Original Research

Novel artificial intelligence machine learning approaches to precisely predict survival and site-specific recurrence in cervical cancer: A multi-institutional study

Chenyan Guo [a,b,1], Jue Wang [a,b,1], Yongming Wang [c,1], Xinyu Qu [a,b], Zhiwen Shi [a,b], Yan Meng [a,b], Junjun Qiu [a,b,*], Keqin Hua [a,b,*]

[a] Department of Gynecology, Obstetrics and Gynecology Hospital, Fudan University, 419 Fangxie Road, Shanghai 200011, China
[b] Shanghai Key Laboratory of Female Reproductive Endocrine-Related Diseases, 413 Zhaozhou Road, Shanghai 200011, China
[c] Shanghai Changjiang Science and Technology Development Co. LTD, China

A R T I C L E   I N F O

A B S T R A C T

Background: Machine learning (ML) has been gradually integrated into oncologic research but seldom applied to predict cervical cancer (CC), and no model has been reported to predict survival and site-specific recurrence simultaneously. Thus, we aimed to develop ML models to predict survival and site-specific recurrence in CC and to guide individual surveillance.
Methods: We retrospectively collected data on CC patients from 2006 to 2017 in four hospitals. The survival or recurrence predictive value of the variables was analyzed using multivariate Cox, principal component, and K-means clustering analyses. The predictive performances of eight ML models were compared with logistic or Cox models. A novel web-based predictive calculator was developed based on the ML algorithms.
Results: This study included 5112 women for analysis (268 deaths, 343 recurrences): (1) For site-specific recurrence, larger tumor size was associated with local recurrence, while positive lymph nodes were associated with distant recurrence. (2) The ML models exhibited better prognostic predictive performance than traditional models. (3) The ML models were superior to traditional models when multiple variables were used. (4) A novel predictive web-based calculator was developed and externally validated to predict survival and site-specific recurrence.
Conclusion: ML models might be a better analytic approach in CC prognostic prediction than traditional models as they can predict survival and site-specific recurrence simultaneously, especially when using multiple variables. Moreover, our novel web-based calculator may provide clinicians with useful information and help them make individual postoperative follow-up plans and further treatment strategies.

Research in context

Evidence before this study

Accurate and personalized prognosis prediction of cervical cancer is required to detect early recurrence and optimize the postoperative follow-up plan. Traditionally, logistic and Cox regression models have been used as the mainstay survival analyses for oncologic research; however, they are incapable of dealing non-linear correlations and processing big data in clinical practice. Moreover, we now lack effective tools to predict high-risk recurrence sites and guide appropriate screening. Under this situation, physicians can only assign individuals into crude categories as low- or high-risk groups without accurately accounting for the specifics of each unique patient. Therefore, a user-friendly, individual-based model that can accurate predict individual survival and site-specific recurrence simultaneously is strongly needed.

Added value of this study

Machine learning models have recently been considered to be useful analytic approaches for oncologic research. In this study of women with cervical cancer, we applied various machine learning methods to develop a model that can accurately predict individual risk of survival, the conditional risk of site-specific recurrence, and the specific time of recurrence-free survival or overall survival. The machine learning model exhibited better performance than traditional models, especially when using multiple variables. The results were validated using a cohort of 5112 patients from four hospitals, which is likely the largest sample size to date. To better apply the model into clinical use, we then built a web-based predictive calculator (available on https://aicer.fckyy.org.cn).

Implications of all the available evidence

Our machine learning predictive model can help doctors identify patients who are at high risk of postoperative recurrence or death, remind them of high-risk recurrence sites, and estimate recurrence-free survival or overall survival time period. Our web-based predictive calculator can provide clinicians with useful information for treatment decision-making and follow-up plan formulation.

Introduction

As the fourth most frequently diagnosed cancer and the fourth leading cause of cancer-related death, cervical cancer (CC) accounted for 570,000 new cases and 311,000 deaths in 2018 worldwide [1]. In China, CC is responsible for 18.4% of cancer-related deaths in women [2]. Surgical resection offers the best opportunity for a cure for early-stage CC patients. However, high recurrence rates are still common and are a main obstacle for long-term survival. To this end, accurate individual prognosis prediction and appropriate postoperative surveillance are therefore necessary for the early detection of recurrence, which may greatly aid in the timely administration of therapies and potentially improve patients' survival prognosis.

Traditionally, the International Federation of Gynecology and Obstetrics staging system is considered the main tool for estimating general prognosis and guiding treatment. However, because of personal differences, it is differences to use FIGO staging to predict individual survival in precision medicine. In addition, even though the new classification added pathologic and imaging evidence, it still does not include all possible prognostic factors, such as histologic type, lymphovascular space invasion (LVSI), operation-related variables, and variables associated with treatment. To integrate more clinicopathologic variables into prediction models, previous studies have used the logistic and Cox proportional hazards methods to estimate individual prognosis [3,4]. Nevertheless, these methods are based on linearity assumptions that make it difficult to explain the nonlinear relationships between variables in real-world settings. Additionally, the precise estimation of site-specific recurrence risk is also of great importance and can not only avoid unnecessary screening in low-risk regions and save medical resources but also guide appropriate postoperative surveillance. However, few studies have addressed this issue. Therefore, new models that can manage nonlinear variables, including all potential prognostic factors, and predict individual survival and site-specific recurrence are urgently needed.

In the present study, we aimed to (1) comprehensively investigate the postoperative survival and recurrence patterns of a large multi-institutional cohort of 5112 CC patients; (2) develop various machine learning models and compare their prognostic predictive performance outcomes with those of traditional logistic or Cox models; and (3) establish a novel user-friendly web-based calculator to estimate individual survival, the conditional risk of site-specific recurrence, and the specific time of recurrence-free survival (RFS) or overall survival (OS) to develop better postoperative follow-up plans and further treatment strategies.

Methods

This retrospective multicenter cohort study was approved by the Institutional Ethics Committee of Fudan University Obstetrics and Gynecology Hospital (2019-87). This study was registered in the Chinese Clinical Trial Registry (ChiCTR1900028702).

Patients

We identified 5112 patients with CC who underwent surgical resection from January 2006 to December 2017 in four tertiary hospitals as the study population. The inclusion criteria for this study included patients with pathologically confirmed stage IA1 (LVSI) to IIB2 CC with complete resection. The exclusion criteria included patients with a history of prior malignancy, a preexisting history of chemotherapy or radiotherapy for other conditions, and death due to surgical complications.

Clinical information

For the eligible patients, patient demographics, laboratory test results, therapeutic data, tumor characteristics, and survival outcomes were collected from medical records. All records were reviewed simultaneously by three experts and were independently checked by two experts to ensure accuracy. The demographic variables included age and comorbidity (hypertension/diabetes). The laboratory test results included human papillomavirus (HPV) infection status. The therapeutic data included surgical approach, operative time, blood loss, transfusion, history of loop electrosurgical excision procedure (LEEP), and adjuvant treatment. The tumor characteristics included stage; tumor size; histology; depth of stromal invasion (DSI); LVSI; surgical margin; parametrial involvement; lymph node (LN) status; keratinization; differentiation; and P53, P16, and Ki67 expression.

The primary outcomes were RFS and OS. RFS was defined as the interval from the initial CC diagnosis to the first finding of any recurrence or the last follow-up. OS was defined as the interval from the initial diagnosis to CC-related death or the last follow-up. Patients who failed to reach survival events at the last follow-up were censored. Local recurrences were defined by pathologic proof of cancer in the vagina/cervix, which was confined to the pelvis, or an imaging study showing the regrowth of the tumor or an enlargement of any pelvic LN. Distant recurrences were defined as any recurrence outside of the pelvis including peritoneal spread or the involvement of supraclavicular LNs, the lung, the liver, the bone, the brain, etc. based on pathologic, cytologic, or radiologic evidence [5]. The definition of local or distant recurrence was determined according to the lesions detected at the time of the first relapse after a complete workup.

According to the National Comprehensive Cancer Network (NCCN) guidelines, the preoperative workup for patients with suspicious symptoms includes history, physical examination, cervical cytologic screening, routine blood tests (including platelets), liver and renal function, electrocardiography (ECG), and imaging examinations. Radiologic imaging included chest X-ray, pelvic computed tomography (CT)/magnetic resonance imaging (MRI), or combined positron emission tomography (PET)-CT, as indicated. Cone biopsy was performed if the cervical biopsy was inadequate to define invasiveness or if an accurate assessment of microinvasive disease was required. For patients older than 60 years, echocardiography, pulmonary function tests, and urodynamic tests were also performed.

The patients were treated with adjuvant treatment after radical hysterectomy when they met one of the following two criteria: (a) patients who presented any one of several high-risk factors (surgical margin, parametrial involvement, and LN metastasis) and (b) patients who satisfied the Sedlis et al. [6] criteria for intermediate-risk factors (tumor size, LVSI, and DSI). After hospital discharge, the patients received regular follow-up in accordance with the NCCN guidelines [5]. HPV, liquid-based cytology (LCT), tumor markers, and ultrasonography were per-
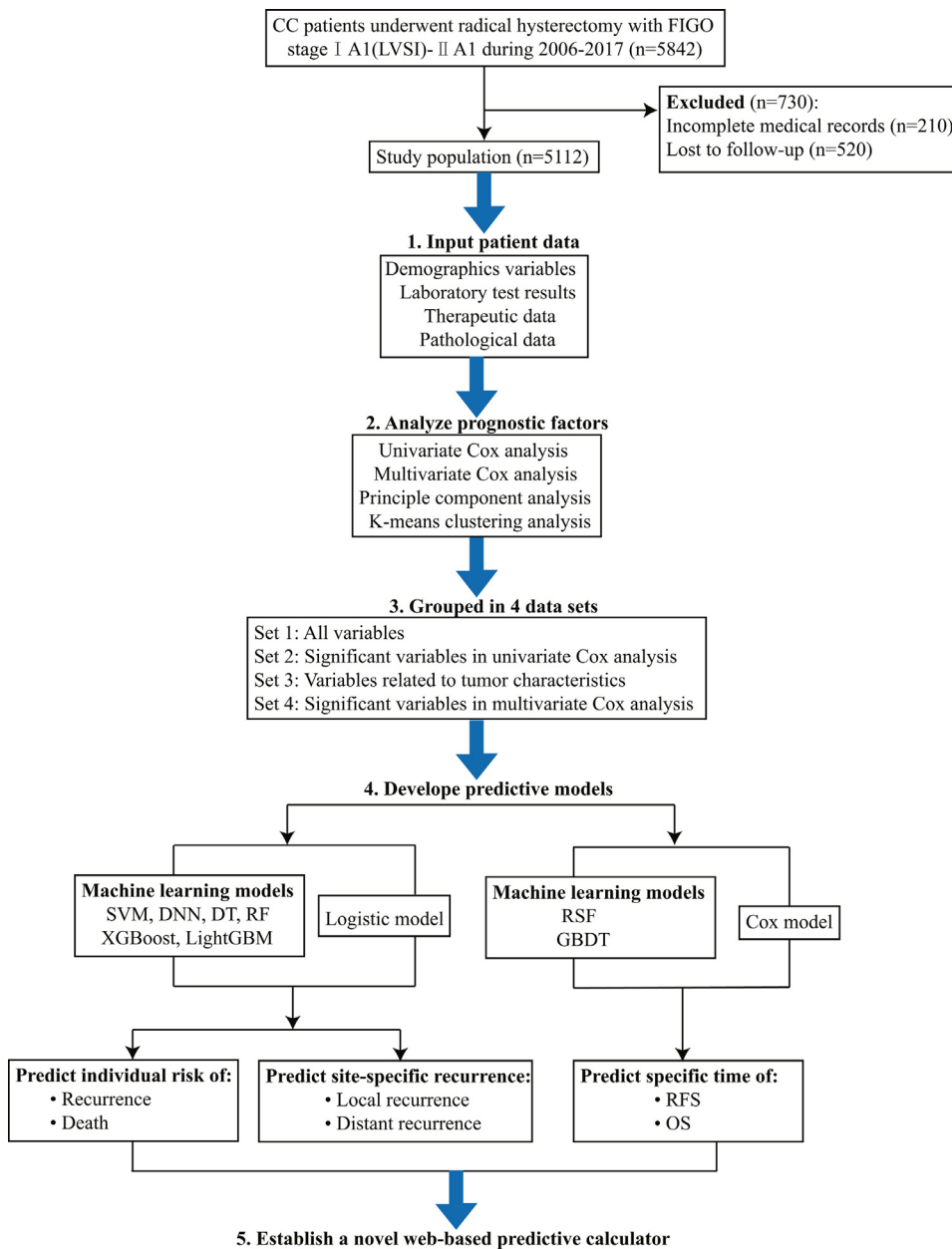
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│ CC patients underwent radical hysterectomy   │
│ with FIGO stage ⅠA1(LVSI)- ⅡA1 during        │
│ 2006-2017 (n=5842)                            │
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Fig. 1. Study schema for survival and recurrence analysis.

formed every 3 months for the first 2 years, every 6 months for 3 to 5 years, and annually after 5 years. Chest CT scans, upper abdominal CT scans with enhancement, and pelvic MRI were performed annually. We also performed telephone follow-up and suggested that patients who had clinical symptoms undergo imaging tests. For suspected organ or LN metastasis diagnosed by ultrasound, other imaging tests (MRI, CT, or PET/CT scan) were usually performed, and needle aspiration biopsy was conducted when necessary. The median follow-up time was 102 (36–168) months.

Statistical analysis

Continuous variables are reported as medians with interquartile ranges (IQRs) or means with standard deviations (SDs). Categorical variables are reported as numbers and proportions. The collinearity of all variables was evaluated using correlation matrices, and no significant interactions were identified. The associations of variables with RFS and OS were evaluated using Cox proportional hazards regression models. Variables with a *P* value less than 0.05 in univariate analysis were entered into multivariate survival analysis (backward selection) to

identify independent predictors. The proportional hazards assumption of Cox regression was tested. Principal component analysis (PCA) and clustering analysis were also performed to further explore the relationships between clinicopathologic factors and survival outcomes. PCA was used for dimensionality reduction and feature extraction. Both the variance contribution and cumulative variance contribution were calculated to determine the number of principal components. K-means clustering analysis was performed based on the results of PCA. Hazard ratios (HRs) are presented with 95% confidence intervals (CIs).

To examine the clinicopathologic prognostic factors across traditional models (Cox and logistic models) and machine learning models, 4 datasets were examined for each separate model. Set 1 represents all basic characteristics (22 variables), including age; comorbidity; HPV infection status; surgical approach; operative time; blood loss; transfusion; history of LEEP; adjuvant treatment; FIGO stage; tumor size; histology; DSI; LVSI; surgical margin; parametrial involvement; LN status; keratinization; differentiation; and P53, P16, and Ki67 expression; Set 2 represents 19 statistically significant variables in univariate Cox analysis (Supplementary Table 1); Set 3 represents 13 variables related to tumor characteristics, including FIGO stage; tumor size; histology; DSI; LVSI;

surgical margin; parametrial involvement; LN status; keratinization; differentiation; and P53, P16, and Ki67 expression; and Set 4 represents 7 statistically significant variables in multivariate Cox analysis (Table 2).

Eight machine learning models were developed for survival prediction as a novel approach (Fig. 1). Support vector machine (SVM), deep neural network (DNN), decision tree (DT), random forest (RF), XGBoost, and LightGBM were used to predict the individual risk of recurrence/death and were compared with the traditional logistic model. Random survival forest (RSF, https://github.com/sebp/scikit-survival) and gradient boosting decision tree (GBDT) were used to predict individual specific times of RFS/OS and were compared with the traditional Cox regression model.

To train and test the generalization performance of these models, the whole dataset from four tertiary hospitals was randomly split into training and test sets (8:2) using stratified random sampling, which can ensure the consistency between patients who experienced events (recurrence/death) and those who had not. To improve the class balance in our datasets, the adaptive synthetic sampling (ADASYN) algorithm was applied to the training set [7]. To determine the optimal model parameters and avoid overfitting, we adopted the method of 5-fold cross validation (CV) based on grid search in the evaluation of the model training performance. The performance metrics of all models are the average performance metrics in the 5 validation sets.

The concordance index (C-index) and mean absolute error (MAE) were used to evaluate the performance of the models that predict individual RFS and OS. The area under the curve (AUC), sensitivity, and specificity were used to evaluate the performance of models predicting survival or recurrence probabilities. All performance parameters were calculated with 5-fold CV and an external test set.

Statistical analysis was performed in SPSS (version 21.0; SPSS Inc., Chicago, IL, USA), R 3.4.3 (Vienna, Austria; http://www.R-project.org/), and Python 3.7 (https://www.python.org/). A web-based predictive calculator was developed using Python. All tests were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Analysis of patient baseline characteristics

A total of 5842 patients with CC met the inclusion criteria. Of them, 730 patients who had incomplete medical records or were lost to follow-up were excluded. The detailed clinicopathologic characteristics of the remaining 5112 patients are listed in Table 1. The median age was 47.7 years, and 2989 (58.5%) patients underwent adjuvant treatment. Most tumors were stage I (74.5%) and of the squamous histologic type (81.7%). The median follow-up time was 102 (36–168) months. There were 343 (6.71%) women who experienced recurrence and 268 (5.24%) who died during the follow-up time. There were 179 (52.2%) patients with initial recurrence in the local region, 71 (20.7%) in the thoracic region, 43 (12.5%) in the abdominal region, 31 (9%) in the bone, and 19 (5.8%) in other regions (brain, bladder, and supraclavicular LN metastasis).

Analyses of clinicopathologic variables and recurrence patterns

In univariate analysis, 15 variables were significantly associated with OS and recurrence, including age, FIGO stage, HPV status, adjuvant treatment, history of LEEP, tumor size, histology, DSI, LVSI, surgical margin, parametrial involvement, LN status, keratinization, differentiation, and immunohistochemistry (P53, P16, and Ki67) (Supplementary Table 1). Factors significant in univariate analysis regarding the specific recurrence site are shown in Supplementary Table 2. It is worth noting that FIGO stage, parametrial involvement, LN status, and adjuvant treatment were associated with recurrence in any specific site based on the univariate analysis.

Table 1
Baseline characteristics of stage IA1(LVSI)- IIB2 cervical cancer patients.

Characteristics	Number of patients ($n = 5112$)
Clinical variables	
Age, years	47.7 (± 9.6)
FIGO stage	
IA1 (LVSI)	27 (0.5)
IA2	136 (2.7%)
IB1	3202 (62.6%)
IB2	605 (11.8%)
IIA1	734 (14.4%)
IIA2	338 (6.6%)
IIB1	39 (0.8%)
IIB2	31 (0.6%)
Comorbidity	
Yes	768 (15%)
No	4344 (85%)
HPV infection	
Yes	1963 (38.4%)
No	594 (11.6%)
Unknown	2555 (50%)
Adjuvant treatment	
Yes	2989 (58.5%)
No	2123 (41.5%)
Surgery related variables	
Surgery approach	
MH	4040 (79%)
LMH	3799 (74.3%)
RMH	236 (4.6%)
Trans-vaginal	5 (0.1%)
OH	1072 (21%)
Operative time, min	213.5 (165, 251)
Blood loss, ml	335.9 (150,400)
Transfusion	
Yes	369 (7.2%)
No	4743 (92.8%)
LEEP	
Yes	982 (19.2%)
No	4130 (80.8%)
Pathologic variables	
Tumor size, cm	
>0.5	975 (19.1%)
[0.5,1)	96 (1.9%)
[1,1.5)	338 (6.6%)
[1.5,2)	428 (8.4%)
[2,2.5)	422 (8.3%)
[2.5,3)	518 (10.1%)
[3,3.5)	727 (14.2%)
[3.5,4)	623 (12.2%)
[4,4.5)	375 (7.3%)
[4.5,5)	188 (3.7%)
≥5	422 (8.3%)
Histology	
SCC	4179 (81.7%)
AC	576 (11.3%)
AS	281 (5.5%)
Rare type	76 (1.5%)
DSI	
Negative	1219 (23.8%)
Inner 2/3	1542 (30.2%)
Outer 1/3	2351 (46%)
LVSI	
Yes	2129 (41.6%)
No	2983 (58.4%)
Surgical margin	
Yes	399 (7.8%)
No	4713 (2.2%)
Parametrial involvement	
Yes	255 (5%)
No	4857 (95%)
LN metastasis	
Yes	1000 (19.6%)
Pelvic LNs	710 (13.9%)
Common iliac LNs	248 (4.9%)
Para-aortic LNs	42 (0.8%)
No	4112 (80.4%)

Table 1 (*continued*)

Characteristics	Number of patients (*n* = 5112)
Keratinization	
Yes	1168 (22.8%)
No	2012 (39.4%)
Non-SCC	933 (18.3%)
Unknown	999 (19.5%)
Differentiation	
Low	105 (2.1%)
Intermediate	232 (4.5%)
High	31 (0.6%)
Unknown	4744 (92.8%)
P53	
Negative	1642 (32.1%)
+	2215 (43.3%)
++	76 (1.5%)
+++	26 (0.5%)
++++	2 (0%)
Unknown	1151 (22.5%)
P16	
Negative	213 (4.2%)
+	2909 (56.9%)
++	339 (6.6%)
+++	583 (11.4%)
++++	58 (1.1%)
Unknown	1010 (9.8%)
Ki67	
Negative	15 (0.3%)
0–20%	517 (10.1%)
20–40%	997 (19.5%)
40–60%	1038 (20.3%)
60–80%	1147 (22.4%)
80–100%	389 (7.6%)
Unknown	1009 (19.7%)
Follow-up, months	90 (18–162)

Multivariate Cox analysis showed that (1) the following seven variables were independent predictors of both OS and recurrence: FIGO stage, adjuvant therapy, tumor size, histology, DSI, parametrial involvement, and LN status (Table 2). (2) The following seven variables were independent predictors of local recurrence: FIGO stage, adjuvant therapy, tumor size, histology, DSI, surgical margin, and parametrial involvement. (3) The following five variables were independent predictors of thoracic recurrence: FIGO stage, adjuvant therapy, histology, parametrial involvement, and LN status. (4) The following three variables were independent predictors of abdominal recurrence: FIGO stage, parametrial involvement, and LN status. (5) The following two variables were independent predictors of bone recurrence: FIGO stage and LN status (Table 3). Notably, for site-specific recurrence, larger tumor size was associated with local recurrence, while positive LNs were associated with distant recurrence based on the multivariate Cox analysis.

To further investigate the associations between multiple variables and patient prognosis, PCA and clustering analysis were performed. After applying one-hot encoding on all variables, the first 40 principal components explained more than 85% of the total variance (Supplementary Table 3). Clustering analysis was then performed based on the results of PCA, and two prognosis-related clinical phenotypes (groups A and B, which represent good prognosis and poor prognosis, respectively) were determined according to the elbow method (Fig. 2). Group B had significantly worse RFS (HR 3.863, 95% CI 2.508–5.95) and OS (HR 5.987, 95% CI 3.317–10.808) than group A (Fig. 3). Compared to patients in group A, patients in group B had significantly higher FIGO stages, more comorbidities, a higher frequency of LEEP, and positive HPV. In addition, larger tumor sizes, non-squamous cell carcinoma, deeper stromal invasion, LVSI, positive surgical margins, positive parametrial involvement, and LN metastasis were more common in group B (Supplementary Table 4).

Collectively, based on univariate analysis, multivariate analysis, PCA, and clustering analysis, we identified certain potential variables associated with patient prognosis, which were selected for the following prognostic model development.
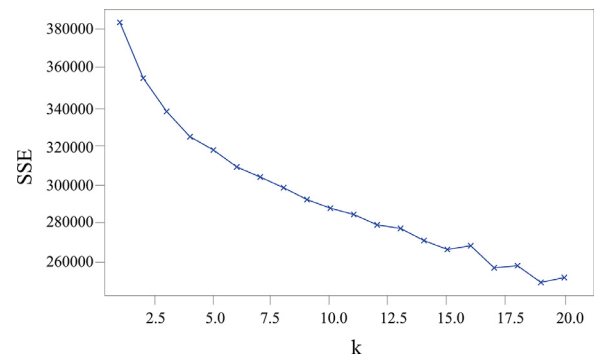

Fig. 2. K for K-means was determined using the elbow method.

Comparison of the prognostic predictive performance between machine learning models and traditional models in 4 datasets

To predict the individual risk of recurrence or death, 6 machine learning algorithms were tested in 4 datasets (22, 19, 13, and 7 variables in set 1, set 2, set 3, and set 4, respectively) and were compared with the logistic model. The average AUC value, sensitivity, and specificity obtained from all machine learning models and the logistic model in both the validation group and test group are presented in Tables 4 and 5. For predicting the risk of recurrence, SVM exhibited the best performance with higher accuracy, sensitivity, and specificity values than the logistic model in 4 datasets. For estimating the individual risk of death, the best predictive performance was obtained by RF. Regarding the specific recurrence site (local or distant recurrence), we again found that the AUC of SVM significantly surpassed those of the remaining models.

To predict the specific time of RFS and OS, we selected RSF and GBDT as the machine learning methods for their superiority in time prediction. The comparison was then made between these two models and the Cox regression model in 4 datasets (Table 6). The C-index of the two machine learning models was markedly higher than that of the Cox model in all 4 datasets. Similar findings were observed for MAE. These findings suggest that machine learning models showed better predictive performance with a higher C-index and lower MAE than the Cox regression model.

To evaluate model performance with different variables, we compared machine learning models and the Cox model across 4 datasets (22, 19, 13, and 7 variables in set 1, set 2, set 3, and set 4, respectively) for predicting RFS and OS (Table 6). The Cox model exhibited the best performance in dataset 4 (7 significant variables in multivariate analysis) but the worst performance in dataset 1 (all 22 variables). In contrast, the performance of machine learning models improved as more variables were added to the models. These findings indicate that the prognostic predictive performance of machine learning models outperformed that of traditional logistic or Cox models, especially when using multiple variables.

Establishment of a novel web-based predictive calculator based on the machine learning models

To better apply the prediction models in clinical practice and create user-friendly access, the statistical formulas were implemented in a web-based predictive calculator. After entering the clinicopathologic information of the patient and time of current follow-up after surgery, physicians/users can estimate the patient's individual conditional risk of death, risk of recurrence, risk of site-specific recurrence, RFS, and OS. For example, as the screenshot shows in Fig. 4, the estimated conditional probabilities of overall death, overall recurrence, local recurrence, and distant recurrence were 10.2%, 11.17%, 2.68%, and 2.16%, respectively. This calculator may help physicians identify patients who are at high risk of recurrence or death, remind them of

Table 2

Multivariate Cox analysis: factors associated with recurrence-free survival and overall survival in stage IA1 (LVSI) to IIB2 cervical cancer patients.

| Characteristics	No.	Multivariate			
		RFS		OS	
		HR (95%CI)	P	HR (95%CI)	P
FIGO (%)			<0.001		<0.001
IA1 (LVSI)	27	1		1	
IA2	136	0.502 [0.081,3.105]		1.005 [0.136,7.347]	
IB1	3202	0.633 [0.196,2.044]		0.735 [0.176,3.073]	
IB2	605	1.019 [0.312,3.326]		1.678 [0.4,7.037]	
IIA1	734	1.137 [0.349,3.708]		1.347 [0.319,5.682]	
IIA2	338	1.506 [0.458,4.949]		1.828 [0.431,7.759]	
IIB1	39	1.062 [0.249,4.530]		1.299 [0.233,7.246]	
IIB2	31	1.444 [0.368,5.667]		2.133 [0.425,10.71]	
Adjuvant therapy (%)			0.009		0.041
No	2123	1		1	
Yes	2989	1.51 [1.109,2.055]		1.44 [1.016,2.041]	
Tumor size, cm			<0.001		<0.001
<0.5	975	1		1	
[0.5,1)	96	0.517 [0.188,1.423]		0.59 [0.188,1.856]	
[1,1.5)	338	0.458 [0.217,0.968]		0.373 [0.157,0.89]	
[1.5,2)	428	1.873 [1.053,3.332]		1.701 [0.867,3.337]	
[2,2.5)	422	0.886 [0.448,1.753]		0.552 [0.233,1.309]	
[2.5,3)	518	0.956 [0.526,1.738]		0.862 [0.432,1.719]	
[3,3.5)	727	0.884 [0.481,1.625]		0.838 [0.416,1.687]	
[3.5,4)	623	1.141 [0.637,2.042]		1.054 [0.537,2.071]	
[4,4.5)	375	0.9 [0.439,1.844]		0.723 [0.31,1.685]	
[4.5,5)	188	1.33 [0.684,2.588]		1.257 [0.589,2.682]	
≥5	422	1.808 [0.948,3.448]		1.488 [0.696,3.18]	
Histology			<0.001		<0.001
SCC	4179	1		1	
AC	576	1.706 [1.241,2.345]		1.921 [1.351,2.733]	
AS	281	1.69 [1.14,2.506]		1.949 [1.27,2.991]	
Rare type	76	2.395 [1.341,4.277]		2.134 [1.062,4.29]	
DSI			0.006		0.001
Negative	1219	1		1	
<2/3	1542	1.007 [0.627,1.618]		1.435 [0.771,2.668]	
≥2/3	2351	1.609 [1.032,2.507]		2.414 [1.336,4.36]	
Parametrial involvement			<0.001		<0.001
No	4857	1		1	
Yes	255	2.034 [1.509,2.742]		1.851 [1.324,2.59]	
LN metastasis			<0.001		<0.001
No	4112	1		1	
Pelvic LNs	710	1.414 [1.066,1.876]		1.513 [1.096,2.089]	
Common iliac LNs	248	3.078 [2.263,4.186]		3.5 [2.494,4.911]	
Para-aortic	42	4.503 [2.523.8.04]		6.543 [3.485,12.285]	
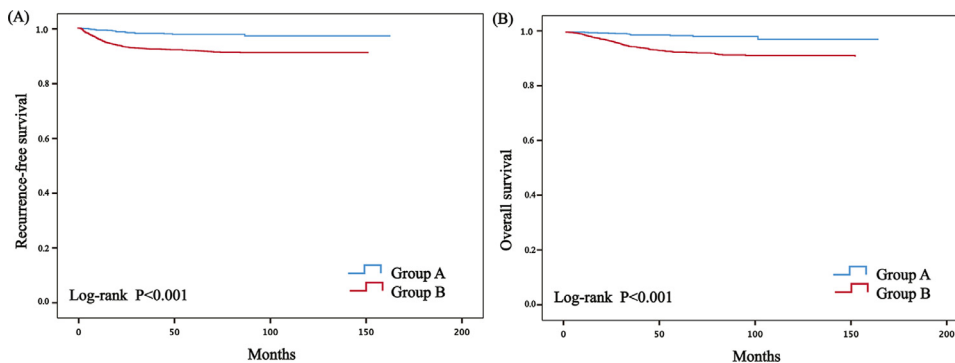
Fig. 3. Survival outcome comparisons between group A and B. Recurrence-free survival (A); Overall survival (B).

high-risk recurrence sites and make individual postoperative follow-up plans and further treatment strategies for CC patients (available on https://aicer.fckyy.org.cn).

Discussion

In this study, 5112 women from four tertiary hospitals were included in the analysis. There were 268 deaths and 343 recurrences during the follow-up period of 102 (36–168) months, of which 179 were local recurrences and 164 were distant recurrences. (1) Based on multivariate analysis for site-specific recurrence, we found that larger tumor sizes were associated with local recurrence, while positive LNs were associated with distant recurrence. (2) The machine learning models exhibited a better performance than traditional logistic or Cox regression models in estimating prognostic outcomes. With regard to the prediction of the individual risk of recurrence and death, the best results were obtained

Table 3

Multivariate Cox analysis for predictors of site-specific recurrence.

Characteristics	Local recurrence (n = 179)		Thorax recurrence (n = 61)		Abdomen recurrence (n = 34)		Bone recurrence (n = 22)	
	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
FIGO (%)		0.013		<0.001		0.006		0.003
I	1		1		1		1	
II	1.517 [1.094,2.103]		2.623 [1.599,4.304]		2.421 [1.288,4.551]		3.04 [1.466,6.306]	
Adjuvant treatment		0.012		0.02		0.487		0.213
No	1		1		1		1	
Yes	1.714 [1.123,2.616]		2.194 [1.13,4.26]		1.335 [0.591,3.011]		1.813 [0.711,4.619]	
Tumor size, cm		0.005						
<2	1		NC		NC		NC	
[2,4)	0.997 [0.693,1.434]							
≥4	1.782 [1.162,2.732]							
Histology		0.012		<0.001				
SCC	1		1		NC		NC	
AC	1.606 [1.034,2.494]		2.161 [1.078,4.331]					
AS	1.392 [0.769,2.521]		4.559 [2.406,8.638]					
Rare type	2.787 [1.299,5.978]		4.673 [1.669,13.08]					
DSI		0.004		0.152		0.222		0.818
Negative	1		1		1		1	
<2/3	0.921 [0.508,1.671]		1.054 [0.352,3.158]		3.694 [0.817,16.707]		1.5 [0.385,5.841]	
≥2/3	1.849 [1.073,3.184]		1.996 [0.745,5.346]		3.488 [0.797,15.261]		1.498 [0.401,5.597]	
Surgical margin		0.023		0.886				0.387
No	1		1		NC		1	
Yes	1.602 [1.068,2.403]		1.050 [0.536,2.058]				1.511 [0.593,3.851]	
Parametrial involvement		0.002		<0.001		<0.001		0.274
No	1		1		1		1	
Yes	2.005 [1.301,3.09]		2.862 [1.602,5.111]		3.778 [1.82,7.845]		1.756 [0.64,4.822]	
LN metastasis		0.059		<0.001		0.001		0.002
No	1		1		1		1	
Yes	1.379 [0.988,1.925]		3.047 [1.824,5.091]		3.051 [1.583,5.881]		3.159 [1.524,6.546]	

NC: not calculated because variables show no significance in univariate analysis.

Fig. 4. Screenshot for the web-based predictive calculator predicting individual conditional risk of death, risk of recurrence, risk of site-specific recurrence, RFS, and OS. The calculator is available at https://aicer.fckyy.org.cn. Choose or enter the value for each variable, and then press the "Submit" button.

by SVM. For predicting the specific time of RFS and OS, all machine learning models outperformed the Cox regression model. (3) The machine learning models were superior to traditional models when using multiple variables, and the performance of the machine learning models improved as more variables were added to the models. (4) A novel simple and efficient user-friendly web-based calculator was developed and externally validated to precisely predict postoperative survival and site-specific recurrence in CC patients.

Tumor recurrence after surgical resection remains a challenge in treating CC patients. A major barrier to the effective prevention of postoperative recurrence is the inability to identify "at risk" and "high-risk" recurrence sites. Traditionally, the estimation of risk was based on clinicians' experience and knowledge by assigning individuals into crude categories as low- or high-risk groups without accurately accounting for the specifics of each unique patient. Considering these shortcomings, the development of accurate clinical models to predict an individual's future risk of site-specific recurrence and death is urgently needed and will be an effective prevention approach and will also greatly optimize follow-up strategies.

In a review of the previous literature, most studies applied logistic or Cox proportional hazards regression models with nomograms to predict oncologic prognostic outcomes [3,4],. However, because of the inability of these models to address nonlinear relationships, which occur in real-world settings, an increasing number of studies have started to apply artificial intelligence and machine learning in the prediction of survival outcomes [8–10]. As a novel analytic approach, machine learning models are able to automatically learn feature characteristics from raw data, fit censored survival data, and exhibit better performance when processing larger datasets and dealing with nonlinear relationships between variables. However, only a few studies have integrated machine learning methods into the prediction of oncologic survival outcomes in the area of CC. The sample sizes of these studies were relatively small;

Table 4.
Comparison of model performance (probability prediction of recurrence and survival, **happen or not**).

	Recurrence						Survival					
	Validation group (n = 1023)			Test group (n = 1023)			Validation group (n = 1023)			Test group (n = 1023)		
Model	AUC	Sen	Spe	AUC	Sen	Spe	AUC	Sen	Spe	AUC	Sen	Spe
Set 1												
Logistic	0.701(0.016)	0.727(0.039)	0.675(0.014)	0.785	0.725	0.679	0.860(0.012)	0.872(0.014)	0.849(0.002)	0.775	0.889	0.512
SVM	0.703(0.016)	0.769(0.033)	0.636(0.011)	0.794	0.768	0.659	0.771(0.026)	0.853(0.040)	0.688(0.025)	0.836	0.796	0.714
ANN	0.853(0.022)	0.739(0.037)	0.768(0.009)	0.728	0.561	0.749	0.967(0.014)	0.966(0.022)	0.968(0.006)	0.867	0.556	0.975
DT	0.685(0.017)	0.857(0.115)	0.515(0.109)	0.607	0.768	0.445	0.942(0.029)	0.925(0.063)	0.958(0.006)	0.777	0.593	0.961
RF	0.845(0.041)	0.876(0.072)	0.814(0.015)	0.741	0.522	0.874	0.981(0.032)	0.965(0.064)	0.997(0.002)	0.890	0.352	0.994
XGBoost	0.778(0.025)	0.881(0.056)	0.740(0.020)	0.751	0.667	0.674	0.980(0.032)	0.966(0.065)	0.994(0.004)	0.906	0.593	0.991
LightGBM	0.897(0.051)	0.879(0.110)	0.915(0.011)	0.757	0.464	0.929	0.981(0.026)	0.970(0.055)	0.992(0.004)	0.895	0.611	0.988
Set 2												
Logistic	0.699(0.026)	0.719(0.053)	0.679(0.014)	0.783	0.696	0.684	0.718(0.014)	0.739(0.039)	0.697(0.030)	0.773	0.667	0.715
SVM	0.701(0.021)	0.762(0.042)	0.939(0.015)	0.790	0.783	0.655	0.722(0.017)	0.780(0.045)	0.663(0.035)	0.782	0.741	0.668
ANN	0.697(0.024)	0.758(0.068)	0.637(0.057)	0.652	0.536	0.710	0.768(0.065)	0.819(0.060)	0.717(0.065)	0.682	0.481	0.835
DT	0.712(0.029)	0.728(0.059)	0.696(0.055)	0.645	0.580	0.681	0.597(0.008)	0.998(0.004)	0.196(0.013)	0.591	0.963	0.220
RF	0.823(0.031)	0.883(0.060)	0.763(0.010)	0.752	0.623	0.780	0.855(0.025)	0.899(0.048)	0.811(0.008)	0.783	0.556	0.807
XGBoost	0.803(0.030)	0.844(0.055)	0.762(0.010)	0.744	0.594	0.791	0.830(0.024)	0.873(0.047)	0.786(0.010)	0.759	0.611	0.770
LightGBM	0.811(0.031)	0.858(0.059)	0.764(0.010)	0.747	0.623	0.747	0.675(0.019)	0.832(0.105)	0.518(0.071)	0.748	0.852	0.577
Set 3												
Logistic	0.688(0.024)	0.677(0.059)	0.688(0.020)	0.802	0.783	0.714	0.710(0.025)	0.725(0.056)	0.694(0.023)	0.784	0.704	0.695
SVM	0.696(0.020)	0.711(0.043)	0.680(0.019)	0.803	0.797	0.708	0.706(0.022)	0.716(0.055)	0.695(0.039)	0.789	0.796	0.651
ANN	0.718(0.030)	0.750(0.053)	0.687(0.068)	0.728	0.681	0.644	0.745(0.025)	0.712(0.053)	0.778(0.025)	0.758	0.611	0.767
DT	0.649(0.009)	0.869(0.012)	0.430(0.025)	0.699	0.855	0.431	0.612(0.020)	0.645(0.161)	0.578(0.172)	0.742	0.667	0.719
RF	0.740(0.033)	0.738(0.051)	0.743(0.020)	0.751	0.609	0.767	0.787(0.013)	0.830(0.017)	0.744(0.014)	0.785	0.722	0.737
XGBoost	0.679(0.015)	0.801(0.046)	0.556(0.022)	0.764	0.754	0.594	0.654(0.044)	0.768(0.081)	0.541(0.055)	0.751	0.759	0.609
LightGBM	0.804(0.038)	0.833(0.062)	0.776(0.018)	0.766	0.609	0.766	0.633(0.046)	0.779(0.087)	0.487(0.053)	0.782	0.889	0.442
Set 4												
Logistic	0.634(0.030)	0.679(0.054)	0.590(0.008)	0.752	0.725	0.605	0.717(0.034)	0.763(0.063)	0.672(0.035)	0.792	0.722	0.670
SVM	0.682(0.018)	0.760(0.029)	0.604(0.020)	0.778	0.768	0.612	0.716(0.031)	0.731(0.055)	0.702(0.031)	0.790	0.704	0.707
ANN	0.644(0.024)	0.780(0.790)	0.508(0.049)	0.764	0.754	0.630	0.663(0.043)	0.825(0.094)	0.501(0.016)	0.779	0.889	0.492
DT	0.659(0.034)	0.663(0.117)	0.655(0.059)	0.732	0.725	0.624	0.663(0.049)	0.774(0.097)	0.552(0.035)	0.799	0.907	0.562
RF	0.855(0.035)	0.872(0.063)	0.837(0.112)	0.738	0.754	0.835	0.660(0.047)	0.763(0.096)	0.557(0.028)	0.803	0.870	0.564
XGBoost	0.664(0.032)	0.739(0.057)	0.591(0.012)	0.770	0.696	0.798	0.662(0.043)	0.763(0.098)	0.561(0.029)	0.808	0.870	0.559
LightGBM	0.647(0.026)	0.734(0.065)	0.560(0.047)	0.780	0.754	0.566	0.695(0.019)	0.733(0.051)	0.658(0.023)	0.798	0.778	0.651

Table 5
Comparison of model performance (probability prediction of recurrence site).

| Model | Validation group (n = 4089) 5-flod CV | | | | | Test group (n = 1023) | | | | |
| | | Local | | Distant | | | Local | | Distant | |
	AUC(std)	Sensitivity(std)	Specificity(std)	Sensitivity(std)	Specificity(std)	AUC	Sensitivity	Specificity	Sensitivity	Specificity
Set 1										
LR	0.767(±0.034)	0.494(±0.066)	0.663(±0.018)	0.662(±0.057)	0.773(±0.027)	0.776	0.389	0.757	0.455	0.842
SVM	0.767(±0.026)	0.556(±0.082)	0.662(±0.026)	0.656(±0.059)	0.802(±0.035)	0.781	0.472	0.750	0.424	0.844
ANN	0.944(±0.012)	0.837(±0.042)	0.690(±0.004)	0.850(±0.050)	0.949(±0.015)	0.637	0.167	0.920	0.273	0.932
DT	0.725(±0.029)	0.539(±0.159)	0.705(±0.062)	0.764(±0.142)	0.671(±0.070)	0.731	0.583	0.623	0.485	0.762
RF	0.847(±0.032)	0.568(±0.061)	0.632(±0.023)	0.722(±0.078)	0.773(±0.027)	0.737	0.306	0.861	0.515	0.863
XGBoost	0.823(±0.041)	0.524(±0.086)	0.632(±0.027)	0.695(±0.082)	0.764(±0.033)	0.715	0.333	0.823	0.515	0.837
LightGBM	0.823(±0.041)	0.524(±0.086)	0.632(±0.027)	0.695(±0.082)	0.764(±0.033)	0.716	0.333	0.823	0.545	0.864

Table 6
. Comparison of model performance (prediction of RFS and OS).

| Model | RFS (344 events) | | | | OS (268 events) | | | |
| | Validation group (n = 1023) | | Test group (n = 1023) | | Validation group (n = 1023) | | Test group (n = 1023) | |
	C-index	Mean absolute error	C-index	Mean absolute error	C-index	Mean absolute error	C-index	Mean absolute error
Set 1								
Cox	0.753(±0.028)	14.391(±1.119)	0.782	11.717	0.797(±0.020)	25.630(±2.077)	0.794	23.390
RF	0.783(±0.028)	12.951(±1.343)	0.785	11.396	0.802(±0.028)	22.475 (±2.169)	0.850	20.085
GDBT	0.766(±0.025)	12.358(±1.103)	0.786	11.079	0.787(±0.034)	22.171(±2.083)	0.825	21.415
Set 2								
Cox	0.753(±0.025)	14.318(±1.168)	0.783	11.107	0.796(±0.022)	25.335(±2.174)	0.801	23.595
RF	0.773(±0.030)	13.248 (±1.448)	0.789	10.933	0.802(±0.027)	22.478(±2.093)	0.847	20.232
GDBT	0.768(±0.031)	14.399(±1.099)	0.784	12.025	0.794(±0.021)	22.846(±2.057)	0.820	22.060
Set 3								
Cox	0.753(±0.021)	15.268(±1.147)	0.786	11.955	0.791(±0.021)	24.403(±2.186)	0.801	23.619
RF	0.774(±0.013)	12.823(±1.277)	0.808	11.416	0.789(±0.028)	22.715(+2.110)	0.849	20.548
GDBT	0.771(±0.018)	15.227(±1.102)	0.798	11.916	0.787(±0.034)	23.335(±2.111)	0.833	22.437
Set 4								
Cox	0.762(±0.028)	14.825(±1.078)	0.767	11.593	0.793(±0.023)	25.249(±2.1.71)	0.815	23.387
RF	0.780(±0.026)	13.921(±1.236)	0.771	12.432	0.796(±0.023)	22.921(±1.965)	0.823	21.180
GDBT	0.765(±0.032)	13.154(±1.117)	0.775	11.247	0.780(±0.021)	23.087(±2.049)	0.815	23.355

to our knowledge, the largest dataset (n = 768) was reported by Matsuo et al. [11]. Additionally, the majority of these studies were conducted in single institutions and lacked external validation [11–13]. Their main prediction outcomes were the probability of recurrence or death, but they seldom took specific recurrence sites (local or distant recurrence) into consideration, which is essential for planning appropriate follow-up strategies.

Considering the deficiencies of previous studies and the promising application value of machine learning algorithms, in the present study, we applied 6 machine learning methods to predict the risk of recurrence/death and 2 machine learning methods to predict the specific time of RFS/OS based on the data of 5112 CC patients, and we externally validated these models using data from four tertiary hospitals. In our study, we observed that the machine learning models exhibited superior prognostic predictive performance compared to linear regression models (logistic and Cox models) in estimating individual risk of recurrence/death or RFS/OS. It is worth noting that the machine learning models also outperformed the traditional logistic model in predicting site-specific recurrence (local or distant metastasis). In addition, the performance of the machine learning models improved when more features were added to the models. These findings revealed that machine learning might be a better analytic approach in prognostic prediction, especially when using multiple variables.

Admittedly, although many studies have identified clinicopathologic predictors for OS and recurrence after radical hysterectomy of CC, additional information on site-specific recurrence is still needed to select diagnostic procedures during surveillance. In the current study,

we identified FIGO stage, adjuvant therapy, tumor size, histology, DSI, parametrial involvement, and LN status as independent predictors of OS and recurrence using multivariate analysis. For site-specific recurrence, larger tumor size was an independent predictor of local recurrence in multivariate analysis but not a significant predictor of distant recurrence. This finding was consistent with those of previous studies which reported that tumor size was strongly correlated with local recurrence rather than distant recurrence [14–17]. In addition, consistent with the findings of certain published studies [16,18,19], we found that positive LNs were independent predictors of distant recurrence (thoracic, abdominal, and bone recurrence), whereas they were not significant for local recurrence. Collectively, our study supported the identification of risk factors for recurrence in each specific site, which also ensures the rationality for building models to estimate site-specific recurrence.

Of note, in this study, we were the first group to establish a web-based calculator that inputs the clinicopathologic features of individual patients into the developed machine learning algorithms. Clinicians can estimate the conditional risk of death and site-specific recurrence and generate personalized surveillance strategies accordingly, including when to follow up patients and what strategies to use for further diagnosis and treatment. For example, if a patient shows a high recurrence risk in the local region, then the clinician can recommend pelvic MRI for effective screening. If a patient is estimated to have a high thoracic recurrence risk, then chest CT might be a better choice. This can greatly save medical resources and optimize individualized surveillance in precision medicine.

There are several limitations in this study. First, considering the retrospective nature of this study, future prospective studies are still warranted. Second, our models were developed and validated based on Chinese patients, and the generalizability needs further validation with non-Chinese patient data. Third, as the follow-up time was relatively short (<5 years), caution should be taken in applying this model to estimate long-term prognostic outcomes.

In conclusion, this study used machine learning technology as a novel approach to develop prediction models to precisely estimate survival and site-specific recurrence in CC patients. We trained and externally validated the models based on the data of 5112 CC patients from four tertiary hospitals, which is the largest multicenter cohort to date. Our models can provide multitask prediction using various machine learning methods, which can estimate the individual probability of overall survival, overall recurrence, and site-specific recurrence as well as RFS and OS times at the same time. The machine learning models outperformed traditional logistic or Cox models, especially when using multiple variables. Of note, we built a novel user-friendly web-based calculator based on our machine learning algorithms for the first time. This calculator can help to identify patients who are at high risk of postoperative recurrence or death and provide clinicians with useful information for treatment decision-making and follow-up plan formulation.

Contributors

Conceptualization: Chenyan Guo, Junjun Qiu,
Methodology: Chenyan Guo, Jue Wang, Yongming Wang
Data acquisition: Chenyan Guo, Xinyu Qu, Zhiwen Shi, Yan Meng
Validation: Keqin Hua, Junjun Qiu
Writing-original draft: Chenyan Guo
Writing-review & editing: all authors
Supervision: Keqin Hua, Junjun Qiu

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data sharing statement

The data that support the findings of this study are available upon request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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