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ORIGINAL RESEARCH

Predicting Prostate Cancer Upgrading of Biopsy Gleason Grade Group at Radical Prostatectomy Using Machine Learning-Assisted Decision-Support Models

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Objective: This study aimed to develop a machine learning (ML)-assisted model capable of accurately predicting the probability of biopsy Gleason grade group upgrading before making treatment decisions.

Methods: We retrospectively collected data from prostate cancer (PCa) patients. Four ML-assisted models were developed from 16 clinical features using logistic regression (LR), logistic regression optimized by least absolute shrinkage and selection operator (Lasso) regularization (Lasso-LR), random forest (RF), and support vector machine (SVM). The area under the curve (AUC) was applied to determine the model with the highest discrimination. Calibration plots and decision curve analysis (DCA) were performed to evaluate the calibration and clinical usefulness of each model.

Results: A total of 530 PCa patients were included in this study. The Lasso-LR model showed good discrimination with an AUC, accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 0.776, 0.712, 0.679, 0.745, 0.730, and 0.695, respectively, followed by SVM (AUC=0.740, 95% confidence interval [CI] =0.690–0.790), LR (AUC=0.725, 95% CI=0.674–0.776) and RF (AUC=0.666, 95% CI=0.618–0.714). Validation of the model showed that the Lasso-LR model had the best discriminative power (AUC=0.735, 95% CI=0.656–0.813), followed by SVM (AUC=0.723, 95% CI=0.644–0.802), LR (AUC=0.697, 95% CI=0.615–0.778) and RF (AUC=0.607, 95% CI=0.531–0.684) in the testing dataset. Both the Lasso-LR and SVM models were well-calibrated. DCA plots demonstrated that the predictive models except RF were clinically useful.

Conclusion: The Lasso-LR model had good discrimination in the prediction of patients at high risk of harboring incorrect Gleason grade group assignment, and the use of this model may be greatly beneficial to urologists in treatment planning, patient selection, and the decision-making process for PCa patients.

Keywords: prostate cancer, biopsy cores, Gleason grade group, upgrading, machine learning

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Background

Despite first being introduced in 1966, the Gleason score (GS) remains the most widely used grading system for prostate cancer (PCa).[1] The GS grading system was updated in 2005 and 2014 and a new five-tier grade group (GG) system was proposed and developed: GG 1 (GS≤6), GG 2 (GS3+4=7), GG 3 (GS 4+3=7), GG 4 (GS 8), and

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GG 5 (GS 9 and 10).[2,3] Appropriate clinical management for PCa patients depends on accurate risk stratification, which is mainly reliant on the pretreatment prostate-specific antigen (PSA) level, Gleason grade group (GG) of positive biopsy cores, and tumor stage. However, up to 56% of high-grade patients at initial biopsy tend to be overestimated, compared with prostatectomy specimens due to the sampling error of biopsy and the multifocal nature of PCa.[3,4] In addition, some low risk patients who embark on active surveillance (AS) will be upgraded to higher grade at RP so they are not suitable candidates for AS.[5,6] The discordance between initial biopsy GG and radical prostatectomy (RP) GG can potentially impact over- and under-treatment.[7] Therefore, for the management of PCa, it is of pivotal importance to identify PCa patients at a higher risk of upgrading at RP before making treatment-related decisions.

Machine learning (ML) is the semi-automated extraction of knowledge and insight from data.[8] Developed within the fields of statistics, computer science and artificial intelligence, it allows the training of algorithms that can discover and identify complex patterns and relationships faster than conventional statistical models that focus on only a handful of patient variables.[8] Owing to the ability of ML algorithms to improve the accuracy of predicting diseases and subsequent outcomes over the use of traditional statistical models, they have been applied extensively in the field of clinical research.[9,10] In the present study, we apply ML algorithms to the dataset, with the goal of identifying those patients at high risk of harboring upgrading at RP before making treatment decisions, and to determine the best predictive models.

Additionally, there is still no consensus on how to choose a "case level" biopsy GG (GS) for patients regarding the reporting of the "worst/highest" and "global/overall" GG (GS).[7,11] Considering that the biopsy global GG is more likely be in line with RP GG, we selected global GG together with other preoperative clinical parameters to construct predictive models to calculate the probability of upgrading for each PCa patient.

Methods

Patient Selection and Study Parameters

Patients who underwent radical prostatectomy at Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology between January 2015 and December 2019 were retrospectively enrolled in this study. This retrospective study was approved by the Ethics Committee of Tongji Hospital, Huazhong University of Science and Technology. The need for informed consent from all patients was waived due to its retrospective nature. All patient information was strictly confidential and our procedures were carried out according to the Declaration of Helsinki. The inclusion criteria were as follows: 1) multi-parametric magnetic resonance imaging (mp-MRI) performed for all patients before surgery; 2) standard systematic (12-core) transrectal ultrasonography (TRUS)-guided biopsy prior to surgery performed for all patients; and 3) final pathological results of each patient including a detailed description of Gleason grade group. The following exclusion criteria were applied: 1) neoadjuvant therapy prior to MRI examination; 2) patients with incomplete clinical data; and 3) MRI images of unsatisfactory quality. The clinical parameters included patient age, total prostate-specific antigen (TPSA), prostate volume (PV=Height×Width×Length×0.52), PSA density (PSAD), %fPSA (free PSA/TPSA), maximum diameter of index lesion (D-max), the Prostate Imaging Reporting and Data System (PI-RADS) score, clinical and pathological T stage (T1-2, T3a, T3b and T4), apical involvement at MRI, global biopsy GG, number of positive cores, number of cores with clinically significant PCa (csPCa, defined as cores with GG≥2), maximum tumor length at biopsy core, percentage of tumor in total biopsy cores, and GG at RP. The MRI findings were re-reported and scored by the same dedicated radiologist on a five-point scale using the modified PI-RADS version 2 criteria.[12] If multiple tumor foci existed on the MRI, only the highest PI-RADS score of index lesions and the maximum diameter of the largest tumor were included in the analysis. GG of the biopsy specimen was assigned following the 2014 International Society of Urological Pathology (ISUP) criteria.[13] The global GG of the biopsy was defined as the most prevalent GG among all positive cores. The upgrades from biopsy to RP represented at least one grade difference in the GG.

Development, Validation, and Performance of ML-Based Models

The dataset was randomly split into two datasets: 70% for model training and 30% for model testing. For model training, data from the training set were used to approximate model parameters. Four ML algorithms were performed to build predictive models: logistic regression (LR), logistic regression optimized by least absolute shrinkage and

Table 1 Characteristics of Total Population, Training Dataset, and Testing Dataset

	Overall (n=530)	Training Dataset (n=371)	Testing Dataset (n=159)
Age (years), median (IQR)	69 (63–75)	69 (63–75)	69 (62–73)
PV (mL), median (IQR)	37.5 (29.7–49.3)	37.1 (30.0–47.8)	38.2 (28.5–52.0)
D-max (cm), median (IQR)	1.9 (1.3–2.7)	1.9 (1.3–2.7)	1.8 (1.3–2.7)
TPSA (ng/mL), median (IQR)	21.0 (10.9–42.2)	20.9 (10.9–42.4)	21.4 (10.7–41.0)
%fPSA (fPSA/TPSA) (n, %)			
≤0.16	423 (79.8)	293 (79.0)	130 (81.8)
>0.16	107 (20.2)	78 (21.0)	29 (18.2)
PSAD (n, %)			
≤0.20	70 (13.2)	49 (13.2)	21 (13.2)
>0.20	460 (86.8)	322 (86.8)	138 (86.8)
Clinical T stage at MRI (n, %)			
T1–2	307 (57.9)	218 (58.8)	89 (56.0)
T3a	75 (14.2)	50 (13.5)	25 (15.7)
T3b	140 (26.4)	100 (27.0)	40 (25.2)
T4	8 (1.5)	3 (0.7)	5 (3.1)
PI-RADS score (n, %)			
1–2	24 (4.5)	20 (5.4)	4 (2.5)
3	67 (12.6)	47 (12.7)	20 (12.6)
4	129 (24.3)	90 (24.3)	39 (24.5)
5	310 (58.6)	214 (57.6)	96 (60.4)
Apical involvement at MRI (n, %)			
Yes	301 (56.8)	207 (55.8)	94 (59.1)
No	229 (43.2)	164 (44.2)	65 (40.9)
Biopsy grade group (n, %)			
1	166 (31.3)	118 (31.8)	48 (30.2)
2	138 (26.0)	98 (26.4)	40 (25.2)
3	111 (20.9)	76 (20.5)	35 (22.0)
4	115 (21.8)	79 (21.3)	36 (22.6)
No. of positive biopsies, median (IQR)	5 (3–9)	5 (3–9)	6 (3–9)
Presence of cores with csPCa, (n, %)			
Yes	433 (81.7)	301 (81.1)	132 (83.0)
No	97 (18.3)	70 (18.9)	27 (17.0)
Presence of cores with tumor length ≥0.6 cm, median (IQR)			
Yes	402 (75.8)	290 (78.2)	112 (70.4)
No	128 (24.2)	81 (21.8)	47 (29.6)
Maximum tumor length in single core (cm), median (IQR)	0.9 (0.6–1.4)	0.9 (0.6–1.4)	0.9 (0.5–1.3)
Total tumor length of positive cores (cm), median (IQR)	2.7 (1.2–5.4)	2.8 (1.3–5.6)	2.7 (1.0–5.2)
Percentage of tumor in total biopsy cores (%), median (IQR)	18.7 (7.9–36.0)	17.3 (8.3–35.9)	21.3 (7.1–36.7)
Presence of upgrading at final pathology (n, %)			
Yes	262 (49.4)	187 (50.4)	75 (47.2)
No	268 (50.6)	184 (49.6)	84 (52.8)

Abbreviations: IQR, interquartile range; PV, prostate volume; D-max, maximum diameter of the index lesion on MRI; TPSA, total prostate-specific antigen; fPSA, free prostate-specific antigen; PSAD, prostate-specific antigen density; MRI, magnetic resonance imaging; csPCa, clinically significantly prostate cancer; PI-RADS, the Prostate Imaging Reporting and Data System.

selection operator (Lasso) regularization (Lasso-LR), random forest classifier (RF), and support vector machine (SVM) integrated with recursive feature elimination (RFE).

Model evaluation was carried out by examining discrimination and calibration. The receiver operating characteristic (ROC) curve analysis was used to evaluate the discrimination ability of predictive models in both the training dataset and testing dataset; the discrimination ability of each model was quantified by the area under the ROC curve (AUC). Moreover, discrimination metrics including accuracy, sensitivity, specificity, Youden index (YI), positive predictive value (PPV), and negative predictive value (NPV) were also applied to assess the discriminative power of predictive models. Comparisons between ROC Curves were performed using the method described by DeLong et al.[14] As logistic regression analysis was one of the most widely used statistical methods in binary data classification, we used the LR model as the reference in the pairwise comparison of AUC. Calibration plots were used to investigate the extent of over- or under-estimation of predicted probabilities relative to the observed probabilities. Decision curve analysis (DCA) was conducted to determine the clinical net benefit associated with the use of the predictive models at different threshold probabilities in the patient cohort.

Statistical analyses were performed using R software (Version 3.6.0; https://www.R-project.org) with the following packages: "rms", "glmnet", "caret", "rpart", "randomForest", "gplots", "e1071", "kernlab", "pROC",and "MachineShop". $P<0.05$ was considered statistically significant.

Results

Baseline Characteristics and Pathological Results

Table 1 lists patient characteristics and pathological results in the total population, training dataset and testing dataset. The median patient age of the overall cohort was 69 (interquartile range [IQR]=63–75) years. The median TPSA value was 21.0 (IQR=10.9–42.2) ng/mL. The median D-max on MRI was 1.9 (IQR=1.3–2.7) cm. Most patients had clinical stage T1–2 (57.9%, n=307) and PI-RADS score 5 (58.6%, n=310). Table 2 details the concordance between the biopsy global GG and the final RP GG, and the corresponding downgrades and upgrades for GG 1–4. The most prevalent GGs assigned on biopsy were GG 1 (31.3%, n=166) and GG 2 (26.0%, n=138). Overall, 262 patients (49.4%) experienced upgrading at final pathology. The overall incidence of biopsy GG 1 upgrading was 120 (72.3%) of 166 patients, of which most were to GG 2 (50.0%, n=83), followed by GG 3 (12.7%, n=21), GG 4 (6.6%, n=11), and GG 5 (3.0%, n=5). Biopsy GG 3 (47.7%) and GG 4 (44.3%) showed the highest agreements when compared with RP GG. Patients with lower biopsy GG were more likely to harbor upgrading at RP.

ML-Assisted Models

In multivariable analysis, %fPSA (>0.16 vs ≤0.16) (OR=0.52; 95% CI=0.27–0.995; $P=0.048$), apical involvement (No vs Yes) (OR=1.80; 95% CI=1.02–3.19; $P=0.042$) on MRI and biopsy GG 1 ($P<0.001$) were significantly associated with upgrading at RP (Table 3). According to their respective coefficients, the LR model was constructed using the following formula: $Y=2.29-0.65\times(\%fPSA)-0.59\times(\text{apical involvement})-0.97\times(\text{biopsy GG})$ (where Y is the output value of predictive models).

Based on the results of Lasso analysis, those clinical features with coefficients >0.1 were selected as the parameters included in the construction of the Lasso-LR model. Finally, %fPSA, apical involvement, PI-RADS score, clinical T stage, and biopsy GG were the selected features (Figure 1). The Lasso-LR was constructed by using the following formula: $Y=1.81-0.41\times(\%fPSA)-0.25\times$

Table 2 Global Grade Groups on Biopsy and Radical Prostatectomy and Change in Grade

Biopsy GS (GG)	N	GS (GG) at RP (N [% of GS/GG])					Change in Score (N [% of GS/GG])		
		6	3+4	4+3	8	9–10			
		(GG1)	(GG2)	(GG3)	(GG4)	(GG5)	Upgrade	No Change	Downgrade
6 (GG1)	166	46 (27.7)	83 (50.0)	21 (12.7)	11 (6.6)	5 (3.0)	120 (72.3)	46 (27.7)	–
3+4 (GG2)	138	5 (3.6)	58 (42.0)	43 (31.2)	17 (12.3)	15 (10.9)	75 (54.4)	58 (42.0)	5 (3.6)
4+3 (GG3)	111	6 (5.4)	19 (17.1)	53 (47.7)	20 (18.0)	13 (11.8)	33 (29.8)	53 (47.7)	25 (22.5)
8 (GG4)	115	1 (0.9)	8 (7.0)	21 (18.3)	51 (44.3)	34 (29.5)	34 (29.5)	51 (44.3)	30 (26.2)
Total	530	58 (10.9)	168 (31.7)	138 (26.0)	99 (18.7)	67 (12.7)	262 (49.4)	208 (39.2)	60 (11.3)

Abbreviations: GS, Gleason score; GG, Gleason grade group; RP, radical prostatectomy.

Table 3 Factors Associated with Upgrading on Multivariable Logistic Regression Analyses

	Multivariable Analysis	*P*-value
	OR (95% CI)	
Age (years)	0.97 (0.94–1.001)	0.055
PV (mL)	1.004 (0.99–1.02)	0.527
D-max (cm)	0.92 (0.64–1.30)	0.628
TPSA (ng/mL)	1.00 (0.99–1.01)	0.892
%fPSA		
≤0.16	1 (reference)	
>0.16	0.52 (0.27–0.995)	0.048
PSAD		
≤0.20	1 (reference)	
>0.20	1.44 (0.63–3.29)	0.389
PI-RADS score		
<3	1 (reference)	
3	1.87 (0.53–6.53)	0.329
4	2.55 (0.76–8.50)	0.129
5	2.40 (0.69–8.30)	0.167
Apical involvement		
Yes	1 (reference)	
No	1.80 (1.02–3.19)	0.042
Clinical T stage at MRI		
T1–2	1 (reference)	
T3a	2.53 (1.07–5.99)	0.034
T3b	1.67 (0.73–3.79)	0.223
T4	4.41 (0.30–64.07)	0.277
No. of positive cores	1.03 (0.88–1.21)	0.676
Presence of csPCa at core		
Yes	1 (reference)	
No	0.57 (0.20–1.61)	0.285
Presence of core with tumor length >0.6 cm		
Yes	1 (reference)	
No	0.97 (0.40–2.34)	0.944
Maximum tumor length in single core	0.74 (0.29–1.91)	0.535
Total tumor length	1.12 (0.88–1.44)	0.364
Percentage of tumor in total biopsy cores	1.01 (0.97–1.06)	0.557
Biopsy grade group		
1	1 (reference)	
2	0.17 (0.06–0.44)	< 0.001
3	0.04 (0.02–0.12)	< 0.001
4	0.05 (0.02–0.13)	< 0.001

Abbreviations: IQR, interquartile range; PV, prostate volume; D-max, maximum diameter of the index lesion on MRI; TPSA, total prostate-specific antigen; fPSA, free prostate-specific antigen; PSAD, prostate-specific antigen density; MRI, magnetic resonance imaging; csPCa, clinically significantly prostate cancer; PI-RADS, the Prostate Imaging Reporting and Data System.

(apical involvement) − 0.81 × (biopsy GG) + 0.15 × (clinical T stage) + 0.11 × (PI-RADS score) (where *Y* is the output value of predictive model).

In the RFE-SVM analysis, 10 clinical parameters were selected as the final candidates for constructing the predictive model without impacting the prediction accuracy of the model, including biopsy GG, apical involvement, maximum tumor length in single core, %fPSA, PSAD, presence of core with tumor length >0.6 cm, presence of csPCa at core, PI-RADS score, D-max, and clinical T stage (Figure 2A). As depicted in Figure 2B, with the selected features being added to the SVM model one by one, the AUC value of model also increased little by little.

The process of feature selection by RF model and the importance of features are illustrated in Figure 3. Based on different combinations of clinical parameters, each tree in the forest votes for the major classification, and the final classification of the RF model is derived from the majority of these votes (Figure 3A). The best number of trees and the best number of variables tried at each split were 131 and 4, respectively. The out of bag (OOB) estimate of error rate was 33.42%, suggesting that the generalization error was quite unsatisfactory.

Comparison Between ML-Based Models

Among these models, the Lasso-LR model had the highest AUC (0.776, 95% confidence interval [CI]=0.729–0.822), followed by SVM (AUC=0.740, 95% CI=0.690–0.790), LR (AUC=0.725, 95% CI=0.674–0.776) and RF (AUC=0.666, 95% CI=0.618–0.714) (Figure 4A). Similarly, in the testing dataset, the Lasso-LR model had the highest AUC (0.735, 95% CI=0.656–0.813), followed by SVM (AUC=0.723, 95% CI=0.644–0.802), LR (AUC=0.697, 95% CI=0.615–0.778), and RF (AUC=0.607, 95% CI=0.531–0.684) (Figure 4B). The Lasso-LR model illustrated an accuracy of 0.712, a sensitivity of 0.679, and a specificity of 0.745, indicating that this model correctly identified 67.9% of PCa patients who experienced upgrading at RP and 74.5% of PCa patients who did not experience upgrading at RP (Table 4). In addition, the Lasso-LR model had the highest YI (0.424) compared with other models. Due to the fact that the YI was calculated as a summation of the sensitivity and specificity minus 1, the highest YI indicated that both the sensitivity and specificity of the Lasso-LR model are reasonably good relative to other models. Pairwise comparison of ROC curves showed that the AUC of the Lasso-LR model was significantly higher than that of LR (*P*=0.002), while the AUCs of SVM and RF

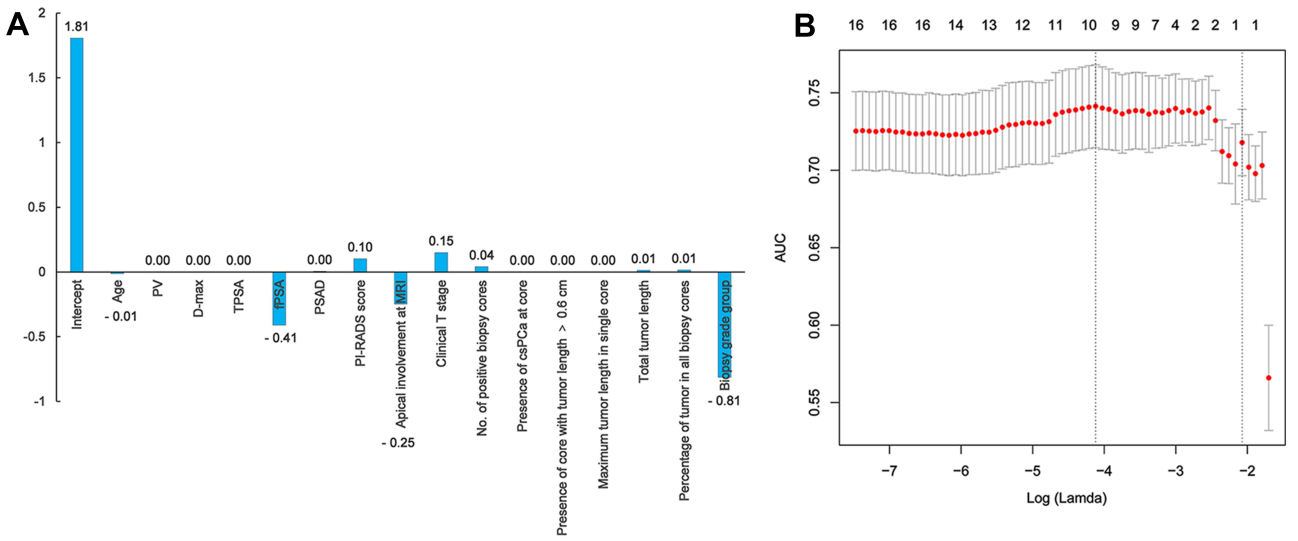


Figure 1 Distribution of feature coefficients estimated by Lasso-LR analysis (**A**) and the optimal features are those with a coefficient >0.1 and produced best accuracy (**B**).
Abbreviations: AUC, area under the ROC curve; PV, prostate volume; D-max, maximum diameter of the index lesion on MRI; TPSA, total prostate-specific antigen; fPSA, free prostate-specific antigen; PSAD, prostate-specific antigen density; MRI, magnetic resonance imaging; csPCa, clinically significantly prostate cancer; PI-RADS, the Prostate Imaging Reporting and Data System.

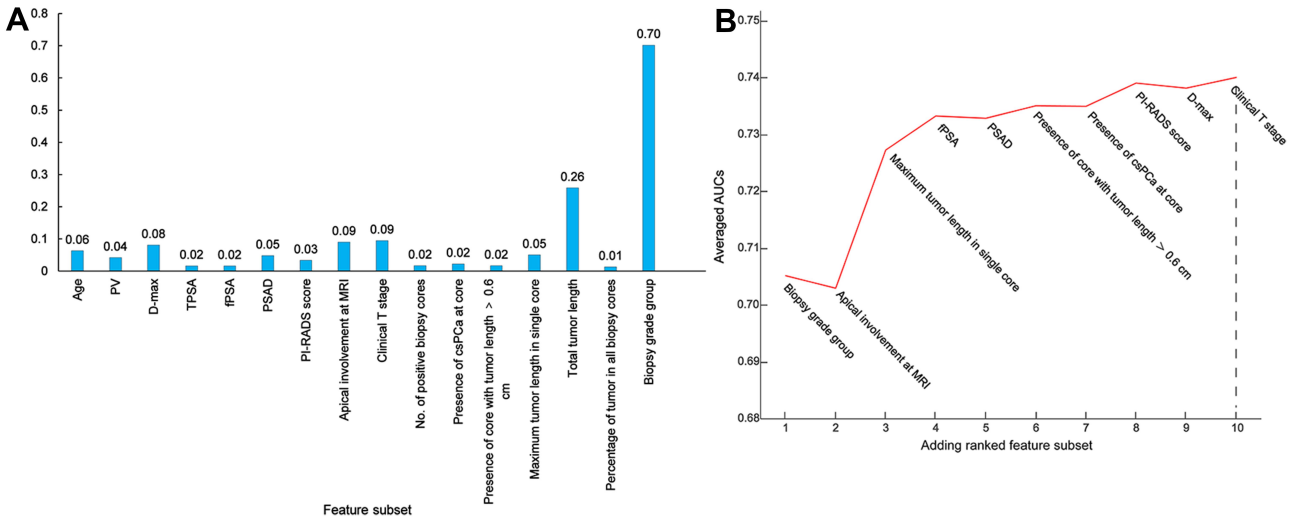


Figure 2 Results of feature selection, feature ranking, and model construction with RFE-SVM analysis. (**A**) Distribution of weight for features with RFE-SVM analysis. (**B**) Influence on AUC with incrementally adding ranked features in RFE-SVM. RFE-SVM classifier is trained by adding ranked feature one by one. The iteration repeated until the desired number of features was reached.
Abbreviations: RFE, recursive feature elimination; SVM, support vector machine; AUC, area under the ROC curve; PV, prostate volume; D-max, maximum diameter of the index lesion on MRI; TPSA, total prostate-specific antigen; fPSA, free prostate-specific antigen; PSAD, prostate-specific antigen density; MRI, magnetic resonance imaging; csPCa, clinically significantly prostate cancer; PI-RADS, the Prostate Imaging Reporting and Data System.

were not significantly different to that of LR (P>0.05) (Figure 4A).

The calibration of ML-based models was evaluated graphically by the formulation of calibration curves (Figure 5). The green line represented the fit of the model. Deviations from the 45° line indicated miscalibration. Part of the green line below the 45° line indicated that higher predicted probabilities might overestimate the true outcome, and part of the green line upon the 45° line indicated that lower predicted probabilities might under-predict the true probability of upgrading. The SVM model was well-calibrated (Figure 5D), followed by Lasso-LR (Figure 5B), RF (Figure 5C), and LR (Figure 5A). Moreover, the bootstrapped DCA also suggested higher net benefits of the

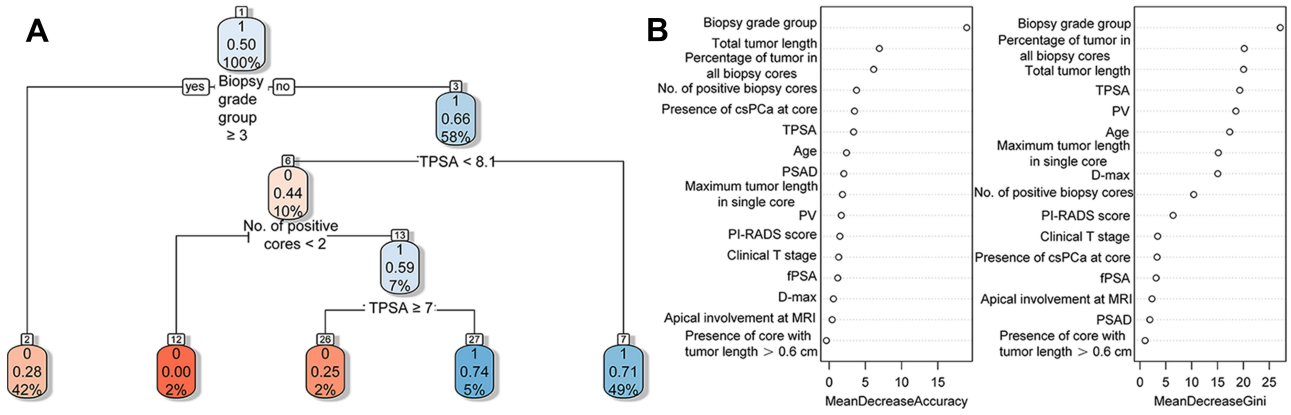


Figure 3 Results of model analysis with RF. (**A**) The detail distribution of classification trees. Orange leaf or node represents the upgrading class (1). Blue leaf or node represents the non-upgrading class (0). The number at the top of leaf or node is the class value, and whichever class occurs the most within the leaf or node will be selected as the class value (0 or 1). The value at the middle of leaf or node is the Gini score, which is a metric that quantifies the purity of the node or leaf. The value at the bottom of leaf or node represents the number of samples. (**B**) The importance of features ranked by mean decrease accuracy and mean decrease Gini.

Abbreviations: PV, prostate volume; D-max, maximum diameter of the index lesion on MRI; TPSA, total prostate-specific antigen; fPSA, free prostate-specific antigen; PSAD, prostate-specific antigen density; MRI, magnetic resonance imaging; csPCa, clinically significantly prostate cancer; PI-RADS, the Prostate Imaging Reporting and Data System.

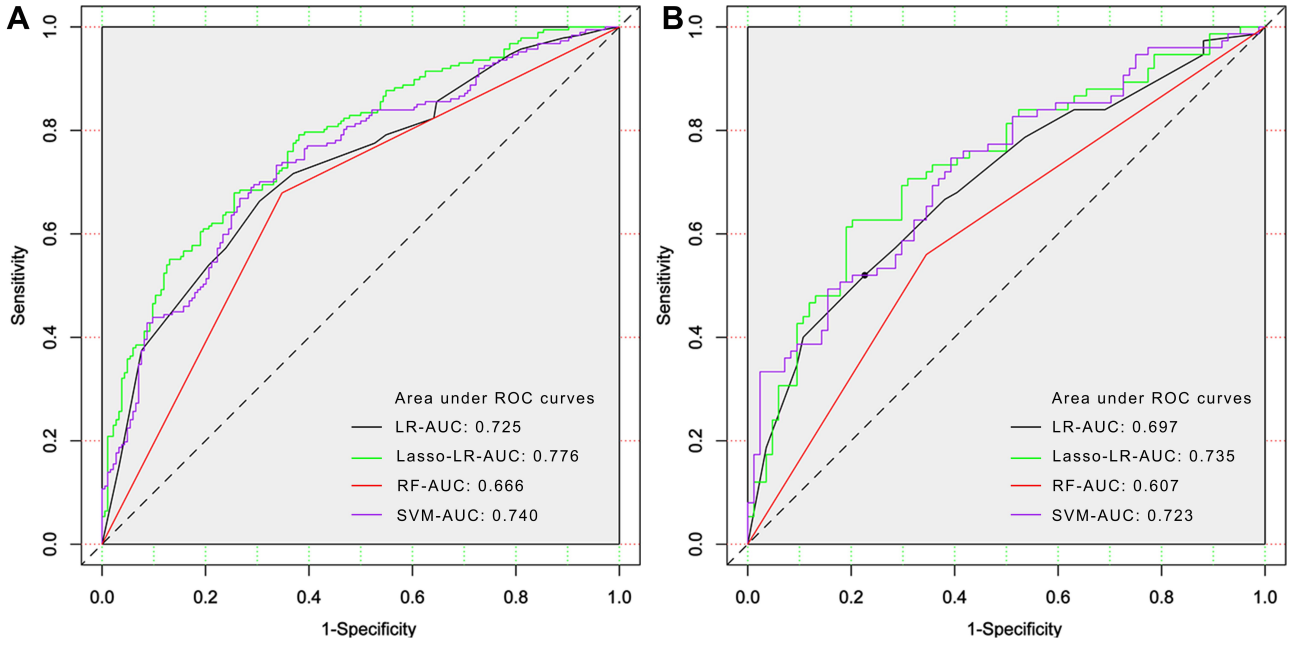


Figure 4 The ROC results of ML-based models in the training dataset (**A**) and testing dataset (**B**).

Abbreviations: ROC, receiver operating characteristic curve; AUC, area under the ROC curve; LR, logistic regression, Lasso least absolute shrinkage and selection operator; SVM, support vector machine; RF, random forest.

three predictive models with threshold probabilities between 30% and 78% for LR, threshold probabilities between 50% and 75% for SVM and threshold probabilities between 30% and 90% for Lasso-LR (Figure 6).

Discussion

Accurate risk stratification, which mainly depends on PSA level, biopsy grade group, and stage classification, plays a pivotal role in guiding treatment management for PCa patients. However, it has been demonstrated that prostate biopsy often underestimates the cancer and incorrectly assigns National Comprehensive Cancer Network (NCCN) risk stratification.[3,4] There are several reasons accounting for the discrepancies between the biopsy and RP grades: sampled cores and indications for biopsy, differences in biopsy techniques, erroneous diagnostic interpretation, tumor heterogeneity,

Table 4 Discrimination of Prediction Models

	LR	Lasso-LR	SVM	RF
Accuracy	0.679	0.712	0.701	0.666
Sensitivity	0.663	0.679	0.668	0.679
Specificity	0.696	0.745	0.734	0.652
YI	0.359	0.424	0.402	0.331
PPV	0.689	0.730	0.718	0.665
NPV	0.670	0.695	0.685	0.667
AUC	0.725	0.776	0.740	0.666

Abbreviations: LR, logistic regression Lasso least absolute shrinkage and selection operator; SVM, support vector machine; RF, random forest; YI, Youden index; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the ROC curve.

sampling error on biopsy, clinician interpretation of the biopsy GG (global vs highest/composite/overall score), and practice variations regarding biopsy grade assignment.[7,16] The incorrect risk stratification may impact treatment planning, patient selection, and decision-making processes. Therefore, it is extremely important to identify risk factors associated with upgrading to avoid under-treatment, especially among those PCa patients who are considered appropriate candidates for AS. Unfortunately, there are currently no widely accepted predictive models to accurately predict the final individualized GG at RP and the discrimination ability of various models remains modest.[17–20] ML has been previously used for predicting outcomes in other fields of medicine, including the identification of lung cancer based on routine blood indices and the in-hospital rupture of type A aortic dissection.[21,22] Given the excellent performance of machine learning algorithms in classification, four machine learning algorithms were employed in our study to determine relevant risk factors; we then developed and validated four novel prediction models to identify those PCa patients at high risk of harboring upgrading at RP before making treatment decisions.

Overall, up to 49.4% included patients were upgraded at RP, especially biopsy GG 1 patients, with the proportion of upgrading being 72.3%. Similarly, Altok et al[23] reported that 70.9% of biopsy GG 1 patients in their study cohort were upgraded at RP, and most were upgraded to GG 2. These observations explain why some patients with GG 1 disease at biopsy suffer metastases or die of prostate cancer and suggest that a substantial proportion of biopsy GG 1 patients who embark on active surveillance are not, in fact, suitable candidates.[24] Given the known risk of underestimation in biopsy specimens, the prediction of GG upgrade plays a major role when considering individualized therapy for PCa patients, especially AS.[25] In our series, %fPSA (>0.16 vs ≤0.16), apical involvement at MRI (No vs Yes), and biopsy grade group (GG 4, GG 3, GG 2 vs GG 1) were independent factors in multivariable LR analysis. %fPSA, apical involvement at MRI, biopsy grade group, and clinical T stage at MRI were significantly associated with upgrading in Lasso-LR and SVM models. However, in a comparable study, Alshak et al[15] demonstrated that only the PI-RADS score was a significant predictor of upgrading. Besides, Gandaglia et al[26] reported that preoperative PSA level, GG at MRI-targeted biopsy, and clinically significant PCa at systematic biopsy were independent risk factors of upgrading at RP. The differences in results between our study and the latter two studies might be due to the fact that the latter two studies did not include detailed core biopsy information, which has been successfully shown to contain huge potential predictive value.

In our study, imaging factors such as apical involvement at MRI and clinical T stage at MRI, were more important predictors than clinical parameters according to the results of ML-based feature ranking analyses, except for RF analysis. This implied that mp-MRI had great potential in predicting upgrading, irrespective of its important role in detecting csPCa and assigning accurate risk stratification for PCa patients. The routine mp-MRI examination for patients with suspected PCa before biopsy was indeed beneficial and helpful.[27] Among those biopsy-related variables, biopsy GG was always the strongest predictor. In the LR and Lasso-LR model, the number of positive cores, presence of csPCa at core, presence of a core with a tumor length >0.6 cm, maximum tumor length in a single core, total tumor length, and percentage of tumor in total biopsy cores demonstrated almost no value in the prediction of upgrading at RP, while the number of positive cores, total tumor length and percentage of tumor in total biopsy cores ranked ahead in the RF model. This is not in line with the findings of Pepe et al.[28] As these features, including D-max, were reliable proxies of tumor volume, the size of tumor should not be considered relevant to the presence of upgrading.[29] Nonetheless, Corcoran et al[16] reported that tumor volume of PCa was a significant predictor of upgrading in multivariable analysis, and the measurement of surrogate of tumor volume might predict those at greatest risk of Gleason score upgrade. One thing to be noted was that the patient cohort in the study of Corcoran et al[16] did not include those patients with biopsy GG 3 and 4. %fPSA outperformed TPSA and PSAD in the prediction of upgrading in the LR, Lasso-LR, and SVM models. On the contrary, in the mean decrease accuracy and mean decrease Gini

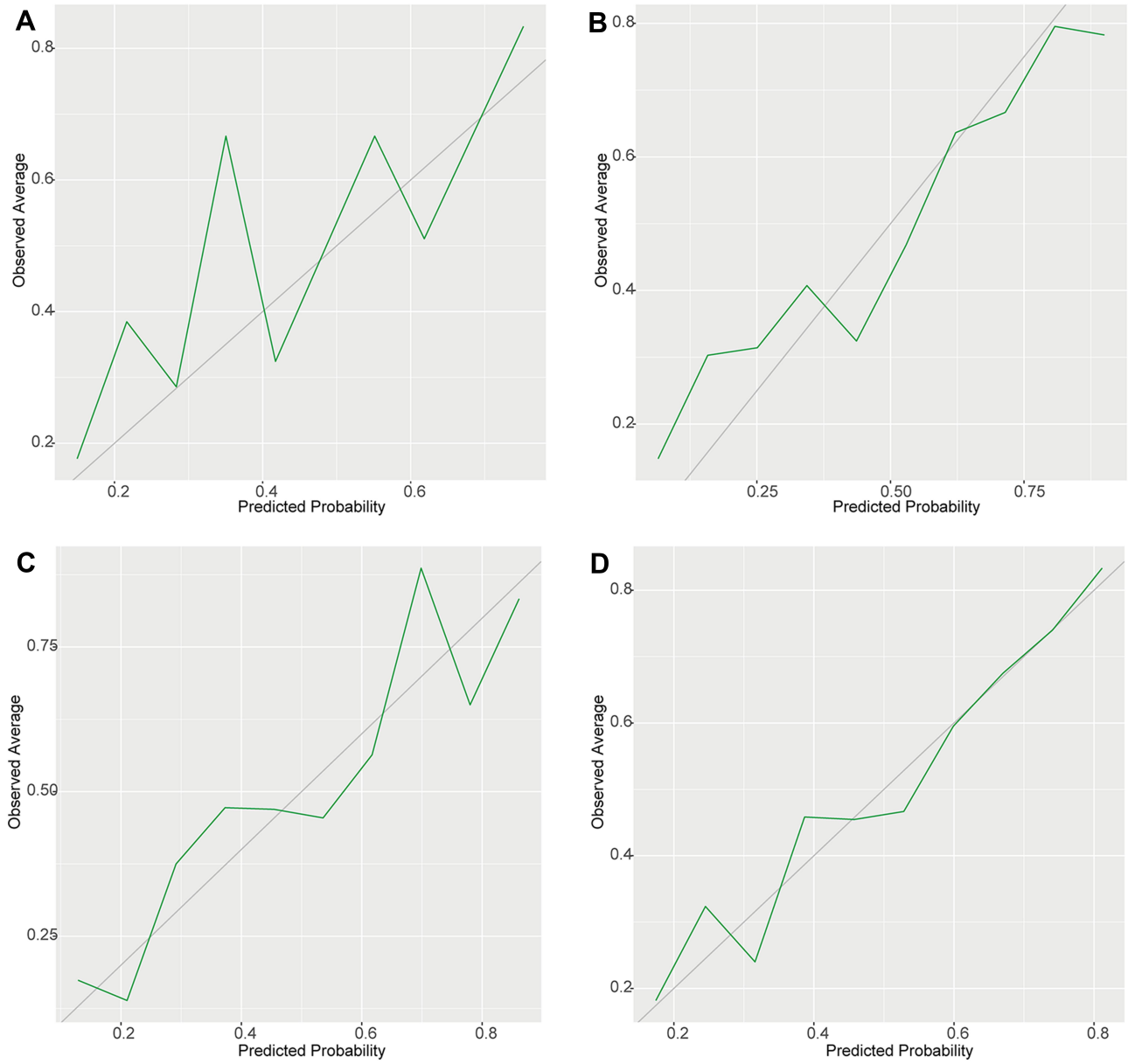


Figure 5 Calibration plots of LR (**A**), Lasso-LR (**B**), RF (**C**), and SVM (**D**).
Abbreviations: LR, logistic regression, Lasso least absolute shrinkage and selection operator; SVM, support vector machine; RF, random forest.

evaluation of RF models, TPSA and PSAD ranked higher than %fPSA. Apart from those variables included in our models, Ferro et al[30–32] have successfully demonstrated that the serum total testosterone level and biomarkers including prostate cancer antigen 3, prostate health index, and sarcosine play an important role in predicting GG upgrading. Regrettably, our center has not yet launched these tests in the management of PCa.

For the performance of ML-based models, the Lasso-LR model showed the best discriminative power with an AUC of 0.776 (95% CI=0.729–0.822), followed by SVM (AUC=0.740; 95% CI=0.690–0.790), LR (AUC=0.725, 95% CI=0.674–0.776), and RF (AUC=0.666; 95% CI=0.618–0.714). The nomogram developed by He et al[33] achieved an AUC of 0.753 in the prediction of upgrading, which was higher than that of LR but lower than Lasso-LR in the present study. Also, Moussa et al[34] constructed a nomogram for predicting the possibility of upgrading, with a concordance index of 0.68. Additionally, all of the ML-based models except for RF outperformed the predictive models constructed by Kulkarni et al[35] and Athanazio et al[7], with AUC values of 0.71 and 0.699 in the respective studies. Of note, in a study consisting of 2,982 PCa patients treated with RP, the model for predicting upgrading based

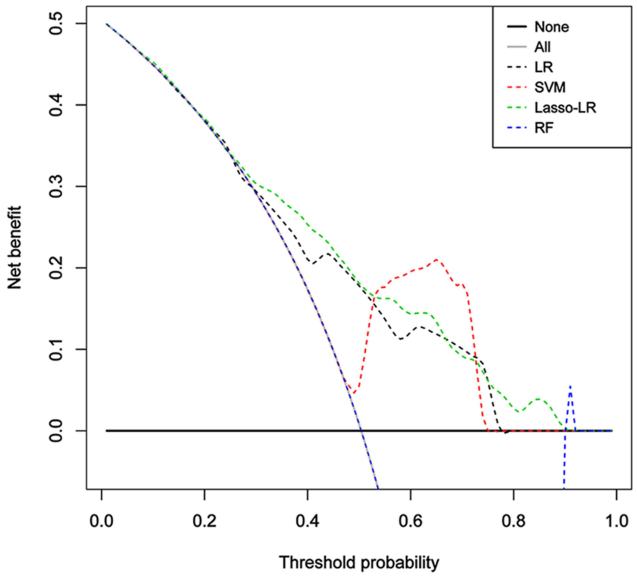


Figure 6 Decision curve analysis for ML-based models.
Abbreviations: LR, logistic regression, Lasso least absolute shrinkage and selection operator; SVM, support vector machine; RF, random forest.

on LR analysis showed a predictive accuracy of 0.804; in contrast, in our study, the Lasso-LR model presented the best predictive accuracy of 0.712.[19] Despite the better predictive accuracy of the model in the study of Chun et al,[19] it was still difficult to determine the model with best performance when compared with our ML-based models as there was no other discrimination metrics such as AUC, sensitivity, specificity, PPV, and NPV in their study. It should be noted that the good performance of our ML-based models might be related to the inclusion of mp-MRI information and detailed biopsy information.

Limitations

Despite several strengths, our study has certain limitations. First, the data on PCa patients who underwent RP enrolled in our study cohort were retrospectively collected at a single institution, which may have resulted in selection bias. Second, the case-level highest Gleason grade group was more commonly assigned to patients undergoing systematic TRUS-guided biopsy in our country; hence, we should also construct predictive models to identify risk factors associated with upgrading using a comparison between the highest biopsy GG and final RP samples. Moreover, we did not include the radiomic features of PCa in the construction of prediction models. Considering that the radiomic features play an important role in the detection of PCa, the inclusion of radiomic features may significantly improve the performance of models.

Conclusions

In summary, we developed four ML-based models to help clinicians identify the individualized risk of upgrading for PCa patients after prostate needle biopsy. The Lasso-LR model had the best discriminative power according to the results of pairwise comparisons. We believe that our research findings can make a significant difference in the process of treatment decision-making by more accurately identifying patients at high risk of harboring upgrading at RP. Of course, further validation in multiple institutions with a large sample size is warranted.

Abbreviations

AS, Active surveillance; AUC, Area under the ROC curve; CI, Confidence interval; csPCa, Clinically significantly prostate cancer; D-max, Maximum diameter of the index lesion on MRI; fPSA, Free prostate-specific antigen; GG, Gleason grade group; IQR, Interquartile range; Lasso, least absolute shrinkage and selection operator; LR, Logistic regression; ML, Machine learning; mp-MRI, Multi-parametric MRI; MRI, Magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; NPV, Negative predictive value; OOB, Out of bag; PCa, Prostate cancer; PI-RADS, The Prostate Imaging Reporting and Data System; PPV, Positive predictive value; PSA, Prostate-specific antigen; PSAD, Prostate-specific antigen density; PV, Prostate volume; RF, Random forest; RFE, recursive feature elimination; SVM, Super vector machine; TPSA, Total prostate-specific antigen; TRUS, Transrectal ultrasonography; YI, Youden index.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest for this work.

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