Preoperative prediction for periprosthetic bone loss and individual evaluation of bisphosphonate effect after total hip arthroplasty using artificial intelligence

From Yokohama City University, Yokohama, Japan

Cite this article:
Bone Joint Res 2024;13(4): 184–192.

DOI: 10.1302/2046-3758.134.BJR-2023-0188.R1

Correspondence should be sent to Yutaka Inaba
yute0131@yokohama-cu.ac.jp

A. Morita,[1] Y. Iida,[1,2,3] Y. Inaba,[1] T. Tezuka,[1] N. Kobayashi,[4] H. Choe,[1] H. Ike,[1] E. Kawakami[2,3,5]

[1]Department of Orthopaedic Surgery, Yokohama City University, Yokohama, Japan
[2]Medical Sciences Innovation Hub Program, RIKEN, Yokohama, Japan
[3]Advanced Data Science Project, RIKEN Information R&D and Strategy Headquarters, RIKEN, Yokohama, Japan
[4]Department of Orthopaedic Surgery, Yokohama City University Medical Center, Yokohama, Japan
[5]Department Artificial Intelligence Medicine, Graduate School of Medicine, Chiba University, Chiba, Japan

Aims
This study was designed to develop a model for predicting bone mineral density (BMD) loss of the femur after total hip arthroplasty (THA) using artificial intelligence (AI), and to identify factors that influence the prediction. Additionally, we virtually examined the efficacy of administration of bisphosphonate for cases with severe BMD loss based on the predictive model.

Methods
The study included 538 joints that underwent primary THA. The patients were divided into groups using unsupervised time series clustering for five-year BMD loss of Gruen zone 7 postoperatively, and a machine-learning model to predict the BMD loss was developed. Additionally, the predictor for BMD loss was extracted using SHapley Additive exPlanations (SHAP). The patient-specific efficacy of bisphosphonate, which is the most important categorical predictor for BMD loss, was examined by calculating the change in predictive probability when hypothetically switching between the inclusion and exclusion of bisphosphonate.

Results
Time series clustering allowed us to divide the patients into two groups, and the predictive factors were identified including patient- and operation-related factors. The area under the receiver operating characteristic (ROC) curve (AUC) for the BMD loss prediction averaged 0.734. Virtual administration of bisphosphonate showed on average 14% efficacy in preventing BMD loss of zone 7. Additionally, stem types and preoperative triglyceride (TG), creatinine (Cr), estimated glomerular filtration rate (eGFR), and creatine kinase (CK) showed significant association with the estimated patient-specific efficacy of bisphosphonate.

Conclusion
Periprosthetic BMD loss after THA is predictable based on patient- and operation-related factors, and optimal prescription of bisphosphonate based on the prediction may prevent BMD loss.

Bone & Joint Research

Article focus

- Can artificial intelligence (AI) be used to develop a model to predict periprosthetic bone mineral density (BMD) loss after total hip arthroplasty (THA)?
- Based on the predictive model, can we hypothetically examine the efficacy of bisphosphonate administration in patients with severe BMD loss?

Key messages

- Periprosthetic BMD loss after THA can be predicted based on patient- and operation-related factors using AI.
- Optimal prescription of bisphosphonate based on the prediction may prevent BMD loss.

Strengths and limitations

- The strength of this study is the design of an AI-based model to predict periprosthetic BMD loss.
- An important limitation is that the groups were divided using time series clustering and not according to threshold values.

Introduction

Stress shielding and bone loss in the proximal medial femur after total hip arthroplasty (THA) remain unresolved issues. It has been reported that bone mineral density (BMD) loss around implants may be related to periprosthetic fractures and later loosening,[1,2] and it is expected that revision THA for cases with severe bone loss will be difficult; therefore, preventing periprosthetic BMD loss is desirable. Many factors influence the BMD loss of the THA, and these factors can be divided into operation- and patient-related factors. Operation-related factors include the implant shape,[3] stem size,[4] material component,[5] and surgical approach.[6] Meanwhile, patient-related factors include preoperative lumbar spine BMD,[7] femoral canal shape,[8] and postoperative clinical score.[9]

Identifying and preventing these factors before or immediately after surgery would be important because periprosthetic BMD loss occurs within one year.[10] Anti-receptor activator of NF-kappa B ligand (RANKL) antibody,[11] parathyroid hormone,[3] and bisphosphonate[10] have been reported to be effective in preventing periprosthetic BMD loss. Particularly, bisphosphonates are the most popular drugs that are effective in preventing BMD loss for the lumbar spine, femoral neck,[12,13] and periprosthetic bone, and they reduce the risk of revision THA due to aseptic loosening.[14] However, it has been reported that osteonecrosis of the jaw[15] and atypical femoral fractures[16] have emerged as potential complications of bisphosphonate therapy. Therefore, regarding complications, bisphosphonate should only be used in cases where periprosthetic BMD is expected to decrease severely after THA.

To date, no model has been developed to predict postoperative periprosthetic BMD loss in advance. In addition, the lack of clear prescribing criteria and efficacy assessment methods for drugs makes it difficult to assess their effect on periprosthetic BMD. To improve prognosis after THA, it is essential to accurately predict periprosthetic BMD, and to develop drug prescription criteria

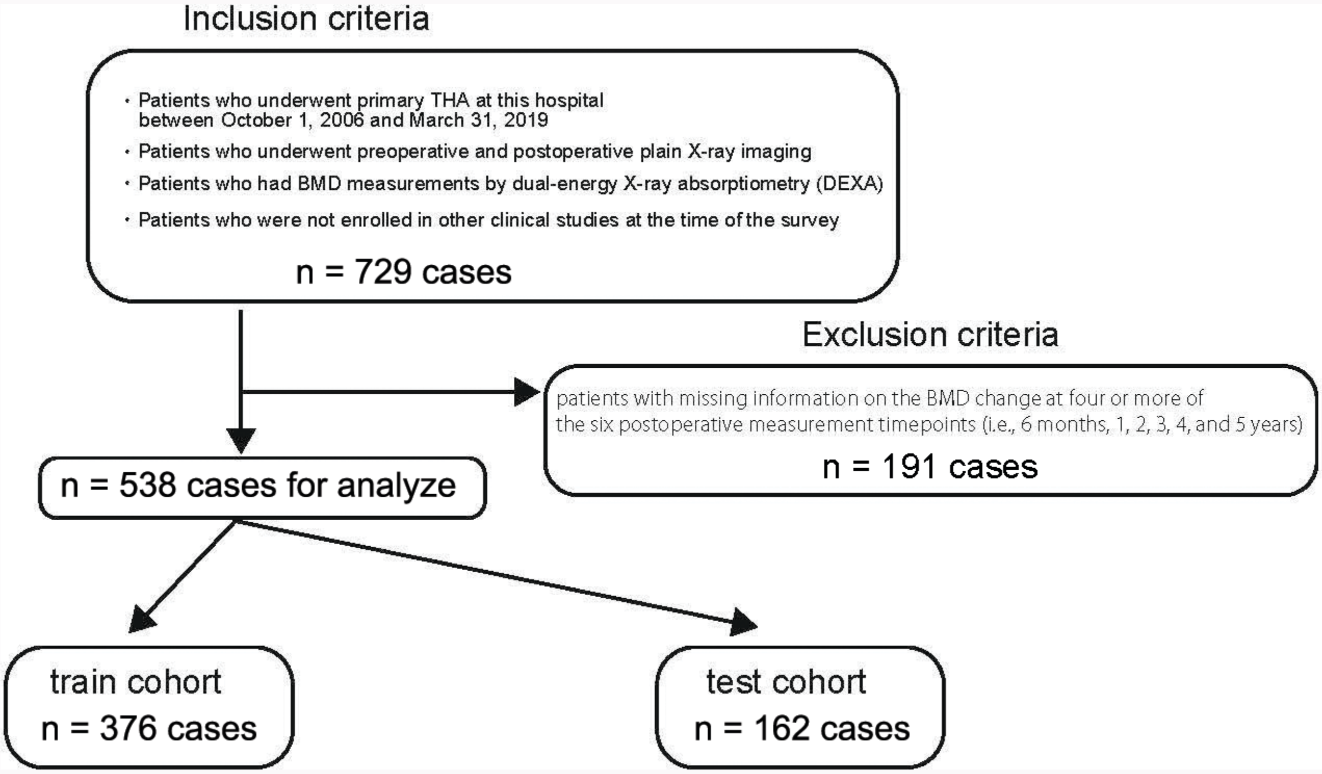

Fig. 1

Flow chart showing inclusion and exclusion criteria. A total of 538 patients were enrolled in the study. BMD, bone mineral density; DXA, dual energy X-ray absorptiometry; THA, total hip arthroplasty.

Table I. Explanatory variables.

Variable	Information
Demographic data	Sex, age, height, weight, BMI, operation side, smoking, alcohol, PSL, previous medical history, diagnosis*, CDH, implant types, medicine before operation, medicine in first year
Laboratory test	WBC, RBC, Hb, Hct, PLT, TP, Alb, CK, AST, ALT, LDH, ALP, γ-GTP, BUN, Cr, eGFR, UA, Glu, T-cho, TG, Na, K, Cl, Ca, CRP, APTT, PT-INR, D-dimer
Preoperative clinical data	JOA hip score, HHS[21]
Preoperative imaging data (including radiograph, CT, and DXA images)	Femoral anteversion angle, canal flare index, isthmus, A,[8] Dorr classification, Tönnis classification, preoperative lumbar BMD on the frontal/lateral side
Postoperative imaging data (including radiograph and CT images)	Abs error, stem anteversion, distance A, distance B

*Diagnosis of disease that caused the surgery.
Abs error, absolute difference between stem anteversion and femoral neck anteversion; Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BMD, bone mineral density; BUN, blood urea nitrogen; CDH, congenital dislocation of the hip; CK, creatine kinase; Cr, creatinine; DXA, dual energy X-ray absorptiometry; eGFR, estimated glomerular filtration rate; Glu, glucose; Hb, haemoglobin; Hct, haematocrit; HHS, Harris Hip Score; JOA, Japanese Orthopaedic Association; LDH, lactate dehydrogenase; PLT, platelets; PSL, prednisolone; PT-INR, prothrombin time-international normalized ratio; RBC, red blood cells; T-cho, total cholesterol; TG, triglyceride; TP, total protein; UA, uric acid; WBC, white blood cells; γ-GTP, γ-glutamyl transpeptidase.

Table II. Stem types (n = 538).

Stem	Manufacturer	n
SL-PLUS MIA	Smith & Nephew	108
Accolade TMZF	Stryker	101
VerSys Fiber Metal MidCoat	Zimmer Biomet	78
Accolade II	Stryker	96
SL-PLUS	Smith & Nephew	52
SL-PLUS MIA HA	Smith & Nephew	85
VerSys Fiber Metal TAPER	Zimmer Biomet	18

Table III. Types of medication for osteoporosis.

Medicine	Before operation, n	First year after operation, n
Bisphosphonate	59	123
Anti-RANKL antibody	6	13
PTH	2	23
SERM	7	5
VD3	53	86

PTH, parathyroid hormone; RANKL, receptor activator of NF-kappa B ligand; SERM, selective oestrogen receptor modulator; VD3, vitamin D3.

and drug efficacy assessment methods according to the characteristics of each patient.

In the field of orthopaedics, the use of artificial intelligence (AI) has also accelerated in recent years because information from various methods, such as imaging features, blood tests, and physiological data, contributes to disease onset and prognosis.[17,18] Some studies have shown that AI is promising for orthopaedic surgeons.[19,20] On the other hand, AI-based forecasting models are based on finite data, so reproducibility and interpretability require attention. To improve these qualities in AI models and make them usable in clinical practice, some 'explainable AI' (XAI) technologies have been proposed. SHapley Additive exPlanations (SHAP) is an XAI technique that quantitatively calculates the impact of each explanatory variable on the predicted results output by the model.

This study was designed to develop an AI model for predicting periprosthetic BMD loss in Gruen zone 7, which will become the area with the lowest periprosthetic BMD after THA. We also aimed to identify preoperative and operative factors that influence prediction by using SHAP. Additionally, we virtually examined the individual efficacy of bisphosphonate in preventing BMD loss based on the predictive model.

Methods

Patients

This study was approved by Yokohama City University's Institutional Review Board (number F211000006), and informed consent was obtained as an opt-out option on the website. The inclusion criteria for this study were as follows: 1) patients who underwent primary THA, including bilateral THA, at our hospital between 1 October 2006 and 31 March 2019; 2) those who underwent preoperative and postoperative plain radiograph imaging; 3) those who underwent BMD measurements using dual energy X-ray absorptiometry (DXA); and 4) those who were not enrolled in other clinical studies at the time of the survey. During the study period, 729 patients were included. The exclusion criterion was missing information on BMD change at four or more of the six postoperative measurement timepoints (i.e. six months and one, two, three, four, and five years). Overall, 191 cases were excluded because more than half of the BMD change information was missing. Therefore, 538 patients were enrolled in this study (Figure 1).

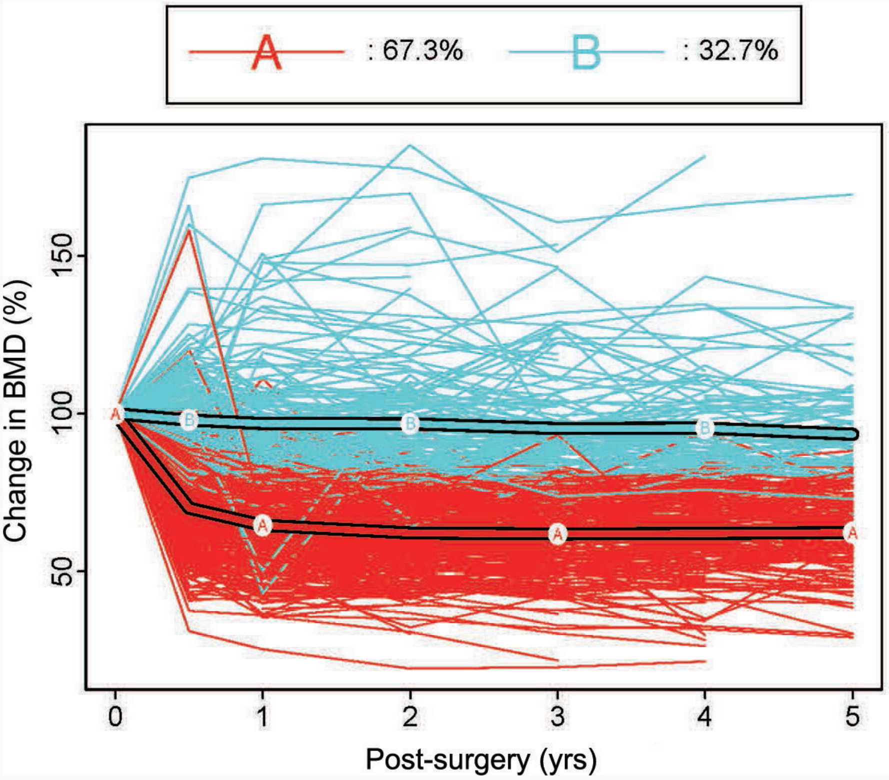

Fig. 2

Bone mineral density (BMD) change rate clustering. Longitudinal clustering by five-year postoperative trajectory was shown, with group A being the low BMD group (67.3%, n = 362) and group B being the non-low BMD group (32.7%, n = 176).

We retrospectively reviewed the patients' backgrounds and clinical and radiological parameters (Table I and Supplementary Table i). The implants used in this study are shown in Table II. Furthermore, osteoporosis drugs used in this study are shown in Table III.

Radiological assessment

In this study, we defined distance A as the distance from the top of the greater trochanter to the stem shoulder and distance B as the distance from the stem shoulder to the tip of the lesser trochanter (Supplementary Figure a).

The definitions of other radiological parameters related to THA measured in this study are summarized in Supplementary Table ii.

Unsupervised clustering of the five-year postoperative BMD change rate

Prior to developing a supervised machine-learning model to predict postoperative BMD change, we performed unsupervised clustering of BMD change rates over a five-year postoperative period. For BMD change rates, BMD measured one week after surgery was used as the baseline. The regions of interest were centred on the periprosthetic zones, as described by Gruen et al.[22] BMD has large measurement variability and missing measurements, and there is no commonly used threshold. To reduce the influence of measurement error and reveal potential patterns of postoperative BMD change, we employed k-means clustering for time series data. Groups according to the five-year postoperative rate of change in BMD were identified using a longitudinal k-means clustering method implemented in the kml package in R (R Foundation for Statistical Computing, Austria).[23] The kml package allows for clustering based on changes in longitudinal data over time. The optimal number of clusters was selected using the statistical criteria proposed by Calinski and Harabasz.[24]

Data preprocessing

Explanatory variables with < 30% missing were used.[25] As a result, 85 variables were used in the BMD prediction (Supplementary Tables i, iii, and iv). In this study, missing value completion was not performed because LightGBM,[26] which can handle missing values without completion, was employed. Next, using the train_test_split function of the scikit-learn package in Python (Python Software Foundation, USA), the data were split into training and test data at a ratio of 7:3, to preserve the proportion of the objective variable. Statistical tests were performed between the training and test data using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. The Python package scipy was used for the statistical tests. No significant differences were found between the training and test data for the aforementioned variables.

Supervised classification using machine learning

A supervised classification model using LightGBM was constructed with groups of postoperative BMD changes identified by longitudinal k-means clustering as the objective variable. Logistic regression was used as the

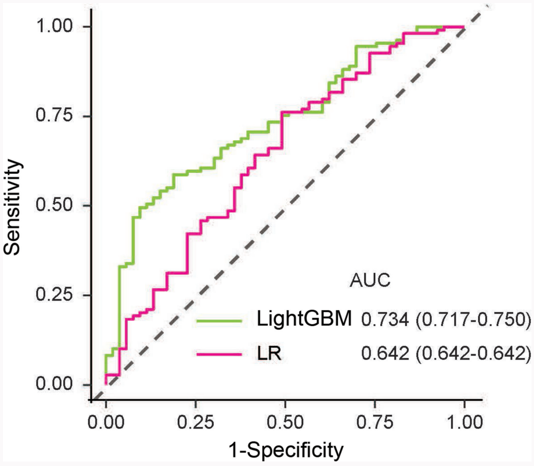

Fig. 3

Supervised prediction of bone mineral density (BMD) loss using patient- and operation-related variables. LightGBM showed a higher area under the receiver operating characteristic curve (AUC) than logistic regression (LR). The LightGBM classifier outperformed the LR model with a mean AUC of 0.734.

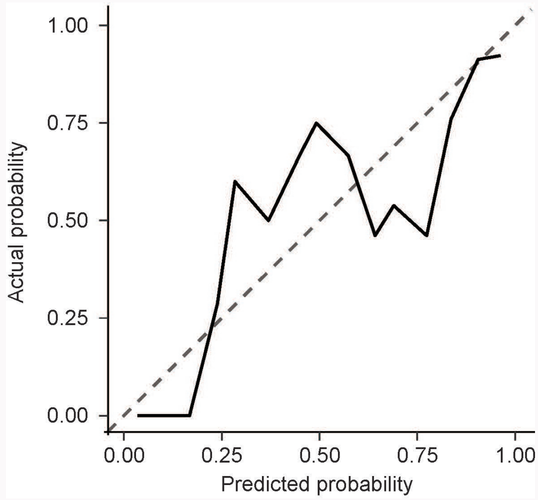

Fig. 4

The calibration curves for the predicted and observed probabilities of LightGBM, with a Brier score of 0.196.

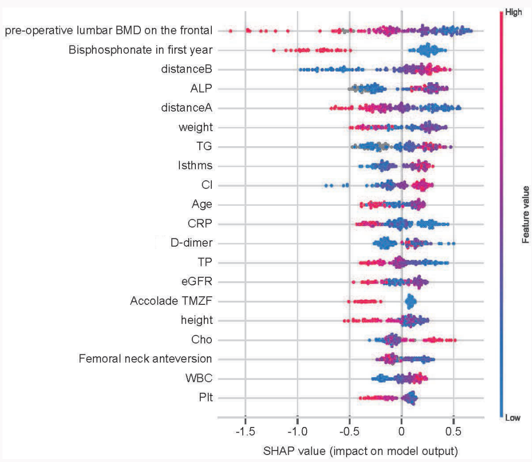

Fig. 5

The top 20 SHapley Additive exPlanations (SHAP) values for the impact of variables on the discrimination in the machine learning classifier (LightGBM). The higher the SHAP value of the feature, the higher the patient's risk of BMI loss. ALP, alkaline phosphatase; BMD, bone mineral density; Cho, cholesterol; Cl, chlorine; eGFR, estimated glomerular filtration rate; Isthms, isthmus; Plt, platelet; TG, triglyceride; TP, total protein; WBC, white blood cell.

baseline. Hyperparameters were tuned by fivefold cross-validation on the training data using the Optuna package in Python.[27] Optuna is an automatic hyperparameter optimization software framework for machine learning. Performances of the classification models were evaluated on test data with the area under the ROC curve (AUC). For each algorithm, we trained ten times with different random seed values and calculated means and the 95% confidence intervals for the performance measures. The SHAP value was used to evaluate the importance of the explanatory variables in the classification.[28] SHAP represents the contribution of each feature to the model predictions using the Shapley value from cooperative game theory. The SHAP package in Python was used to calculate the SHAP value. Calibration performances of the classification models were evaluated by comparing predictions and observations in each predicted probability bin. We used a total of ten bins in this study. Based on the predictive model for postoperative BMD changes, we then examined the individual efficacy of bisphosphonate in preventing BMD loss. We calculated the change in the predicted probability of the BMD prediction model when virtually changing the bisphosphonate prescription. The predicted probability was the probability of being classified into the group with a significant decrease in BMD within one year after surgery.

Statistical analysis

The association between change in the predicted probability and explanatory variables was assessed with Welch's *t*-test for binary variables, analysis of variance (ANOVA) and Tukey's test for categorical data of three or more types, and Spearman's rank correlation coefficient for continuous variables. Furthermore, false discovery rate (FDR) correction was performed to address the multiple testing issue using the Benjamini-Hochberg method implemented in stats R package.

Results

Unsupervised clustering of the postoperative BMD changes over five years

With longitudinal k-means clustering analysis, it was determined that the change in BMD loss ratio over the five-year postoperative period could best be divided into two groups (Supplementary Figure b). The clustering results are shown in Figure 2. Group A had a marked decrease in BMD within one year postoperatively, averaging 62.3% of the preoperative level five years after surgery, while group B had a lesser decrease, averaging 93.4% of the preoperative level five years after surgery. The characteristics of each group are shown in Supplementary Tables i, iii, iv, and v.

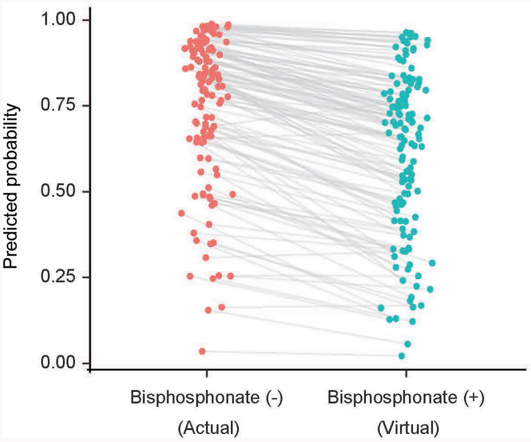

Fig. 6
Predicted probability of group A classification for those who did not use bisphosphonate (n = 127) versus for those who used bisphosphonate in virtual. Predicted probability decreased in most cases except for three.

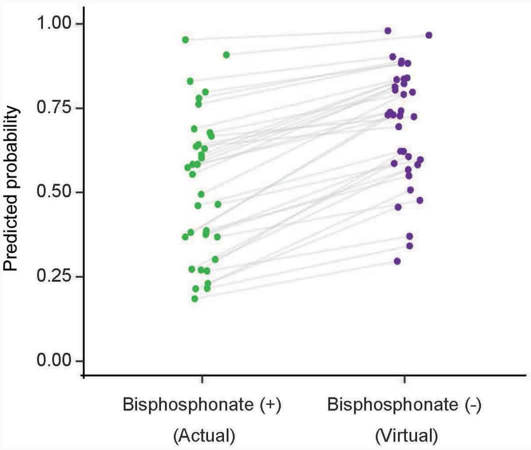

Fig. 7
Predicted probability to group A classification for those who did use bisphosphonate (n = 35) versus for those who had not used bisphosphonate in virtual. All had an increased predicted probability.

Supervised prediction of BMD loss using patient- and operation-related variables

We next developed a supervised predictive model with the group A/B obtained by unsupervised time series clustering as an objective variable. Figure 3 shows the receiver operating characteristic curve (ROC) of the predictions using LR and LightGBM. The LightGBM classifier outperformed the LR model with a mean AUC of 0.734 (SD 0.017; 0.717 to 0.750). Figure 4 shows the calibration curve for the predicted and observed probabilities for LightGBM classifier, with a Brier score of 0.196. Next, we examined the importance of explanatory variables in predicting BMD loss in the LightGBM classifier. In addition to bisphosphonate prescription during the first postoperative year, anatomical variables, such as preoperative lumbar BMD on the frontal side, distance A, distance B, and stem type (Accolade TMZF), as well as blood biomarker factors such as alkaline phosphatase (ALP) and triglyceride (TG), were identified as important predictors (Figure 5).

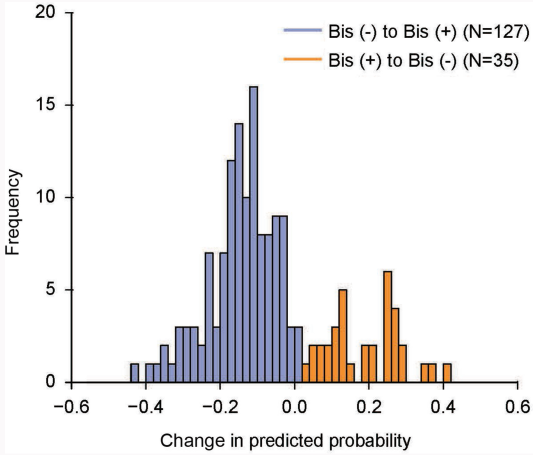

Fig. 8
Amount of change in the predicted probability in the with and without bisphosphonate groups. The virtual administration of bisphosphonate increased the efficacy by approximately 14%, and without virtual administration the efficacy decreased by approximately 19%.

Examination of the individual efficacy of bisphosphonate in preventing loss of BMD

To examine the patient-specific efficacy of bisphosphonate, which was the most important categorical predictor of BMD change, we calculated the change in predicted probability when virtually changing the bisphosphonate prescription. When virtually prescribing bisphosphonate to those who were not prescribed bisphosphonate (n = 127), the predicted probability decreased in most cases except for three (Figure 6). In contrast, for those who were originally prescribed bisphosphonate (n = 35), all had an increased predicted probability with the virtual cancellation of bisphosphonate (Figure 7). The change in predicted probability varied widely from patient to patient, ranging from -0.43 to 0.075 (mean = -0.14) in the virtual prescription group and from 0.035 to 0.41 (mean = 0.19) in the virtual cancellation group (Figure 8).

In the virtual prescription group, statistical examination of the association between changes in predicted probability and explanatory variables showed that implant type and TG, creatinine (Cr), estimated glomerular filtration rate (eGFR), creatine kinase (CK), and predicted probability were significantly associated (adjusted $p < 0.05$, Welch's *t*-test and Tukey's test) (all results are summarized in Supplementary Tables i and vi). Among these results, TG was particularly strongly associated. Figure 9 shows the changes in predicted probability for each implant type. When Tukey's test was performed to examine differences between implants, a significant difference was observed between the SL-PLUS MIA stem (Smith & Nephew, USA) and the SL-PLUS stem (Smith & Nephew), as well as between the SL-PLUS MIA stem and the VerSys Fiber Metal MidCoat stem (Zimmer Biomet, USA). The SL-PLUS stem and VerSys Fiber Metal MidCoat stem showed significantly higher predicted probability change than the SL-PLUS MIA stem ($p < 0.05$, Tukey's test). TG was associated with a difference in the predicted probability, with an adjusted p-value < 0.001 (Welch's *t*-test). The association between the difference in predicted probability and TG, eGFR, Cr, and CK values is illustrated in Figure 10 as scatter plots.

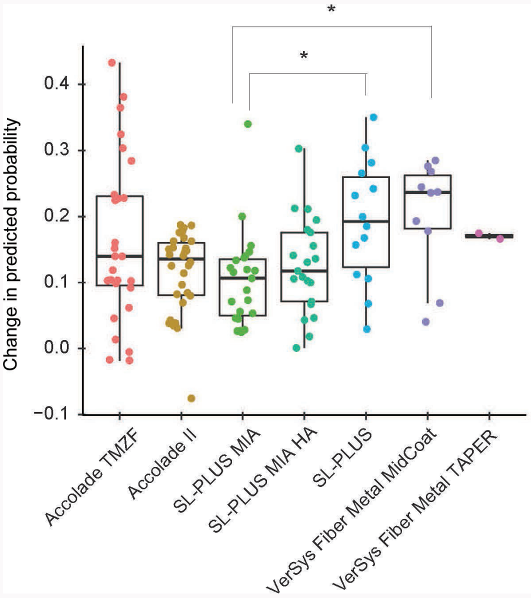

Fig. 9

Relationship between implant types and predicted probability change. SL-Plus and VerSys Fiber Metal MidCoat stems were significantly more likely to produce bisphosphonate efficacy than SL MIA stem. *Adjusted p-value < 0.05, Tukey's test.

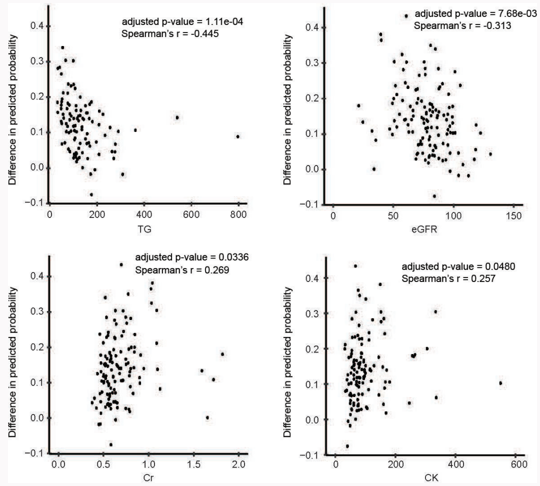

Fig. 10

Relationship between continuous variables (TG, eGFR, Cr, and CK) and predicted probability change. The lower the preoperative TG levels, the more effective the bisphosphonate treatment. Statistics were performed using Welch's *t*-test. CK, creatine kinase; Cr, creatinine; eGFR, estimated glomerular filtration rate; TG, triglyceride.

Discussion

Identifying predictors for periprosthetic BMD loss using conventional statistical analysis is difficult, because many factors are associated with each other and confound each other. In this study, AI made it possible to deal with multimodal data related to THA. In the results of the current study, (67.3%,n=362) of the patients were classified into a group with a marked decrease in BMD (group A), whereas the remaining (32.7%,n=176) were classified into a group with postoperative BMD at the same level as before surgery (group B). These groups could be predicted with reasonable accuracy by operation- and patient-related factors. The important categorical predictor for the two groups was the use of bisphosphonate one year after surgery, suggesting the efficacy of bisphosphonate use immediately after THA. Distance A and distance B, anatomical distances related to how the implant stem is placed, were also identified as important predictors for BMD change. Analysis using SHAP revealed that a smaller distance A and a larger distance B increased the probability of having a lower postoperative BMD (i.e. being classified as group A). It could be explained that deep stem placement prevented stress shielding to the medial proximal femur. Accolade TMZF stem was also identified as an important factor. Accolade TMZF stem is a β titanium alloy with a low Young's modulus, and has been reported to prevent stress shielding to the proximal femur; the results of the present study were the same as those reported previously.[5] Regarding patient-related factors, preoperative lumbar BMD was the most important factor, as shown in a previous report.[7] Additionally, ALP and TG were identified as important predictors among preoperative blood biomarkers, and patients with higher levels of ALP and TG tended to be classified into group A. ALP is related to bone metabolism and may reflect the preoperative osteoporosis status. The more osteoporotic the condition, the more likely zone 7 BMD tends to decrease postoperatively. TG is related to osteoporosis, and osteogenesis is decreased in patients with hyperlipidaemia.[29] Postoperatively, bone formation in zone 7 may be suppressed in patients with hyperlipidaemia.

In this study, we also examined the efficacy and factors affecting the virtual administration of bisphosphonate to prevent BMD loss, because the risk of complications makes the use of bisphosphonates difficult in all patients. The results showed that virtual administration of bisphosphonate reduced the probability of BMD loss by an average of 14%, but the effect varied widely from patient to patient. The differences in efficacy were associated with stem types, with SL-PLUS stem and VerSys Fiber Metal MidCoat stem being significantly more effective than SL-PLUS MIA stem. Identifying the cause of the differences in bisphosphonate effects between stems is difficult, and further research is needed to elucidate this. However, it is important to confirm the existence of differences in bisphosphonate effects among stem types, considering the aim to prevent periprosthetic BMD loss. Additionally, TG, Cr, eGFR, and CK were identified as factors related to the efficacy of bisphosphonate. TG is related to osteogenesis; however, differences in the effects of bisphosphonate depending on blood TG levels have rarely been reported previously. Generally, TG metabolism is related to the peroxisome proliferator-activated receptor gamma (PPARγ) signalling pathway,[30] which plays a substantial role in the relationship between lipid biomarkers and BMD.[31] When the PPARγ level increases, osteogenesis is inhibited.[32] Cr and eGFR are factors that reflect renal function, and bisphosphonate becomes more effective due to decreases excretion and enhances efficacy by renal dysfunction.[33] Similar results were obtained in this study, with preoperative high Cr levels and low eGFR levels leading to a greater effect of bisphosphonate. From these results, TG and renal function may play an important role in the difference in the effects of bisphosphonate, and caution should be taken when using bisphosphonate in patients with high TG levels, as their efficacy may be attenuated in contrast to renal dysfunction such as Cr and eGFR. We were unable to find any previous studies that could explain the association between CK and the effect of bisphosphonates; further studies are needed to explore this.

There are several limitations to our study. First, the sample size is not large, and it was a single-centre study. Therefore, in the future we intend to demonstrate the validity and reproducibility of our working hypothesis using a larger multicentre cohort. Second, the groups were divided using time series clustering and not according to threshold values. The absence of clear clinical criteria for BMD loss is one of the factors that make its prevention difficult, so future studies will need to establish these criteria. Third, although we found that certain stems and TG affect the efficacy of bisphosphonates, we could not identify a clear mechanism. However, we believe that these factors, which could not be identified using conventional statistical analysis, are essential in preventing periprosthetic BMD loss and require further study. Fourth, we only investigated medical history that might be associated with periprosthetic BMD loss.

In conclusion, periprosthetic BMD loss after THA is reasonably predictable based on patient- and operation-related factors, and optimal prescription of bisphosphonates based on the prediction related to stem types and TG, Cr, eGFR, and CK will be effective in preventing periprosthetic BMD loss.

Supplementary material

Figures showing the definitions of distances A and B and the statistical criteria proposed by Calinski and Harabasz. Tables showing the results of Welch's *t*-test for the difference of predicted probability and binary variables, radiological measurements, preoperative peripheral blood tests, patient background and clinical scores, patient background and radiological data, and the results of Spearman's rank correlation coefficient for the difference of predicted probability and continuous variables.

References

1. **Yamada H**, **Yoshihara Y**, **Henmi O**, **et al**. Cementless total hip replacement: past, present, and future. *J Orthop Sci*. 2009;14(2):228–241.
2. **Leonardsson O**, **Kärrholm J**, **Åkesson K**, **Garellick G**, **Rogmark C**. Higher risk of reoperation for bipolar and uncemented hemiarthroplasty. *Acta Orthop*. 2012;83(5):459–466.
3. **Kobayashi N**, **Inaba Y**, **Uchiyama M**, **Ike H**, **Kubota S**, **Saito T**. Teriparatide versus alendronate for the preservation of bone mineral density after total hip arthroplasty - a randomized controlled trial. *J Arthroplasty*. 2016;31(1):333–338.
4. **Oba M**, **Inaba Y**, **Kobayashi N**, **Ike H**, **Tezuka T**, **Saito T**. Effect of femoral canal shape on mechanical stress distribution and adaptive bone remodelling around a cementless tapered-wedge stem. *Bone Joint Res*. 2016;5(9):362–369.
5. **Morita A**, **Kobayashi N**, **Choe H**, **Tezuka T**, **Misumi T**, **Inaba Y**. Effect of implant composition on periprosthetic bone mineral density after total hip arthroplasty. *Arch Orthop Trauma Surg*. 2023;143(5):2763–2771.
6. **Ugland TO**, **Haugeberg G**, **Svenningsen S**, **et al**. Less periprosthetic bone loss following the anterolateral approach to the hip compared with the direct lateral approach. *Acta Orthop*. 2018;89(1):23–28.
7. **Alm JJ**, **Mäkinen TJ**, **Lankinen P**, **Moritz N**, **Vahlberg T**, **Aro HT**. Female patients with low systemic BMD are prone to bone loss in Gruen zone 7 after cementless total hip arthroplasty. *Acta Orthop*. 2009;80(5):531–537.
8. **Morita A**, **Kobayashi N**, **Choe H**, **Tezuka T**, **Higashihira S**, **Inaba Y**. Preoperative factors predicting the severity of BMD loss around the implant after total hip arthroplasty. *BMC Musculoskelet Disord*. 2021;22(1):290.
9. **Hayashi S**, **Hashimoto S**, **Kanzaki N**, **Kuroda R**, **Kurosaka M**. Daily activity and initial bone mineral density are associated with periprosthetic bone mineral density after total hip arthroplasty. *Hip Int*. 2016;26(2):169–174.
10. **Morita A**, **Kobayashi N**, **Choe H**, **et al**. Effect of switching administration of alendronate after teriparatide for the prevention of BMD loss around the implant after total hip arthroplasty, 2-year follow-up: a randomized controlled trial. *J Orthop Surg Res*. 2020;15(1):17.
11. **Nagoya S**, **Tateda K**, **Okazaki S**, **Kosukegawa I**, **Shimizu J**, **Yamashita T**. Restoration of proximal periprosthetic bone loss by denosumab in cementless total hip arthroplasty. *Eur J Orthop Surg Traumatol*. 2018;28(8):1601–1607.
12. **Liberman UA**, **Weiss SR**, **Bröll J**, **et al**. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. *N Engl J Med*. 1995;333(22):1437–1443.
13. **Black DM**, **Cummings SR**, **Karpf DB**, **et al**. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. *Lancet*. 1996;348(9041):1535–1541.
14. **Khatod M**, **Inacio MCS**, **Dell RM**, **Bini SA**, **Paxton EW**, **Namba RS**. Association of bisphosphonate use and risk of revision after THA: outcomes from a US total joint replacement registry. *Clin Orthop Relat Res*. 2015;473(11):3412–3420.
15. **Durie BGM**, **Katz M**, **Crowley J**. Osteonecrosis of the jaw and bisphosphonates. *N Engl J Med*. 2005;353(1):99–102.
16. **Shane E**, **Burr D**, **Ebeling PR**, **et al**. Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res*. 2010;25(11):2267–2294.
17. **Lisacek-Kiosoglous AB**, **Powling AS**, **Fontalis A**, **Gabr A**, **Mazomenos E**, **Haddad FS**. Artificial intelligence in orthopaedic surgery. *Bone Joint Res*. 2023;12(7):447–454.
18. **Kunze KN**, **Orr M**, **Krebs V**, **Bhandari M**, **Piuzzi NS**. Potential benefits, unintended consequences, and future roles of artificial intelligence in orthopaedic surgery research: a call to emphasize data quality and indications. *Bone Jt Open*. 2022;3(1):93–97.
19. **Langenberger B**, **Schrednitzki D**, **Halder AM**, **Busse R**, **Pross CM**. Predicting whether patients will achieve minimal clinically important differences following hip or knee arthroplasty. *Bone Joint Res*. 2023;12(9):512–521.
20. **Gurung B**, **Liu P**, **Harris PDR**, **et al**. Artificial intelligence for image analysis in total hip and total knee arthroplasty: a scoping review. *Bone Joint J*. 2022;104-B(8):929–937.
21. **Harris WH**. Traumatic arthritis of the hip after dislocation and acetabular fractures: treatment by mold arthroplasty. An end-result study using a new method of result evaluation. *J Bone Joint Surg Am*. 1969;51-A(4):737–755.
22. **Gruen TA**, **McNeice GM**, **Amstutz HC**. "Modes of failure" of cemented stem-type femoral components: a radiographic analysis of loosening. *Clin Orthop Relat Res*. 1979;141:17–27.
23. **Genolini C**, **Falissard B**. KmL: k-means for longitudinal data. *Comput Stat*. 2010;25(2):317–328.
24. **Calinski T**, **Harabasz J**. A dendrite method for cluster analysis. *Comm in Stats - Theory & Methods*. 1974;3(1):1–27.
25. **Juhola M**, **Laurikkala J**. Missing values: how many can they be to preserve classification reliability? *Artif Intell Rev*. 2013;40(3):231–245.
26. **Ke G**, **Meng Q**, **Finley T**, **et al**. LightGBM: A Highly Efficient Gradient Boosting Decision Tree. Advances in Neural Information Processing Systems 30 (NIPS 2017). 2017. https://proceedings.neurips.cc/paper_files/paper/2017/file/6449f44a102fde848669bdd9eb6b76fa-Paper.pdf (date last accessed 8 February 2024).
27. **Akiba T**, **Sano S**, **Yanase T**, **Ohta T**, **Koyama M**. Optuna: A Next-generation Hyperparameter Optimization Framework. KDD'19: Proceedings of the 25th ACM SIGKDD International Conference on Knowledge Discovery & Data Mining. 2019. https://dl.acm.org/doi/10.1145/3292500.3330701 (date last accessed 8 February 2024).

28. **Lundberg SM**, **Lee SI**. A unified approach to interpreting model predictions. NIPS'17: Proceedings of the 31st International Conference on Neural Information Processing Systems. 2017. https://dl.acm.org/doi/10.5555/3295222.3295230 (date last accessed 8 February 2024).
29. **Nuttall ME**, **Gimble JM**. Controlling the balance between osteoblastogenesis and adipogenesis and the consequent therapeutic implications. *Curr Opin Pharmacol*. 2004;4(3):290–294.
30. **Ye G**, **Gao H**, **Wang Z**, **et al**. PPARα and PPARγ activation attenuates total free fatty acid and triglyceride accumulation in macrophages via the inhibition of Fatp1 expression. *Cell Death Dis*. 2019;10(2):39.
31. **Kan B**, **Zhao Q**, **Wang L**, **Xue S**, **Cai H**, **Yang S**. Association between lipid biomarkers and osteoporosis: a cross-sectional study. *BMC Musculoskelet Disord*. 2021;22(1):759.
32. **Akune T**, **Ohba S**, **Kamekura S**, **et al**. PPARgamma insufficiency enhances osteogenesis through osteoblast formation from bone marrow progenitors. *J Clin Invest*. 2004;113(6):846–855.
33. **Mitchell DY**, **St Peter JV**, **Eusebio RA**, **et al**. Effect of renal function on risedronate pharmacokinetics after a single oral dose. *Br J Clin Pharmacol*. 2000;49(3):215–222.

Author information

A. Morita, MD, PhD, Staff Physician
Y. Inaba, MD, PhD, Professor and Chairman
T. Tezuka, MD, PhD, Associate Professor
H. Choe, MD, PhD, Associate Professor
H. Ike, MD, PhD, Associate Professor
Department of Orthopaedic Surgery, Yokohama City University, Yokohama, Japan.

Y. Iida, Department of Orthopaedic Surgery, Yokohama City University, Yokohama, Japan; Medical Sciences Innovation Hub Program, RIKEN, Yokohama, Japan; Advanced Data Science Project, RIKEN Information R&D and Strategy Headquarters, RIKEN, Yokohama, Japan.

N. Kobayashi, MD, PhD, Associate Professor, Department of Orthopaedic Surgery, Yokohama City University Medical Center, Yokohama, Japan.

E. Kawakami, MD, PhD, Team Reader, Medical Sciences Innovation Hub Program, RIKEN, Yokohama, Japan; Advanced Data Science Project, RIKEN Information R&D and Strategy Headquarters, RIKEN, Yokohama, Japan; Department Artificial Intelligence Medicine, Graduate School of Medicine, Chiba University, Chiba, Japan.

Author contributions

A. Morita: Data curation, Investigation, Writing – original draft.
Y. Iida: Formal analysis, Methodology, Writing – original draft.
Y. Inaba: Conceptualization, Project administration, Supervision.
T. Tezuka: Investigation.
N. Kobayashi: Investigation, Methodology.
H. Choe: Investigation.
H. Ike: Methodology.
E. Kawakami: Formal analysis, Project administration, Validation.

A. Morita and Y. Iida are joint first authors.

Funding statement

The authors disclose receipt of the following financial or material support for the research, authorship, and/or publication of this article: funding from JSPS KAKENHI (Grant Number JP23K08635).

ICMJE COI statement

Y. Inaba reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Stryker, Smith & Nephew, and Zimmer Biomet, not related to this study.

Data sharing

The data that support the findings for this study are available to other researchers from the corresponding author upon reasonable request.

Ethical review statement

This study was approved by the Institutional Review Board of Yokohama City University (B200700017), and informed consent was obtained as an opt-out option on the website (https://www.yokohama-cu.ac.jp/amedrc/ethics/ethical/fuzoku_optout.html).

Open access funding

The authors report that they received open access funding for their manuscript from JSPS KAKENHI (Grant Number JP23K08635).