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Original Article

Prevalence, risk factors, prediction of robust callus formation and accelerated fracture healing in traumatic brain injury patients: a five-year study

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ABSTRACT

Background: Traumatic brain injury (TBI) usually induces robust callus formation at early stage and then subsequent acceleration of fracture union, as supported by both clinical and preclinical studies. However, risk factors and predictive tools to identify TBI patients most likely to experience this accelerated healing response are lacking and subject to future development.This study aimed to study the prevalence, risk factors, and develop machine learning (ML) models to predict robust callus formation and healing acceleration of fractures in TBI patients.

Methods: Between January 2018 and 2023, patients sustaining concomitant TBI and diaphyseal fractures who were admitted into the First Affiliated Hospital of Shantou University Medical College were evaluated retrospectively. The TBI patients were categorized into robust callus formation group (RCF) and normal callus formation group (NCF) based on follow-up radiographic fracture callus index assessments. Risk factors for RCF occurrence were first identified using traditional univariate and multivariate regression model, and predictive models were developed using 12 ML models (including traditional logistic regression model). The performance and interpretations of ML models were evaluated using the area under the receiver operating characteristic curve (AUC) and Shapley Additive Explanations (SHAP).

Results: Of the 723 patients reviewed, 150 cases were enrolled for final analysis. The prevalence of robust callus formation was 40.67 % (61/150) with significantly wider callus index (2.01 ± 0.61 vs 1.17 ± 0.12, $P < 0.001$) and acceleration in time to initial callus formation (22.92 ± 11.98 days vs 90.18 ± 34.52 days, $P < 0.001$). Brain contusions (OR 5.914, 95 % CI:2.479–14.108,$P < 0.001$), greater TBI severity levels evaluated using Glasgow Coma Scale (GCS, OR 3.074, 95 % CI:1.149–8.222,$P = 0.025$) and Marshall CT classifications (OR 2.845, 95 % CI:1.095–7.390,$P = 0.032$) were identified as independent risk factors for RCF occurrence. The gradient boosting

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decision tree (GBDT) algorithm demonstrated optimal predictive performance using TBI-specific variables, achieving an AUC of 0.86 ± 0.03. SHAP analysis revealed brain contusion, GCS scores, and Marshall CT classification scores as the three most influential clinical features.

Conclusions: For the first time, this study provided the prevalence and risk factors contributing to RCF occurrence in TBI patients with combined diaphyseal fractures, and also developed ML models for its prediction, for which it may optimize orthopedics treatment strategies and decision making in these unique set of TBI patients.

The translational potential of this article: The findings from this study offer crucial insights to enhance clinical decision-making and treatment approaches for managing fractures in TBI patients. Furthermore, our research establishes a groundwork for future investigations into the mechanisms linking TBI and enhanced osteogenesis, potentially aiding in addressing intricate bone regeneration obstacles like non-unions and critical-size defects.

1. Introduction

Both TBI and fracture are common forms of trauma-related injuries contributing to high mortality and disability [1]. Interestingly, the acceleration of fracture union, characterized by robust fracture callus formation in the early stage, is frequently encountered in clinics [2–4]. This intriguing occurrence has drawn significant interest within the orthopaedic community and initiated quest on investigation of its underlying mechanisms, which may offer promise for translation of innovative treatments to enhance fracture healing and prevent fracture non-union. Previous studies have enrolled fracture populations without TBI as control groups, none has specifically focused on the cases with combined TBI and fracture(s) as the main study population [5,6]. As a result, the incidence, identification of risk factors and TBI patterns associated with accelerated fracture healing within the TBI patients, is insufficient. This also leads to a lack of predictive ability for these cases, hindering the provision of an optimal time window for orthopaedic intervention and the selection of the appropriate treatment strategy. For instance, in TBI patients, the acceleration of fracture healing may result in much earlier formation of bridging calluses, which could already be observed on the operating table or before adequate reduction, potentially leading to malalignment.

In recent years, as machine learning has advanced in the medical field, many promising algorithms have emerged. The traditional logistic regression model commonly used in medical research is also a type of machine learning model. However, the main limitations of traditional logistic regression model are their restricted modeling capabilities, susceptibility to overfitting, and lack of interpretability [7]. while emerging machine learning algorithms like gradient boosting decision tree (GBDT) better overcome these shortcomings, making them more powerful and practical predictive modeling tools [8]. GBDT is a highly accurate and flexible algorithm that excels at handling non-linear relationships and feature selection. It also provides excellent model interpretability through SHapley Additive exPlanations (SHAP) analysis, making it an ideal choice for developing high-performance predictive models [9]. Research on using ML models to predict robust fracture callus formation and accelerate fracture healing in TBI patients is however lacking.

To fill this gap in existing studies, this five-year retrospective study was conducted in a teaching hospital at a city with highest motorcycle ownership and its traffic accidents in China, to representatively screen for polytrauma subjects demonstrating this unique clinical manifestation. Here, its prevalence, potential risk factors were investigated, and 12 kinds of ML models (including traditional logistic regression model) were further developed based on TBI variables that can be assessed in routine clinical work to enhance prompt and appropriate treatment strategy in this population suffering from TBI and bone fractures. The models with the highest predictive accuracy (based on AUC) were selected and compared with the result of traditional logistic regression model. Each feature in this model was subsequently subjected to a quantitative assessment of its contribution. This research may therefore provide clinicians with a solid therapeutic rationale and actionable recommendations.

2. Methods

2.1. Study design and patient selection

This is a single center retrospective study that reviewed data from admitted patients with traumatic brain injury presenting with concomitant fracture(s), which enrolled those with TBI of all severities from August 2018 to August 2023. The institutional review board of the ethics committee at First affiliated hospital of Shantou University approved this study (B-2023-106). Informed consent was waived by the IRB per the Declaration of Helsinki (2013), Article 32, as this study involved secondary analysis of electronial health records, with justification for no additional risk to participants, and obtaining consent was impracticable due to the difficulty to re-contact patients treated across over a 5-year period in TBI patients with low prognosis and high mortality. This study is part of the multi-phase "TBI Fracture" project which includes retrospective, prospective clinical and preclinical studies to investigate the risk factors and underlying mechanism of "accelerated fracture healing accompanied with TBI".

Inclusion criteria were: (1) patients' age from 18 to 55; (2) patient diagnosed with TBI with or without skull fractures, intracranial hemorrhages, and brain contusions; (3) diaphysis fractures at the upper and lower limb including the femur, tibia, humerus, ulnar, radius, and at the clavicle; (4) fraction fixation methods: cast, external fixation, internal fixation with intramedullary nails and/or plates and screws; (5) patient follow up period of at least 6 months. Exclusion criteria: (1) concomitant vertebral fractures and/or spinal cord injuries; (2) concomitant pelvic fractures, pathological fractures, infections, open fractures; (3) medical history of endocrinal diseases and/or use of steroids; (4) medical history of anti-osteoporosis regimens (denosumab, RANKL inhibitors, teriparatide, etc.); (5) patient with incomplete clinical and radiographical data, loss of follow up (Fig. 1).

Data extracted for analysis comprised demographics, admission details acquired during the acute stages of the initial injury, operations and procedures, fracture fixation modalities, and discharge information. The severity of the injury was assessed upon admission using the Glasgow Coma Scale (GCS) scores and classified into three categories: mild (GCS = 13–15), moderate (GCS = 9–12), severe traumatic brain injury (TBI) (GCS = 3–8) [10].The presence of intracranial abnormalities was identified from the first computed tomography (CT) scan and were further classified according to the Marshall CT classification system [6]. Glasgow Coma Scale (GCS) scores were assessed by the admitting physician during the initial clinical evaluation on the day of injury. Marshall CT classification was determined by a board-certified radiologist based on the initial trauma imaging.TBI variables were further examined, including the site of contusions, presence of bilateral and unilateral contusions, hematoma types including subdural hematoma (SDH), epidural hematoma, subarachnoid hematoma, and multiple hematomas (where two or more hematoma types were present in each patient). Presence of skull fractures and any neurosurgical procedures performed before orthopedic intervention were also obtained.

The main outcome measures for fracture healing response after TBI were the time to initial callus formation based on serial radiographs on anteroposterior and/or lateral radiographs and widest callus index

during follow-up. Callus index was measured as the widest diameter of the callus divided by the diameter of the bone at or adjacent to the fracture site (Fig. 2F), according to previously published method described by Spencer [11]. For the purposes of this investigation, robust callus formation (RCF) was defined as fracture callus index equal to or greater than 1.4, which is the callus index value of fracture injury without TBI from previous studies [5,12]. All radiographic reviews and measurements on fracture(s) prior and after orthopedic intervention were performed by two independent senior-level orthopedic surgeons (ZY.J, JC.C). Further, surgical records were also thoroughly reviewed for observation of RCF occurrence found during surgery. These cases were further allocated into the RCF group and radiographical measurements were excluded from analysis as observations of "robust callus formation" were absent during follow-up after callus removal for implant placement.

2.2. Statistical analysis

Statistical analysis was performed by SPSS 28.0 (IBM) and GraphPad Prism 10.0 (GraphPad Software Inc.) software. Descriptive analysis used count and proportion or mean and standard deviation, as appropriate. The continuous variables were distributed using either the t-test, as mean ± SD. The categorical variables were analyzed using the $\chi 2$or Fisher's exact test. To assess the association between TBI and robust fracture callus formation in the study population, we performed binary logistic regression for univariate analysis to screen for the potential risk factors from TBI injury variable(s), brain CT abnormalities for patients with RCF, and all variables with statistical significance were further enrolled into multivariate logistic regression models for adjustment of confounding factors using step-wise (forward selection) method. Odds ratios (OR) for each variable were reported with corresponding 95 % confidence intervals (CI). For all tests, two-sided P value < 0.05 were considered as statistically significant.

2.3. Machine learning and predictive model development

To compare the traditional logistic regression model, this study introduces a tree-based model and some other common machine learning models, including the following 12 models: Linear Discriminant Analysis, Gaussian Naive Bayes, Multinomial Naive Bayes Classifier, SVM Classifier, K-Neighbors Classifier, Decision Tree Classifier, Random Forest, GBDT (Gradient Boosting Decision Tree) Classifier, AdaBoost Classifier, XGBoost, and Neural Network (MLP). These models were used to make predictions of fracture healing after TBI. To determine the optimal feature subset for each model, this study used the recursive feature elimination (RFE) method. RFE involved training the models multiple times, using a different number of features in each round, and recording the performance on the test set. The optimal feature combination was then selected based on the corresponding evaluation metrics. After completing the feature selection, this study employed grid search to tune the model hyperparameters and maximize the evaluation metrics. The feature selection process was then repeated with the updated parameters. This iterative process continued until the results of the feature screening no longer changed. At this point, the model parameters and feature combinations were considered the optimal configuration for the current model.

2.4. Cross validation

To avoid the effect of data partitioning randomness on model evaluation, this study used the 5-fold cross-validation method. A total of 150 samples were randomly divided into five groups. When evaluating each model, four groups were used as the training set, and the remaining group was used as the test set. The final evaluation result was the average of the five tests.

3. Results

3.1. Demographics and incidence of RCF

The flow chart of patient screening process is shown in Fig. 1. We identified a total of 723 patients with concomitant TBI and fracture between 2018 and 2023 at the first affiliated hospital of Shantou University Medical College. Of these, 150 patients (mean age = 37.67 ± 9.17; 113 (75.33 % males) met the criteria for inclusion for our preliminary analysis. 61 patients (40.67 %) developed robust callus formation with a wider callus index of 1.91 ± 0.62 than patients without presence of RCF (n = 89, callus index = 1.17 ± 0.12) during follow-up.

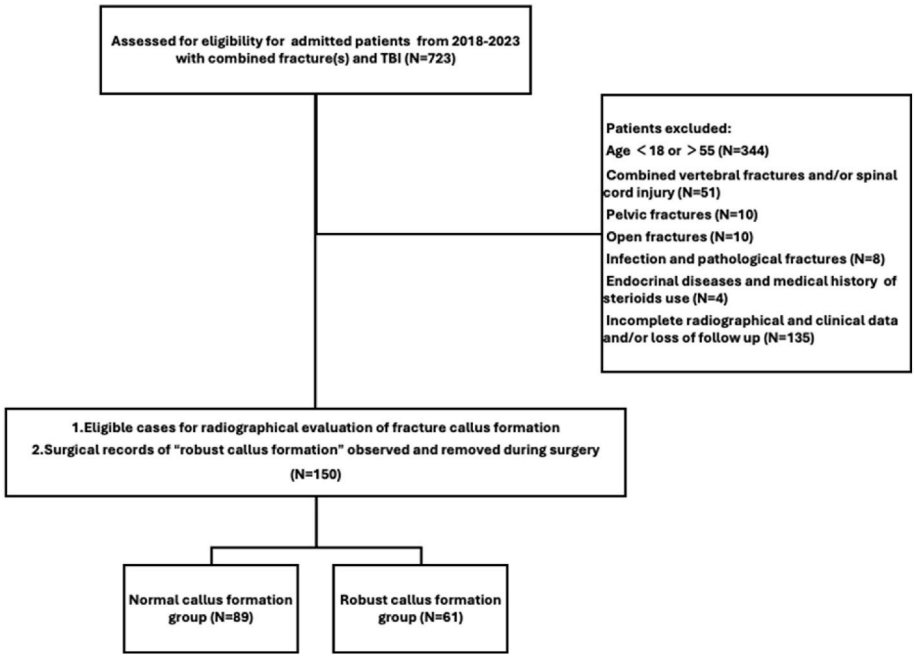

Fig. 1. Data acquisition and fracture callus assessments.

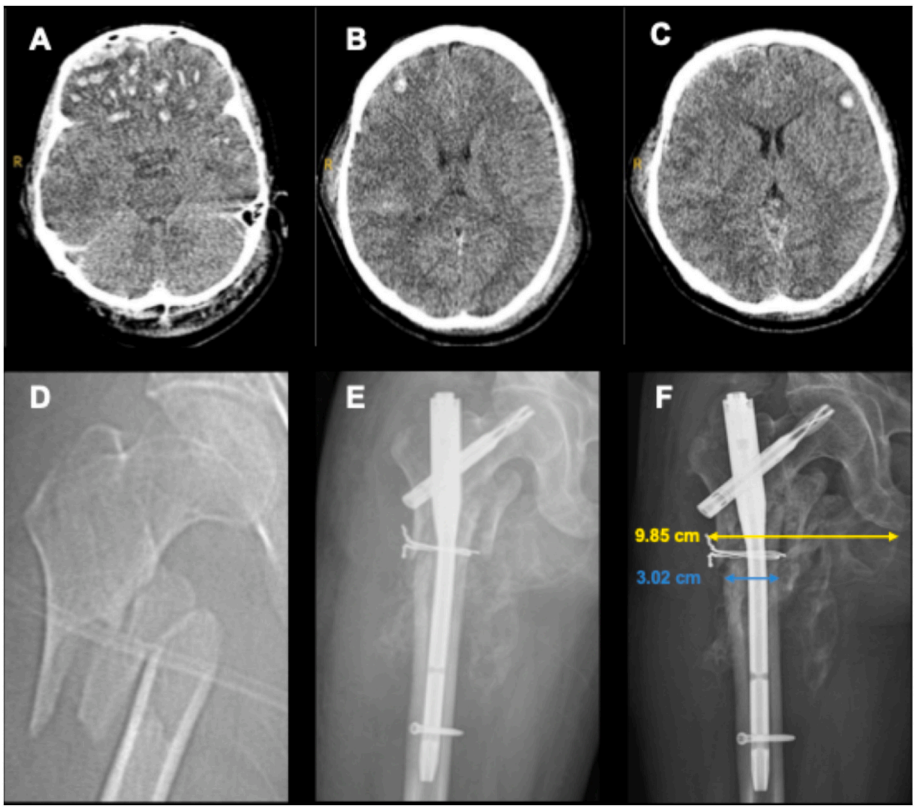

Fig. 2. Representative case and callus index calculation. A 45-year-old male, an electric moped cyclist, sustained polytrauma with a traumatic brain injury (GCS = 9). Brain CT upon admission showed multiple brain contusions involving the bilateral frontal lobe, temporal lobe, and parietal lobe (A–C), along with a comminuted right femur fracture(D). The surgical notes indicated the observation of robust callus formation at 22 days after initial injury, and radiographs taken at 1 months (E) and 2 months (F) follow-up showed widest callus index of 3.26. Callus index is calculated by the widest diameter of the callus (yellow arrow) divided by the diameter of the bone at or adjacent to the fracture site (blue arrow).

Among those, 9 additional RCF cases were enrolled after reviewing surgical records, where robust callus formations were accidently found and later removed during surgical implantation for internal fixators, where the mean time to fracture callus formation was 14.67 ± 2.29 days and the occurrence of RCF were not observed on radiographs during later follow-up. Overall, the mean time to initial callus formation was also significantly shorter in RCF group (22.92 ± 11.98 days) than patients without RCF (90.18 ± 34.52 days, $P < 0.001$), demonstrating acceleration of fracture healing in the RCF group (Fig. 3).

Patients' age (39.40 ± 10.14 vs 37.18 ± 12.09) and gender (Male = 71.91 % vs 80.33 %) were comparable between the NCF and RCF groups. The most common cause of injury were road traffic accidents (70 %) due to motorcycle accidents (58.67 %). The clavicles (60.67 %) and the femurs (21.33 %) were two most frequently injured fractures sites for both groups, and no significant difference were found in fracture fixation methods among NCF group and RCF group. Further, significant higher proportion of RCF patients required neurosurgical procedures (39.34 % vs11.24 %, $P < 0.001$) prior orthopedic surgery, significantly longer time to orthopedics surgery (16.67 ± 7.33 days vs 10.13 ± 4.57 days, $P < 0.001$) and longer total hospital stay (43.00 ± 26.57 days vs 27.99 ± 24.78 days, $P < 0.001$) were also observed. The patients' baseline demographics and clinical data are shown in Table 1.

3.2. TBI risk factors for robust callus formation

Based on univariate analysis of CT findings of TBI variables (Table 2),

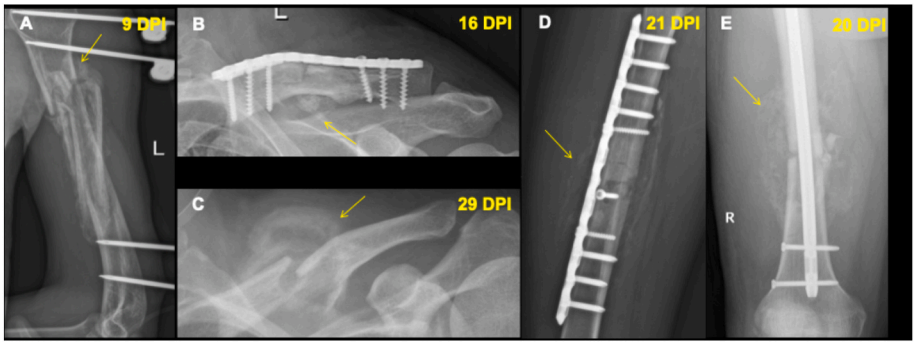

Fig. 3. Representative cases that show that time to initial visible callus formation is accelerated in patients accompanied with TBI at multiple fracture site including (A) humerus shaft fracture treated with external fixators at 9 DPI, (B) clavicle fractures treated with plates or (C) conservatively at 16 DPI and 29 DPI respectively, and the femur shaft fractures treated with (D) locking plate or (E) intramedullary nail at 21 DPI and 20 DPI respectively. DPI: day(s) post injury.

Table 1
Demographics, fracture injury characteristics and outcome in TBI patients.

	Total	NCF	RCF	*P* value
Patients #	150	89 (59.33 %)	61 (40.67 %)	
Age (year)	37.67 ± 9.17	39.40 ± 10.14	37.18 ± 12.09	0.22
Male (%)	113 (75.33 %)	64 (71.91 %)	49 (80.33 %)	0.24
Cause of injury				0.068
Road traffic incident	105 (70 %)	61 (67.41 %)	44 (72.13 %)	
Vehicles	20 (13.33)	16 (17.98 %)	4 (6.56 %)	
Motorcycles	88 (58.67 %)	47 (52.81 %)	40 (65.58 %)	
Incidental fall	30 (20.00 %)	21 (23.59 %)	10 (16.39 %)	
Unspecified	12 (8.00 %)	5 (5.62 %)	7 (11.48 %)	
Fracture sites				**<0.001**
Clavicle	91 (60.67 %)	67 (75.28 %)	24 (39.34 %)	
Femur	32 (21.33 %)	7 (7.86 %)	25 (40.98 %)	
Tibia	14 (9.33 %)	9 (10.11 %)	5 (8.19 %)	
Others (humerus, fibula, ulnar)	13 (8.67 %)	6 (7.74 %)	7 (11.47 %)	
Fixation methods				0.0921
Plates	133 (88.67 %)	80 (89.88 %)	50 (81.97 %)	
Intramedullary nail	4 (2.67 %)	4 (4.49 %)	3 (4.92 %)	
Cast or external fixators	13 (8.67 %)	5 (5.62 %)	8 (13.11 %)	
Neurosurgical procedures	34 (22.67 %)	10 (11.24 %)	24 (39.34 %)	**<0.001**
Time to orthopedic surgery	11.62 ± 5.18	10.13 ± 4.57	16.67 ± 7.33	**<0.001**
Total hospital stays	27.24 ± 27.63	27.99 ± 24.78	43.00 ± 26.57	**<0.001**
Fracture callus index	1.48 ± 0.56	1.17 ± 0.12	2.01 ± 0.61	**<0.001**
Time to callus formation	81.67 ± 33.50	90.18 ± 34.52	22.92 ± 11.98	**<0.001**

the prevalence of following findings was associated with occurrence of RCF, including the lower GCS scores, higher Marshall CT classification scores, brain contusions, frontal and temporal lobe lesions, subdural hematoma (SDH), epidural hematoma (EDH), subarachnoid hematoma (SAH), and multiple type hematomas.

TBI-specific variables included in the multivariate analysis are shown in Table 2. TBI patients with brain contusions had 5.914 (95 %CI: 2.479–14.108) time the risk of developing RCF compared to those without. Further, TBI patients with a GCS score of 3–12 (moderate to severe injury) had 3.074 (95 %CI: 1.149–8.222) times the risk of RCF compared with patients with mild TBI, and patients with Marshall CT classification higher than III had 2.845 (95 % CI:1.095–7.390) times the risk of RCF than patients with lower-level Marshall CT grades.

3.3. Machine learning

As shown in Table 3, the evaluated algorithms included logistic regression, linear discriminant analysis, quadratic discriminant analysis, Gaussian naive Bayes, multinomial naive Bayes, support vector machine (SVM), k-nearest neighbors, decision tree, random forest, gradient boosting decision tree (GBDT), AdaBoost, and XGBoost, all applied to predict robust callus formation (RCF) and accelerated fracture healing (AFH) in TBI patients. When compared against traditional logistic regression using AUC as the primary performance indicator, the GBDT model demonstrated superior predictive capability with an AUC of 0.86 (95 % CI: 0.83–0.89) versus 0.81 (95 % CI: 0.78–0.83) for logistic regression. Fig. 4 displays the ROC curves for both models on the test set, with annotation thresholds indicating optimal performance probabilities. Table 3 additionally presents feature counts, accuracy metrics, and four principal confusion matrix parameters: sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The GBDT model's outperformance of other machine learning approaches suggests particular efficacy in handling nonlinear relationships within this dataset.

Calibration curves assess the reliability of model-derived probability estimates by quantifying potential overconfidence or underconfidence in predictions, thereby enabling model optimization and enhanced decision-making capacity. Probability calibration curves were employed to evaluate model performance, with ideal calibration manifesting as alignment along the diagonal reference line (Fig. 5). The GBDT demonstrated superior calibration fidelity, while the logistic regression classifier exhibited substantial deviation from the reference standard.

Table 2
Univariate and multivariate and TBI-specific risk factors for robust callus formation occurrence.

	Total	NCF	RCF	*P* value[a]	OR (95 %CI)	*P* value[b]
GCS score	12.09 ± 3.77	13.54 ± 2.73	9.98 ± 4.10	**<0.001**	**3.074(1.149–8.222)**	**0.025**
Mild (13–15)	93(62.00 %)	70(78.65 %)	23(37.70 %)			
Moderate (9–12)	22(14.67 %)	10(11.24 %)	12(19.67 %)			
Severe (3–8)	35(23.33 %)	9(10.11 %)	26(42.62 %)			
Marshall CT classification				**<0.001**	**2.845(1.095–7.390)**	**0.032**
<III	93(62.00 %)	71(79.77 %)	22(36.07 %)			
>III	57(38.00 %)	18(20.23 %)	39(63.93 %)			
Brain contusions	90(60.00 %)	39(43.82 %)	51(83.61 %)	**<0.001**	**5.914(2.479–14.108)**	**<0.001**
Site of contusion						
Frontal lobe	60(40.00)	21(21.21 %)	39(63.93 %)	**<0.001**		0.081
Temporal lobe	68(45.33 %)	30(33.71 %)	38(62.30 %)	**<0.001**		0.721
Parietal lobe	18 (12.00 %)	8(8.99 %)	10(16.39 %)	0.17		
Occipital lobe	11(7.33 %)	3(3.37 %)	8(13.11 %)	0.05		
Hematomas						
Multiple	81(54.00 %)	37(41.57 %)	44(72.13 %)	**<0.001**		**0.353**
SDH	100(66.67 %)	50(56.18 %)	50(81.97 %)	**<0.001**		0.136
EDH	38(25.33 %)	16(17.98 %)	22(36.07 %)	**0.01**		0.233
SAH	82(54.67 %)	42(47.19 %)	40(65.57 %)	**0.03**		0.502
Skull fracture(s)	105(70.00 %)	58(65.17 %)	47(77.05 %)	0.12		

Note. OR:odds ratio; CI: Confidence interval.
P value[a] was calculated with t-test or Chi-square test.
P value[b] was calculated with logistic regression analysis.

Table 3
5-fold cross validation yielded the average scores of the patient models.

Classifier	n features	AUC	ACC	SEN	SPE	PPV	NPV
Logistic Regression Classifier	12	0.8074 ± 0.0232	0.78 ± 0.034	0.6554 ± 0.0658	0.8615 ± 0.0388	0.7588 ± 0.0721	0.7794 ± 0.0724
SGD	18	0.8081 ± 0.0179	0.6933 ± 0.0389	0.725 ± 0.1263	0.6785 ± 0.126	0.6105 ± 0.1332	0.7859 ± 0.0767
Linear Discriminant Analysis	9	0.8317 ± 0.0246	0.7467 ± 0.034	0.6268 ± 0.065	0.8223 ± 0.0636	0.6929 ± 0.1335	0.764 ± 0.0522
Quadratic Discriminant Analysis	7	0.8392 ± 0.0734	0.76 ± 0.049	0.6264 ± 0.1321	0.8669 ± 0.075	0.7758 ± 0.1469	0.7619 ± 0.1023
Gaussian NB	7	0.8516 ± 0.0251	0.7533 ± 0.034	0.6753 ± 0.0653	0.813 ± 0.0684	0.7017 ± 0.1265	0.7807 ± 0.0735
Multinomial Nave Bayes Classifier	12	0.8326 ± 0.0463	0.74 ± 0.0442	0.6093 ± 0.0921	0.8485 ± 0.0484	0.7225 ± 0.1164	0.7518 ± 0.1011
SVM Classifier	9	0.8176 ± 0.011	0.7467 ± 0.0452	0.615 ± 0.0814	0.8485 ± 0.0484	0.7178 ± 0.132	0.7565 ± 0.086
Kneighbors Classifier	9	0.8491 ± 0.0157	0.7733 ± 0.0133	0.5885 ± 0.0975	0.8893 ± 0.0459	0.7662 ± 0.1437	0.7638 ± 0.054
Decision Tree Classifier	14	0.697 ± 0.0549	0.7067 ± 0.0646	0.6851 ± 0.0781	0.7089 ± 0.1413	0.6268 ± 0.0863	0.7585 ± 0.0775
Random Forest	7	0.7897 ± 0.0347	0.7067 ± 0.0249	0.6211 ± 0.0483	0.7645 ± 0.0615	0.6369 ± 0.1183	0.7431 ± 0.0784
GBDT (Gradient Boosting Decision Tree) Classifier	8	0.8623 ± 0.0319	0.78 ± 0.0163	0.6286 ± 0.0837	0.8831 ± 0.0664	0.7671 ± 0.1596	0.7798 ± 0.0555
AdaBoost Classifier	12	0.8354 ± 0.0368	0.76 ± 0.0389	0.6315 ± 0.093	0.8504 ± 0.0492	0.7215 ± 0.16	0.7741 ± 0.0706
XGBoost	7	0.8023 ± 0.0233	0.74 ± 0.0389	0.5914 ± 0.0291	0.8435 ± 0.0549	0.7131 ± 0.1073	0.7452 ± 0.0797

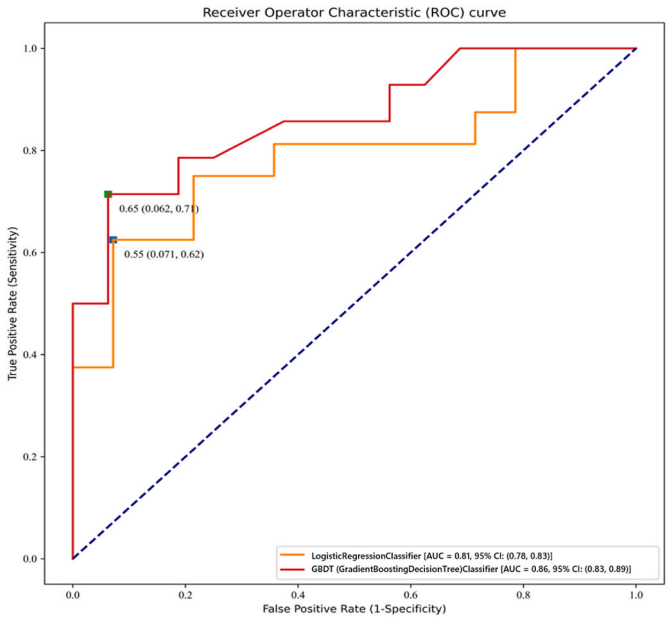

Fig. 4. ROC curves from traditional logistic regression and GBDT on the test group for robust callus formation occurrence in TBI patients.

These findings collectively indicate that the GBDT model maintains strong calibration alignment with the observed outcome distribution.

3.4. Model interpretation

SHAP values represent a game theory-based explanatory framework for machine learning models, quantifying individual feature contributions to predictive outcomes through additive feature attribution. This analysis enhances model interpretability by elucidating the decision-making mechanisms of the GBDT algorithm. We employed SHAP analysis to evaluate feature importance in the optimized GBDT model (post-feature selection) and compared these results against multivariate logistic regression outputs. Fig. 6A displays the beeswarm plot of the 8 selected features, where the x-axis represents SHAP values - positive values indicating increased probability of RCF occurence and negative values corresponding to reduced likelihood. Feature ranking by mean absolute SHAP values identified brain contusion, Marshall CT classification, and GCS scores as the three most influential predictors. Fig. 6B presents the waterfall plot demonstrating individual prediction decomposition, visually mapping how each feature contributes to final model outputs for representative cases.

4. Discussion

This is the first clinical study to investigate the prevalence and TBI-specific risk factors for the occurrence of RCF and accelerated fracture healing in patients with combined TBI and fracture injuries. The presence of RCF after TBI has been noted for a long time in orthopaedic community. The mechanisms behind such magnificent clinical phenomenon may inspire discovery of novel biological factors or signaling pathways to improve fracture healing and prevent non-union of fractures [13–16]. This study provides clinical evidence for the first time that demonstrates a direct association between TBI severity, brain contusion incidence, and accelerated fracture callus formation, thereby advancing our understanding of the systemic interplay between neurotrauma and skeletal repair mechanisms.

The traditional logistic regression model showed that brain contusions, greater TBI severity measurement including lower GCS scores, and higher Marshall CT classification are independent factors for RCF and AFH in TBI patients, which are also among the top 3 contributing features in the GBDT models. Our study has identified the brain contusions as independent risk factor for RCF occurrence after TBI. This seems to support the classic hypothesis of accelerated fracture healing in TBI, suggesting that the release of osteogenic factors from the injured brain tissue into peripheral fracture microenvironment may be a key mechanism. Based on this hypothesis, after confirming the osteogenic effect of TBI patients' serum and cerebral spinal fluid [12,17–20], clinical and preclinical studies have proposed myriads biological cytokines including neuropeptides, exosomes with or without mi-RNAs, hormones, and other humoral proteins after TBI that can induce osteogenesis of bone marrow stem cells and osteoblast cell lines in vitro [21–25]. This finding is also in line with current animal models, where accelerated fracture healing has been demonstrated in rodent studies with cortical brain contusions [14,21,26,27]. However, high-quality evidence is still lacking to determine the main contributing brain-derived biological factor and further linking its connection to its downstream target cell population and molecular mechanisms behind this phenomenon and potential translation into clinical practice [28]. We observed the incidence of RCF following combined TBI and fracture injury was 40.67 %, and occurred across multiple fracture sites, including the femur, the clavicle, tibia, humerus, which were also independent of fracture fixation methods. These findings are consistent with that of previously published studies [6,29–31]. Its incidences are associated with risk factors related to greater TBI severity, as indicted by GCS scores, and Marshall CT classification at admission. These risk factors also echo with the other findings of our current study, including the higher rate of requirement of neurosurgeries, longer duration prior orthopedics intervention, and overall mean duration of hospital stay found in TBI patients demonstrating robust callus formation (Table 1). There are many limitations of traditional logistic models to handle complex data. To achieve better

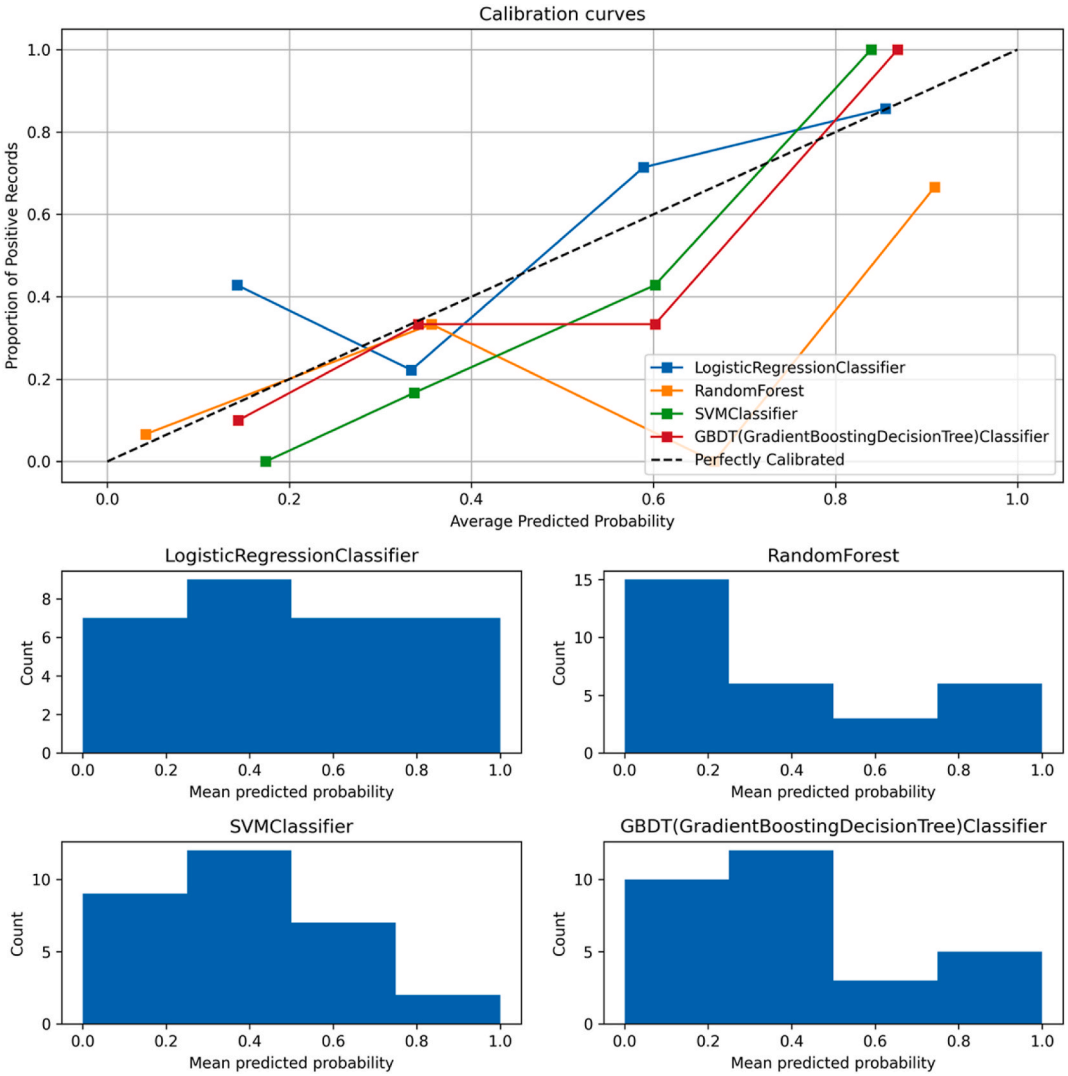

Fig. 5. The horizontal coordinate is the predicted probability and below the black standard line indicates that the predicted value is greater than the actual (or observed) value, i.e. the risk is overestimated. Therefore, a better model was defined as that around the standard line.

prediction accuracy than traditional statistical models, we tested various classical machine learning models using research data and compared them with traditional logistic models. Finally, we found that the GBDT model demonstrated excellent data handling and prediction accuracy (AUC) compared to the traditional logistic regression model and other ML models. The GBDT model had an AUC of 0.86 (95 % CI: 0.83–0.89), while the logistic regression model had an AUC of 0.81 (95 % CI: 0.78–0.83). The SHAP analysis effectively mitigated the black-box effect of the GBDT model and showed how much each feature contributes to the model's predictions [9].

Previous study reported a trend of SDH over other types of extra cranial and incra-axial hematoma associated with RCF occurrence under TBI scenario [32]. In this study, presence of SDH, EDH, SAH were all higher in RCF group and those with multiple types of hematomas, suggesting no isolated type of hematoma type are strongly associated with robust callus formation and accelerated fracture healing in TBI scenario. The clinical features of TBI injury is complex and potentially difficult to interpret, we suspect higher motorcycle accidents (65.58 %) found in RCF group lead to a greater severity in TBI injuries and higher rate of frontal and temporal lobe lesions upon direct impact on brain. Recent preclinical studies have identified the crosstalk between the central nervous system and peripheral skeletal system, where specific brain areas can regulate bone homeostasis and bone mass, which can also possibly regulate the fracture healing process [33,34]. Whether there is a direct link between specific brain regions that are affected after TBI that alter fracture healing response requires further investigation in future clinical and animal experimental models. A validated preclinical brain contusion model is required to confirm TBI severity-associated effects on fracture healing, integrate multi-omics analysis to identify key brain-derived biological drivers of robust callus formation post-TBI, and cross-validate findings with clinical specimens identified using predictive models in future prospective multi-center clinical study.

The research on RCF has progressed from sporadic case reports to recent retrospective case series and cohort studies, exploring potential mechanisms and risk factors. The unexpected occurrence of RCF in TBI patients during orthopaedic surgery may also lead to complications, including fracture malunion due to accelerated healing prior surgery. It may also occur in those fractures with optimal reduction, as fractures may displace later in these unconscious TBI patients due to involuntary movements (see Fig. 7). Currently, there is no recommended timing for surgical fixation after combined TBI and fracture injuries. The mean time to visible fracture callus formation or the ossification phase was significantly shorter in the RCF group, being 3.93 times faster at 22.92 ± 11.98 days, compared to patients without RCF, whose mean time was 90.18 ± 34.52 days. Optimal orthopedic intervention, including conservative and open reduction, should be performed before this phase. In

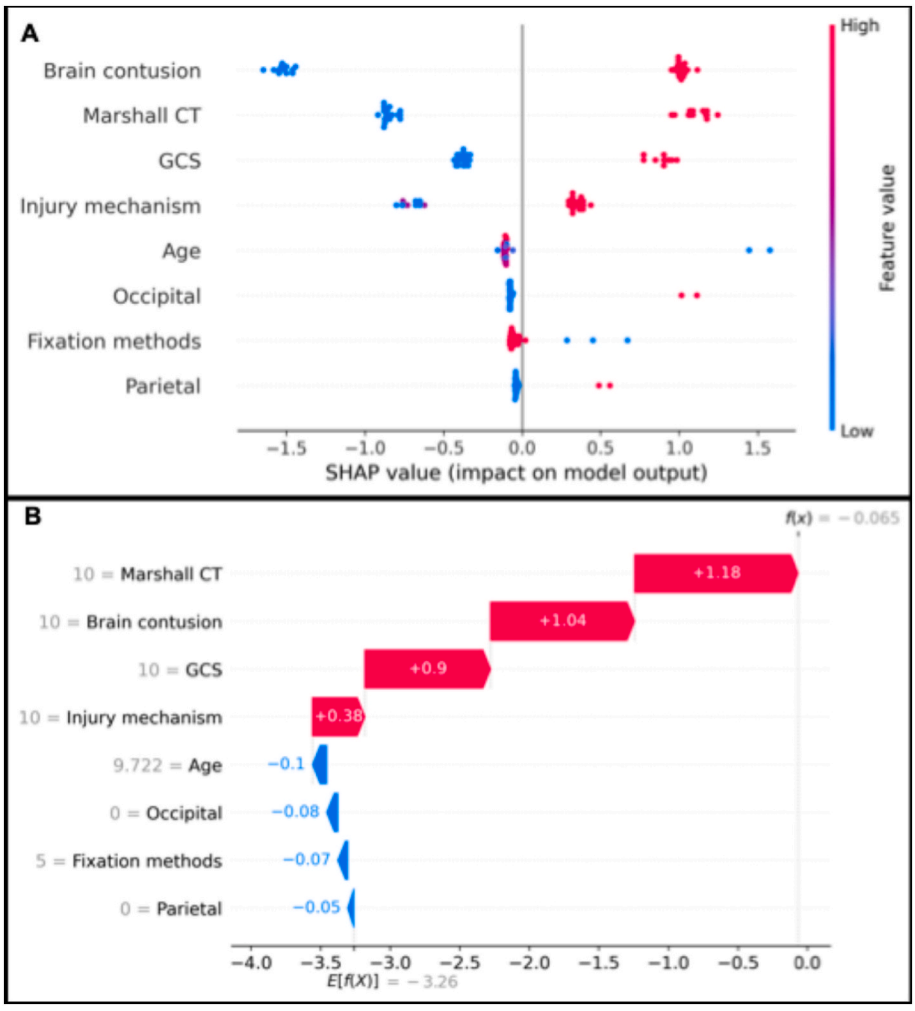

Fig. 6. Interpretation of model built by GBDT algorithm using selecting features. (A) The beeswarm plot displays the SHAP values for each feature. Each dot corresponds to each patient in each feature, with red indicating higher feature values and blue indicating lower values. (B) The row in the waterfall plot repreasents how each feature contributes to the outcome. GCS: Glasgo Coma Scale.

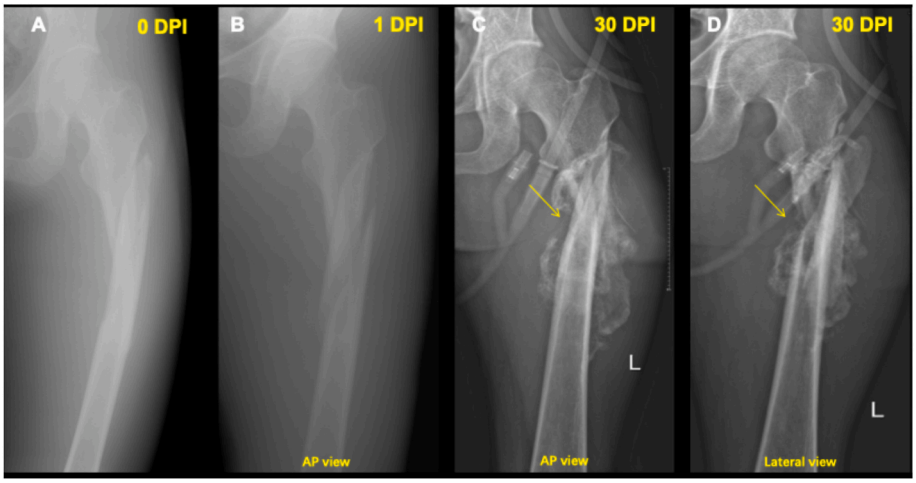

Fig. 7. Case demonstrating robust callus formation and malalignment. Optimal alignment was achieved after manual reduction at 1 DPI (A, B). Preoperative radiographs show extensive bony callus formation with malalignment due to displacement of the fracture parts (C, D).

clinical practice, patients with TBI requiring surgical fixation for fractures are typically managed after preanesthetic evaluation following resuscitation and hemodynamic stabilization. Consequently, the timing of surgical intervention is often delayed beyond the immediate post-injury period. The fracture callus may not be visible on bedside radiographs for early diagnosis before the ossification phase, often being

incidentally discovered and removed for proper reduction and implant fixation during surgery. In this study, nine additional TBI patients with RCF were identified through surgical records. Their fractures healed successfully after the removal of the robust fibrocartilaginous callus, with no recurrence of RCF during subsequent follow-ups. However, callus removal can lead to significant intraoperative bleeding, prolonged surgery duration, and other complications that can further complicate the condition of TBI patients. Therefore, the ability to anticipate RCF before surgery is crucial for determining the timing of orthopedic intervention and optimizing the overall treatment strategy.

4.1. Limitations

This study included patients from one of the cities in China with highest traffic accidents and its related trauma population, treated at a highly experienced and specialized hospital center with high patient volumes sustaining combined fracture and TBI. Thus, the severity of the TBI and incidence of robust callus formation in patients accompanied with TBI in this study population may be higher. Further, the present study focused on the occurrence of RCF incidence, and overall follow-up were short in general, the long-term effect of TBI on fracture healing including the delayed-union and non-union, and long-term prognosis in this specific set of patients were not assessed. While preliminary findings in nine patients with robust callus formation (RCF) demonstrated uneventful fracture healing following immature callus removal for implant fixation, larger cohorts are necessary to evaluate long-term outcomes, including recurrence, delayed union, or non-union, a future large multicenter cohort study is desirable to investigate associations between RCF and isolated hematoma types (volume or timing), as well as to rigorously validate and optimize the machine learning model. Although we have identified brain contusion and TBI severity levels as independent risk factors for RCF occurrence and accelerated fracture healing, the exact underlying mechanism and the main contributing brain derived factors remain to be validated before future potential clinical translation. Furthermore, we specifically focused on diaphyseal fractures at selected sites to facilitate radiographic evaluations of fracture callus formation, with the periosteum playing a predominant role in fracture repair. Therefore, the potential acceleration of fracture healing in other skeletal sites, such as the vertebrae and femoral neck fractures—where cancellous bone is more prominent—remains to be investigated.

5. Conclusions

To the best of our knowledge, this study is the first to present the prevalence and risk factors for robust callus formation in TBI patients across multiple fracture sites and developed ML models to predict its occurrence. The results suggested that brain contusions and greater TBI severity levels are significant risk factors for robust callus formation and acceleration of fracture healing in TBI patients. We found that GBDT model outperformed other ML models and traditional regression method in predicting RCF occurrence in TBI patients, for which can aid in decision making and optimizing treatment strategies in this unique set of patients. A high index of clinical suspicions is also required as to diagnose this condition adequately can be challenging, especially since the formation of bony callus may not be detectable prior ossification phase on radiographs. This study also lays the groundwork for future clinical and preclinical investigations into the mechanisms underlying robust callus formation following TBI, for which presents translation of its discoveries to accelerate fracture healing and prevent non-union.

Authorship

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Each author certifies that this material or part thereof has not been published in another journal, that it is not currently submitted elsewhere, and that it will not be submitted elsewhere until a final decision regarding publication of the manuscript in Journal of Orthopaedic Translation has been made.

Indicate the specific contributions made by each author (list the authors' initials followed by their surnames, e.g., Y.L. Cheung). The name of each author must appear at least once in each of the three categories below.

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Conception and design of study: Zheyu Jin, Jun Hu, Ling Qin, Jiankun Xu; acquisition of data: Zheyu Jin, Jiechen Chen, Zhengming Shan, Tongzhou Liang, Weiyang Liu, Zhenkang Wen, Hongwei Shao, analysis and/or interpretation of data: Zheyu Jin, Zhengming Shan, Dianhui Tan, Jiechen Chen, Ziyi Chen, Xuesong Ren, Dianhui Tan.

Category 2.

Drafting the manuscript: Zheyu Jin, Ling Qin, Jiankun Xu

revising the manuscript critically for important intellectual content: Ling Qin, Jiankun Xu.

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Declaration of competing interest

The authors declare they have no competing interests.

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