Title: Machine Learning Model Can Predict Periprosthetic Joint Infection Following Total Knee Arthroplasty

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Abstract

Introduction:

Periprosthetic joint infection (PJI) is a significant complication of primary total knee arthroplasty (TKA). A prediction tool to assist clinical preoperative risk assessment is important. However, no such model is tailored for Hong Kong patients. This study aimed to develop a machine learning (ML)-based model for predicting PJI following primary TKA in Hong Kong.

Materials and Methods:

A retrospective analysis was conducted in a local teaching hospital on 3,483 primary TKA (81 with PJI) from 1998 to 2021. We gathered 61 features, encompassing patient demographics, operation-related variables, laboratory findings and comorbidities. Six of them were selected by univariate and multivariate analysis. We trained a Balanced Random Forest classifier using stratified 10-fold cross-validation and compared it with Logistic Regression to verify ML performance.

Results:

The ML model demonstrated stable and robust performance across all ten folds, with average metrics of 0.963 for area under the receiver operating curve, 0.920 for balanced accuracy, 0.938 for sensitivity, and 0.902 for specificity, outperforming the Logistic Regression model (AUC, 0.728). The significant risk factors identified were long operative time (HR, 9.07; p=0.018), male (HR, 3.11; p<0.001), ASA>2 (HR, 1.68; p=0.028), history of anaemia (HR, 2.17; p=0.023) and history of septic arthritis (HR, 4.35; p=0.030). Spinal anaesthesia (HR, 0.55; p=0.022) was a significant protective factor.

Discussion and conclusion:

We developed the first ML-based model for predicting PJI following primary TKA in Hong Kong, demonstrating its superiority over statistical methods. It may assist the preoperative treatment decision-making and patient health optimization.

1. Introduction:

A common surgical treatment option for severe knee osteoarthritis is the primary total knee arthroplasty (TKA). The demand for TKA is high and was estimated to have an increase of 673% to 3.48 million by 2030 in the United States (1). In view of the aging population, there is a surging demand of TKA in Hong Kong. Periprosthetic joint infection (PJI), a significant complication of TKA, is expected to increase in number of cases, hence requires more attention. PJI is the leading cause of revision knee replacement which occurs in 1%-2% of primary joint replacements (2, 3). It is expected to devastate patient outcomes and increase hospital resource utilisation by causing greater pain and mortality, longer antibiotic treatment and length of stay in hospital, more revision surgeries, and a higher economic cost which was estimated to cost USD$1.1 billion by 2030 (4, 5). Hence, there is a pressing need for preoperative PJI risk stratification.

Machine learning (ML) is a subset of artificial intelligence which learns the pattern from experience and improves along the learning progress (6). ML is rapidly gaining prominence in Orthopaedics due to its promising potential in discerning underlying patterns within data in complex and non-linear tasks, and overcoming difficulties in imbalanced classification tasks. ML has shown to have a great ability in the prediction of the failure rate of debridement, antibiotics and implant retention for PJI and the prediction of recurrent PJI following revision TKA (7, 8), demonstrating its potential in prediction and classification tasks.

While recent attempts have been made to stratify PJI risk following primary TKA by statistical or ML-based methods (9-15), to our best knowledge, there is a knowledge gap: No such model has been designed specifically for Hong Kong patients. Regarding the variation in lifestyles and risk factors among different countries, prior studies may be unsuitable for the local population. Moreover, previous models often included only a limited set of risk factors, failing to comprehensively investigate potential predictors such as operative duration, less common comorbidities and preoperative laboratory test results. Furthermore, some prior risk models require many selected predictors to form a prediction, increasing data collection, input and computational time in clinical settings, thereby hindering clinical utility.

In light of these limitations, this study aimed to develop a comprehensive ML model for predicting PJI risk following primary TKA in Hong Kong and to identify predictors. We examined a broad range of potential risk factors and minimised the number of predictors required, thereby providing accurate predictions with fewer inputs. This study also aimed to solve the imbalanced classification task of PJI.

2. Methods

2.1 Patient Cohort

This single-centred retrospective study of a local teaching hospital was approved by the Institutional-Review-Board (UW23-328). Between 1998 and 2021, the ipsilateral, staged or simultaneous bilateral primary TKA with electronic patient record of the operation and a minimum follow-up time of one year was included. Episodes of unicompartmental or bicompartmental knee arthroplasty and TKA with a prior revision were excluded. *TKA was searched by the* ICD-9-CM procedure code 81.54 (total knee replacement) in the Clinical Data Analysis and Reporting System of our hospital. Patient chart review was performed using the electronic patient record system of our hospital to exclude ineligible TKAs according to our exclusion criteria.

The final cohort included 3483 TKAs, divided into infected class (PJI developed following TKA) and non-infected class (No evidence of PJI following TKA). PJI was defined according to the endorsed Musculoskeletal Infection Society criteria at the 2013 international consensus meeting (16).

2.2 Feature Collection and Preprocessing

From the electronic patient record system and Clinical Data Analysis and Reporting System, we collected 61 features, including patient demographics (eg. age, gender, ethnicity and American Society of Anesthesiology (ASA) score), operation-related variables (eg. operative time, anaesthesia type and indication for operation.), laboratory findings (eg. preoperative albumin, haemoglobin and international normalized ratio) and comorbidities (eg. diabetes mellitus, tuberculosis, systemic lupus erythematosus and septic arthritis). The characteristics of the cohort were summarized in Table 1.

Missing data was imputed with the mean for continuous variables and the mode for discrete variables. The effect of outliers was reduced by Winsorization. MaxAbsScaler was applied to continuous variables for re-scaling.

By univariate analysis, the p-value was calculated for all features and summarized in Table 1. 16 features ($p<0.05$) were selected for an iterative multivariate analysis. 6 significant features ($p<0.05$) were selected as our final set of predictors, including operative time, male, ASA>2, spinal anaesthesia, history of anaemia and history of septic arthritis.

2.3 Model Development

In this research, we employed the Balanced Random Forest Classifier to predict the risk of PJI following primary TKA. Random Forest classifier is a popular and easy-to-use ML algorithm which involved a technique called bagging (bootstrap aggregation) (17). Bootstrap involved a random sampling of the dataset with replacement. Our dataset was a highly imbalanced dataset with a small sample size of the minority class (with PJI). Dealing with a significantly imbalanced dataset, the bootstrap samples may consist of very few or even none of the minority class, leading to a poor predictive capability of the model on the minority class. However, by using the Balanced Random Forest classifier, the imbalance problem could be solved. In each iteration of the classifier, a bootstrap sample was drawn from the minority class. Then, the same number of majority class was randomly sampled with replacement. By down-sampling the majority class, a balanced boostrap sample could be resulted to induce a classification tree. The predictions of the ensemble, which consisted of all classification trees, were aggregated and reached the final prediction by majority voting (18).

We also developed a Logistic Regression (LR) model, a common statistical method, for comparison to verify our ML model's performance. Both models were trained using a stratified 10-fold cross-validation method with hyperparameters tuned. The stratified 10-fold cross validation method involved a random splitting of the complete dataset into 10 folds with the same stratified class ratio between the majority and minority classes as the ratio of the complete dataset (19). Within one iteration, all folds were used for model training except for one fold which was used for model validation and assessing the performance of the model. The cross-validation process was repeated for 10 iterations. The final performance of the model was the average of the performance in each iteration.

Both models performance were evaluated by several metrics, including the area under the receiver operating curve (AUC), balanced accuracy, sensitivity, specificity, precision, F1 score and Brier score. AUC is the most common metric for evaluating the performance of the model. It is the area under a probability curve plotted with true positive rates against false positive rates, representing the degree of predictive performance. The value of AUC ranges from 0 to 1. A model with an AUC higher than 0.7 is considered to have a good performance with clinical significance, while an AUC of 1 is considered as perfect (20). The rest of the metrics range from 0 to 1, with a higher score indicating a better performance except for Brier score which reflects a better performance when approaching 0.

In order to increase the transparency and interpretability of the prediction model, a global explanation was provided. Global explanation was delivered through the feature importance which were visualized by a SHapley Additive exPlanations (SHAP) summary plot of each feature. The summary plot described how the features contributed to the model prediction output and their importance, enabling an interpretable risk stratification model.

All statistical analysis, ML model development and evaluation were performed with the use of Python (Python Software Foundation, Wilmington, DE, USA) and Anaconda (Anaconda Inc., Austin, TX, USA).

3. Results

81 (2.3%) TKAs developed PJI. Most of the patients were Chinese (98.2%) female (73%), with a mean age of 70.4 years, had an ASA class 2 (57.5%) and mean BMI of 27.8 kg/m^2. Most of the TKAs lasted for 116.6 minutes, using spinal anaesthesia (48.9%), and with primary osteoarthritis as the indication of operation (92.6%). The mean preoperative laboratory findings were 42.3 g/L for albumin, 12.8g/dL for haemoglobin, 1.0 for international normalized ratio and 1.8x10^9/L for absolute lymphocyte count. Common comorbidities were hypertension (71.3%), diabetes mellitus (41.3%) and hyperlipidaemia (11.3%) (Table 1).

The ML model outperformed the LR model, demonstrating stable and robust performances across all ten folds (Fig.1), with excellent average AUC (ML: 0.963 Vs LR: 0.728), balanced accuracy (ML: 0.920 Vs LR: 0.654), sensitivity (ML: 0.938 Vs LR: 0.744), and specificity (ML: 0.902 Vs LR: 0.564) (Table 2).

Predictors identified in order of significance were operative time (HR, 9.07; 95% CI, 1.47-56.14; p=0.018), male gender (HR, 3.11; 95% CI, 1.97-4.90; p<0.001), ASA>2 (HR, 1.68; 95% CI, 1.06-2.67; p=0.028), spinal anaesthesia (HR, 0.55; 95% CI, 0.33-0.92; p=0.022), history of anaemia (HR, 2.17; 95% CI, 1.11-4.24; p=0.023) and history of septic arthritis (HR, 4.35; 95% CI, 1.15-16.41; p=0.030). Spinal anaesthesia was a protective factor among all risk factors. Their effect on the model output was visualized in the SHAP summary plot (Fig. 2).

4. Discussion and conclusion:

This study developed the first PJI prediction model for the local population. A recent study developed a ML-based artificial neural network for PJI risk prediction (AUC, 0.84) (15). In this study, our ML model (AUC, 0.963) outperformed prior models, demonstrating its excellent discriminative capability and potential for identifying high-risk patients in the clinical environment.

The predictors identified were supported by existing literatures. The strongest predictor identified was operative time. A longer operative time was found to be associated with higher PJI risk. With a 15-minute increase in operative time, a 18% (95% CI, 11-26) increased PJI risk was found by a retrospective study of 11,840 primary TKAs performed between 2014 and 2017 (21), and a 9% (95% CI, 4-13) increased deep wound infection risk was found by a registry-based study of 56,216 primary TKAs performed between 2001 and 2009 (22). The underlying mechanism may be multifactorial. In TKAs, large incisions are inevitable. With a longer operative time, there is a higher risk for contamination of the open wound by airborne bacteria (23, 24), and an increased risk of tissue desiccation around the incisions (25), which is prone to contamination and delay the wound healing process (26). Also, a longer tourniquet duration may prolong wound hypoxia and increase infection risk. (27)

The second significant predictor was male gender. Male was revealed to be a significant PJI risk factor in an analysis of 64,566 TKAs from the New Zealand Joint Registry performed between 1999 and 2012 (OR 1.84, 95% CI 1.24-2.73) (28) and an analysis of 56,216 TKAs from an American registry performed from 2001 to 2009 (HR, 1.89) (29). The underlying mechanism is controversial. Male gender may not necessarily be the risk factor, it may be related to multiple behavioural factors that were not recorded in our electronic patient record

system and thus not investigated in this study, including smoking, alcohol, diet and hygiene which are more prevalent in males than females (30, 31).

The third significant predictor was ASA>2. ASA score is a score assessed by an anaesthetist preoperatively which indicates the physical status of the patient, estimating the comorbidity and preoperative risk. ASA > 2 indicates the presence of significant systemic disease (32). We found that ASA score > 2 was associated with an increased risk of PJI following TKA. This observation was consistent with the findings of other studies. In the meta-analysis by Kong et al (32), it was concluded that ASA score > 2 was a high risk factor (OR, 2·06; 95% CI, 1.77–2.39) among all risk factors investigated. The multivariable analysis by Panula et al (33) also found that ASA 2 had a 1.2 lower hazard ratio than ASA > 2 compared with ASA 1 for PJI following total hip arthroplasty.

Spinal anaesthesia was the only protective factor identified among all risk factors. Scholten et al (34) suggested less association between spinal anesthesia and early PJI after TKA compared to general anesthesia. The analysis showed an odds ratio for PJI of 2.0 (95% CI, 1.0–3.7) after general anesthesia relative to spinal anesthesia. Similar result was obtained by several literatures (35-37). Although the underlying mechanism is not fully understood, the association between spinal anaesthesia and less blood loss, less blood transfusions required and less incidence of hyperglycaemia are some possible reasons for its protective nature from PJI since these factors suppress immunity (34, 38, 39).

Our study has several strengths. We demonstrated that ML outperformed statistical methods (LR) in this imbalanced classification task, as ML automates pattern learning without the need for manual specification of the relationship between data. Furthermore, the model's reliance on only six selected predictors enhances its ease of use. Moreover, the extensive investigation of potential predictors makes our study particularly comprehensive.

Our study has strong clinical implications. Five predictors of our model were modifiable. By applying our model in real clinical settings, we could identify high-risk patients and their modifiable risk factors preoperatively. Adequate health optimization and surgical plans could be performed accordingly, thereby reducing PJI risk preoperatively. Patient could also make a thorough preoperative treatment decision by weighing TKA risks against benefits. Healthcare sectors could allocate clinical resources better and reduce expenditure as well.

However, there are limitations. The 'black box' nature of ML causes an opaque decision making process which the users could not fully understand (40). To increase the interpretability and transparency of the model, we provided a global interpretation of the model prediction that visualized the significant features and their contribution to the model prediction output. Moreover, as a single-centered retrospective study with a small cohort size, pre-existing misclassification, selection and recall bias may be inherent, possibly leading to prevalent risk factors for PJI, such as diabetes, hypertension, and body mass index (BMI) (41, 42), being classified as insignificant predictors which their p-values in our univariate analysis were 0.742 for diabetes mellitus, 0.157 for hypertension, and 0.148 for BMI, higher than our significant level 0.05. Future multi-centred prospective studies with a larger cohort are warranted to validate the model predictive ability in clinical settings. Furthermore, our study only incorporated internal validation. The model's generalizability may require future external validation for confirmation.

We developed the first ML model for predicting PJI following primary TKA in Hong Kong, identifying operative time and gender as the strongest predictors. We also demonstrated its superiority over statistical methods and provided a global interpretation for the model to increase transparency in the ML prediction process. This model may assist the preoperative treatment decision-making and patient health optimization.

Figure 1. The confusion matrices and receiver operating characteristics curve of all ten folds.

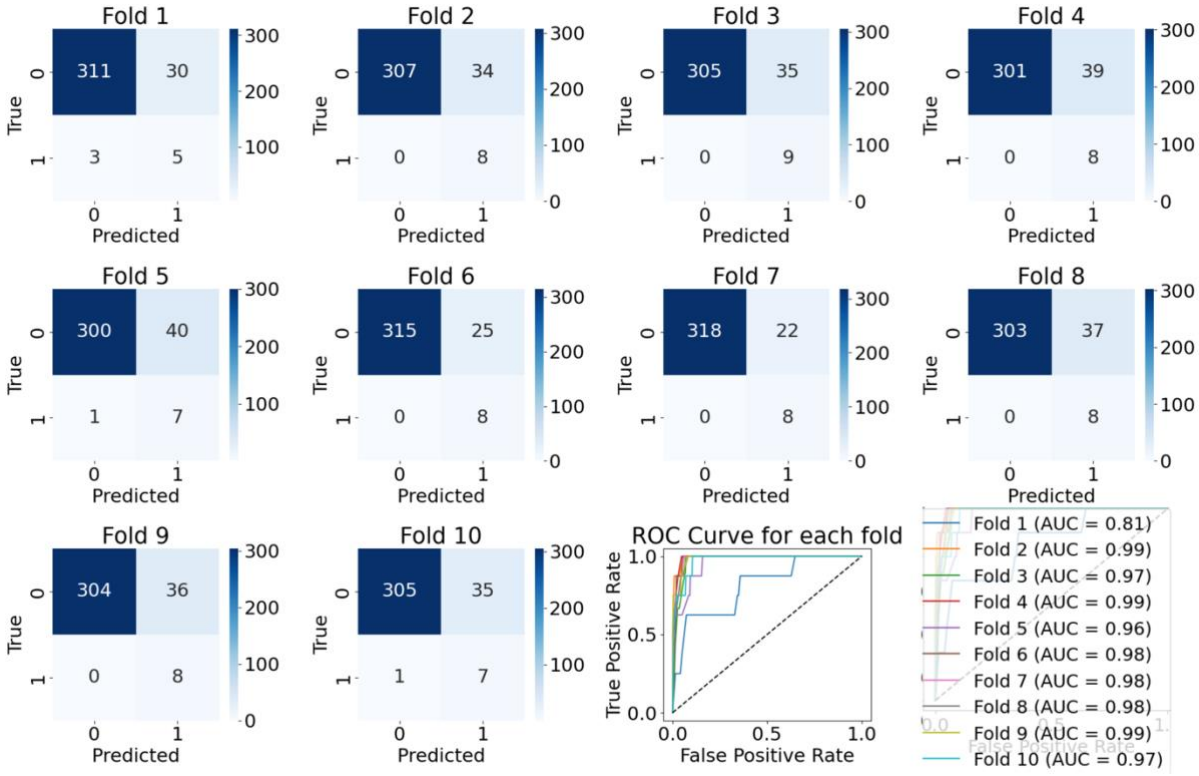

Figure 2. The SHAP summary plot

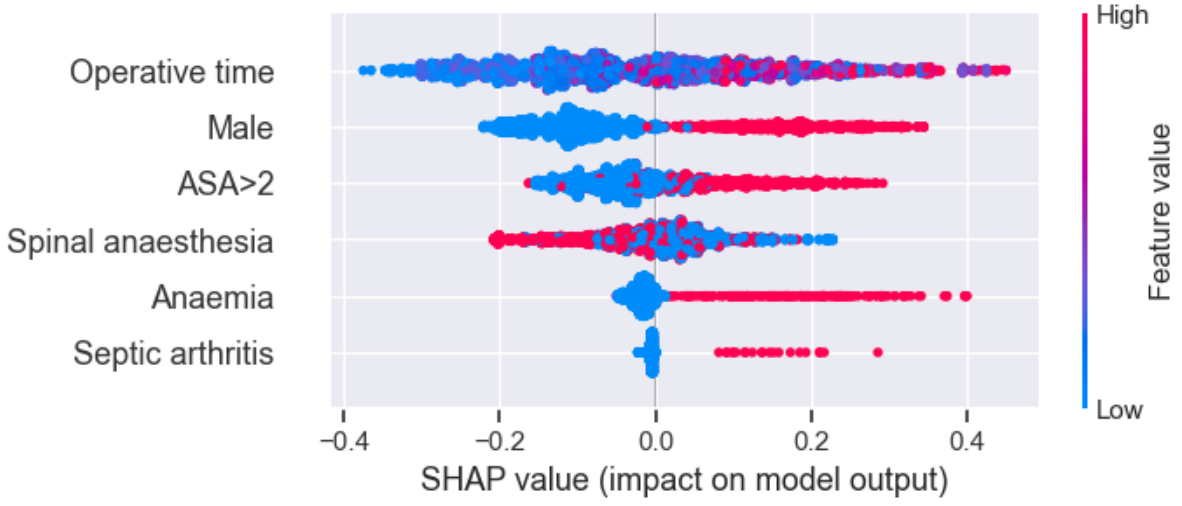

Table 1. Characteristics of the cohort

Characteristics	Primary total knee arthroplasty patients (N=3483)	P-value from univariate analysis
Patient demographics		
Age (years)	70.4± 10.0	**<0.001**
Male gender	939 (27.0%)	**<0.001**
Ethnicity	Chinese 3421 (98.2%); Other Asians 33 (0.9%); British 22 (0.6%); Non-Asians 7 (0.2%)	0.436
American Society of Anaesthesiology score	ASA 1, 146 (4.2%); ASA 2, 2002 (57.5%); ASA 3, 1077 (30.9%); ASA 4, 3 (0.1%); Missing, 255 (7.3%)	ASA>2: **0.016**
Body mass index (kg/m^2)	27.8 ± 4.6	0.148
Operation-related variables		
Laterality	Left 1458 (41.9%); Right 1457 (41.8%); Bilateral 568 (16.3%)	0.229
Operative time (minutes)	116.6 ± 75.8	**<0.001**
Month of operation (months)	6.7 ± 3.5	0.667
Preoperative length of stay (days)	1.2 ± 1.8	0.081
Anaesthesia type		
General anaesthesia	1233 (35.4%)	**0.002**
Spinal anaesthesia	1703 (48.9%)	**0.003**
Combined-spinal epidural anaesthesia	428 (12.3%)	0.987
Epidural anaesthesia	22 (0.6%)	0.497
Other	97 (2.8%)	0.861
Indication for operation		
Primary osteoarthritis	3226 (92.6%)	**<0.001**
Rheumatoid arthritis	114 (3.3%)	0.826
Neoplasm	56 (1.6%)	**<0.001**
Secondary osteoarthritis	89 (2.6%)	**0.008**
Other	32 (0.9%)	0.157
Laboratory findings		
Preoperative albumin (g/L)	42.3 ± 3.3	**0.014**
Preoperative haemoglobin (g/dL)	12.8 ± 1.4	0.058
Preoperative international normalized ratio	1.0 ± 0.1	**0.028**
Preoperative absolute lymphocyte count (x10^9/L)	1.8 ± 0.6	0.102
Comorbidities		
Diabetes mellitus	1438 (41.3%)	0.742
Uncomplicated	1339 (38.4%)	0.469
Complicated	99 (2.8%)	0.258
Hypertension	2482 (71.3%)	0.157
Renal disease	109 (3.1%)	0.995
Renal failure	60 (1.7%)	0.999
Renal impairment	49 (1.4%)	1.000
Heart failure	107 (3.1%)	0.751
Chronic ischaemic heart disease	251 (7.2%)	0.716
Atrial fibrillation	137 (3.9%)	0.914
Dysrhythmia	53 (1.5%)	0.831
Myocardial infarction	17 (0.5%)	1.000
Angina pectoris	36 (1.0%)	0.857
Atherosclerosis	38 (1.1%)	0.241
Peripheral vascular disease	6 (0.2%)	0.052
Asthma	90 (2.6%)	0.450
Chronic obstructive pulmonary disease	38 (1.1%)	0.900
Cerebrovascular disease	85 (2.4%)	0.460
Neoplasm	339 (9.7%)	0.056
Non-malignant neoplasm	206 (5.9%)	0.565
Malignant neoplasm	133 (3.8%)	**0.027**
Organic brain syndrome	14 (0.4%)	0.258
Epilepsy	13 (0.4%)	0.976
Hemiplegia	10 (0.3%)	0.996
Alzheimer's disease	12 (0.3%)	0.999

Dementia	7 (0.2%)	0.999
Depression	110 (3.2%)	0.359
Psychosis	79 (2.3%)	0.385
Anxiety	54 (1.6%)	0.999
Liver disease	90 (2.6%)	0.523
Hyperlipidaemia	392 (11.3%)	0.692
Anaemia	215 (6.2%)	**0.002**
Thrombocytopenia	16 (0.5%)	**0.018**
Agranulocytosis	12 (0.3%)	**0.006**
Tuberculosis	156 (4.5%)	0.384
Rheumatoid disease	181 (5.2%)	0.689
Systemic lupus erythematosus	11 (0.3%)	0.995
Septic arthritis	21 (0.6%)	**0.002**

*Bolded p-values are p-values > 0.05.

Table 2. Average performances across all 10 folds

Metrics	Balanced Random Forest	Logistic Regression
Area under Receiver Operating Curve	0.963	0.728
Balanced Accuracy	0.920	0.654
Sensitivity	0.938	0.744
Specificity	0.902	0.564
Precision	0.189	0.039
F1 score	0.314	0.074
Brier-score	0.097	0.432

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