model.	Table 2, eTable 6, 11
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	Table 2, eTable 6
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	N/A
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	17-19

Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	17-19
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	17-19
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	17-19
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	19-20
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	19

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

BMJ Open

Development of prediction models for complications after primary total hip and knee arthroplasty: a single-centre retrospective cohort study in the Netherlands.

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Keywords:	Hip < ORTHOPAEDIC & TRAUMA SURGERY, Knee < ORTHOPAEDIC & TRAUMA SURGERY, ORTHOPAEDIC & TRAUMA SURGERY

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Title Page

(1) Title

Development of prediction models for complications after primary total hip and knee arthroplasty: a single-centre retrospective cohort study in the Netherlands.

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Abstract

Objective. The aim of the study was to develop prediction models for patients with THA and TKA to predict the risk for surgical complications based on personal factors, comorbidities, and medication use.

Design. Retrospective cohort study.

Setting. Tertiary Care in outpatient clinic of university medical center.

Participants. 3,776 patients with a primary THA or TKA between 2004 and 2018.

Primary and secondary outcome measures. Multivariable logistic regression models were developed for primary outcome surgical site infection (SSI), and secondary outcomes venous thromboembolism (VTE), postoperative bleeding (POB), luxation, delirium, and nerve damage (NER).

Results. For SSI, age, smoking status, BMI, presence of immunological disorder, diabetes mellitus, liver disease, and use of NSAID's were included. An area under the receiver operating characteristic curve (AUC) of 71.9%(95%CI=69.4-74.4) was found. For this model, liver disease showed to be the strongest predictor with an odds ratio of 10.7(95%CI=2.4-46.6). The models for POB and NER showed AUCs of 73.0%(95%CI=70.7-75.4) and 76.6%(95%CI=73.2-80.0), respectively. For delirium an AUC of 85.9%(95%CI=83.8-87.9) was found, and for the predictive algorithms for luxation and VTE we found least favorable results (AUC= 58.4%(95%CI=55.0-61.8) and 66.3%(95%CI=62.7-69.9)). Included predictors for secondary outcomes are presented in Table 2 and eTable 5.

Conclusions. Discriminative ability was reasonable for SSI and predicted probabilities ranged from 0.01%-51.0%. We expect this to enhance shared decision making in considering THA or TKA since current counseling is predicated on population-based probability of risk, rather than using personalized prediction. We consider our models for SSI, delirium and NER appropriate for clinical use when taking under- and overestimation of predicted risk into account. For VTE and POB, caution concerning overestimation exceeding a predicted probability of 0.08 for VTE and 0.05 for POB should be taken into account. Furthermore, future studies should evaluate clinical impact and whether the models are feasible in an external population.

Keywords. total hip arthroplasty; total knee arthroplasty; surgical complications; prediction; prognosis; comorbidities; medication use

Strengths and limitations of this study.

- This study included multivariable logistic regression models to predict postoperative complications after primary total hip- and knee arthroplasty based on personal factors, comorbidities, and medication use.
- The present study was conducted and reported according the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guidelines.
- Purposive selection of predictors by clinical reasoning and literature search.
- Limitations include only internal validation of the prediction models by bootstrapping.
- Used data were not primarily registered for research purposes, and therefore, their detail and accuracy could be less than optimal.

Introduction

Joint replacement is a recommended intervention for people with end stage hip or knee osteoarthritis.[1] Whether surgery is the best solution depends on many individual factors such as severity of the disease, level of experienced pain and discomfort, medication use, personal circumstances, comorbid diseases, and intended type of surgery.[2-4] Because the decision to have surgery or not is complex, a shared decision making (SDM) process is warranted. This process allows patients and clinicians to discuss treatment options consistent with the patient's values and preferences.[5]

Information on most likely prognosis is central in this dialogue as the clinician provides guidance and information about expected outcomes, including the risk on surgical complications, when facing the decision to pursue or forgo surgery. However, providing personalized information about the risk on surgical complications, based on personal characteristics of the patient, is challenging. Available evidence often consists of average outcomes and current guidelines on prediction of outcome still recommend counselling predicated on population-based probability of risk, rather than using personalized prediction.[6] This is remarkable, as discussing potential personal risks is an important aspect of SDM.[7 8]

To overcome this problem, the development of prediction models is emerging. It has been shown that useful prediction on postoperative outcome can be made predicated on preoperative data like demographic factors, pain scores, and physical functioning measured with Patient Reported Outcome Measures (PROMs), to identify patients at risk of not benefitting from total knee arthroplasty (TKA) in general.[9-11] Another study developed a preoperative prediction model to predict residual complaints on pain, functional outcome and treatment success for individual patients after TKA.[12] Also useful electronic risk calculators predicting complications and mortality for patients and clinicians are available for specific populations.[13 14] In one study, data of patients registered in the Medicare database, the federal health insurance program for individuals aged ≥65 years, are used for development of a risk calculator. However, the exact patient characteristics of the study population are not reported and the effect of the predictors remain unclear.[14] In another study, regression models are based on the results of univariate analyses on a broad range of data as demographics, comorbidities, and laboratory, or test values of a mainly male Veteran population, and the authors reported suboptimal performance scores for prediction of most outcomes.[13] Generalizability of prediction models based on specific patient populations may be

limited, and further evaluation of potential risk factors is needed to validate prediction models for complications after primary total hip- and knee replacement.

As it is known from literature that personal factors including demographic characteristics and comorbidities have an impact on surgical complications,[3] these assumed caused relationships might therefore serve as basis for a risk prediction model. Therefore, the aim of this study is to develop a prediction model for clinicians and patients with hip- or knee osteoarthritis considering surgery, by predicting risk for surgical complications based on personal factors, comorbidities and medication use.

Methods

Study design and setting

For this retrospective cohort study, we established a cohort of patients who underwent primary total hip- (THA) or TKA between 2004 and 2018 at the Orthopedic department of Radboud university medical center Nijmegen, the Netherlands. Datasets were merged into one centralized database based on patient number, birthdate and date of surgery.

This study was performed and reported in line with transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guidelines.[15]

Data collection

Data used for this study were extracted from (electronic) medical records of Radboudumc, Dutch Arthroplasty Register (LROI), and Radboudumc registry of complications. We primarily extracted comorbidities and medication use from medical records. These data were extracted based on coding and were obtained by three researchers (LS, TW and AT) by use of a standardized operating procedure, and stored in a centralized platform (Castor Electronic Data Capture (EDC)).[16] Data about patient characteristics like age, sex, BMI, smoking status, American Society of Anesthesiologists (ASA) classification and diagnosis for surgery were extracted from LROI. Furthermore, date of surgery, type of surgery (primary or revision), surgery side, and type of implant were extracted.[17] From the register of complications we extracted all surgeries and complications which occurred within one year after THA or TKA.[18] In this registry, surgery related orthopedic complications were registered as well as other medical complications.[19] All complications were registered by location code combined with a code for the nature of the complication.[18] Some registrations were unclear and could refer to one of predefined complications and were therefore checked in medical records by LS. For all included location- and nature of complication codes per surgical complication, see eTable 1.

Inclusion and exclusion criteria

Patients were eligible for inclusion in the cohort if the surgery concerned primary THA or TKA. We defined primary THA or TKA as the first time a total prosthesis is placed. Revision arthroplasty was defined as any change (replacement, removal, or addition) of one or several components of the joint

prosthesis.[17] We expected revision arthroplasty to influence risk for complications negatively, therefore revision arthroplasty was excluded for this study.

Outcome (dependent variables)

Prediction models were developed over the pooled THA and TKA data for six predefined surgical complications. Primary outcome was surgical site infection (SSI), and secondary outcomes included venous thromboembolism (VTE), postoperative bleeding (POB), luxation, delirium, and nerve damage (NER). All prediction models were developed based on primary THA and TKA data, except for the models for luxation and NER which were developed based on primary THA data. These surgical complications are uncommon in TKA.

Predictors (independent variables)

In total sixteen predictor candidates were selected based on evidence from previous reports and clinical reasoning in relation to the outcomes. These included patient characteristics, comorbidities, and medication use (as specified in eTable 2 and 3). Note that we made a purposive selection from the sixteen predictors candidates to serve as predictors for the different surgical complications.

Comorbidities extracted from medical records were categorized according to the English National Health Service (NHS). The NHS considered these categories relevant comorbid categories in terms of outcome prediction.[3] Medication use was reduced to the active substance of the drug and was categorized to drug groups according the Dutch pharmacotherapeutic compass.[20]

Sample size

It is recommended that at least five events are collected for each predictor that is evaluated in multivariable regression analysis.[21 22] An event was defined as the least frequent outcome status, which in our case was the presence of surgical complication. In the Netherlands, the estimated risk of a complication like SSI is 3%[23]; therefore, in order to develop a model with six predictors, at least 30 events were required, and so a sample size of at least 1000 patients was required.

Missing data

Data were checked for completeness by investigating patterns of missingness to assess presence of a nonrandom element. Incomplete data were double checked. Missing data were imputed using multiple imputation, as the omission of patients who have one or more predictor variables missing from analysis can cause considerable loss of precision and might bias the results.[24 25] The number of imputations was set to ten. The imputation was checked for accuracy by visual inspection and frequencies.

Statistical analysis methods

Model development

Evidence from literature, clinical reasoning and eyeballing guided selection of predictors to be included in the models. Eyeballing was done by evaluation of potential higher frequencies of predictors in relation to the outcome.[26] All selected predictors were entered into a multivariable logistic regression model, using the occurrence of a surgical complication as outcome variable. The prediction model was pooled over the imputed datasets.[27]

Internal validation

To reduce risk of overfitting, we internally validated the model using bootstrapping. In this step, B-bootstrap samples of B=1000 were drawn with replacement from original data, which reflects drawing samples from underlying population. Due to the drawing with replacement, a bootstrapped dataset allows for containing the same original cases. Other validation methods resample without replacement and thereby such validation datasets are produced through a pre-specified number of surrogate datasets, and each of the original cases will be left out exactly once, which results in a smaller dataset. Since our dataset is not very large, we decided to use bootstrapping as internal validation method. Bootstrapping was performed to estimate the performance in future patients, and to adjust the model by the calculated shrinkage factor so that future predictions will be less extreme.[21]

Performance of the model

We quantified measures of performance, discrimination and calibration. Overall model performance is the distance between predicted- and actual outcome.[25] To quantify overall model performance, we assessed Brier, $Brier_{scaled}$ and Nagelkerke's R^2. For Brier, squared differences between actual outcome and predictions were calculated. Brier can range from 0 for a perfect model to 0.25 for a noninformative

model with 50% incidence of the outcome. $Brier_{scaled}$ is scaled by its maximum under a noninformative model and range between 0-100%. Nagelkerke's R^2 is a measure of explained variation.[28] The ability of the model to discriminate between those with and without the outcome was quantified as the area under the receiver operating characteristic curve (AUC). This can range from 50% (no discriminative capacity) to 100% (perfect discriminative capacity). The discriminative capacity was interpreted as reasonable when AUC was >0.70 and good when AUC was >0.80.[29] Calibration of the model is the agreement between predicted probabilities (probability of an event calculated with the model) and observed frequencies of outcome (accuracy) and was assessed by visually inspecting the calibration plot.[25] Furthermore, we computed Hosmer and Lemeshow (H-L) goodness-of-fit as a quantitative measure of calibration. A high H-L statistic is related to a low P-value, and indicates a poor fit.[21]

All statistical analyses were performed using R 3.5.3. Packages vim, mice, rms, pROC, and generalhoslem were used.

Patient and Public Involvement

Patients were involved in the design of the study which included consultation during grant writing and advice in setting up the study design. Furthermore, patients were involved in the process of incorporating the prediction models in a patient decision aid. Focus groups were held and patients and clinicians together were asked for their opinion regarding incorporation of the models in the preoperative process.

Results

Participants

In total 3,776 patients with primary THA or TKA were identified as eligible for the present study. Of these patients, 2,494 patients underwent THA and 1,282 patients underwent TKA. See Figure 1 for participant flow. Baseline characteristics of the final cohort are presented in Table 1.

Model development

The number of missing values per predictor are shown in Table 1. For the majority of potential predictors, there was only a small quantity of missing data; however, smoking status was missing in 24.7%. After imputation, all patients were available for multivariable modelling. There were no missing values in surgical complications.

Model specification

According to our selection of predictor candidates per outcome (depicted in eTable 4), we entered all selected predictors in the model. For SSI, these predictors were: age, smoking status, BMI, presence of an immunological disorder, diabetes mellitus, liver disease, and use of Non-Steroidal Anti-Inflammatory Drugs (NSAID's). We found a significant influence of age, immunological disorder, diabetes mellitus and liver disease of which the presence of liver disease showed to be the strongest predictor with an odds ratio of 10.7 (95%CI=2.4–46.6). The bootstrap yielded a shrinkage factor of 0.984, which was used to adjust the regression coefficients. Table 2 shows the adjusted prediction models and odds ratios that estimates the risk for SSI and secondary outcomes. For original prediction models and adjusted coefficients, see eTable 5.

Model performance

Brier, $Brier_{scaled}$ and Nagelkerke's R^2, to assess overall performance of the model for SSI, were 0.010, 0.026 and 0.081 respectively.

The discriminative performance of the model for SSI is shown in Figure 2. The AUC was 71.9 (95%CI=69.4–74.4%), which indicates reasonable discriminative ability. Predicted probabilities ranged between 0.01%-51.0%, with a mean of 1.0% (SD=1.5%). Calibration was poor, indicated by significant H-L statistic ($p<0.001$). The corresponding calibration plot that represents the accuracy of the model is

shown in Figure 3. The calibration plot showed quite accurate prediction, especially when the risk is low. The model underestimates the risk with a predicted probability >0.10.

The performance, discrimination and calibration of SSI and secondary outcomes are presented in Table 3. The predictive algorithms for POB and NER showed reasonable discriminative values (AUC=73.0 and 76.6) and explained fraction of variance by a Nagelkerke's R^2 of 0.072 and 0.086 respectively. The prediction model for delirium showed good discriminative value (AUC=85.9) and explained fraction of variance of 0.193. The models for luxation and VTE showed least favorable results on discrimination (AUC=58.4 and 66.3 respectively) and explained fraction of variance of 0.010 and 0.047 respectively. The ROC curves and calibration plots for secondary outcomes are presented in eFigure 1.

Table 1. Patient characteristics

Patient characteristics	Missing values	Total population (n=3776)	Total hip replacement (n=2494)	Total knee replacement (n=1282)
Age, mean (SD), years	0.1%	60.2 (15.8)	57.7 (17.0)	65.1 (11.7)
Gender: female No. (%)	0.1%	2298 (60.9%)	1468 (58.9%)	829 (64.7%)
BMI, mean (SD), kg/m^2	2.6%	27.5 (5.2)	26.6 (4.7)	29.3 (5.6)
Smoking: yes No. (%)	24.7%	498 (13.2)	341 (13.7)	157 (12.2)
ASA classification No. (%)	0.4%			
I		839 (22.2)	669 (26.8)	170 (13.3)
II		2091 (55.4)	1314 (52.7)	777 (60.6)
III		829 (22.0)	500 (20.0)	329 (25.7)
Diagnosis hip No. (%)	0.4%			
arthrosis			1599 (64.1)	
rheumatoid arthritis			68 (2.7)	
dysplasia			241 (9.7)	
osteonecrosis			228 (9.1)	
other			349 (14.0)	
Diagnosis knee No. (%)	0.9%			
arthrosis				1037 (80.9)
rheumatoid arthritis				123 (9.6)
other				111 (8.7)
Side affected: right No. (%)	0.3%	1915 (50.9)	1257 (50.4)	658 (51.3)
Surgical complications No. (%)	0%			
surgical site infection		38 (1.0)	25 (1.0)	13 (1.0)
venous thromboembolism		26 (0.7)	17 (0.7)	9 (0.7)
postoperative bleeding		47 (1.2)	28 (1.1)	19 (1.5)
luxation		32 (0.8)	31 (1.2)	1 (0.1)

delirium nerve damage		24 (0.6) 24 (0.6)	20 (0.8) 21 (0.8)	4 (0.3) 3 (0.2)

Table 2. Models including the coefficient per predictor per surgical outcome

	Surgical site infection		Venous thromboembolism		Postoperative bleeding		Luxation		Delirium		Nerve damage	
Variable	Coefficient *	Odds Ratio (95% CI)	Coefficient *	Odds Ratio (95% CI)	Coefficient *	Odds Ratio (95% CI)	Coefficient *	Odds Ratio (95% CI)	Coefficient *	Odds Ratio (95% CI)	Coefficient *	Odds Ratio (95% CI)
Intercept	-7.272	-	-4.790	-	-7.172	-	-5.864	-	-14.307	-	-2.250	-
Age (years)	0.031	1.032 (1.005-1.059)	-0.008	0.991 (0.966-1.018)	0.033	1.034 (1.006-1.062)	0.013	1.014 (0.991-1.038)	0.127	1.137 (1.067-1.212)	-0.051	0.949 (0.926-0.974)
Gender (male/female)	-	-	-0.168	0.844 (0.377-1.888)	-	-	-	-	-	-	-0.254	0.772 (0.319-1.868)
BMI (kg/m^2)	-0.002	0.998 (0.937-1.063)	-	-	0.012	1.012 (0.954-1.073)	0.021	1.023 (0.951-1.099)	-	-	-	-
Obesity (yes/no)	-	-	1.376	4.040 (1.462-11.159)	-	-	-	-	-	-	-	-
Smoking status (yes/no)	0.757	2.145 (0.883-5.213)	-	-	-0.023	0.952 (0.336-2.701)	0.491	1.667 (0.651-4.268)	-	-	0.572	1.754 (0.510-6.029)
Lung disease (yes/no)	-	-	-	-	-	-	-	-	-	-	-	-
Immunological disorder (yes/no)	0.891	2.474 (1.186-5.158)	-	-	-	-	-	-	-	-	-	-
Rheumatoid arthritis (yes/no)	-	-	-	-	-	-	0.538	1.752 (0.408-7.530)	-	-	-	-
Diabetes mellitus (yes/no)	0.904	2.494 (1.125 - 5.529)	0.829	2.317 (0.870-6.173)	-	-	-	-	-	-	-	-
Liver disease (yes/no)	2.345	10.659 (2.441-46.555)	-	-	-	-	-	-	-	-	-	-
Heart disease (yes/no)	-	-	-	-	0.729	2.086 (1.040-4.183)	-	-	0.348	1.422 (0.590-3.428)	-	-
Disease of central nervous system (yes/no)	-	-	-	-	-	-	0.106	1.113 (0.324-3.822)	0.898	2.465 (0.936-6.490)	-	-
Thromboembolic event (yes/no)	-	-	1.501	4.586 (1.521-13.826)	-	-	-	-	-	-	-	-
Dysplasia (yes/no)	-	-	-	-	-	-	-	-	-	-	-0.009	0.993

												(0.217-4.552)
Vitamin K antagonist use (yes/no)	-	-	-	-	0.787	2.220 (1.022-4.821)	-	-	-	-	-	-
NSAID's (yes/no)	0.619	1.877 (0.946-3.725)	-	-	-	-	-	-	-	-	-	-
To calculate the absolute risk for the surgical complications: $P_{(surgical\ complication)}$= 1/(1+exp- linear part) x 100%. Linear part = intercept + (coefficients * variables). *adjustment for over-fitting by shrinkage factor (SF); the intercept was re-estimated. BMI: Body Mass Index, NSAID's: Non-Steroidal Anti-Inflammatory Drugs												

Table 3. Model performance

	Surgical site infection	Venous Thrombo-embolism	Post-operative bleeding	Luxation	Delirium	Nerve damage
Brier score	0.010	0.007	0.012	0.012	0.006	0.008
$Brier_{scaled}$	0.026	0.007	0.010	0.003	0.027	0.012
Nagelkerke's R^2	0.081	0.047	0.072	0.010	0.193	0.086
AUC (95%CI)	71.9 (69.4-74.4)	66.3 (62.7-69.9)	73.0 (70.7-75.4)	58.4 (55.0-61.8)	85.9 (83.8-87.9)	76.6 (73.2-80.0)
H-L statistic (p-value)	p < 0.001	p < 0.001	p < 0.001	p < 0.001	p < 0.001	p < 0.001
Predicted possibilities						
Mean	0.010	0.007	0.012	0.012	<0.001	0.008
SD	0.015	0.007	0.012	0.004	0.012	0.010
Range	0.001-0.510	0.003-0.147	0.001-0.090	0.005-0.045	<0.001-0.147	0.001-0.072
Shrinkage factor	0.984	0.986	0.989	0.941	0.993	0.987

Discussion

The prediction models developed in this study are aimed for personalized counselling and SDM in orthopedic outpatient clinics. With our models, risk for surgical site infection (SSI), venous thromboembolism (VTE), postoperative bleeding (POB), luxation, delirium, and nerve damage (NER) can be predicted by patient characteristics, comorbidities and medication use. For SSI, predicted probabilities range between 0.01%-51.0%, which makes the model useful in adding relevant personalized information for adequate SDM compared to the previously used population-based probability of risk of 3%.[23] However, it is important to state that the model showed moderately accurate prediction, especially when the risk is low. The model underestimates the risk with a predicted probability >10%. Therefore, predicted probabilities exceeding 10% should be interpreted with caution. Furthermore, other performance measures were moderate to reasonable, indicating moderate overall performance of the model for SSI. We found similar results for other outcomes, except for the model for luxation; this model seriously underestimates the risk for luxation and could therefore not be used for personalized counselling.

Our results are comparable with the results of a recent meta-analysis on impact of comorbidities on SSI in THA or TKA. The authors stated diabetes and liver disease to contribute to a higher risk for SSI.[3] Another study with similar discriminative capacity found BMI, use of immunosuppression, ASA-score, procedure duration, and prior surgeries as risk factors for SSI.[30] Some of these predictors did not contribute to a higher performance in our model and were therefore not included. We additionally found age to be a significant predictor for SSI. For the already available prediction model based on data of Veterans with osteoarthritis of Harris et al., independent variables of the model cannot be compared for SSI since these results have not been reported.[13] We found a slightly better c-statistic (AUC) of 0.72 compared to 0.66 in their boosted model. Also comparison with Bozic et al., is difficult since applicability to non-Medicare population is questionable, as they also describe in their discussion.[14]

Based on literature we expected use of thromboprophylaxis, such as platelet aggregation inhibitors, direct oral anticoagulants, low-molecular-weight heparin, and/or vitamin K antagonists to be important predictors for POB. However, we could not demonstrate this finding in our model.[31] This is perhaps due to low frequencies of these predictors in our participants with POB and due to improved preoperative care regarding anticoagulant therapy. Our model for delirium included comparable predictors as other studies; they showed that age and preexisting cognitive impairment are important predictors for

delirium.[32 33] Our model confirms this finding. Kalisvaart et al., 2006 developed a comparable model based on acute- and elective hip surgery patients and found comparable predictors. The authors additionally found acute admission as predictor for delirium.[32] We cannot confirm this in our model since we focused on primary THA and TKA and these interventions are not primarily preferred in acute admissions due to hip fracture. The AUC indicates that our model is more accurate in estimating the risk for delirium (85.9 vs. 73).[32]

For VTE we only found obesity and thromboembolic event as significant risk factors.[3 34] This can be explained by the fact that the recurrence rate is high after earlier thromboembolic events.[35] We could not demonstrate diabetes to be a significant predictor for VTE.[3] For the risk of luxation, it is known that causes of dislocation are multifactorial and also caused by non-patient modifiable factors such as implant-related, surgery-related, and hospital-related factors. It is unclear to what extent these factors contribute to the occurrence of luxation, but we expect these factors to be of influence the model.[36 37] For these reasons, and the poor performance of the model for luxation, we consider this model of insufficient quality for use in patient information documents. Since we aimed our models to support preoperative SDM, we only used patient related variables as these variables are considered modifiable.[36 38]

Strengths and limitations

A strong point is that we thoroughly created a big dataset and we used state-of-the-art statistics for our analyses. Furthermore, the simplicity of our models is a strength because we used predictors collected in usual care. The predictors are easily to assess and thereby easily to implement in care. Several limitations in this study should be noted. We retrospectively analyzed prospectively collected data. These data were not primarily registered for research purposes and therefore their detail and accuracy could be less than optimal. Moreover, changes in reporting systems took place during the studied period, for instance the introduction of electronic medical records. It is known that changes in coding practice may change completeness of data.[39 40] Although researchers performed data collection thoroughly, data about comorbidities and medication use could be missed because it was reported elsewhere. Moreover, we expect a small quantity of underreporting regarding comorbidities since physicians and anesthesiologists perchance make a selection of important comorbidities in their report. We tried to correct for this limitation by including medication use since all drugs are registered in preoperative

anesthesia report. Also, data from 2004 until 2018 were used. In this period preoperative care has been changed. To evaluate the effect of this change on our outcome, we checked our patterns of complications and found no differences in this period. Furthermore, due to a low estimated event rate (1-3%) we needed a large population to have enough events to include predictors into our models. However, since not all predictors were significant in our final models, we expect that inclusion of more predictors would not lead to a considerably different model, as also discussed above. The models were developed based on pooled THA and TKA data. It is expected that the influence of patient characteristics, comorbidities and medication use is comparable for both THA and TKA.[41] The influence of comorbidities on outcomes is studied together quite often.[3] Furthermore, we tested this assumption by performing the analysis on THA and TKA data only. The models with corresponding performance measures were still consistent with the main analysis. Another limitation is that we only performed internal validation by bootstrapping, and were not yet able to determine external validity and clinical impact of the models. For clinical impact it is also important to determine the Minimal Clinically Important Difference of the outcomes.

Conclusion

Clinical prediction models were developed to contribute to more unbiased and accurate counselling in considering THA or TKA and are expected to be useful for identifying patients at risk for surgical complications. For SSI, the discriminative ability was reasonable and predicted risk varied between 0.01%-51.0%. We expect the individual predicted risk to enhance SDM and support a well-founded choice. We consider our models for SSI, delirium, and NER appropriate for clinical use when taking under- and overestimation of predicted risk into account. For clinical use of the models VTE and POB, caution concerning overestimation exceeding predicted probability of 0.08 and 0.05 (data presented in calibration plots in eFigure 1), respectively, should be taken into account. Future studies should evaluate clinical impact and whether our models are feasible in an external population.

Supplementary information

In the supplementary file, an excel file with the prediction models calculator is provided, see Appendix 1. The decision aid including the prediction models is published in Dutch at the website of the Radboud university medical center.

Ethics Statement

Approval for this study was obtained at the Medical Ethical Committee of Radboudumc (2018-4880).

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Competing interests

P. Van der Wees participates in the Scientific Advisory Panel of the American Physical Therapy Association (APTA)

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Author's contribution

All authors confirm authorship on all four ICMJE criteria.

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Data availability statement

Raw data will not be shared via a public data repository. Data will be available upon request via the Data repository from Radboudumc.

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Abbreviations used in manuscript

ASA: American Society of Anesthesiologists

AUC: Area under the receiver operating characteristic curve

H-L: Hosmer and Lemeshow

LROI: Dutch Arthroplasty Register

NER: Nerve damage

NHS: National Health Service

NOV: Dutch Orthopaedic Association

NSAID's: Non-Steroidal Anti-Inflammatory Drugs

POB: Postoperative bleeding

PROMs: Patient Reported Outcome Measures

SDM: Shared decision making

SSI: Surgical site infection

THA: Total hip arthroplasty

TKA: Total knee arthroplasty

VTE: Venous Thromboembolism

Figure 1. Flow chart for inclusion and exclusion of patients. Variables indicated with an asterisk* were primarily extracted from the LROI database. When these data were missing, the data were extracted from the (electronic) medical record. Castor EDC is indicated by Castor

Figure 2. Receiver Operating Characteristic curve of the prediction model for surgical site infection

AUC=71.9 (95% CI = 69.4–74.4%)

Figure 3. Calibration plot with the actual probability against the predicted probability for the model for surgical site infection. The triangles indicate quantiles (g=10) of patients with a similar predicted probability of success. The grey diagonal line represents perfect agreement between predicted and actual probability

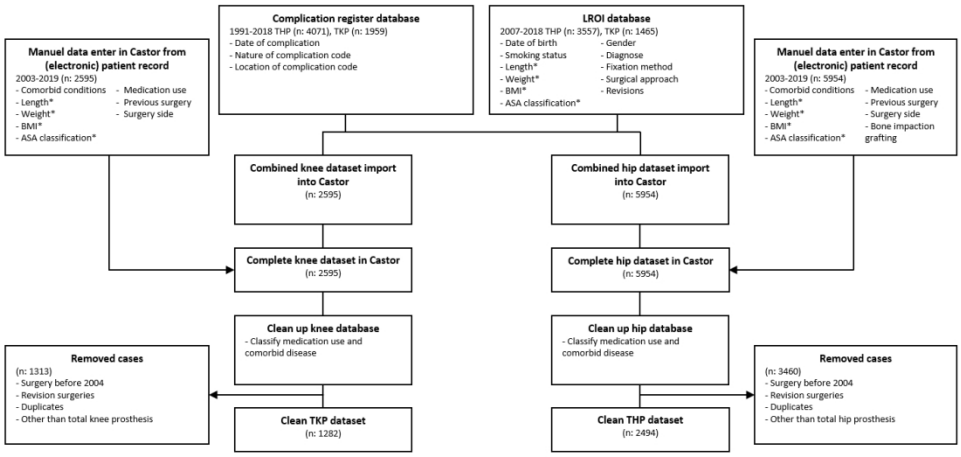

Figure 1. Flow chart for inclusion and exclusion of patients. Variables indicated with an asterisk* were primarily extracted from the LROI database. When these data were missing, the data were extracted from the (electronic) medical record. Castor EDC is indicated by Castor

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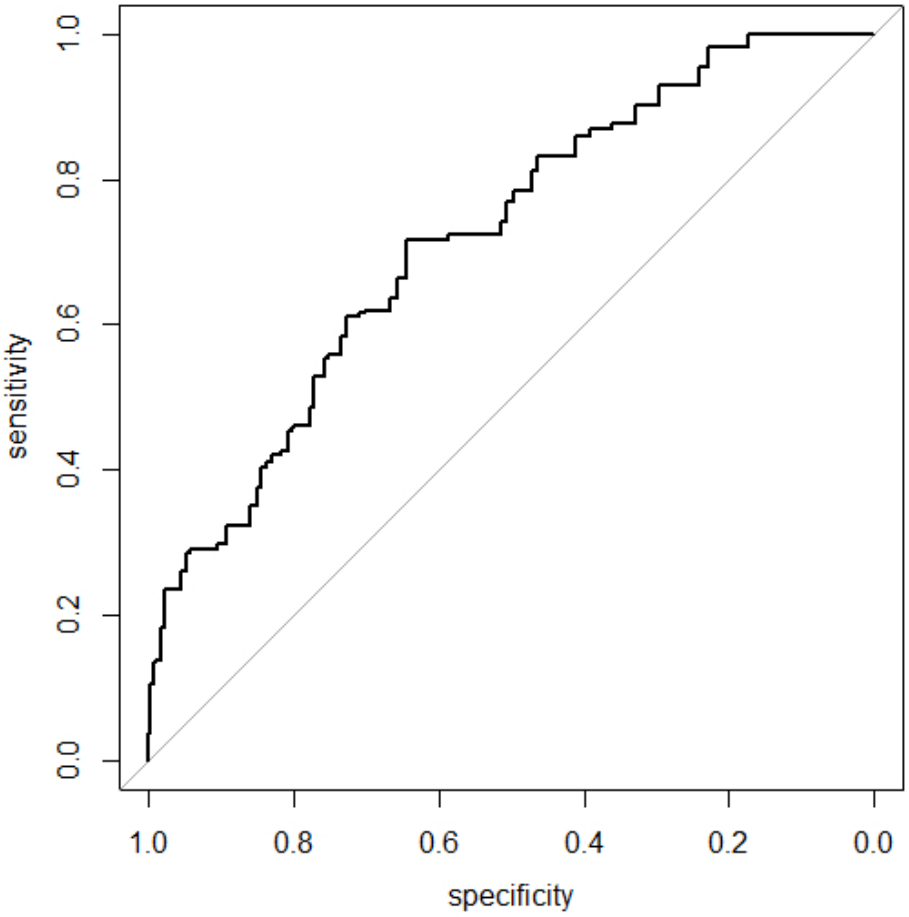


Figure 2. Receiver Operating Characteristic curve of the prediction model for surgical site infection
AUC=71.9 (95%-CI = 69.4–74.4%)

145x145mm (96 x 96 DPI)

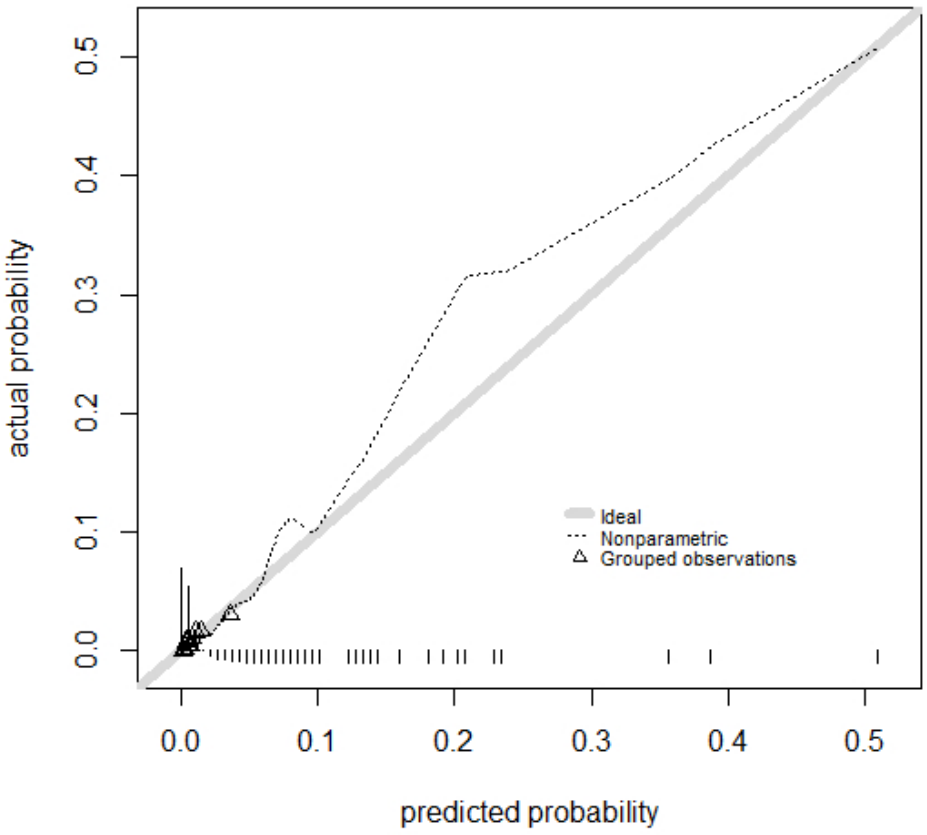


Figure 3. Calibration plot with the actual probability against the predicted probability for the model for surgical site infection. The triangles indicate quantiles (g=10) of patients with a similar predicted probability of success. The grey diagonal line represents perfect agreement between predicted and actual probability

145x145mm (96 x 96 DPI)

Supplemental Material

eTable 1. Categorization of surgical complications

Location code**	Location**	Code nature of complication**	Nature of complication**
Surgical site infection*			
24	Pelvis	012	Prosthesis infection
40	Hip	083	Deep infection
42	Knee	134	Infected organ
Venous thromboembolism			
24	Pelvis	104	Thrombosis
40	Hip	105	Embolus
41	Femur/upper leg		
42	Knee		
43	Lower leg		
50	Lung		
56	Venous system		
Luxation			
40	Hip	041	Luxation
		086	Disconnection prosthesis
Delirium			
54	Central nervous system	141	Psychological decompensation
58	Total		
Nerve damage			
40	Hip	094	Nerve lesion
41	Femur/upper leg		
43	Lower leg		
57	Arterial system		
Postoperative bleeding			
40	Hip	014	Wound leakage
41	Femur/upper leg	022	Bleeding

42 56	Knee Venous system	100 136	Secondary bleeding/hematoma Bleeding organ

* the records registered with the nature of complication 010 (infection around sutures), 011 (superficial infection), 013 (local wound necrosis) and 014 (wound leakage) are checked for occurrence of surgical site infection and added to the outcome surgical site infection when this was the case.

** only depicted when location code or code of the nature of complication occurred in the register.

Furthermore records registered with nature of complication 125 (interruption of sterility) were checked for occurrence of a surgical complication.

eTable 2. Predictors per outcome

	OR*/RR** (95% CI)	Study
Surgical site infection		
Age		
THA (>70years)	0.7** (0.3-1.5)	Almustafa et al (2018) (1)
TKA (>70years)	1.7** (0.9-3.3)	Almustafa et al (2018) (1)
Smoking status	0.16** (0.05-0.52)	Møller et al (2002) (2)
BMI	6.7* (NR)	Namba et al (2005) (3)
	4.8** (1.9-12.0)	Almustafa et al (2018) (1)
	2.53* (1.25-5.13)	Chen et al (2013) (4)
Immunological disorder	-	*Clinical reasoning*
NSAID's	-	*Clinical reasoning*
Diabetes mellitus	1.90* (1.32-2.74)	Podmore et al (2018) (5)
Liver disease	2.46* (1.46-4.12)	Podmore et al (2018) (5)
Venous thromboembolism		
Age		
THA(≥75years)	1.82* (1.15-2.87)	Migita et al (2014) (6)
TKA(≥75years)	1.30* (0.99-1.71)	Migita et al (2014) (6)
Sex		
THA(female>risk)	2.31* (1.03-5.18)	Migita et al (2014) (6)
TKA(female>risk)	1.58* (1.08-2.31)	Migita et al (2014) (6)
Diabetes mellitus	1.26* (0.92-1.72)	Podmore et al (2018) (5)
(TKA)	1.36* (1.07-1.72)	Yang et al (2015) (7)
Thromboembolic event *(TKA)*	1.11* (0.36-3.46)	Migita et al (2014) (6)
Obesity		
THA(BMI>30)	0.89* (0.36-2.20)	Migita et al (2014) (6)
TKA(BMI>30)	0.90* (0.58-1.38)	Migita et al (2014) (6)
Postoperative bleeding		
Age		
THA(>70 years)	2.61** (1.50-4.53)	Quintero et al (2016) (8)

TKA(>70years)	2.25** (1.03-4.94)	Quintero et al (2016) (8)
BMI	-	*Clinical reasoning*
Heart disease	-	*Univariate analysis*
Vitamin K antagonists	-	*Clinical reasoning*
Smoking status	-	*Univariate analysis*
Luxation		
Age	1.27* (1.02-1.57)	Kunutsor et al (2019) (9)
Smoking status	1.08* (0.96-1.21)	Kunutsor et al (2019) (9)
BMI	1.38* (1.03-1.85)	Kunutsor et al (2019) (9)
Rheumatoid arthritis	1.50* (1.05-2.15)	Kunutsor et al (2019) (9)
Disease of the central nervous system	2.54* (1.86-3.48)	Kunutsor et al (2019) (9)
Delirium		
Age	2.20* (1.80-2.71)	Huang et al (2019) (10)
Disease of the central nervous system *(dementia)*	7.44* (3.54-14.60)	Huang et al (2019) (10)
Heart disease *(congestive)*	0.83* (0.39-1.61)	Huang et al (2019) (10)
Nerve damage		
Age *(<45 (vs 65-74)*	7.17* (1.17-44.00)	Shetty et al (2016) (11)
BMI *(<BMI >risk)*	0.96* (0.77-1.21)	Kawano et al (2018) (12)
Sex *(female > risk)*	Not reported	Shetty et al (2016) (11)
Smoking status	1.90* (1.06-3.38)	Shetty et al (2016) (11)
Dysplasia	3.69* (1.65-8.28)	Farrell et al (2005) (13)
*results reported as odds ratio (OR); ** results reported as risk ratio (RR).		

eTable 3. Categorization of comorbidities

Categorization of comorbidities	
Comorbid category*	**Included comorbid conditions****
Bleeding diseases	Hemophilia
Blood quality	Anemia
Cancer	Prostate cancer Leukemia Breast cancer Lymph node cancer Bowen's disease
Central nervous system	Parkinson's disease Dementia TIA CVA
Cognitive impairment	Down syndrome
Diabetes mellitus	Diabetes mellitus
Heart disease	Ischemia of the heart Valve damage blood regurgitation Valve damage reduced blood flow Valve replacement Cardiomyopathy decreased contraction Cardiomyopathy decreased relaxation Heart decompensation Heart attack Angina pectoris Atrial fibrillation
High blood pressure	Hypertension
Hyper hormonal	Hyper hormonal
Hypo hormonal	Hypo hormonal

Immunological disorder	Scleroderma Rheumatoid arthritis Gout Psoriasis Artritides Dermal barrier disease General immune disorder Organ transplantation
Inflammation	Chronic bladder infection
Kidney disease	Kidney insufficiency
Liver disease	Liver cirrhosis
Lung disease	Chronic bronchitis Asthma COPD Emphysema Dyspnea
Mood sickness	Depression Psychosis
Obesity	Obesity
Peripheral nervous system	Nerve compression Lumbar vertebral stenosis
Poor peripheral blood flow	Atherosclerosis Claudication intermittent
Thromboembolic event	Deep venous thromboembolism Pulmonary embolism

* the comorbid categories are used for analysis.

** comorbid conditions are depicted when the frequency was ≥ 10 or when the comorbid condition was considered as a relevant comorbid condition in terms of outcome prediction.

eTable 4. Categorization of drug groups

Categorization of medication use	
Drug category	**Drugs groups according to the Dutch pharmacotherapeutic compass** (14)
Acenocoumarol	Acenocoumarol*
Antifibrinolytica	Antifibrinolytica
Antimycotics	Antimycotic antibiotics Others
Antiretroviral agents	Antiretroviral agents
Bisfosfonates	Bisfosfonates
Colchinine group	Colchinine group
Directly working oral anticoagulants	Directly working oral anticoagulants
DMARD's biologicals	Immunosuppresives selective Immunosuppresives others
Factors in blood coagulance	Factors in blood coagulance
Fenprocoumon	Fenprocoumon*
Imidazoles	Cutane imidazoles Others
Immunosuppressives	Interferons Interleukin antagonists Monoclonal antibodies
Local antibacterial agents	Cutaneous antibacterial agents Ocular antibacterial agents
Local corticosteroids	Cutane corticosteroids Nasal corticosteroids Corticosteroides for inhalation
Low molecular weight heparins	Low molecular weight heparins
Methotrexate	Methotrexate

NSAID's**	Coxib's Others
Oncology related detoxificants	Oncology related detoxificants
Salicylates	Analgetic salicylates Trombocytic salicylates
Statins	Statins
Systemic antibacterial agents	Cephalosporins Macrolides Penicillin's Tetracyclines Carbapenems Ceftriaxone Glycopeptides Aminoglycosides Rifamycins tuberculose Sulfonamides and trimethroprimides Triazoles Fluoroquinolones Others
Thrombocyte-aggregationblockers	P2y12 blockers Others
Xanthineoxidase inhibitor	Xanthineoxidase inhibitor

* according the Dutch pharmacotherapeutic compass, acenocoumarol and fenprocoumon belong to the drug group 'vitamin k antagonists'. Based on expert opinion, acenocoumarol and fenprocoumon were included separately in the analysis because of the differences in half-life.

** Non-Steroidal Anti-Inflammatory Drugs

eTable 5. Original prediction models and adjusted coefficients

Prediction model for estimation of risk for surgical site infection

Variable	Regression coefficient	Regression coefficient (adjusted with SF)*	Odds Ratio (95% CI)
Intercept	-7.305	-7.272	-
Age (years)	0.031	0.031	1.032 (1.005-1.059)
BMI (kg/m²)	-0.002	-0.002	0.998 (0.937-1.063)
Smoking status (yes/no)	0.769	0.757	2.145 (0.883-5.213)
Immunological disorder (yes/no)	0.905	0.891	2.474 (1.186-5.158)
Diabetes mellitus (yes/no)	0.918	0.904	2.494 (1.125-5.529)
Liver disease (yes/no)	2.382	2.345	10.659 (2.441-46.555)
NSAID's (yes/no)	0.629	0.619	1.877 (0.946-3.725)
To calculate the absolute risk of surgical site infection: $P_{(\text{surgical site infection})} = 1/(1+e^{-\text{linear part}}) \times 100\%$; Linear part = -7.272 + (0.031 x age – 0.002 x BMI + 0.757 x smoking status + 0.891 x immunological disorder + 0.904 x diabetes mellitus + 2.345 x liver disease + 0.619 x NSAID's). *adjustment for over-fitting by shrinkage factor (SF) (SF = 0.984); the intercept was re-estimated.			

Prediction model for estimation of risk for venous thromboembolism

Variable	Regression coefficient	Regression coefficient (adjusted with SF)*	Odds Ratio (95% CI)
Intercept	-4.764	-4.790	-
Age (years)	-0.009	-0.008	0.991

			(0.966-1.018)
Gender (male/female)	-0.170	-0.168	0.844 (0.377-1.888)
Obesity (yes/no)	1.396	1.376	4.040 (1.462-11.159)
Diabetes mellitus (yes/no)	0.841	0.829	2.317 (0.870-6.173)
Thromboembolic event (yes/no)	1.523	1.501	4.586 (1.521-13.826)
To calculate the absolute risk of venous thromboembolism: $P_{(\text{venous thromboembolism})} = 1/(1+e^{-\text{linear part}}) \times 100\%$; Linear part = -4.790 + (-0.008 x age – 0.168 x gender + 1.376 x obesity + 0.829 x diabetes mellitus + 1.501 x thromboembolic event). *adjustment for over-fitting by shrinkage factor (SF) (SF = 0.986); the intercept was re-estimated.			

Prediction model for estimation of risk for postoperative bleeding.

Variable	Regression coefficient	Regression coefficient (adjusted with SF)*	Odds Ratio (95% CI)
Intercept	-7.182	-7.172	-
Age (years)	0.033	0.033	1.034 (1.006-1.062)
BMI (kg/m²)	0.012	0.012	1.012 (0.954-1.073)
Smoking status (yes/no)	-0.023	-0.023	0.952 (0.336-2.701)
Heart disease (yes/no)	0.737	0.729	2.086 (1.040-4.183)
Vitamin K antagonist use (yes/no)	0.796	0.787	2.220 (1.022-4.821)
To calculate the absolute risk of postoperative bleeding: $P_{(\text{postoperative bleeding})} = 1/(1+e^{-\text{linear part}}) \times 100\%$;			

Linear part = -7.172 + (0.033 x age + 0.012 x BMI – 0.023 x smoking status + 0.729 x heart disease + 0.787 x vitamin K antagonist use). *adjustment for over-fitting by shrinkage factor (SF) (SF = 0.989); the intercept was re-estimated.

Prediction model for estimation of risk for luxation.

Variable	Regression coefficient	Regression coefficient (adjusted with SF)*	Odds Ratio (95% CI)
Intercept	-5.976	-5.800	-
Age (years)	0.014	0.013	1.014 (0.991-1.038)
BMI (kg/m²)	0.022	0.021	1.023 (0.951-1.099)
Smoking status (yes/no)	0.521	0.491	1.667 (0.651-4.268)
Rheumatoid arthritis (yes/no)	0.572	0.538	1.752 (0.408-7.530)
Disease of central nervous system (yes/no)	0.113	0.106	1.113 (0.324-3.822)
To calculate the absolute risk of luxation: $P_{(luxation)} = 1/(1+e^{-\text{linear part}}) \times 100\%$; Linear part = -5.800 + (0.013 x age + 0.021 x BMI + 0.491 x smoking status + 0.538 x rheumatoid arthritis + 0.106 x disease of central nervous system). *adjustment for over-fitting by shrinkage factor (SF) (SF = 0.941); the intercept was re-estimated.			

Prediction model for estimation of risk for delirium.

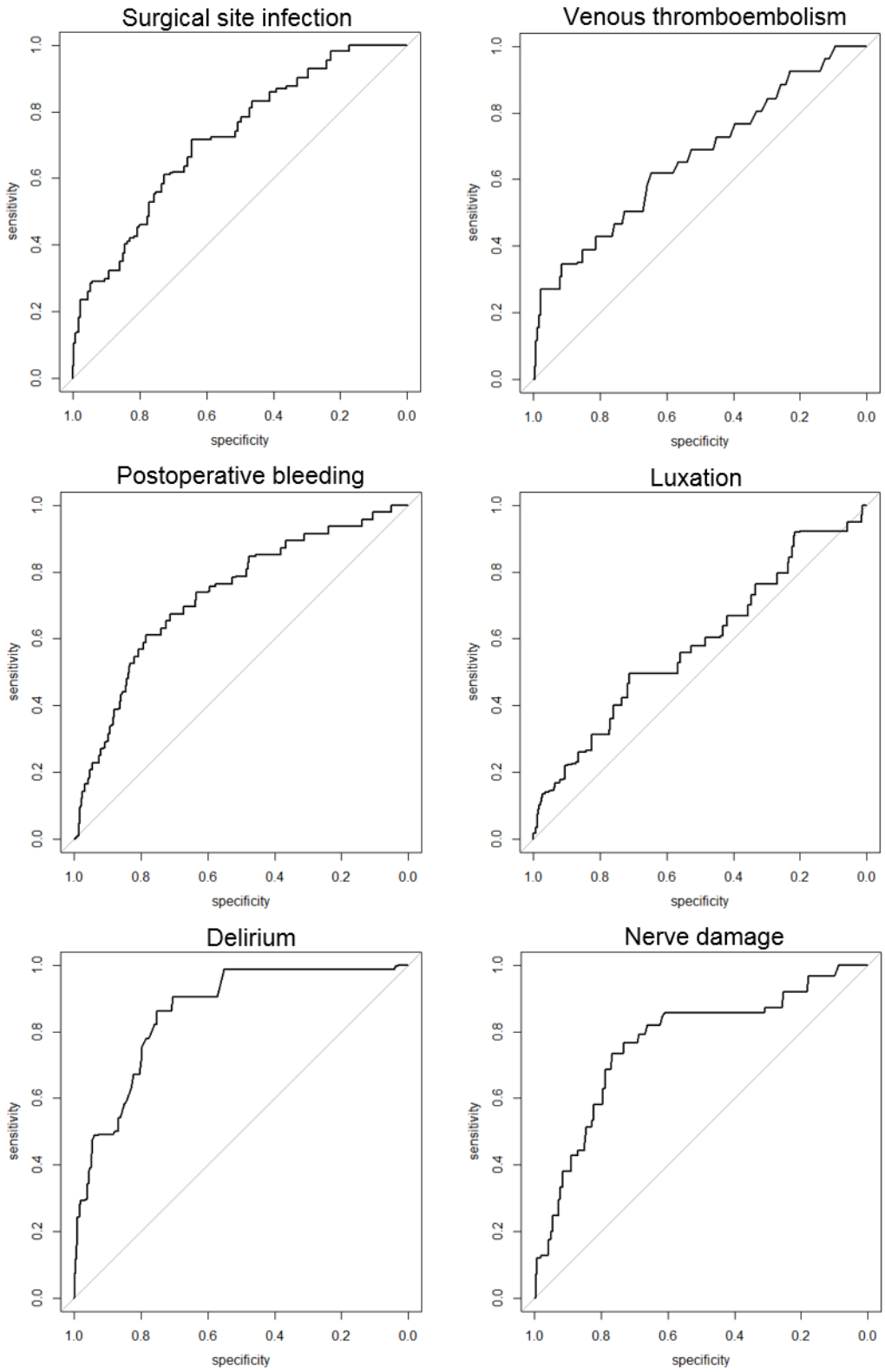
Variable	Regression coefficient	Regression coefficient (adjusted with SF)*	Odds Ratio (95% CI)
Intercept	-14.368	-14.307	-
Age (years)	0.129	0.127	1.137 (1.067-1.212)
Heart disease (yes/no)	0.351	0.348	1.422

			(0.590-3.428)
Disease of central nervous system (yes/no)	0.904	0.898	2.465 (0.936-6.490)
To calculate the absolute risk of delirium: $P_{(delirium)} = 1/(1+e^{-\text{linear part}}) \times 100\%$; Linear part = -14.307 + (0.127 x age + 0.348 x heart disease + 0.898 x disease of central nervous system). *adjustment for over-fitting by shrinkage factor (SF) (SF = 0.993); the intercept was re-estimated.			

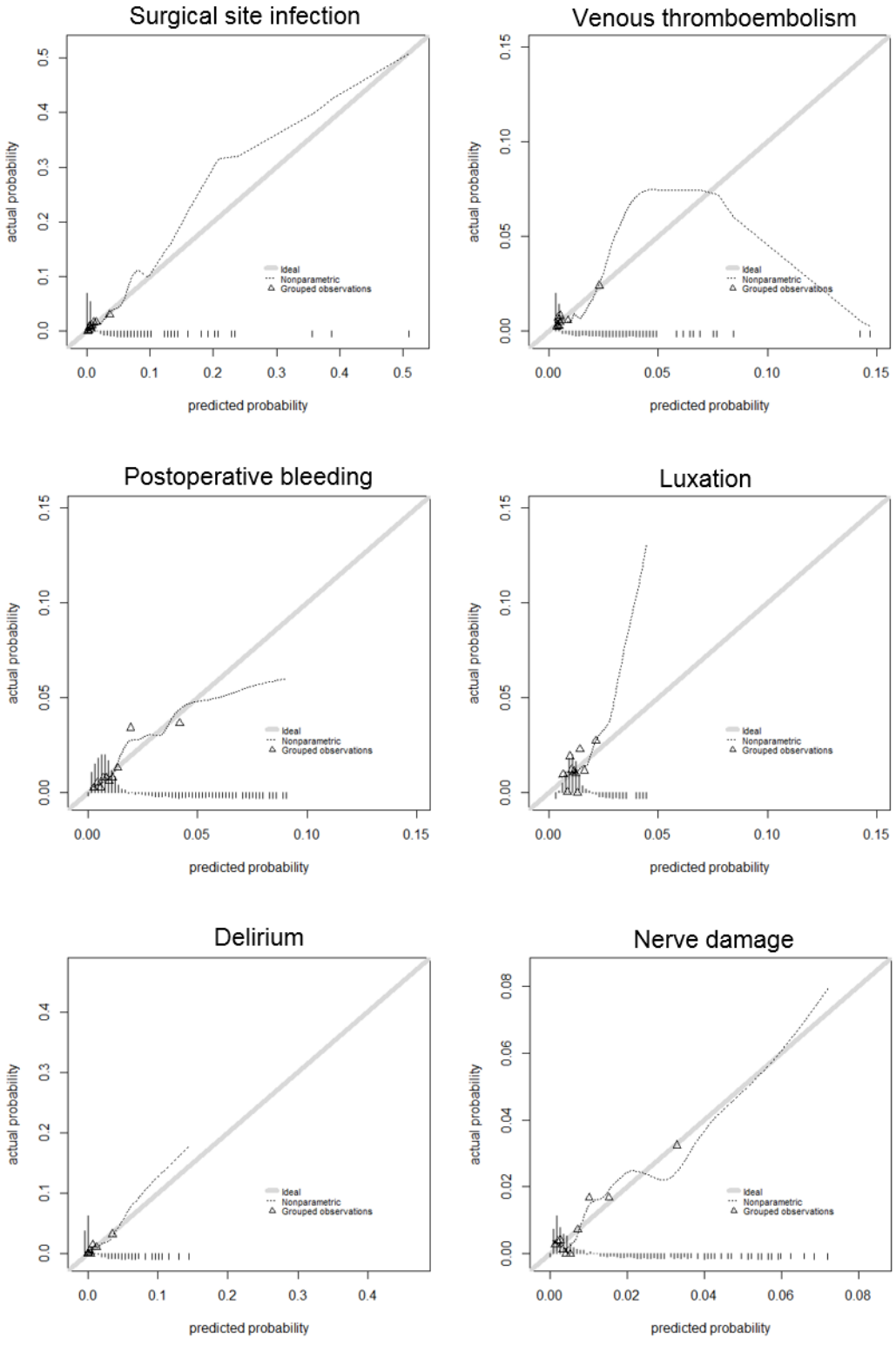
Prediction model for estimation of risk for nerve damage.

Variable	Regression coefficient	Regression coefficient (adjusted with SF)*	Odds Ratio (95% CI)
Intercept	-2.209	-2.250	-
Age (years)	-0.052	-0.051	0.949 (0.926-0.974)
Gender (man/woman)	-0.258	-0.254	0.772 (0.319-1.868)
Smoking status (yes/no)	0.580	0.572	1.754 (0.510-6.029)
Dysplasia (yes/no)	-0.009	-0.009	0.993 (0.217-4.552)
To calculate the absolute risk of nerve damage: $P_{(nerve\ damage)} = 1/(1+e^{-\text{linear part}}) \times 100\%$; Linear part = -2.250 + (-0.051 x age – 0.254 x gender + 0.572 x smoking status – 0.009 x dysplasia). *adjustment for over-fitting by shrinkage factor (SF) (SF = 0.987); the intercept was re-estimated.			

eFigure 1. ROC curves and Calibration plots



eFigure 1.1. Receiver Operating Characteristic curves of the prediction models for surgical site infection, venous thromboembolism, postoperative bleeding, luxation, delirium and nerve damage



eFigure 1.2. Calibration plots with actual probability against the predicted probability for the models for surgical site infection, venous thromboembolism, postoperative bleeding, luxation, delirium and nerve damage. The triangles indicate quantiles (g=10) of patients with a similar predicted probability of success. The grey diagonal line represents perfect agreement between predicted and actual probability

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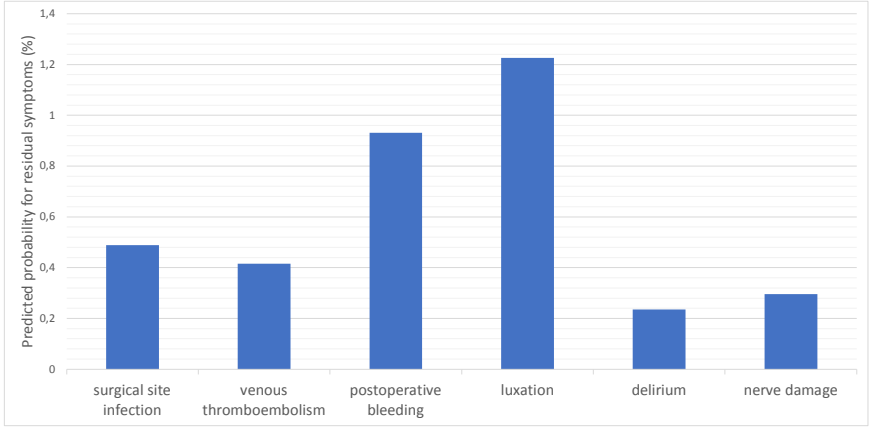
Input variables*		Surgical site infection		Venous thromboembolism		Postoperative bleeding		Luxation		Delirium		Nerve damage	
Age (years)	65	0,031	2,015	-0,008	-0,52	0,033	2,145	0,013	0,845	0,127	8,255	-0,051	-3,315
Gender (male/female)	1		0	-0,168	-0,168		0		0		0	-0,254	-0,254
BMI (kg/m2)	30	-0,002	-0,06		0	0,012	0,36	0,021	0,63		0		0
Obesity (yes/no)	0		0	1,376	0		0		0		0		0
Smoking status (yes/no)	0	0,757	0		0	-0,023	0	0,491	0		0	0,572	0
Lung disease (yes/no)	0		0		0		0		0		0		0
Immunological disorder (yes/no)	0	0,891	0		0		0		0		0		0
Rheumatoid arthritis (yes/no)	0		0		0		0	0,538	0		0		0
Diabetes mellitus (yes/no)	0	0,904	0	0,829	0		0		0		0		0
Liver disease (yes/no)	0	2,345	0		0		0		0		0		0
Heart disease (yes/no)	0		0		0	0,729	0		0	0,348	0		0
Disease of central nervous system (yes/no)	0		0		0		0	0,106	0	0,898	0		0
Thromboembolic event (yes/no)	0		0	1,501	0		0		0		0		0
Dysplasia (yes/no)	0		0		0		0		0		0	-0,009	0
Vitamin K antagonist use (yes/no)	0		0		0	0,787	0		0		0		0
NSAID use (yes/no)	0	0,619	0		0		0		0		0		0
		-7,272	1,955	-4,79	-0,688	-7,172	2,505	-5,864	1,475	-14,307	8,255	-2,25	-3,569
			-5,317		-5,478		-4,667		-4,389		-6,052		-5,819
Predicted probability for residual symptoms (%)		**0,48834885**		**0,41602963**		**0,93128835**		**1,22609394**		**0,23476267**		**0,29617761**	
		surgical site infection		venous thromboembolism		postoperative bleeding		luxation		delirium		nerve damage	

* Age: in years, Gender: male scored as 1 and female scored as 2, BMI: in kg/m2, Obesity: no scored as 0 and yes as 1, Smoking status: no scored as 0 and yes as 1, Lung disease: no scored as 0 and yes as 1, Immunological disorder: no scored as 0 and yes as 1



embolic event: no scored as 0 and yes as 1, Dysplasia: no scored as 0 and yes as 1, Vitamin K antagonists use: no scored as 0 and yes as 1, NSAID's: no scored as 0 and yes as 1

Research checklist. TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	3
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	5-6
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	6
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	7
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	7
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	7
	5b	D;V	Describe eligibility criteria for participants.	7-8
	5c	D;V	Give details of treatments received, if relevant.	7-8
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	8
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	N/A
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	8
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	N/A
Sample size	8	D;V	Explain how the study size was arrived at.	8
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	8-9

Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	9-10
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	9-10
	10c	V	For validation, describe how the predictions were calculated.	9-10
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	9-10
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	N/A
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	N/A
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	N/A
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	11, Figure 1
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	11, Table 1
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	N/A
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	11, Table 1
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	eTable 5
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	Table 2, eTable 5
	15b	D	Explain how to the use the prediction model.	Table 2, eTable 5, 11-12
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	Table 2, eTable 5
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	N/A
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample,	18-20

			few events per predictor, missing data).	
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	18-20
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	18-20
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	18-20
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	20
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	21

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

BMJ Open

Development of prediction models for complications after primary total hip and knee arthroplasty: a single-centre retrospective cohort study in the Netherlands.

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Title Page

(1) Title

Development of prediction models for complications after primary total hip and knee arthroplasty: a single-centre retrospective cohort study in the Netherlands.

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Abstract

Objective. The aim of the study was to develop prediction models for patients with THA and TKA to predict the risk for surgical complications based on personal factors, comorbidities, and medication use.

Design. Retrospective cohort study.

Setting. Tertiary Care in outpatient clinic of university medical center.

Participants. 3,776 patients with a primary THA or TKA between 2004 and 2018.

Primary and secondary outcome measures. Multivariable logistic regression models were developed for primary outcome surgical site infection (SSI), and secondary outcomes venous thromboembolism (VTE), postoperative bleeding (POB), luxation, delirium, and nerve damage (NER).

Results. For SSI, age, smoking status, BMI, presence of immunological disorder, diabetes mellitus, liver disease, and use of NSAID's were included. An area under the receiver operating characteristic curve (AUC) of 71.9%(95%CI=69.4-74.4) was found. For this model, liver disease showed to be the strongest predictor with an odds ratio of 10.7(95%CI=2.4-46.6). The models for POB and NER showed AUCs of 73.0%(95%CI=70.7-75.4) and 76.6%(95%CI=73.2-80.0), respectively. For delirium an AUC of 85.9%(95%CI=83.8-87.9) was found, and for the predictive algorithms for luxation and VTE we found least favorable results (AUC= 58.4%(95%CI=55.0-61.8) and 66.3%(95%CI=62.7-69.9)).

Conclusions. Discriminative ability was reasonable for SSI and predicted probabilities ranged from 0.01%-51.0%. We expect this to enhance shared decision making in considering THA or TKA since current counseling is predicated on population-based probability of risk, rather than using personalized prediction. We consider our models for SSI, delirium and NER appropriate for clinical use when taking under- and overestimation of predicted risk into account. For VTE and POB, caution concerning overestimation exceeding a predicted probability of 0.08 for VTE and 0.05 for POB should be taken into account. Furthermore, future studies should evaluate clinical impact and whether the models are feasible in an external population.

Keywords. total hip arthroplasty; total knee arthroplasty; surgical complications; prediction; prognosis; comorbidities; medication use

Strengths and limitations of this study.

- This study included multivariable logistic regression models to predict postoperative complications after primary total hip- and knee arthroplasty based on personal factors, comorbidities, and medication use.
- The present study was conducted and reported according the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guidelines.
- Purposive selection of predictors by clinical reasoning and literature search.
- Limitations include only internal validation of the prediction models by bootstrapping.
- Used data were not primarily registered for research purposes, and therefore, their detail and accuracy could be less than optimal.

Introduction

Joint replacement is a recommended intervention for people with end stage hip or knee osteoarthritis.[1] Whether surgery is the best solution depends on many individual factors such as severity of the disease, level of experienced pain and discomfort, medication use, personal circumstances, comorbid diseases, and intended type of surgery.[2-4] Because the decision to have surgery or not is complex, a shared decision making (SDM) process is warranted. This process allows patients and clinicians to discuss treatment options consistent with the patient's values and preferences.[5]

Information on most likely prognosis is central in this dialogue as the clinician provides guidance and information about expected outcomes, including the risk on surgical complications, when facing the decision to pursue or forgo surgery. However, providing personalized information about the risk on surgical complications, based on personal characteristics of the patient, is challenging. Available evidence often consists of average outcomes and current guidelines on prediction of outcome still recommend counselling predicated on population-based probability of risk, rather than using personalized prediction.[6] This is remarkable, as discussing potential personal risks is an important aspect of SDM.[7, 8]

To overcome this problem, models that can predict postoperative complications are frequently developed and applied. Several universal surgical prediction models have already been developed based on a big national database.[9] However, before applying these models to orthopedic surgical procedures, performance and accuracy on the specific surgical field needs to be determined. For total joint arthroplasty, this is performed by Trickey et al.[10] As shown by Trickey et al., and others, patients at risk of not benefitting from total hip- or total knee arthroplasty (THA or TKA) can be identified using prediction models based on preoperative data like demographic factors, and pain scores, and physical functioning measured with Patient Reported Outcome Measures (PROMs).[10-13] Another study developed a preoperative prediction model to predict residual complaints on pain, functional outcome and treatment success for individual patients after TKA.[14] Also useful electronic risk calculators predicting complications and mortality for patients and clinicians are available for specific populations.[15-17] In one study, data of patients registered in the Medicare database, the federal health insurance program for individuals aged ≥65 years, are used for development of a risk calculator. However, the exact patient characteristics of the study population are not reported and the effect of the predictors remain unclear.[16] Harris et al. developed prediction models with machine learning

techniques models to determine demographic and clinical predictors for prediction of postoperative complications and mortality. The authors were able to identify predictor variables for their three most accurate models predicting a postoperative renal complication, cardiac complication, and death. However, used predictor variables in the models can only be found for their three most accurate outcomes.[17] Further research is warranted to identify relevant predictors for different postoperative outcomes. In another study, regression models are based on the results of univariate analyses on a broad range of data as demographics, comorbidities, and laboratory, or test values of a mainly male Veteran population, and the authors reported suboptimal performance scores for prediction of most outcomes.[15] Generalizability of prediction models based on specific patient populations may be limited, and further evaluation of potential risk factors is needed to validate prediction models for complications after primary total hip- and knee replacement.

As it is known from literature that personal factors including demographic characteristics and comorbidities have an impact on surgical complications,[3] these assumed caused relationships might therefore serve as basis for a risk prediction model. Therefore, the aim of this study is to develop a prediction model for clinicians and patients with hip- or knee osteoarthritis considering surgery, by predicting risk for surgical complications based on personal factors, comorbidities and medication use.

Methods

Study design and setting

For this retrospective cohort study, we established a cohort of patients who underwent primary THA or TKA between 2004 and 2018 at the Orthopedic department of Radboud university medical center Nijmegen, the Netherlands. Datasets were merged into one centralized database based on patient number, birthdate and date of surgery.

This study was performed and reported in line with transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guidelines.[18]

Data collection

Data used for this study were extracted from (electronic) medical records of Radboudumc, Dutch Arthroplasty Register (LROI), and Radboudumc registry of complications. We primarily extracted comorbidities and medication use from medical records. These data were extracted based on coding and were obtained by three researchers (LS, TW and AT) by use of a standardized operating procedure, and stored in a centralized platform (Castor Electronic Data Capture (EDC)).[19] Data about patient characteristics like age, sex, BMI, smoking status, American Society of Anesthesiologists (ASA) classification and diagnosis for surgery were extracted from LROI. Furthermore, date of surgery, type of surgery (primary or revision), surgery side, and type of implant were extracted.[20] From the register of complications we extracted all surgeries and complications which occurred within one year after THA or TKA.[21] In this registry, surgery related orthopedic complications were registered as well as other medical complications.[22] All complications were registered by location code combined with a code for the nature of the complication.[21] Some registrations were unclear and could refer to one of predefined complications and were therefore checked in medical records by LS. For all included location- and nature of complication codes per surgical complication, see eTable 1.

Inclusion and exclusion criteria

Patients were eligible for inclusion in the cohort if the surgery concerned primary THA or TKA. We defined primary THA or TKA as the first time a total prosthesis is placed. Revision arthroplasty was defined as any change (replacement, removal, or addition) of one or several components of the joint

prosthesis.[20] We expected revision arthroplasty to influence risk for complications negatively, therefore revision arthroplasty was excluded for this study.

Outcome (dependent variables)

Prediction models were developed over the pooled THA and TKA data for six predefined surgical complications. Primary outcome was surgical site infection (SSI), and secondary outcomes included venous thromboembolism (VTE), postoperative bleeding (POB), luxation, delirium, and nerve damage (NER). All prediction models were developed based on primary THA and TKA data, except for the models for luxation and NER which were developed based on primary THA data. These surgical complications are uncommon in TKA.

Predictors (independent variables)

In total sixteen predictor candidates were selected based on evidence from previous reports and clinical reasoning in relation to the outcomes. These included patient characteristics, comorbidities, and medication use (as specified in eTable 2 and 3). Note that we made a purposive selection from the sixteen predictors candidates to serve as predictors for the different surgical complications.

Comorbidities extracted from medical records were categorized according to the English National Health Service (NHS). The NHS considered these categories relevant comorbid categories in terms of outcome prediction.[3] Medication use was reduced to the active substance of the drug and was categorized to drug groups according the Dutch pharmacotherapeutic compass.[23]

Sample size

It is recommended that at least five events are collected for each predictor that is evaluated in multivariable regression analysis.[24, 25] An event was defined as the least frequent outcome status, which in our case was the presence of surgical complication. In the Netherlands, the estimated risk of a complication like SSI is 3%[26]; therefore, in order to develop a model with six predictors, at least 30 events were required, and so a sample size of at least 1000 patients was required.

Missing data

Data were checked for completeness by investigating patterns of missingness to assess presence of a nonrandom element. Incomplete data were double checked. Missing data were imputed using multiple imputation, as the omission of patients who have one or more predictor variables missing from analysis can cause considerable loss of precision and might bias the results.[27, 28] The number of imputations was set to ten. The imputation was checked for accuracy by visual inspection and frequencies.

Statistical analysis methods

Model development

Evidence from literature, clinical reasoning and eyeballing guided selection of predictors to be included in the models. Eyeballing was done by evaluation of potential higher frequencies of predictors in relation to the outcome.[29] All selected predictors were entered into a multivariable logistic regression model, using the occurrence of a surgical complication as outcome variable. The prediction model was pooled over the imputed datasets.[30]

Internal validation

To reduce risk of overfitting, we internally validated the model using bootstrapping. In this step, B-bootstrap samples of B=1000 were drawn with replacement from original data, which reflects drawing samples from underlying population. Due to the drawing with replacement, a bootstrapped dataset allows for containing the same original cases. Other validation methods resample without replacement and thereby such validation datasets are produced through a pre-specified number of surrogate datasets, and each of the original cases will be left out exactly once, which results in a smaller dataset. Since our dataset is not very large, we decided to use bootstrapping as internal validation method. Bootstrapping was performed to estimate the performance in future patients, and to adjust the model by the calculated shrinkage factor so that future predictions will be less extreme.[24]

Performance of the model

We quantified measures of performance, discrimination and calibration. Overall model performance is the distance between predicted- and actual outcome.[28] To quantify overall model performance, we assessed Brier, $Brier_{scaled}$ and Nagelkerke's R^2. For Brier, squared differences between actual outcome and predictions were calculated. Brier can range from 0 for a perfect model to 0.25 for a noninformative

model with 50% incidence of the outcome. $Brier_{scaled}$ is scaled by its maximum under a noninformative model and range between 0-100%. Nagelkerke's R^2 is a measure of explained variation.[31] The ability of the model to discriminate between those with and without the outcome was quantified as the area under the receiver operating characteristic curve (AUC). This can range from 50% (no discriminative capacity) to 100% (perfect discriminative capacity). The discriminative capacity was interpreted as reasonable when AUC was >0.70 and good when AUC was >0.80.[32] Calibration of the model is the agreement between predicted probabilities (probability of an event calculated with the model) and observed frequencies of outcome (accuracy) and was assessed by visually inspecting the calibration plot.[28] Furthermore, we computed Hosmer and Lemeshow (H-L) goodness-of-fit as a quantitative measure of calibration. A high H-L statistic is related to a low P-value, and indicates a poor fit.[24]

All statistical analyses were performed using R 3.5.3. Packages vim, mice, rms, pROC, and generalhoslem were used.

Patient and Public Involvement

Patients were involved in the design of the study which included consultation during grant writing and advice in setting up the study design. Furthermore, patients were involved in the process of incorporating the prediction models in a patient decision aid. Focus groups were held and patients and clinicians together were asked for their opinion regarding incorporation of the models in the preoperative process.

Results

Participants

In total 3,776 patients with primary THA or TKA were identified as eligible for the present study. Of these patients, 2,494 patients underwent THA and 1,282 patients underwent TKA. See Figure 1 for participant flow. Baseline characteristics of the final cohort are presented in Table 1.

Model development

The number of missing values per predictor are shown in Table 1. For the majority of potential predictors, there was only a small quantity of missing data; however, smoking status was missing in 24.7%. After imputation, all patients were available for multivariable modelling. There were no missing values in surgical complications.

Model specification

According to our selection of predictor candidates per outcome (depicted in eTable 4), we entered all selected predictors in the model. For SSI, these predictors were: age, smoking status, BMI, presence of an immunological disorder, diabetes mellitus, liver disease, and use of Non-Steroidal Anti-Inflammatory Drugs (NSAID's). We found a significant influence of age, immunological disorder, diabetes mellitus and liver disease of which the presence of liver disease showed to be the strongest predictor with an odds ratio of 10.7 (95%CI=2.4–46.6). The bootstrap yielded a shrinkage factor of 0.984, which was used to adjust the regression coefficients. Table 2 shows the adjusted prediction models and odds ratios that estimates the risk for SSI and secondary outcomes. For original prediction models and adjusted coefficients, see eTable 5.

Model performance

Brier, $Brier_{scaled}$ and Nagelkerke's R^2, to assess overall performance of the model for SSI, were 0.010, 0.026 and 0.081 respectively.

The discriminative performance of the model for SSI is shown in Figure 2. The AUC was 71.9 (95%CI=69.4–74.4%), which indicates reasonable discriminative ability. Predicted probabilities ranged between 0.01%-51.0%, with a mean of 1.0% (SD=1.5%). Calibration was poor, indicated by significant H-L statistic (p<0.001). The corresponding calibration plot that represents the accuracy of the model is

shown in Figure 3. The calibration plot showed quite accurate prediction, especially when the risk is low. The model underestimates the risk with a predicted probability >0.10.

The performance, discrimination and calibration of SSI and secondary outcomes are presented in Table 3. The predictive algorithms for POB and NER showed reasonable discriminative values (AUC=73.0 and 76.6) and explained fraction of variance by a Nagelkerke's R^2 of 0.072 and 0.086 respectively. The prediction model for delirium showed good discriminative value (AUC=85.9) and explained fraction of variance of 0.193. The models for luxation and VTE showed least favorable results on discrimination (AUC=58.4 and 66.3 respectively) and explained fraction of variance of 0.010 and 0.047 respectively. The ROC curves and calibration plots for secondary outcomes are presented in eFigure 1.

Table 1. Patient characteristics

Patient characteristics	Missing values	Total population (n=3776)	Total hip replacement (n=2494)	Total knee replacement (n=1282)
Age, mean (SD), years	0.1%	60.2 (15.8)	57.7 (17.0)	65.1 (11.7)
Gender: female No. (%)	0.1%	2298 (60.9%)	1468 (58.9%)	829 (64.7%)
BMI, mean (SD), kg/m^2	2.6%	27.5 (5.2)	26.6 (4.7)	29.3 (5.6)
Smoking: yes No. (%)	24.7%	498 (13.2)	341 (13.7)	157 (12.2)
ASA classification No. (%)	0.4%			
I		839 (22.2)	669 (26.8)	170 (13.3)
II		2091 (55.4)	1314 (52.7)	777 (60.6)
III		829 (22.0)	500 (20.0)	329 (25.7)
Diagnosis hip No. (%)	0.4%			
arthrosis			1599 (64.1)	
rheumatoid arthritis			68 (2.7)	
dysplasia			241 (9.7)	
osteonecrosis			228 (9.1)	
other			349 (14.0)	
Diagnosis knee No. (%)	0.9%			
arthrosis				1037 (80.9)
rheumatoid arthritis				123 (9.6)
other				111 (8.7)
Side affected: right No. (%)	0.3%	1915 (50.9)	1257 (50.4)	658 (51.3)
Surgical complications No. (%)	0%			
surgical site infection		38 (1.0)	25 (1.0)	13 (1.0)
venous thromboembolism		26 (0.7)	17 (0.7)	9 (0.7)
postoperative bleeding		47 (1.2)	28 (1.1)	19 (1.5)
luxation		32 (0.8)	31 (1.2)	1 (0.1)

delirium nerve damage		24 (0.6) 24 (0.6)	20 (0.8) 21 (0.8)	4 (0.3) 3 (0.2)

Table 2. Models including the coefficient per predictor per surgical outcome

	Surgical site infection		Venous thromboembolism		Postoperative bleeding		Luxation		Delirium		Nerve damage	
Variable	Coefficient *	Odds Ratio (95% CI)	Coefficient *	Odds Ratio (95% CI)	Coefficient *	Odds Ratio (95% CI)	Coefficient *	Odds Ratio (95% CI)	Coefficient *	Odds Ratio (95% CI)	Coefficient *	Odds Ratio (95% CI)
Intercept	-7.272	-	-4.790	-	-7.172	-	-5.864	-	-14.307	-	-2.250	-
Age (years)	0.031	1.032 (1.005-1.059)	-0.008	0.991 (0.966-1.018)	0.033	1.034 (1.006-1.062)	0.013	1.014 (0.991-1.038)	0.127	1.137 (1.067-1.212)	-0.051	0.949 (0.926-0.974)
Gender (male/female)	-	-	-0.168	0.844 (0.377-1.888)	-	-	-	-	-	-	-0.254	0.772 (0.319-1.868)
BMI (kg/m^2)	-0.002	0.998 (0.937-1.063)	-	-	0.012	1.012 (0.954-1.073)	0.021	1.023 (0.951-1.099)	-	-	-	-
Obesity (yes/no)	-	-	1.376	4.040 (1.462-11.159)	-	-	-	-	-	-	-	-
Smoking status (yes/no)	0.757	2.145 (0.883-5.213)	-	-	-0.023	0.952 (0.336-2.701)	0.491	1.667 (0.651-4.268)	-	-	0.572	1.754 (0.510-6.029)
Lung disease (yes/no)	-	-	-	-	-	-	-	-	-	-	-	-
Immunological disorder (yes/no)	0.891	2.474 (1.186-5.158)	-	-	-	-	-	-	-	-	-	-
Rheumatoid arthritis (yes/no)	-	-	-	-	-	-	0.538	1.752 (0.408-7.530)	-	-	-	-
Diabetes mellitus (yes/no)	0.904	2.494 (1.125 - 5.529)	0.829	2.317 (0.870-6.173)	-	-	-	-	-	-	-	-
Liver disease (yes/no)	2.345	10.659 (2.441-46.555)	-	-	-	-	-	-	-	-	-	-
Heart disease (yes/no)	-	-	-	-	0.729	2.086 (1.040-4.183)	-	-	0.348	1.422 (0.590-3.428)	-	-
Disease of central nervous system (yes/no)	-	-	-	-	-	-	0.106	1.113 (0.324-3.822)	0.898	2.465 (0.936-6.490)	-	-
Thromboembolic event (yes/no)	-	-	1.501	4.586 (1.521-13.826)	-	-	-	-	-	-	-	-
Dysplasia (yes/no)	-	-	-	-	-	-	-	-	-	-	-0.009	0.993

												(0.217-4.552)
Vitamin K antagonist use (yes/no)	-	-	-	-	0.787	2.220 (1.022-4.821)	-	-	-	-	-	-
NSAID's (yes/no)	0.619	1.877 (0.946-3.725)	-	-	-	-	-	-	-	-	-	-
To calculate the absolute risk for the surgical complications: $P_{(surgical\ complication)}$= 1/(1+exp- linear part) x 100%. Linear part = intercept + (coefficients * variables). *adjustment for over-fitting by shrinkage factor (SF); the intercept was re-estimated. BMI: Body Mass Index, NSAID's: Non-Steroidal Anti-Inflammatory Drugs												

Table 3. Model performance

	Surgical site infection	Venous Thrombo-embolism	Post-operative bleeding	Luxation	Delirium	Nerve damage
Brier score	0.010	0.007	0.012	0.012	0.006	0.008
$Brier_{scaled}$	0.026	0.007	0.010	0.003	0.027	0.012
Nagelkerke's R^2	0.081	0.047	0.072	0.010	0.193	0.086
AUC (95%CI)	71.9 (69.4-74.4)	66.3 (62.7-69.9)	73.0 (70.7-75.4)	58.4 (55.0-61.8)	85.9 (83.8-87.9)	76.6 (73.2-80.0)
H-L statistic (p-value)	p < 0.001	p < 0.001	p < 0.001	p < 0.001	p < 0.001	p < 0.001
Predicted possibilities						
Mean	0.010	0.007	0.012	0.012	<0.001	0.008
SD	0.015	0.007	0.012	0.004	0.012	0.010
Range	0.001-0.510	0.003-0.147	0.001-0.090	0.005-0.045	<0.001-0.147	0.001-0.072
Shrinkage factor	0.984	0.986	0.989	0.941	0.993	0.987

Discussion

The prediction models developed in this study are aimed for personalized counselling and SDM in orthopedic outpatient clinics. With our models, risk for surgical site infection (SSI), venous thromboembolism (VTE), postoperative bleeding (POB), luxation, delirium, and nerve damage (NER) can be predicted by patient characteristics, comorbidities and medication use. For SSI, predicted probabilities range between 0.01%-51.0%, which makes the model useful in adding relevant personalized information for adequate SDM compared to the previously used population-based probability of risk of 3%.[26] However, it is important to state that the model showed moderately accurate prediction, especially when the risk is low. The model underestimates the risk with a predicted probability >10%. Therefore, predicted probabilities exceeding 10% should be interpreted with caution. Furthermore, other performance measures were moderate to reasonable, indicating moderate overall performance of the model for SSI. We found similar results for other outcomes, except for the model for luxation; this model seriously underestimates the risk for luxation and could therefore not be used for personalized counselling.

Our results are comparable with the results of a recent meta-analysis on impact of comorbidities on SSI in THA or TKA. The authors stated diabetes and liver disease to contribute to a higher risk for SSI.[3] Another study with similar discriminative capacity found BMI, use of immunosuppression, ASA-score, procedure duration, and prior surgeries as risk factors for SSI.[33] Some of these predictors did not contribute to a higher performance in our model and were therefore not included. We additionally found age to be a significant predictor for SSI. For the already available prediction model based on data of Veterans with osteoarthritis of Harris et al., independent variables of the model cannot be compared for SSI since these results have not been reported.[15] We found a slightly better c-statistic (AUC) of 0.72 compared to 0.66 in their boosted model. Similar variables as those used in our models were used for the development of other models predicting postoperative complications as well, such as the models of Harris et al. Unfortunately, a direct comparison of the predictive capacity of these variables between the models of Harris et al. and our models is not possible, as the postoperative outcomes used in their prediction models were different to the postoperative outcomes used in our models.[17] Also comparison with Bozic et al., is difficult since applicability to non-Medicare population is questionable, as they also describe in their discussion.[16]

Based on literature we expected use of thromboprophylaxis, such as platelet aggregation inhibitors, direct oral anticoagulants, low-molecular-weight heparin, and/or vitamin K antagonists to be important predictors for POB. However, we could not demonstrate this finding in our model.[34] This is perhaps due to low frequencies of these predictors in our participants with POB and due to improved preoperative care regarding anticoagulant therapy. Our model for delirium included comparable predictors as other studies; they showed that age and preexisting cognitive impairment are important predictors for delirium.[35, 36] Our model confirms this finding. Kalisvaart et al., 2006 developed a comparable model based on acute- and elective hip surgery patients and found comparable predictors. The authors additionally found acute admission as predictor for delirium.[35] We cannot confirm this in our model since we focused on primary THA and TKA and these interventions are not primarily preferred in acute admissions due to hip fracture. The AUC indicates that our model is more accurate in estimating the risk for delirium (85.9 vs. 73).[35]

For VTE we only found obesity and thromboembolic event as significant risk factors.[3, 37] This can be explained by the fact that the recurrence rate is high after earlier thromboembolic events.[38] We could not demonstrate diabetes to be a significant predictor for VTE.[3] For the risk of luxation, it is known that causes of dislocation are multifactorial and also caused by non-patient modifiable factors such as implant-related, surgery-related, and hospital-related factors. It is unclear to what extent these factors contribute to the occurrence of luxation, but we expect these factors to be of influence the model.[39, 40] For these reasons, and the poor performance of the model for luxation, we consider this model of insufficient quality for use in patient information documents. Since we aimed our models to support preoperative SDM, we only used patient related variables as these variables are considered modifiable.[39, 41]

Strengths and limitations

A strong point is that we thoroughly created a big dataset and we used state-of-the-art statistics for our analyses. Furthermore, the simplicity of our models is a strength because we used predictors collected in usual care. The predictors are easily to assess and thereby easily to implement in care. Several limitations in this study should be noted. We retrospectively analyzed prospectively collected data. These data were not primarily registered for research purposes and therefore their detail and accuracy could be less than optimal. Moreover, changes in reporting systems took place during the studied period,

for instance the introduction of electronic medical records. It is known that changes in coding practice may change completeness of data.[42, 43] Although researchers performed data collection thoroughly, data about comorbidities and medication use could be missed because it was reported elsewhere. Moreover, we expect a small quantity of underreporting regarding comorbidities since physicians and anesthesiologists perchance make a selection of important comorbidities in their report. We tried to correct for this limitation by including medication use since all drugs are registered in preoperative anesthesia report. Also, data from 2004 until 2018 were used. In this period preoperative care has been changed. To evaluate the effect of this change on our outcome, we checked our patterns of complications and found no differences in this period. Furthermore, due to a low estimated event rate (1-3%) we needed a large population to have enough events to include predictors into our models. However, since not all predictors were significant in our final models, we expect that inclusion of more predictors would not lead to a considerably different model, as also discussed above. The models were developed based on pooled THA and TKA data. It is expected that the influence of patient characteristics, comorbidities and medication use is comparable for both THA and TKA.[44] The influence of comorbidities on outcomes is studied together quite often.[3] Furthermore, we tested this assumption by performing the analysis on THA and TKA data only. The models with corresponding performance measures were still consistent with the main analysis. Another limitation is that we only performed internal validation by bootstrapping, and were not yet able to determine external validity and clinical impact of the models. For clinical impact it is also important to determine the Minimal Clinically Important Difference of the outcomes.

Conclusion

Clinical prediction models were developed to contribute to more unbiased and accurate counselling in considering THA or TKA and are expected to be useful for identifying patients at risk for surgical complications. For SSI, the discriminative ability was reasonable and predicted risk varied between 0.01%-51.0%. We expect the individual predicted risk to enhance SDM and support a well-founded choice. We consider our models for SSI, delirium, and NER appropriate for clinical use when taking under- and overestimation of predicted risk into account. For clinical use of the models VTE and POB, caution concerning overestimation exceeding predicted probability of 0.08 and 0.05 (data presented in

calibration plots in eFigure 1), respectively, should be taken into account. Future studies should evaluate clinical impact and whether our models are feasible in an external population.

Supplementary information

In the supplementary file, an excel file with the prediction models calculator is provided, see Appendix 1. The decision aid including the prediction models is published in Dutch at the website of the Radboud university medical center.

Ethics Statement

Approval for this study was obtained at the Medical Ethical Committee of Radboudumc (2018-4880).

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Competing interests

P. Van der Wees participates in the Scientific Advisory Panel of the American Physical Therapy Association (APTA)

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Author's contribution

All authors confirm authorship on all four ICMJE criteria.

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Project administration – Lieke Sweerts

Resources – Lieke Sweerts, Thierry van Wessel

Software –

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Validation – Lieke Sweerts

Visualization – Lieke Sweerts, Thierry van Wessel

Writing – original draft – Lieke Sweerts

Writing – review & editing – Thomas Hoogeboom, Thierry van Wessel, Philip van der Wees, Sebastiaan van de Groes

Data availability statement

Raw data will not be shared via a public data repository. Data will be available upon request via the Data repository from Radboudumc.

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Abbreviations used in manuscript

ASA: American Society of Anesthesiologists

AUC: Area under the receiver operating characteristic curve

H-L: Hosmer and Lemeshow

LROI: Dutch Arthroplasty Register

NER: Nerve damage

NHS: National Health Service

NOV: Dutch Orthopaedic Association

NSAID's: Non-Steroidal Anti-Inflammatory Drugs

POB: Postoperative bleeding

PROMs: Patient Reported Outcome Measures

SDM: Shared decision making

SSI: Surgical site infection

THA: Total hip arthroplasty

TKA: Total knee arthroplasty

VTE: Venous Thromboembolism

Figure 1. Flow chart for inclusion and exclusion of patients. Variables indicated with an asterisk* were primarily extracted from the LROI database. When these data were missing, the data were extracted from the (electronic) medical record. Castor EDC is indicated by Castor

Figure 2. Receiver Operating Characteristic curve of the prediction model for surgical site infection

AUC=71.9 (95% CI = 69.4–74.4%)

Figure 3. Calibration plot with the actual probability against the predicted probability for the model for surgical site infection. The triangles indicate quantiles (g=10) of patients with a similar predicted probability of success. The grey diagonal line represents perfect agreement between predicted and actual probability

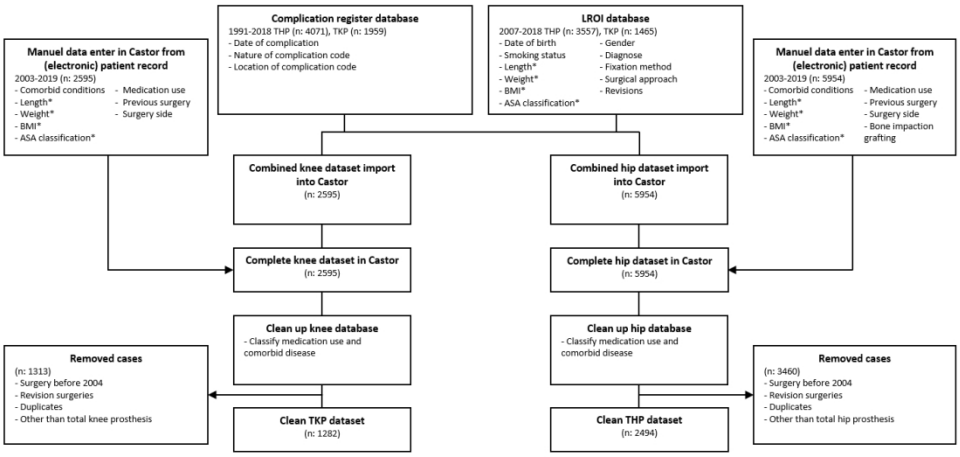

Figure 1. Flow chart for inclusion and exclusion of patients. Variables indicated with an asterisk* were primarily extracted from the LROI database. When these data were missing, the data were extracted from the (electronic) medical record. Castor EDC is indicated by Castor

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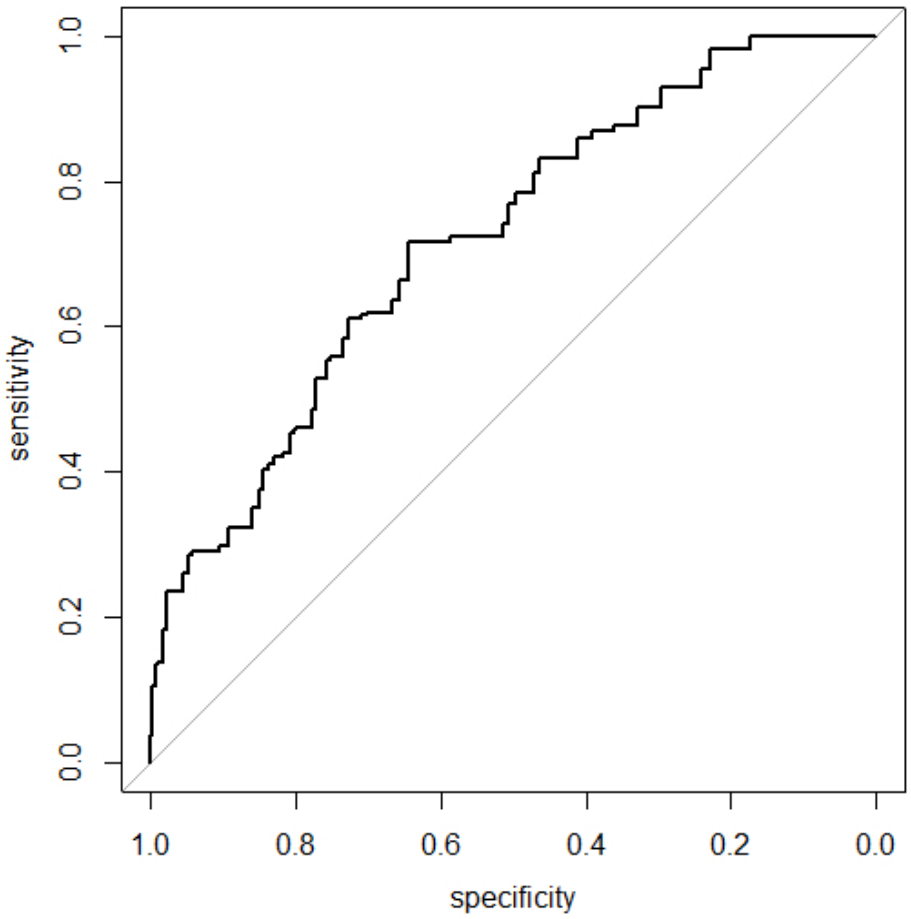


Figure 2. Receiver Operating Characteristic curve of the prediction model for surgical site infection
AUC=71.9 (95%-CI = 69.4–74.4%)

145x145mm (96 x 96 DPI)

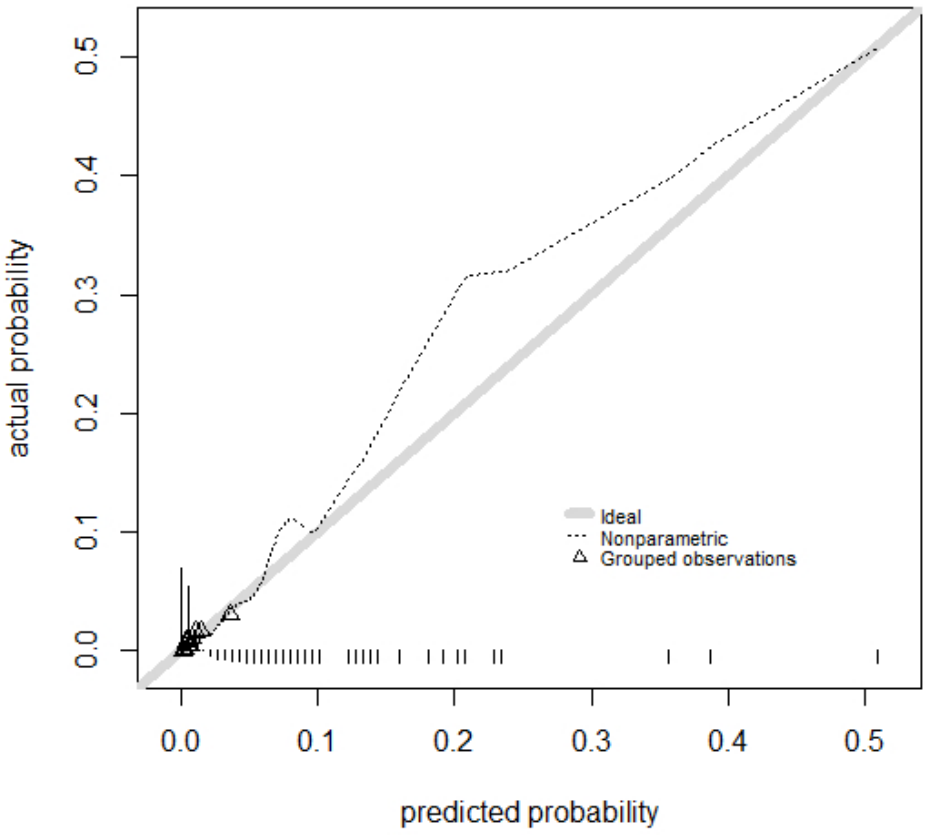


Figure 3. Calibration plot with the actual probability against the predicted probability for the model for surgical site infection. The triangles indicate quantiles (g=10) of patients with a similar predicted probability of success. The grey diagonal line represents perfect agreement between predicted and actual probability

145x145mm (96 x 96 DPI)

Supplemental Material

eTable 1. Categorization of surgical complications

Location code**	Location**	Code nature of complication**	Nature of complication**
Surgical site infection*			
24	Pelvis	012	Prosthesis infection
40	Hip	083	Deep infection
42	Knee	134	Infected organ
Venous thromboembolism			
24	Pelvis	104	Thrombosis
40	Hip	105	Embolus
41	Femur/upper leg		
42	Knee		
43	Lower leg		
50	Lung		
56	Venous system		
Luxation			
40	Hip	041	Luxation
		086	Disconnection prosthesis
Delirium			
54	Central nervous system	141	Psychological decompensation
58	Total		
Nerve damage			
40	Hip	094	Nerve lesion
41	Femur/upper leg		
43	Lower leg		
57	Arterial system		
Postoperative bleeding			
40	Hip	014	Wound leakage
41	Femur/upper leg	022	Bleeding

42 56	Knee Venous system	100 136	Secondary bleeding/hematoma Bleeding organ

* the records registered with the nature of complication 010 (infection around sutures), 011 (superficial infection), 013 (local wound necrosis) and 014 (wound leakage) are checked for occurrence of surgical site infection and added to the outcome surgical site infection when this was the case.

** only depicted when location code or code of the nature of complication occurred in the register.

Furthermore records registered with nature of complication 125 (interruption of sterility) were checked for occurrence of a surgical complication.

eTable 2. Predictors per outcome

	OR*/RR** (95% CI)	Study
Surgical site infection		
Age		
THA (>70years)	0.7** (0.3-1.5)	Almustafa et al (2018) (1)
TKA (>70years)	1.7** (0.9-3.3)	Almustafa et al (2018) (1)
Smoking status	0.16** (0.05-0.52)	Møller et al (2002) (2)
BMI	6.7* (NR)	Namba et al (2005) (3)
	4.8** (1.9-12.0)	Almustafa et al (2018) (1)
	2.53* (1.25-5.13)	Chen et al (2013) (4)
Immunological disorder	-	*Clinical reasoning*
NSAID's	-	*Clinical reasoning*
Diabetes mellitus	1.90* (1.32-2.74)	Podmore et al (2018) (5)
Liver disease	2.46* (1.46-4.12)	Podmore et al (2018) (5)
Venous thromboembolism		
Age		
THA(≥75years)	1.82* (1.15-2.87)	Migita et al (2014) (6)
TKA(≥75years)	1.30* (0.99-1.71)	Migita et al (2014) (6)
Sex		
THA(female>risk)	2.31* (1.03-5.18)	Migita et al (2014) (6)
TKA(female>risk)	1.58* (1.08-2.31)	Migita et al (2014) (6)
Diabetes mellitus	1.26* (0.92-1.72)	Podmore et al (2018) (5)
(TKA)	1.36* (1.07-1.72)	Yang et al (2015) (7)
Thromboembolic event *(TKA)*	1.11* (0.36-3.46)	Migita et al (2014) (6)
Obesity		
THA(BMI>30)	0.89* (0.36-2.20)	Migita et al (2014) (6)
TKA(BMI>30)	0.90* (0.58-1.38)	Migita et al (2014) (6)
Postoperative bleeding		
Age		
THA(>70 years)	2.61** (1.50-4.53)	Quintero et al (2016) (8)

TKA(>70years)	2.25** (1.03-4.94)	Quintero et al (2016) (8)
BMI	-	*Clinical reasoning*
Heart disease	-	*Univariate analysis*
Vitamin K antagonists	-	*Clinical reasoning*
Smoking status	-	*Univariate analysis*
Luxation		
Age	1.27* (1.02-1.57)	Kunutsor et al (2019) (9)
Smoking status	1.08* (0.96-1.21)	Kunutsor et al (2019) (9)
BMI	1.38* (1.03-1.85)	Kunutsor et al (2019) (9)
Rheumatoid arthritis	1.50* (1.05-2.15)	Kunutsor et al (2019) (9)
Disease of the central nervous system	2.54* (1.86-3.48)	Kunutsor et al (2019) (9)
Delirium		
Age	2.20* (1.80-2.71)	Huang et al (2019) (10)
Disease of the central nervous system *(dementia)*	7.44* (3.54-14.60)	Huang et al (2019) (10)
Heart disease *(congestive)*	0.83* (0.39-1.61)	Huang et al (2019) (10)
Nerve damage		
Age *(<45 (vs 65-74)*	7.17* (1.17-44.00)	Shetty et al (2016) (11)
BMI *(<BMI >risk)*	0.96* (0.77-1.21)	Kawano et al (2018) (12)
Sex *(female > risk)*	Not reported	Shetty et al (2016) (11)
Smoking status	1.90* (1.06-3.38)	Shetty et al (2016) (11)
Dysplasia	3.69* (1.65-8.28)	Farrell et al (2005) (13)
*results reported as odds ratio (OR); ** results reported as risk ratio (RR).		

eTable 3. Categorization of comorbidities

Categorization of comorbidities	
Comorbid category*	**Included comorbid conditions****
Bleeding diseases	Hemophilia
Blood quality	Anemia
Cancer	Prostate cancer Leukemia Breast cancer Lymph node cancer Bowen's disease
Central nervous system	Parkinson's disease Dementia TIA CVA
Cognitive impairment	Down syndrome
Diabetes mellitus	Diabetes mellitus
Heart disease	Ischemia of the heart Valve damage blood regurgitation Valve damage reduced blood flow Valve replacement Cardiomyopathy decreased contraction Cardiomyopathy decreased relaxation Heart decompensation Heart attack Angina pectoris Atrial fibrillation
High blood pressure	Hypertension
Hyper hormonal	Hyper hormonal
Hypo hormonal	Hypo hormonal

Immunological disorder	Scleroderma Rheumatoid arthritis Gout Psoriasis Artritides Dermal barrier disease General immune disorder Organ transplantation
Inflammation	Chronic bladder infection
Kidney disease	Kidney insufficiency
Liver disease	Liver cirrhosis
Lung disease	Chronic bronchitis Asthma COPD Emphysema Dyspnea
Mood sickness	Depression Psychosis
Obesity	Obesity
Peripheral nervous system	Nerve compression Lumbar vertebral stenosis
Poor peripheral blood flow	Atherosclerosis Claudication intermittent
Thromboembolic event	Deep venous thromboembolism Pulmonary embolism

* the comorbid categories are used for analysis.

** comorbid conditions are depicted when the frequency was ≥ 10 or when the comorbid condition was considered as a relevant comorbid condition in terms of outcome prediction.

eTable 4. Categorization of drug groups

Categorization of medication use	
Drug category	**Drugs groups according to the Dutch pharmacotherapeutic compass** (14)
Acenocoumarol	Acenocoumarol*
Antifibrinolytica	Antifibrinolytica
Antimycotics	Antimycotic antibiotics Others
Antiretroviral agents	Antiretroviral agents
Bisfosfonates	Bisfosfonates
Colchinine group	Colchinine group
Directly working oral anticoagulants	Directly working oral anticoagulants
DMARD's biologicals	Immunosuppresives selective Immunosuppresives others
Factors in blood coagulance	Factors in blood coagulance
Fenprocoumon	Fenprocoumon*
Imidazoles	Cutane imidazoles Others
Immunosuppressives	Interferons Interleukin antagonists Monoclonal antibodies
Local antibacterial agents	Cutaneous antibacterial agents Ocular antibacterial agents
Local corticosteroids	Cutane corticosteroids Nasal corticosteroids Corticosteroides for inhalation
Low molecular weight heparins	Low molecular weight heparins
Methotrexate	Methotrexate

NSAID's**	Coxib's Others
Oncology related detoxificants	Oncology related detoxificants
Salicylates	Analgetic salicylates Trombocytic salicylates
Statins	Statins
Systemic antibacterial agents	Cephalosporins Macrolides Penicillin's Tetracyclines Carbapenems Ceftriaxone Glycopeptides Aminoglycosides Rifamycins tuberculose Sulfonamides and trimethroprimides Triazoles Fluoroquinolones Others
Thrombocyte-aggregationblockers	P2y12 blockers Others
Xanthineoxidase inhibitor	Xanthineoxidase inhibitor

* according the Dutch pharmacotherapeutic compass, acenocoumarol and fenprocoumon belong to the drug group 'vitamin k antagonists'. Based on expert opinion, acenocoumarol and fenprocoumon were included separately in the analysis because of the differences in half-life.

** Non-Steroidal Anti-Inflammatory Drugs

eTable 5. Original prediction models and adjusted coefficients

Prediction model for estimation of risk for surgical site infection

Variable	Regression coefficient	Regression coefficient (adjusted with SF)*	Odds Ratio (95% CI)
Intercept	-7.305	-7.272	-
Age (years)	0.031	0.031	1.032 (1.005-1.059)
BMI (kg/m²)	-0.002	-0.002	0.998 (0.937-1.063)
Smoking status (yes/no)	0.769	0.757	2.145 (0.883-5.213)
Immunological disorder (yes/no)	0.905	0.891	2.474 (1.186-5.158)
Diabetes mellitus (yes/no)	0.918	0.904	2.494 (1.125-5.529)
Liver disease (yes/no)	2.382	2.345	10.659 (2.441-46.555)
NSAID's (yes/no)	0.629	0.619	1.877 (0.946-3.725)
To calculate the absolute risk of surgical site infection: $P_{(\text{surgical site infection})} = 1/(1+e^{-\text{linear part}}) \times 100\%$; Linear part = -7.272 + (0.031 x age – 0.002 x BMI + 0.757 x smoking status + 0.891 x immunological disorder + 0.904 x diabetes mellitus + 2.345 x liver disease + 0.619 x NSAID's). *adjustment for over-fitting by shrinkage factor (SF) (SF = 0.984); the intercept was re-estimated.			

Prediction model for estimation of risk for venous thromboembolism

Variable	Regression coefficient	Regression coefficient (adjusted with SF)*	Odds Ratio (95% CI)
Intercept	-4.764	-4.790	-
Age (years)	-0.009	-0.008	0.991

			(0.966-1.018)
Gender (male/female)	-0.170	-0.168	0.844 (0.377-1.888)
Obesity (yes/no)	1.396	1.376	4.040 (1.462-11.159)
Diabetes mellitus (yes/no)	0.841	0.829	2.317 (0.870-6.173)
Thromboembolic event (yes/no)	1.523	1.501	4.586 (1.521-13.826)
To calculate the absolute risk of venous thromboembolism: $P_{(\text{venous thromboembolism})} = 1/(1+e^{-\text{linear part}}) \times 100\%$; Linear part = -4.790 + (-0.008 x age – 0.168 x gender + 1.376 x obesity + 0.829 x diabetes mellitus + 1.501 x thromboembolic event). *adjustment for over-fitting by shrinkage factor (SF) (SF = 0.986); the intercept was re-estimated.			

Prediction model for estimation of risk for postoperative bleeding.

Variable	Regression coefficient	Regression coefficient (adjusted with SF)*	Odds Ratio (95% CI)
Intercept	-7.182	-7.172	-
Age (years)	0.033	0.033	1.034 (1.006-1.062)
BMI (kg/m²)	0.012	0.012	1.012 (0.954-1.073)
Smoking status (yes/no)	-0.023	-0.023	0.952 (0.336-2.701)
Heart disease (yes/no)	0.737	0.729	2.086 (1.040-4.183)
Vitamin K antagonist use (yes/no)	0.796	0.787	2.220 (1.022-4.821)
To calculate the absolute risk of postoperative bleeding: $P_{(\text{postoperative bleeding})} = 1/(1+e^{-\text{linear part}}) \times 100\%$;			

Linear part = -7.172 + (0.033 x age + 0.012 x BMI – 0.023 x smoking status + 0.729 x heart disease + 0.787 x vitamin K antagonist use). *adjustment for over-fitting by shrinkage factor (SF) (SF = 0.989); the intercept was re-estimated.

Prediction model for estimation of risk for luxation.

Variable	Regression coefficient	Regression coefficient (adjusted with SF)*	Odds Ratio (95% CI)
Intercept	-5.976	-5.800	-
Age (years)	0.014	0.013	1.014 (0.991-1.038)
BMI (kg/m²)	0.022	0.021	1.023 (0.951-1.099)
Smoking status (yes/no)	0.521	0.491	1.667 (0.651-4.268)
Rheumatoid arthritis (yes/no)	0.572	0.538	1.752 (0.408-7.530)
Disease of central nervous system (yes/no)	0.113	0.106	1.113 (0.324-3.822)
To calculate the absolute risk of luxation: $P_{(luxation)} = 1/(1+e^{-\text{linear part}}) \times 100\%$; Linear part = -5.800 + (0.013 x age + 0.021 x BMI + 0.491 x smoking status + 0.538 x rheumatoid arthritis + 0.106 x disease of central nervous system). *adjustment for over-fitting by shrinkage factor (SF) (SF = 0.941); the intercept was re-estimated.			

Prediction model for estimation of risk for delirium.

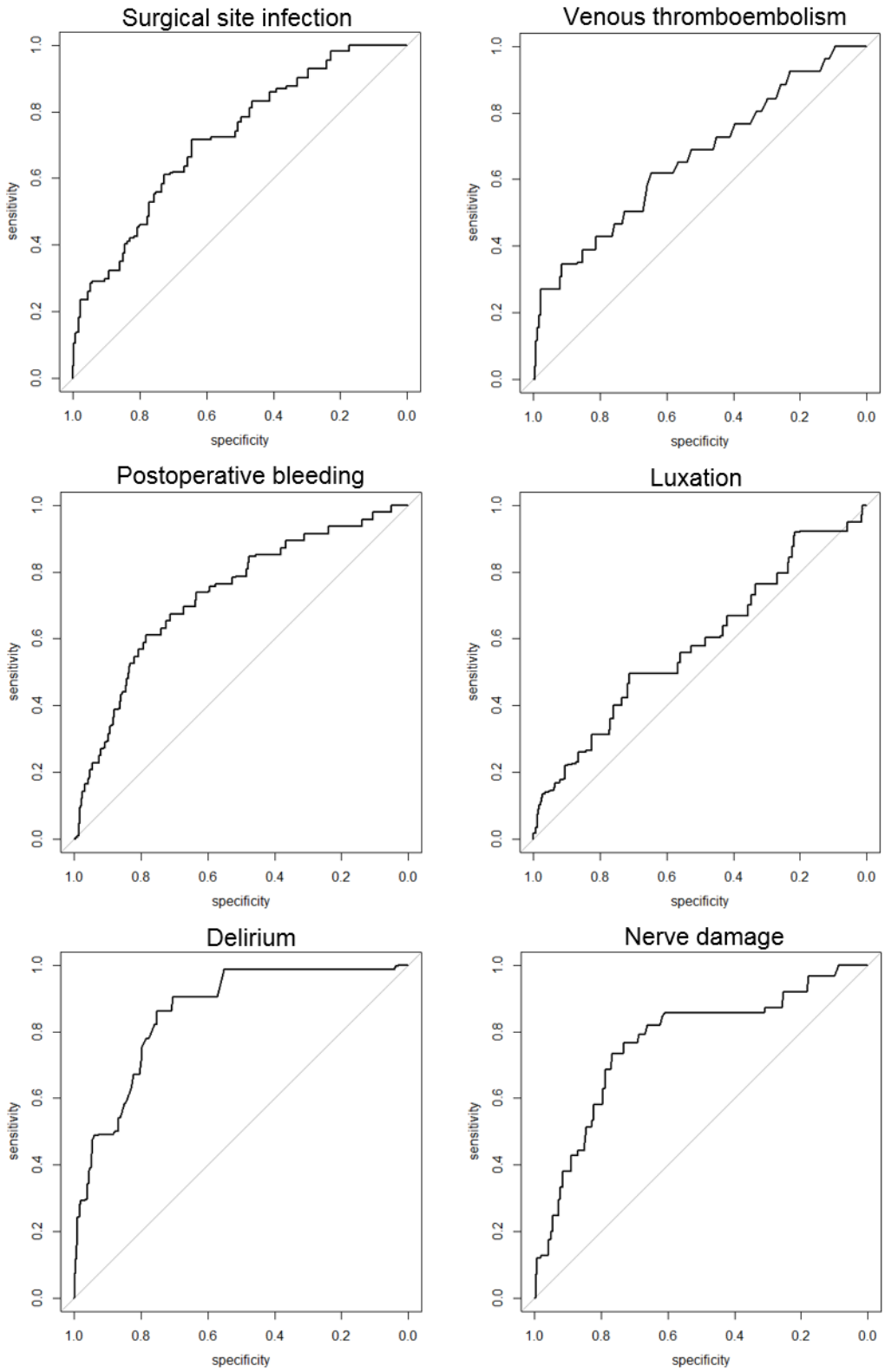
Variable	Regression coefficient	Regression coefficient (adjusted with SF)*	Odds Ratio (95% CI)
Intercept	-14.368	-14.307	-
Age (years)	0.129	0.127	1.137 (1.067-1.212)
Heart disease (yes/no)	0.351	0.348	1.422

			(0.590-3.428)
Disease of central nervous system (yes/no)	0.904	0.898	2.465 (0.936-6.490)
To calculate the absolute risk of delirium: $P_{(delirium)}$= 1/(1+$e^{-\text{linear part}}$) x 100%; Linear part = -14.307 + (0.127 x age + 0.348 x heart disease + 0.898 x disease of central nervous system). *adjustment for over-fitting by shrinkage factor (SF) (SF = 0.993); the intercept was re-estimated.			

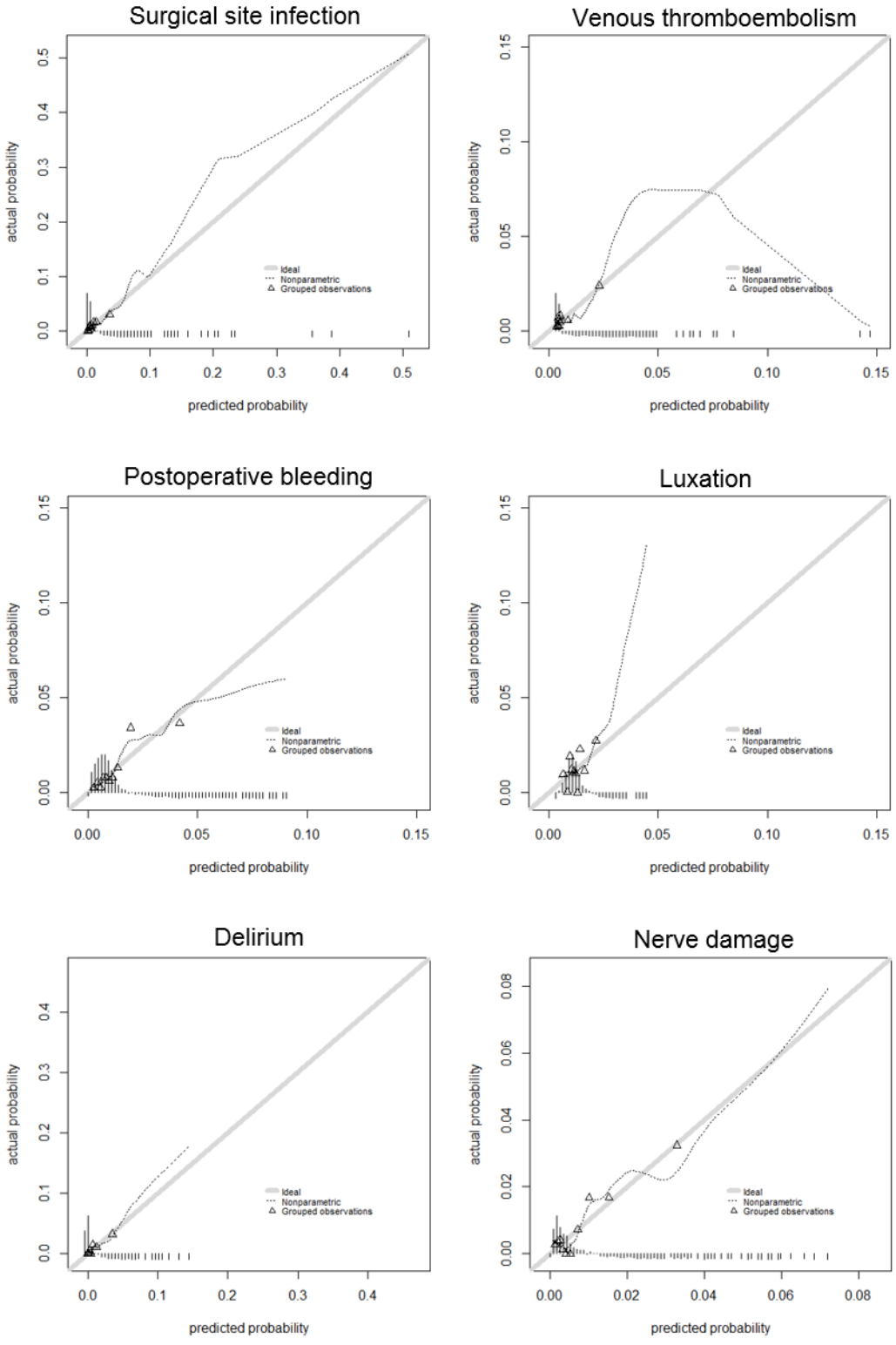
Prediction model for estimation of risk for nerve damage.

Variable	Regression coefficient	Regression coefficient (adjusted with SF)*	Odds Ratio (95% CI)
Intercept	-2.209	-2.250	-
Age (years)	-0.052	-0.051	0.949 (0.926-0.974)
Gender (man/woman)	-0.258	-0.254	0.772 (0.319-1.868)
Smoking status (yes/no)	0.580	0.572	1.754 (0.510-6.029)
Dysplasia (yes/no)	-0.009	-0.009	0.993 (0.217-4.552)
To calculate the absolute risk of nerve damage: $P_{(nerve\ damage)}$= 1/(1+$e^{-\text{linear part}}$) x 100%; Linear part = -2.250 + (-0.051 x age – 0.254 x gender + 0.572 x smoking status – 0.009 x dysplasia). *adjustment for over-fitting by shrinkage factor (SF) (SF = 0.987); the intercept was re-estimated.			

eFigure 1. ROC curves and Calibration plots



eFigure 1.1. Receiver Operating Characteristic curves of the prediction models for surgical site infection, venous thromboembolism, postoperative bleeding, luxation, delirium and nerve damage



eFigure 1.2. Calibration plots with actual probability against the predicted probability for the models for surgical site infection, venous thromboembolism, postoperative bleeding, luxation, delirium and nerve damage. The triangles indicate quantiles (g=10) of patients with a similar predicted probability of success. The grey diagonal line represents perfect agreement between predicted and actual probability

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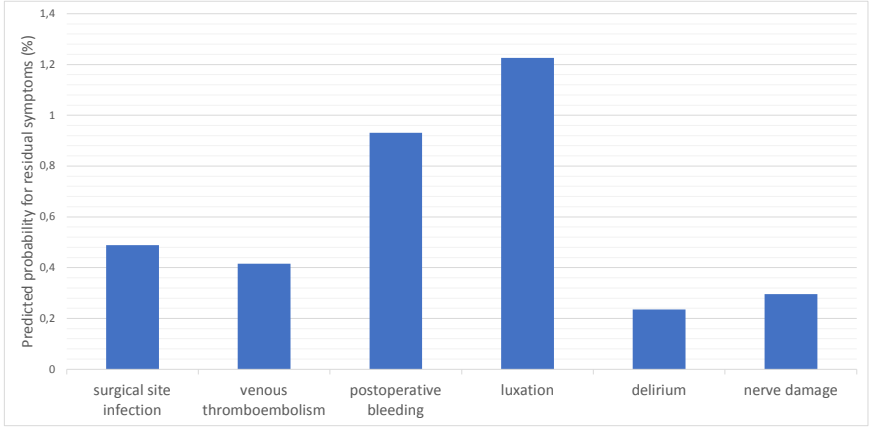
Input variables*		Surgical site infection		Venous thromboembolism		Postoperative bleeding		Luxation		Delirium		Nerve damage	
Age (years)	65	0,031	2,015	-0,008	-0,52	0,033	2,145	0,013	0,845	0,127	8,255	-0,051	-3,315
Gender (male/female)	1		0	-0,168	-0,168		0		0		0	-0,254	-0,254
BMI (kg/m2)	30	-0,002	-0,06		0	0,012	0,36	0,021	0,63		0		0
Obesity (yes/no)	0		0	1,376	0		0		0		0		0
Smoking status (yes/no)	0	0,757	0		0	-0,023	0	0,491	0		0	0,572	0
Lung disease (yes/no)	0		0		0		0		0		0		0
Immunological disorder (yes/no)	0	0,891	0		0		0		0		0		0
Rheumatoid arthritis (yes/no)	0		0		0		0	0,538	0		0		0
Diabetes mellitus (yes/no)	0	0,904	0	0,829	0		0		0		0		0
Liver disease (yes/no)	0	2,345	0		0		0		0		0		0
Heart disease (yes/no)	0		0		0	0,729	0		0	0,348	0		0
Disease of central nervous system (yes/no)	0		0		0		0	0,106	0	0,898	0		0
Thromboembolic event (yes/no)	0		0	1,501	0		0		0		0		0
Dysplasia (yes/no)	0		0		0		0		0		0	-0,009	0
Vitamin K antagonist use (yes/no)	0		0		0	0,787	0		0		0		0
NSAID use (yes/no)	0	0,619	0		0		0		0		0		0
		-7,272	1,955	-4,79	-0,688	-7,172	2,505	-5,864	1,475	-14,307	8,255	-2,25	-3,569
			-5,317		-5,478		-4,667		-4,389		-6,052		-5,819
Predicted probability for residual symptoms (%)		**0,48834885**		**0,41602963**		**0,93128835**		**1,22609394**		**0,23476267**		**0,29617761**	
		surgical site infection		venous thromboembolism		postoperative bleeding		luxation		delirium		nerve damage	

* Age: in years, Gender: male scored as 1 and female scored as 2, BMI: in kg/m2, Obesity: no scored as 0 and yes as 1, Smoking status: no scored as 0 and yes as 1, Lung disease: no scored as 0 and yes as 1, Immunological disorder: no scored as 0 and yes as 1



embolic event: no scored as 0 and yes as 1, Dysplasia: no scored as 0 and yes as 1, Vitamin K antagonists use: no scored as 0 and yes as 1, NSAID's: no scored as 0 and yes as 1

Research checklist. TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	3
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	5-6
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	6
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	7
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	7
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	7
	5b	D;V	Describe eligibility criteria for participants.	7-8
	5c	D;V	Give details of treatments received, if relevant.	7-8
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	8
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	N/A
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	8
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	N/A
Sample size	8	D;V	Explain how the study size was arrived at.	8
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	8-9

Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	9-10
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	9-10
	10c	V	For validation, describe how the predictions were calculated.	9-10
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	9-10
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	N/A
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	N/A
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	N/A
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	11, Figure 1
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	11, Table 1
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	N/A
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	11, Table 1
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	eTable 5
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	Table 2, eTable 5
	15b	D	Explain how to the use the prediction model.	Table 2, eTable 5, 11-12
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	Table 2, eTable 5
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	N/A
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample,	18-20

			few events per predictor, missing data).	
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	18-20
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	18-20
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	18-20
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	20
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	21

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.