Retrospective Study

Support Vector Machine versus Multiple Logistic Regression for Prediction of Postherpetic Neuralgia in Outpatients with Herpes Zoster

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Background: Postherpetic neuralgia (PHN), as the most common complication of herpes zoster (HZ), is very refractory to current therapies. Studies of HZ have indicated that early aggressive pain interventions can effectively prevent PHN; therefore, accurately predicting PHN in outpatients with HZ and treating HZ promptly, would be of great benefit to patients. Multiple logistic regression (MLR) has often been used to predict PHN. However, support vector machine (SVM) has been poorly studied in predicting PHN in outpatients with HZ.

Objective: The aim of our retrospective study was to analyze the data of outpatients with HZ to evaluate the use of SVM for predicting PHN by comparing it with MLR.

Study Design: A retrospective study

Setting: Department of Anesthesiology in China

Methods: The data of 732 outpatients with HZ from January 1, 2015 to May 31, 2020 were reviewed. Risk factors for having PHN in outpatients with HZ were screened using least absolute shrinkage and selection operator (LASSO) algorithm. Then, SVM and MLR were used to predict PHN in outpatients with HZ based on screened risk factors. The data from 600 patients were used for training set and another 132 patients for test set. The receiver operating characteristic (ROC) curve was drawn from the 132 test set of patients. The prediction accuracy of the models was assessed using the area under curve (AUC).

Results: The incidence of having PHN in outpatients with HZ was 19.4%. The risk factors selected by LASSO algorithm were gender, age, VAS scores, skin lesion area, initial treatment time, anxiety, sites of HZ (multiple skin lesions), types of HZ (bullous) and types of pain (knife cutting). The AUC for the SVM and MLR in test set were 0.884 versus 0.853. According to the ROC curve, the specificity and the sensitivity were 0.879 and 0.840 for SVM, and 0.780 and 0.840 for MLR, respectively.

Limitations: Retrospective study and relatively small sample size.

Conclusions: Both SVM and MLR had good discriminative power, but SVM has better performance in predicting PHN in outpatients with HZ, regarding the prediction accuracy and specificity.

Key words: Postherpetic neuralgia, herpes zoster, support vector machine, multiple logistic regression

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Postherpetic neuralgia (PHN), a pain lasting more than 1 month after healing of herpes zoster (HZ) rash, is a common complication of HZ (1). The morbidity of HZ is approximately 3-5/1000 person years and the risk of having PHN varies from 5% to over 30% in outpatients with HZ (2). The risk of having PHN increases with age (3). Approximately 47% and 73% of untreated adult patients aged 60 and 70 years have

PHN, respectively (3). PHN is refractory to medication therapies and interventional treatments (4,5), and most frequently affects a patient's mood and sleep, life enjoyment, anxiety, and depression and causes considerable disease and economic burden (6,7).

Studies of HZ have indicated that early aggressive pain interventions, such as repetitive intracutaneous injections, repetitive paravertebral injections, continuous epidural blockade, and stellate ganglion blockade can effectively prevent PHN (8-12); therefore, accurately predicting PHN in outpatients with HZ and treating HZ promptly, would be of great benefit to patients. A few researches have been performed to predict PHN based on multiple logistic regression (MLR) (13-15). The results of these researches can be helpful for prediction of PHN.

Support vector machine (SVM) is a nonlinear dichotomy model based on the principle of maximum interval in feature space. SVM classifies data points in high-dimensional space by maximizing the edge between classes. The heuristic algorithm of SVM is very different from that of MLR for prediction. SVM has been widely used in cancer genomics (16), disease diagnosis (17,18), imaging diagnosis (19), predicting disease prognosis (20,21), etc. However, there are few studies to predict PHN in outpatients with HZ; thus, the aim of our retrospective research was to analyze the data of outpatients with HZ to investigate the use of SVM for predicting PHN by comparing it with MLR.

Methods

Data Collection

A total of 740 outpatients with HZ from January 1, 2015 to May 31, 2020 in the pain clinic of our hospital were selected and 8 patients with incomplete medical records were excluded. All statistical items were based on references and our own clinical experience. Protocols were approved by the Ethics Committee of Beijing Friendship Hospital (2020-P2-060-01). Informed consent was waived due to the noninterventional study. Medical record data were reviewed. Gender, age, smoking, visual analog scale (VAS) scores, initial treatment time (h), skin lesion area, emotional status, fever, hormone therapy, concomitant diseases (coronary heart disease, hypertension, diabetes, hyperlipidemia, malignant tumor, respiratory diseases, digestive diseases), sites of HZ (head and face, chest and back, waist and abdomen, limbs, multiple skin lesions), involved nerves (trigeminal nerve, intercostal nerve, cervical brachial plexus, lumbosacral plexus), types of HZ (common, extensive, bullous, abortive) and types of pain (burning, knife cutting, and itching) were recorded.

To be calculated, data were processed as follows: Gender was labeled one for men and 0 for women; binomial categorical variables, including smoking, anxiety, fever and hormone therapy, were labeled 1 for yes and 0 for no; multiple categorical variables, including concomitant diseases, sites of HZ, involved nerves, types of HZ and types of pain, were labeled 1 for yes and 0 for no; skin lesion area was calculated using the palmar method, and adult palm size is 1% of total body area; we labeled 1 for yes and 0 for no to indicate whether the patient suffered from PHN.

Risk Factors Screening

Least absolute shrinkage and selection operator (LASSO) algorithm is a variable selection method. Its calculation process is based on the traditional multiple regression or logistic regression model, and the penalty term is added in the form of absolute value, so that the estimated value of the independent variable coefficient (which has little influence on the dependent variable) is compressed to 0, so as to realize the function of variable selection. Compared with traditional logistic regression, the LASSO algorithm was able to extract risk factors with large effects on PHN. In this paper, the LASSO algorithm was solved by R language (3.6.3 version) and the optimal model parameters were selected by 10-fold cross-validation.

Local Regression

Local regression is a nonparametric statistical modeling method, which can obtain the nonlinear correlation between independent variables and dependent variables. In this paper, this method was used to smooth the influence of risk factors on PHN and studied the influence of each risk factor on PHN by smoothing curve. The conclusions of this method can facilitate us to observe in which interval each factor has higher risk for PHN, providing more accurate guidance for clinical practice. In this paper, R language was used to draw the effect of screened risk factors on the relative risk of having PHN.

SVM Modeling

Based on risk factors for PHN screened by LASSO regression, SVM was used to construct a prediction model for the development of PHN. To verify the predictability of the model, 732 samples were randomly divided into

600 patient training set and 132 patient test set. Based on the risk factors screened by the LASSO algorithm, SVM learning was performed on the 600 patients in the training set using R language and the optimal model parameters were selected by 10-fold cross-validation. The receiver operating characteristic (ROC) curve was drawn from the 132 patients in the test set. The prediction accuracy of SVM model was assessed using the area under curve (AUC), and the optimal cut-off value of the prediction model was determined by Youden index. The prediction model based on SVM usually has no explicit expression. It can predict the incidence of having PHN in outpatients with HZ by computer.

MLR Modeling

Based on the risk factors for PHN screened by LASSO regression, MLR was used to construct a prediction model for the development of PHN. MLR attempts to establish a functional relationship between one outcome variable and 2 or more predictors using a weighted least squares algorithm. MLR predicts the probability of an event by fitting the data to a logical function. In this paper, MLR also used the same 600 patients in the training set and the 132 patients in the test set as the SVM model to establish the prediction model. The ROC curve was drawn from the 132 test set patients. The prediction accuracy of MLR model was assessed by the AUC.

Statistical Analysis

SPSS Version 21.0 was used to perform data analysis. Results are reported as mean and SD (as appropriate), median and interquartile range, and percentages. For comparison between the 2 groups, Mann–Whitney test was used for non-normally distributed data, t-test for normally distributed data and Chi-square test for categorical data. $P < 0.05$ was considered significant.

Results

Basic Information

A total of 732 outpatients with HZ were included in our study, 142 of whom had PHN. The incidence of PHN was 19.4% among the patients, 6.03% in men and 29.5% in women ($P = 0.000$). The basic information is shown in Table 1.

Risk Factors Screening

The risk factors for PHN selected by LASSO algo-

Table 1. *Basic information*.

Characteristics	PHN, mean ± SD or n (%)		*P*
	No	Yes	
Age (y)	66.47 ± 13.448	73.80 ± 10.500	0.000
VAS	5.24 ± 1.420	6.17 ± 1/326	0.000
Skin lesion area	3.46 ± 1.260	4.24 ± 1.271	0.000
Initial treatment time (h)	51.47 ± 26.382	80.54 ± 25.496	0.000
Gender			0.000
Women	294 (40.2%)	123 (16.8%)	
Men	296 (40.4%)	19 (2.6%)	
Smoker			0.092
No	524 (71.6%)	133 (18.2%)	
Yes	66 (9.0%)	9 (1.2%)	
Prodromal pain			0.003
No	333 (45.5%)	60 (8.2%)	
Yes	257 (35.1%)	82 (11.2%)	
Anxiety			
No	555 (75.8%)	105 (14.3%)	0.000
Yes	35 (4.7%)	37 (5.1%)	
Fever			
No	559 (76.4%)	132 (18.0%)	0.417
Yes	31 (4.2%)	10 (1.4%)	
Hormone therapy			
No	13 (1.8%)	2 (0.3%)	0.748
Yes	577 (78.8%)	140 (19.1%)	
Coronary heart disease			0.125
No	534 (73.0%)	123 (16.7%)	
Yes	56 (7.7%)	20 (2.7%)	
Hyperlipidemia			0.801
No	568(77.6%)	138(18.9%)	
Yes	22(3.0%)	4(0.5%)	
Hypertension			0.695
No	503(68.7%)	119(16.3%)	
Yes	87(11.9%)	23(3.1%)	
Cancer			0.819
No	563(76.9%)	137(18.7%)	
Yes	27(3.7%)	5(0.7%)	
Diabetes			0.001
No	543(74.2%)	116(15.8%)	
Yes	47(6.4%)	26(3.6%)	
Respiratory diseases			0.098
No	589(80.5%)	140(19.1%)	
Yes	1(0.1%)	2(0.3%)	
Sites of HZ			0.001
Multiple skin lesions	1(0.1%)	5(0.7%)	

Table 1 (cont.). *Basic information.*

Characteristics	PHN, mean ± SD or n (%)		P
	No	Yes	
Limbs	24(3.3%)	5(0.7%)	
Head and face	49(6.7%)	15(2.0%)	
Chest and back	453(61.9%)	97(13.3%)	
Waist and abdomen	63(8.6%)	20(2.7%)	
Types of pain			0.000
Knife cutting	106(14.5%)	51(7.0%)	
Burning	28(3.8%)	9(1.2%)	
Itching	456(62.3%)	82(11.2%)	
Trigeminal nerve	36(4.9%)	10(1.4%)	0.700
Intercostal nerve	454(62.0%)	102(13.9%)	0.229
Cervical brachial plexus	34(4.6%)	13(1.8%)	0.179
Lumbosacral plexus	68(9.3%)	23(3.1%)	0.156
Types of HZ			0.000
common	543(74.2%)	62(8.5%)	
extensive	16(2.2%)	2(0.3%)	
bullous	17(2.3%)	76(10.4%)	
abortive	14(1.9%)	2(0.3%)	

Categorical variables are expressed as number (%), and continuous variables as mean ± SD.
VAS = visual analog scale, HZ = herpes zoster.

rithm were gender, age, VAS scores, skin lesion area, initial treatment time, anxiety, sites of HZ (multiple skin lesions), types of HZ (bullous) and types of pain (knife cutting). The process of screening risk factors by LASSO is shown in Fig. 1.

Local Regression

Four continuous high-risk factors, including age, skin lesion area, VAS scores, and initial treatment time, were subjected to univariate regression using local regression method. The nonlinear curves between the 4 variables and the incidence of PHN are shown in Fig. 2.

The solid line in Fig. 2 shows the relationship between the variable and the risk of PHN, and the gray shadow represents the 95% confidence interval. The narrower the gray shadow was, the more reliable the prediction was. When VAS scores were between 4-8, the risk of having PHN increased with increasing VAS scores. When the initial treatment time was between 50-100 h, the risk of having PHN increased with the increase of initial treatment time. In patients over 40 years old, the risk of having PHN increased with age. When the skin lesion area was between 3-6, the risk of having PHN increased with increasing lesion size.

Model Test Result

In SVM model, the parameters of cost and gamma were selected using 10-fold cross-validation and the optimal parameters were set as cost = 10 and gamma = 0.1. A training set with a sample size of 600 patients was random sampled to train the SVM model and another 132 patients from the test set to make a cross validation. The ROC curve is shown in Fig. 3. Our results showed that the AUC was 0.884, which indicated that SVM model had good extrapolation performance and could well predict the risk of having PHN in outpatients with HZ. According to the ROC curve, the maximum point of the Youden index had a sensitivity of 0.840 and a 1-specificity of 0.121, with a corresponding optimal cutoff value of 0.112. When the output value was greater than 0.112, the SVM predicted that the patient had a higher risk of having PHN.

In MLR model, the ROC curve is shown in Fig. 4. Our results showed that the AUC was 0.853. According to the ROC curve, the maximum point of the Youden index had a sensitivity of 0.840 and a 1-specificity of 0.220.

Discussion

HZ is a self-limited disease with few sequelae after healing in most patients, particularly young adults; however, once HZ progresses to PHN, the condition can be refractory to medication therapies and interventional treatments, and the patient's life is often severely affected (4-6). PHN, as the most common complication of HZ, is often frustrating for patients and represents a challenge for clinicians; therefore, studies on PHN must focus not only on treatment, but moreso on prevention. Accurate prediction of PHN in outpatients with HZ and timely treatment would be beneficial to patients. In this study, 2 popular data mining algorithms were used to predict PHN in outpatients with HZ: one for machine learning (SVM) and another one for statistics (MLR). Our results showed that SVM had better performance for predicting PHN in outpatients with HZ in comparison to MLR regarding the prediction accuracy (0.884 versus 0.853) and specificity (0.879 versus 0.780). For outpatients with HZ at the first visit, SVM model is very helpful for decision making. If the model predicts that the patient will develop PHN one month later, we should pursue more aggressive treatment.

In our study, out of the 23 variables tested by LASSO regression analysis, 9 variables were significantly correlated with the PHN incidence (Fig. 1). Further univariate regression analysis of age, skin lesion area, VAS scores,

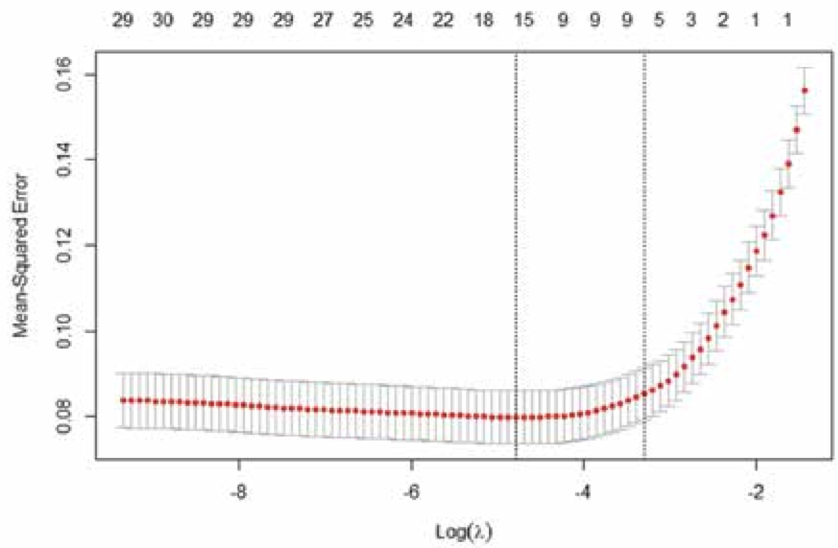

Fig. 1. *Risk factors screening using LASSO.*

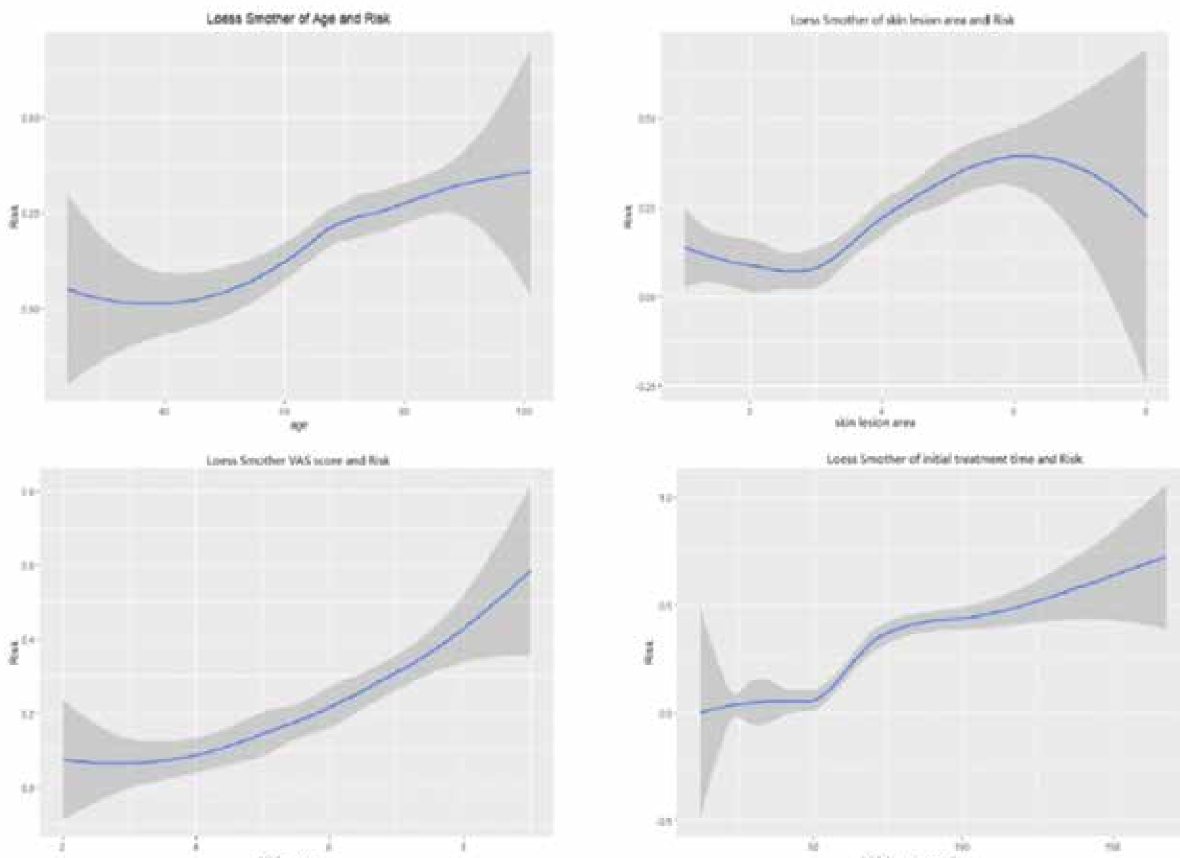

Fig. 2. *The nonlinear curves.*

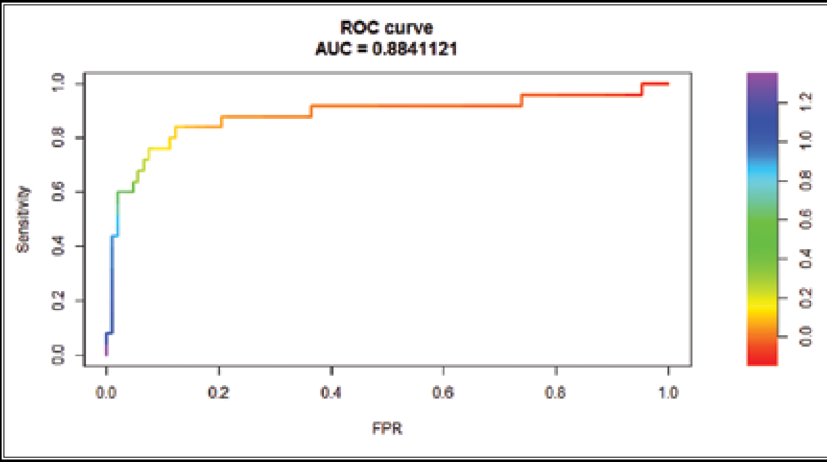

Fig. 3. *The ROC curve of SVM.*

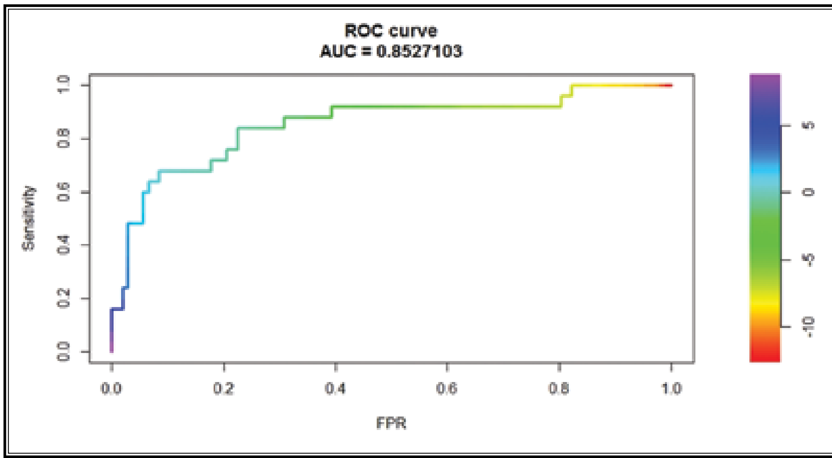

Fig. 4. *The ROC curve of MLR.*

and time to initial treatment using the local regression method found that higher VAS scores, older age, larger skin lesion area, and longer time to initial treatment were associated with higher incidence of PHN. In previous studies, higher VAS scores, older age, larger skin lesion area have been confirmed as independent predictors of PHN and even considered as undisputed predictors (22-24); but, the lack of statistical correlation between other factors and PHN does not necessarily imply a lack of biological connection: the data in our article may be insufficient. For example, HZ is common in immunocompromised populations (25) and severe immunosuppressive status is also an independent risk factor for PHN (23).

In several studies, MLR has been used to build models to predict PHN (13-15). Meister et al (13), built a prediction model using MLR based on age, number of lesions, prodromal pain, hemorrhagic lesions, gender, and location (13). The AUC of their model was not mentioned, and the sensitivity and specificity were 93% and 42%, respectively. Opstelten et al (14), developed a prediction model using MLR based on age, acute pain severity, skin rash severity, and rash duration before consultation (14). The AUC of their model was 0.77, and the sensitivity and specificity were not mentioned. Cho et al (15), used MLR to predict PHN based on VAS (≥ 8), age (≥ 70 years), and S-LANSS (≥15) (15). The AUC of their model was 0.868 and the sensitivity and specificity were 100% and 57.1%, respectively. In our study, the AUC of MLR model was 0.853. The prediction accuracy of MLR model was greater than that of Opstelten et al (14), but less than that of Cho et al (15). The AUC value greater than 0.70 is generally considered to indicate good discrimination (26); therefore, our MLR model can well predict the incidence of PHN in outpatients with HZ.

The superiority of SVM has been demonstrated in some studies. Chao et al (21), used SVM, MLR, and decision tree (DT) to predict the breast cancer survival. SVM outperformed MLR and DT regarding prediction accuracy (95.15% versus 95.1% and 93.95%) (21). In a study which was done to predict obstructive sleep apnea, SVM had a better performance than MLR in terms of the accuracy (0.797 versus 0.729) and the specificity (0.847 versus 0.777) (27). In a study using SVM, artificial neural network, DT, and MLR to evaluate the high-risk population for suicide, the study concluded that SVM achieved the highest accuracy (0.67 versus 0.62, 0.49, and 0.65) and the highest specificity (0.68 versus 0.60, 0.46, and 0.65) for the testing sample (28). The result of our study is consistent with those of other authors: SVM has more predictive power than MLR. The main limitation of this retrospective study is the small sample size. Due to the increase in the amount of data, many data mining algorithms, including SVM, will have better performance, so SVM can be applied to a larger dataset to improve performance.

Conclusions

In conclusion, both SVM and MLR had good discriminative power, but SVM has better performance in predicting PHN in outpatients with HZ regarding the prediction accuracy and specificity. For outpatients with HZ at the first visit, SVM model is very helpful for decision making. Therefore, clinicians are advised to use SVM as an adjunctive screening tool to predicting PHN in outpatients with HZ. This may reduce the incidence of having PHN.

Author Contributions

Jie Zhang contributed to the implementation of the study, data collection, and drafted the manuscript. Xiu-Liang Li and Yi-Wei Hao equally contributed to the design and conception of the experiment and should be co-corresponding authors to this work. Data processing was performed by Qiao Ding and Ying Yang. Yi-Wei Hao performed the statistical analysis. All authors had approved the final manuscript.

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