ORIGINAL RESEARCH

Predictive Value of Simulated CT Radiomics Combined with Ipsilateral Lung Dosimetry Parameters for Radiation Pneumonitis in Patients with Esophageal Cancer: A Machine Learning-Based Retrospective Study

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Objective: To explore how non-surgical esophageal cancer patients can identify high-risk factors for radiation-induced pneumonitis after receiving radiotherapy.

Methods: We retrospectively included 228 esophageal cancer patients who were unable to undergo surgical treatment but received radiotherapy for the first time. By retrospective analysis and identifying potential risk factors for symptomatic radiation-induced pneumonitis (ie ≥grade 2), as well as delineating the affected lung as an area of interest on localized CT and extracting radiomics features, along with extracting dosimetric parameters from the affected lung area. After feature screening, patients were randomly divided into training and testing sets in a 7-to-3 ratio, and a prediction model was established using machine learning algorithms. Finally, the receiver operating characteristic (ROC) curve and decision curve analysis (DCA) were used to validate the predictive performance of the model.

Results: A total of 54 cases of symptomatic radiation pneumonitis occurred in this study, with a total incidence rate of 23.68%. The results of multivariate analysis showed that the occurrence of symptomatic radiation pneumonitis was significantly correlated with the mean lung dose (MLD), esophageal PTVD90, esophageal PTVV50, V5, V10, V15, and V20 in patients. The machine learning prediction model constructed based on candidate prediction variables has a prediction performance interval between 0.751 (95% CI: 0.700–0.802) and 0.891 (95% CI: 0.840–0.942) in the training and validation sets, respectively. Among them, the RFM algorithm has the best prediction performance for radiation-induced pneumonitis, with 0.891 (95% CI: 0.840–0.942) and 0.887 (95% CI: 0.836–0.938) in the training and validation sets, respectively.

Conclusion: The combination of localization CT radiomics features and diseased lung dosimetry parameters has good predictive value for radiation-induced pneumonitis in esophageal cancer patients after radiotherapy. Especially, the radiation-induced pneumonitis prediction model constructed using RF algorithm can be more effectively used to guide clinical decision-making in esophageal cancer patients.

Keywords: esophageal cancer, radiotherapy, radiation pneumonitis, radiomics, prediction model

Introduction

Esophageal cancer is a common malignant tumor of the digestive tract, and radiotherapy is one of the important treatment measures.[1,2] In clinical practice, the dosage of radiotherapy is an important factor determining the efficacy of non-surgical treatment for esophageal cancer patients.[3] However, as the radiation dose increases, the adverse reactions of esophageal cancer patients also increase. During the process of receiving radiation therapy for patients, the high sensitivity of normal lung tissue to radiation limits the application of radiation therapy in chest tumors to a certain

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extent.[4] Previous studies have shown that the incidence of radiation-induced lung injury in chest malignant tumors after radiotherapy ranges from 10% to 30%, and the actual number of patients who experience radiation-induced lung injury in clinical practice is underestimated.[5–7]

In clinical practice, radiation-induced lung injury can be divided into acute radiation-induced pneumonitis and long-term radiation-induced pulmonary fibrosis.[7] Among them, radiation pneumonitis often occurs within 3 months after patients receive radiation therapy, with clinical manifestations including cough, difficulty breathing, and in severe cases, it can further develop into respiratory failure, even endangering the patient's life. At present, the pathogenesis of radiation-induced lung disease is not yet clear, and there is a lack of targeted treatment measures.[8] In view of this, relying on certain early indicators or non-invasive examinations to predict the incidence of radiation pneumonitis has important clinical guidance value for designing personalized treatment plans for high-risk patients.

At present, the parameters used to predict radiation pneumonitis in clinical practice include general clinical information of patients, pulmonary dosimetry parameters, and changes in lung function, etc.[9–11] These indicators have their own advantages and disadvantages in predicting radiation pneumonitis. In recent years, with the rapid development of radiomics and its widespread use in auxiliary diagnosis and prognosis prediction, it has provided the possibility for screening reference predictive factors and improving the predictive efficiency of predicting radiation pneumonitis.[12] In addition, with the continuous application of deep learning in clinical medicine, the diagnosis and treatment of a large number of diseases rely on advanced machine learning algorithms to better serve clinical decision-making.[13] Encouraged by this, this study intends to use radiomics methods to capture features from CT images of esophageal cancer patients, and construct a machine learning prediction model by integrating the dosimetric parameters of the patient's affected lung, in order to explore the predictive value of radiation pneumonitis and guide clinical practice more reasonably.

Materials and Methods
Study Population
We retrospectively included 228 esophageal cancer patients who were admitted to the radiotherapy department of our hospital from January 2017 to December 2023 and were unable to undergo surgical treatment but received radiotherapy for the first time. Inclusion criteria: 1) Patients diagnosed with esophageal squamous cell carcinoma by pathology; 2) Patients with Karnofsky score ≥70; 3) Patients with no abnormal liver or kidney function and no history of chest radiation therapy; 4) Patients with complete dose volume parameters and targeted treatment area located in the chest cavity; 5) Patients who meet the indications for intensity modulated radiation therapy in the trial. Exclusion criteria: 1) Patients with underlying lung diseases such as chronic obstructive pulmonary disease and interstitial lung disease; 2) Patients with low bone marrow hematopoietic function; 3) Patients who have been interrupted by radiotherapy for more than 7 days or do not have a complete radiotherapy plan. This study has been approved by the Medical Ethics Committee of Wuhan First Hospital (NO.202031) and study complies with the Declaration of Helsinki. The personal privacy of all patients included in this study has been kept confidential, and the informed exemption consent of patients for this study has been approved by the ethics committee for implementation. The patient inclusion and prediction model construction process for this study was shown in Figure 1.

CT Image Acquisition and Quality Control Evaluation
All patients received Siemens performing localization scanning using Go.Now type CT. The scanning voltage is 110kV, the tube current is in automatic mode, the layer thickness is set to 5mm, and the matrix size is 512×512 pixels. After the simulation positioning is completed, two physicians with over 10 years of radiation therapy experience can draw the target area and organs at risk in the Monaco planning system. All patient radiotherapy plans are designed by the same radiotherapy physicist, using fixed field intensity modulated radiotherapy technology with 6MV X-ray energy. The radiation field includes two pairs of tangent fields and a zero degree field. The radiotherapy prescription is 50Gy/25fx. All plans are implemented after being reviewed by radiologists and physicists. During radiotherapy, regularly record the values of V5, V10, V15, V20, V25, V30, and mean lung dose (MLD) in the affected lung.
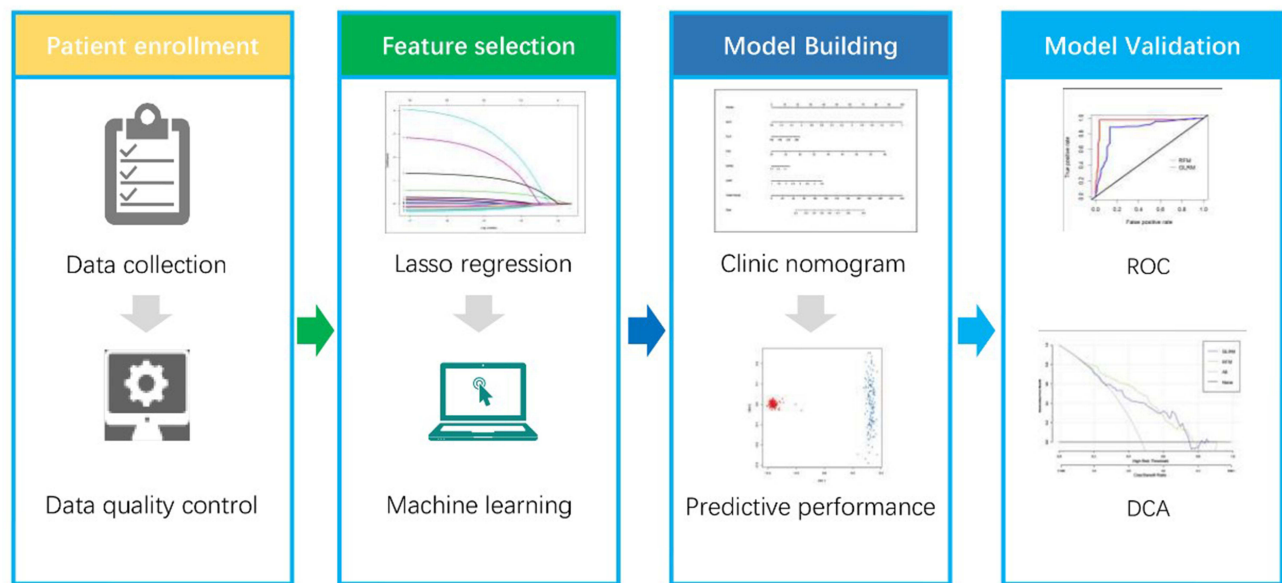
Figure 1 Flow chart of patient collection and data processing in this study.

Image Segmentation and Feature Extraction

We imported the pre radiotherapy positioning CT images of patients into 3D Slicer (version 4.11) software in DICOM format, and used a semi-automatic and manual layer-by-layer correction method to segment the affected lung as the region of interest. The segmentation of the patient's affected lung was completed by an imaging specialist and reviewed by a diagnostic physician with more than 10 years of experience. We used the radiomics plugin in 3D-Slicer software to extract imaging omics features, including original image features, texture features, and intensity and texture features calculated through wavelet decomposition. Before feature extraction, all images were uniformly adjusted to $1 \times 1 \times 1$ pixels using resampling techniques.

Feature Selection and Prediction Model Construction

This study conducted stratified random sampling on patients and divided them into training and testing sets in a 7:3 ratio. Firstly, we calculated the Spearman correlation coefficients for all features and remove feature factors with absolute correlation coefficients greater than 0.9. Then, we used the method of feature recursive elimination to filter and obtain the best set of features. This study used random forests, generalized linear models, decision trees, and neural network algorithms to construct machine learning models. In addition, to avoid overfitting, we used grid search in the training set to facilitate the selection of optimal model parameters, and used 10-fold cross validation for model robustness training and validation.

Statistical Analysis

We used SPSS 26.0 software to conduct a global test on the dosimetric parameters of the affected lung. The *t*-test was used for inter-group comparisons that followed a normal distribution, while the Wilcoxon rank sum test was used for those that did not. In addition, we used R software (version 4.0.2) for feature screening and machine learning model creation, and evaluated the predictive performance of the model through receiver operator characteristic curve (ROC), as well as evaluated the clinical benefits of different predictive models using decision curve analysis (DCA). $P < 0.05$ indicates a statistically significant difference.

Results

Patient Clinical and Treatment Characteristics

A total of 228 patients with esophageal cancer who received radiotherapy were included, including 54 patients diagnosed with radiation pneumonitis (ie grade ≥ 2). These patients were randomly divided into a training group (n = 160) and

a testing group (n = 68). In addition, patient clinical data and total dose, 90% planned target area received dose, corresponding proportion of 50Gy irradiation plan target area, bilateral lung volume, lung dose volume parameters V5~V40, and lung average dose waiting for selection parameters were compared between groups. It was found that clinical staging, radiotherapy mode, and radiotherapy dose were correlated with the occurrence of radiation pneumonitis in esophageal cancer patients after radiotherapy (P values < 0.05). The general information and dose-volume parameters of all patients were summarized in Table 1 and Supplementary Table 1.

Feature Selection

A total of 23 features were obtained from radiomics and dose-volume parameter analysis. We used the LASSO regression model to select eight features, and all radiomics features used wavelet filters, as shown in Figure 2A and B. These features include esophageal PTVD90, esophageal PTVV50, total dose, MLD, V5, V10, V15, V20. The weights selected

Table 1 The Characteristics of Study Population and Clinical Outcome

Variables	Overall (N=228)	Radiation Pneumonitis (N=54)	Non- Radiation Pneumonitis (N=174)	P-value
Age (median [IQR]),year	41.50 [30.00, 56.00]	38.50 [31.50, 54.25]	42.00 [29.25, 56.00]	0.572
Sex (%)				
Male	105 (46.1)	26 (48.1)	79 (45.4)	0.844
Female	123 (53.9)	28 (51.9)	95 (54.6)	
BMI (median [IQR]),kg/m2	24.85 [22.20, 27.72]	24.75 [22.05, 28.08]	24.90 [22.22, 27.67]	0.921
Smoking (%)				
Yes	133 (58.3)	31 (57.4)	102 (58.6)	1.000
No	95 (41.7)	23 (42.6)	72 (41.4)	
Drinking (%)				
Yes	103 (45.2)	24 (44.4)	79 (45.4)	1.000
No	125 (54.8)	30 (55.6)	95 (54.6)	
Site (%)				
Up	78 (34.2)	17 (31.5)	61 (35.1)	0.713
Middle	66 (28.9)	18 (33.3)	48 (27.6)	
Down	84 (36.8)	19 (35.2)	65 (37.4)	
ECOG (%),score				
1	118 (51.8)	30 (55.6)	88 (50.6)	0.628
2	110 (48.2)	24 (44.4)	86 (49.4)	
Chemotherapy (%)				
Yes	112 (49.1)	29 (53.7)	83 (47.7)	0.539
No	116 (50.9)	25 (46.3)	91 (52.3)	
Surgery (%)				
Yes	119 (52.2)	33 (61.1)	86 (49.4)	0.178
No	109 (47.8)	21 (38.9)	88 (50.6)	
Stage (%)				
I–II	127 (55.7)	17 (31.5)	110 (63.2)	<0.001
III–IV	101 (44.3)	37 (68.5)	64 (36.8)	
Mode (%)				
Curative	67 (29.4)	14 (25.9)	53 (30.5)	0.746
Palliative	73 (32.0)	17 (31.5)	56 (32.2)	
Adjuvant	88 (38.6)	23 (42.6)	65 (37.4)	
IMRT (%)				
Late stage	117 (51.3)	30 (55.6)	87 (50.0)	0.577
Full stage	111 (48.7)	24 (44.4)	87 (50.0)	
Dose (%),Gy				
<60	129 (56.6)	19 (35.2)	110 (63.2)	0.001
≥60	99 (43.4)	35 (64.8)	64 (36.8)	

Abbreviation: IQR, Interquartile range; BMI, Body Mass Index; ECOG, Eastern Cooperative Oncology Group; IMRT, Intensity modulated radiation therapy.
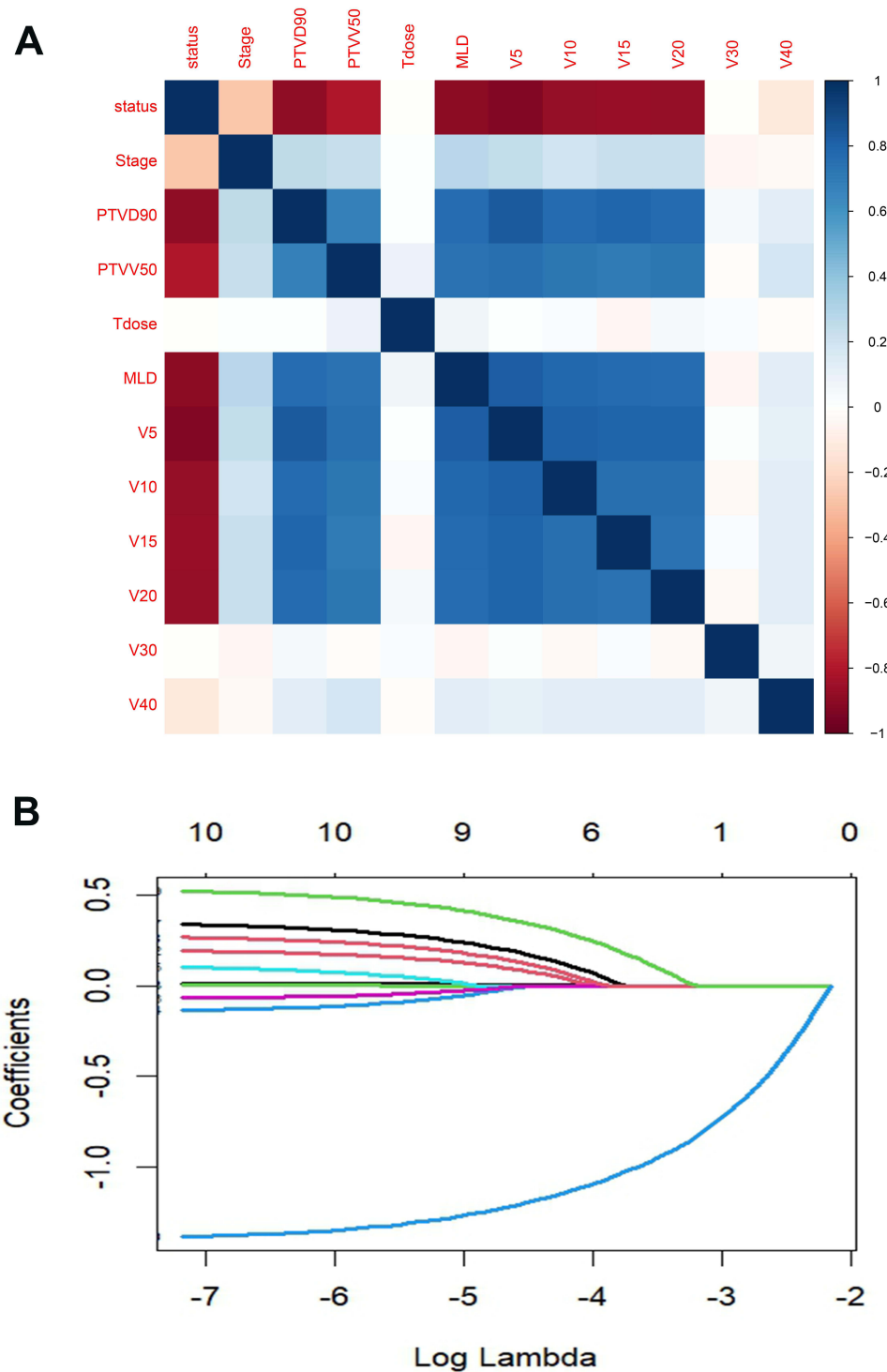
Figure 2 Radiomics features and dose-volume parameter associated with radiation pneumonitis. **(A)** Spearman correlation analysis; **(B)** LASSO regression analysis.

by LASSO regression analysis for the radiomics and dosimetry parameter characteristics related to radiation pneumonitis are shown in Supplementary Table 2.

Radiation Pneumonitis Nomogram Construction

According to univariate analysis, as shown in Table 2, the clinical staging, esophageal PTVD90, esophageal PTVV50, total dose, MLD, V5, V10, V15, V20 were potential high-risk factors for radiation pneumonitis. Multivariate analysis

Table 2 Univariate and Multivariate Logistic Regression Analysis of Risk Factors for Radiation Pneumonitis

Variables	Univariate			Multivariate		
	OR	95% CI	P-value	OR	95% CI	P-value
Age	1.03	0.23~5.39	0.18			
Sex						
Male	1.00					
Female	0.86	0.23~5.27	0.17			
BMI	1.74	0.27~6.74	0.26			
Smoking						
Yes	1.00					
No	0.53	0.12~1.58	0.72			
Drinking						
Yes	1.00					
No	0.49	0.14~7.81	0.43			
Site						
Up	1.00					
Middle	0.86	0.23~5.27	0.53			
Down	1.26	0.14~10.35	0.42			
ECOG						
1	1.00					
2	1.52	0.85~3.56	0.19			
Chemotherapy						
Yes	1.00					
No	0.79	0.52~7.28	0.28			
Surgery						
Yes	1.00					
No	1.15	0.88~4.13	0.17			
Stage						
I–II	1.00					
III–IV	2.35	1.03~14.23	<0.05	2.19	0.75~10.21	<0.05
Mode						
Curative	1.00					
Palliative	0.87	0.23~4.17	0.71			
Adjuvant	0.58	0.15~4.26	0.23			
IMRT						
Late stage	1.00					
Full stage	0.42	0.12~2.38	0.85			
Dose						
<60	1.00			1.00		
≥60	4.13	1.17~10.06	<0.05	3.98	0.17~6.14	0.52
TFLV	2.16	0.22~5.16				
PTVD90	1.78	0.89~2.57	<0.05	1.82	0.71~3.16	<0.05
PTVV50	1.49	0.85~3.97	<0.05	1.57	0.42~4.97	<0.05
Tdose	2.03	0.23~3.87	0.51			
MLD	1.56	0.42~2.89	<0.05	1.72	0.26~3.01	<0.05
V5	1.78	0.58~4.52	<0.05	1.55	0.51~4.72	<0.05
V10	2.23	0.13~2.91	<0.05	2.06	0.23~4.06	<0.05
V15	1.69	0.26~4.09	<0.05	1.71	0.28~4.16	<0.05
V20	4.12	1.03~10.23	<0.05	4.22	1.07~8.57	<0.05

(*Continued*)

Table 2 (Continued).

Variables	Univariate			Multivariate		
	OR	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
V30	2.27	0.28~4.91	1.25			
V40	1.09	0.88~4.17	0.96			

Abbreviation: OR, Odd ratios; 95% CI, 95% confidence interval; BMI, Body Mass Index; ECOG, Eastern Cooperative Oncology Group; IMRT, Intensity modulated radiation therapy; TFLV, Lung volume; PTVD90, 90% planned target area acceptance dose; PTVV50, proportion of 50 Gy irradiation plan target area; Tdose, Total dose; MLD, Lung mean dose.

showed that the esophageal PTVD90, total dose, MLD, V5, V10, V15, V20 were independent predictors of radiation pneumonitis. On the basis of multivariate analysis, we developed a visible radiomics nomogram (Figure 3A) by combining esophageal PTVD90, MLD, V5, V10, V15, V20. In view of this, we also used calibration curves to confirm the consistency between the predicted and actual observed values of the nomogram for radiation pneumonitis. The Hosmer Lemeshow test showed no statistical difference between the predicted and actual values (P = 0.921) (Figure 3B).

Radiation Pneumonitis Machine Learning Based Prediction Model

As for the random forest prediction model, when we set mtry = 5 and ntree = 1200, the model will have the lowest error, that is, selecting esophageal PTVD90, esophageal PTVV50, MLD, V5, V10, V15, V20 as explanatory variables. The average decrease accuracy and average decrease Gini coefficient of each variable are shown in Figure 4A and Supplementary Table 3. Based on the average accuracy reduction index, we construct a decision tree using the top 10 variables. In this decision tree, postoperative menstruation; V5, V10, V15, and V20 was classified as a nodal variable for the occurrence of radiation pneumonitis after radiotherapy (Figure 4B). In addition, using the multi-layer perceptron module of the neural network, the input neurons of the model were sequentially inputted, and the occurrence of radiation pneumonitis was taken as the output neuron, as shown in Figure 4C. Finally, based on the artificial neural network prediction model, the normalized importance ranking of each dependent variable included esophageal PTVD90, esophageal PTVV50, MLD, V5, V10, V15, V20.

Performance Metrics of Four Machine Learning Prediction Models

As shown in Table 3, in the validation and testing queue, the random forest prediction model showed AUC values of 0.891 (95% CI:0.840~0.942) and 0.887 (95% CI: 0.836~0.938), respectively. In the validation and testing queue, the AUC of the neural network prediction model was 0.882 (95% CI: 0.831~0.933) and 0.879 (95% CI: 0.828~0.930), respectively. In contrast, the decision tree prediction model had AUC values of 0.811 (95% CI: 0.760~0.862) and 0.809 (95% CI: 0.758~0.860) in the training and validation sets, respectively. Obviously, as shown in Figure 5, the DCA showed that decision tree predictive ability was worse than that of random forests and neural networks, but it was better than the generalized linear prediction model (ie, the Nomogram) with AUC values of 0.751 (95% CI: 0.700~0.802) and 0.762 (95% CI: 0.711~0.813) in the training and validation sets, respectively.

The Interpretability of the Optimal Radiation Pneumonitis Prediction Model

Due to the best predictive performance of the random forest prediction model, in order to test its predictive performance in clinical practice. We conducted simulation training using clinical impact curve (CIC), as shown in Figure 6. In terms of distinguishing the risk of radiation pneumonitis from non-radiation pneumonitis, the two can achieve the maximum span of differentiation. In view of this, using machine learning techniques from random forests can establish more effective prediction models. This predictive model may be useful in clinical practice and help clinicians tailor precise management and treatment for radiation pneumonitis in esophageal cancer patients.
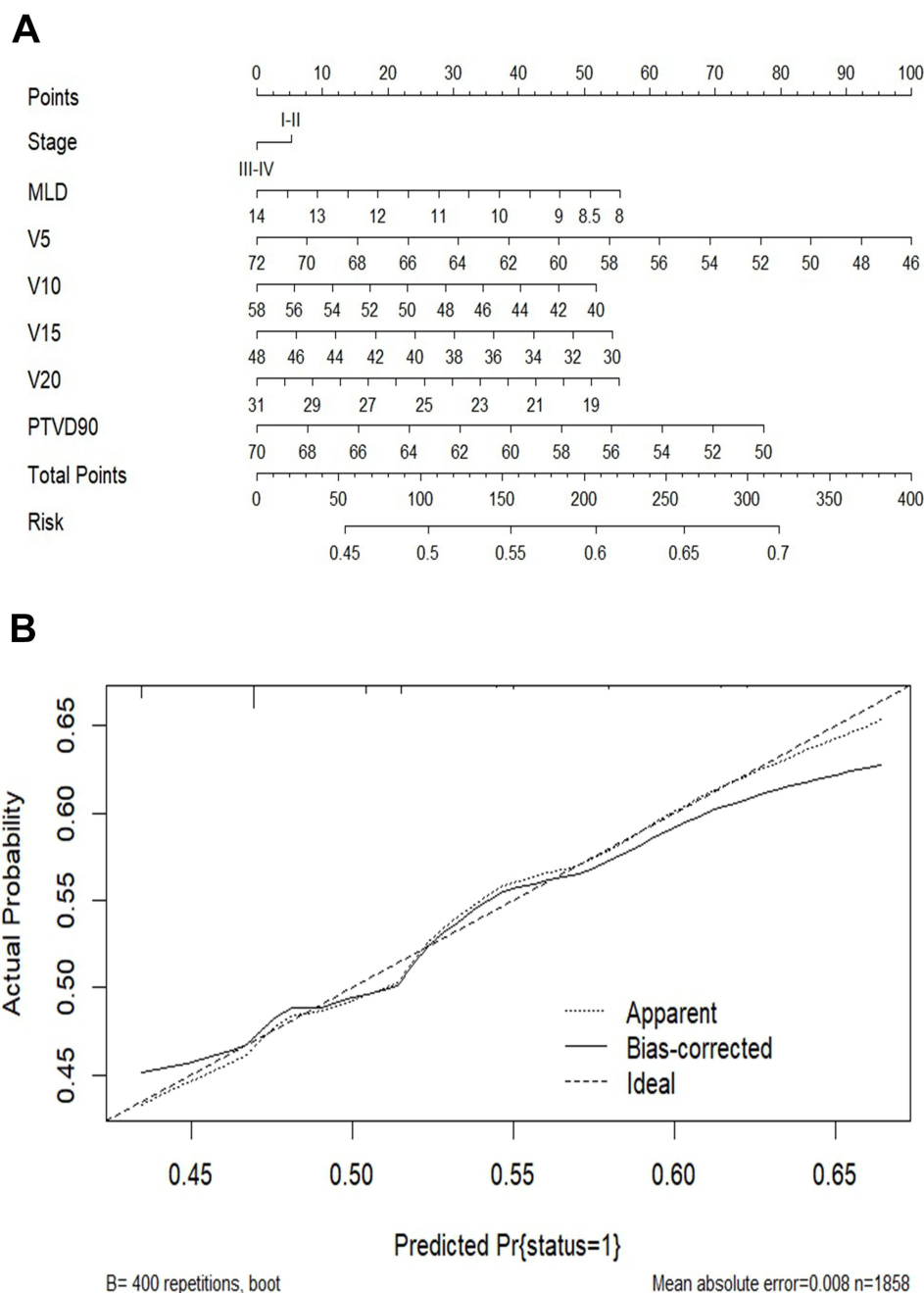
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B

Figure 3 Nomogram visualization model for predicting radiation pneumonitis. (**A**) Nomogram; (**B**) Calibration curve.

Discussion

Radiation lung injury is caused by radiation exposure to normal lung tissue after radiotherapy for malignant tumors such as esophageal cancer in the chest.[6,14] Radiation pneumonitis is an early form of radiation-induced lung injury.[15] Mild cases can recover on their own, but severe cases can progress to pulmonary fibrosis, respiratory dysfunction, and even breathing difficulties. Therefore, accurately predicting the risk of radiation pneumonitis after radiotherapy can guide early intervention for patients and reduce lung damage caused by radiation pneumonitis. However, due to the non-specific early symptoms of radiation pneumonitis compared to other pneumonitis, and the delayed imaging changes in lung CT compared to clinical manifestations by 7 to 10 days, there is still a lack of effective indicators for predicting radiation pneumonitis in esophageal cancer after radiotherapy in clinical practice.[16–18] In this study, we used radiomics methods to
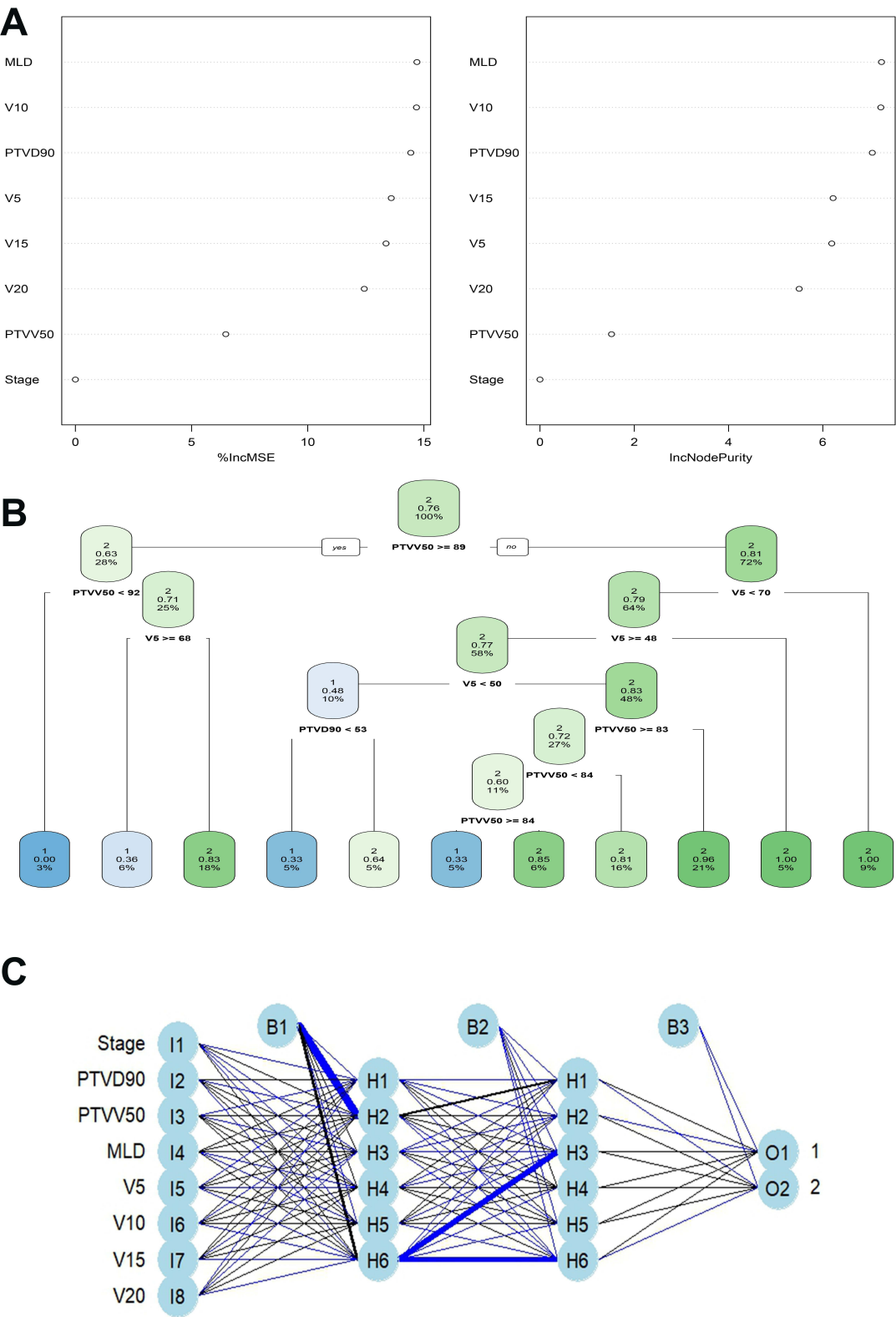
Figure 4 Machine learning based visualization model for predicting radiation pneumonitis. **(A)** Random forest model; **(B)** Decision tree model; **(C)** Artificial neural network model.

Table 3 Comparison of Predictive Performance of Four Types of Radiation-Induced Pneumonitis Prediction Models Through ROC Analysis

Prediction model	Training set				International set			
	AUC	95% CI	PPV	NPV	AUC	95% CI	PPV	NPV
RFM	0.891	0.840~0.942	0.95	0.98	0.887	0.836~0.938	0.96	0.87
DTM	0.811	0.760~0.862	0.80	0.95	0.809	0.758~0.860	0.88	0.63
ANNM	0.882	0.831~0.933	0.89	0.97	0.879	0.828~0.930	0.92	0.75
GLRM	0.751	0.700~0.802	0.70	0.92	0.762	0.711~0.813	0.84	0.44

Abbreviation: AUC, Area under the curve; 95% CI, 95% confidence interval; PPV, Positive predictive value; NPV, negative predictive value; RFM, Random forest model; DTM, Decision tree model; ANNM, Artificial neural network model; GLRM, Generalized linear regression.

extract radiomics features of the patient's affected lung and combined them with lung dosimetry parameters to construct a machine learning algorithm based prediction model for radiation-induced pneumonitis in esophageal cancer after radiotherapy, which is helpful for clinical decision-making.

Our study shows that the incidence of radiation pneumonitis in esophageal cancer patients is 23.68%, which is consistent with previous research reports.[19–21] Our study also found that radiation pneumonitis is related to clinical staging, radiation therapy mode, and radiation dose, especially in patients with esophageal cancer. The more severe the condition, the higher the radiation dose, and the more severe the degree of radiation pneumonitis. This is because curative radiation therapy is often used for patients with advanced esophageal cancer, and the radiation dose is higher than adjuvant and palliative treatment. At the same time, the expansion of the diseased tissue leads to an increase in the target area of radiation therapy and damage to normal lung tissue, resulting in acute radiation injury.

In previous studies, dose volume parameters were often used as the main evaluation factor for radiation therapy.[22–24] In this study, esophageal PTVD90, esophageal PTVV50, total dose, MLD, V5, V10, V15, V20 were associated with the occurrence of radiation pneumonitis and were independent risk factors for radiation pneumonitis. This is closely related to the increase in esophageal PTVD90 radiation dose, the larger the PTVV50 exposure area, the corresponding radiation dose and proportion of lung tissue, and the more severe the radiation defense.[25] This suggests that dose volume parameters are closely related to the occurrence of radiation pneumonitis, and low dose volume parameters have certain value in predicting radiation pneumonitis. Therefore, controlling V5, V10, V15, V20, and MLD is a key element in reducing the occurrence of radiation pneumonitis.

The high dimensionality of feature data is one of the huge challenges faced by machine learning.[26,27] Eliminating a large amount of redundant feature data while retaining key feature information can reduce the training time of the constructed machine learning model and produce good classification performance.[28–30] Our study adopts a machine learning based feature selection method, ultimately selecting and retaining 8 optimal feature combinations, including one dosimetric feature, two first-order features based on wavelet decomposition calculation, and five texture features. Especially, texture features play a very important role in imaging omics research, providing information about organizational structure and spatial distribution. It is encouraging that this study, based on imaging omics and dosimetry models, can effectively predict the risk of radiation pneumonitis after esophageal cancer radiotherapy and has achieved good prediction results in both the training and testing sets, especially reaching an AUC value of 0.891 in the training set. This indicates that the machine learning model has a high net profit and risk threshold range, which also indicates that the radiation pneumonitis prediction model we constructed has high reliability and practicality.

Our study also has some inevitable limitations. Firstly, due to the small sample size of this study, it may have an impact on the stability of the model. Therefore, in the future, large sample cohort studies are still needed to verify the predictive model; Secondly, this study is a single-center study, and all patient data are from the same simulated positioning CT. Therefore, further research and verification are needed to determine whether similar predictive effects can be achieved on different positioning CT data. In view of this, we plan to incorporate multi-center data and analyze CT data from different locations in future research, continuously optimizing the model to
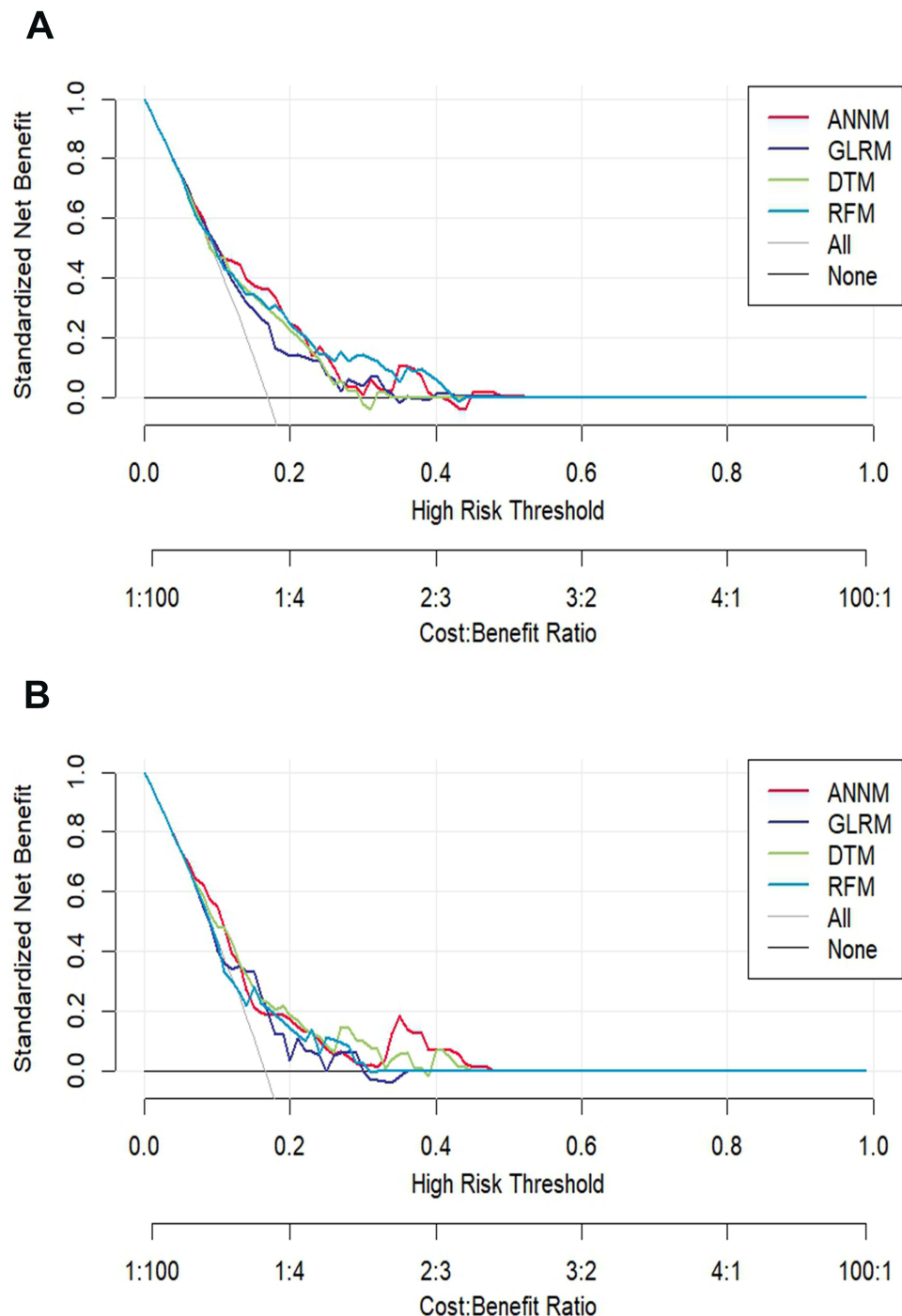
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Figure 5 Comparing the predictive performance of machine learning prediction models using DCA. **(A)** Training set; **(B)** Validation set.

improve its generalization ability. Nonetheless, we cannot deny that the model that combines pre radiotherapy localization CT imaging features with diseased lung dosimetry parameters to predict the occurrence of radiation-induced pneumonitis in esophageal cancer after radiotherapy has certain clinical practical value. The radiation-induced pneumonitis prediction model constructed based on machine learning algorithms can assist doctors in identifying high-risk patients early, providing reference and formulating personalized prevention and treatment strategies to improve treatment effectiveness and reduce adverse reactions, thereby effectively improving patient prognosis.
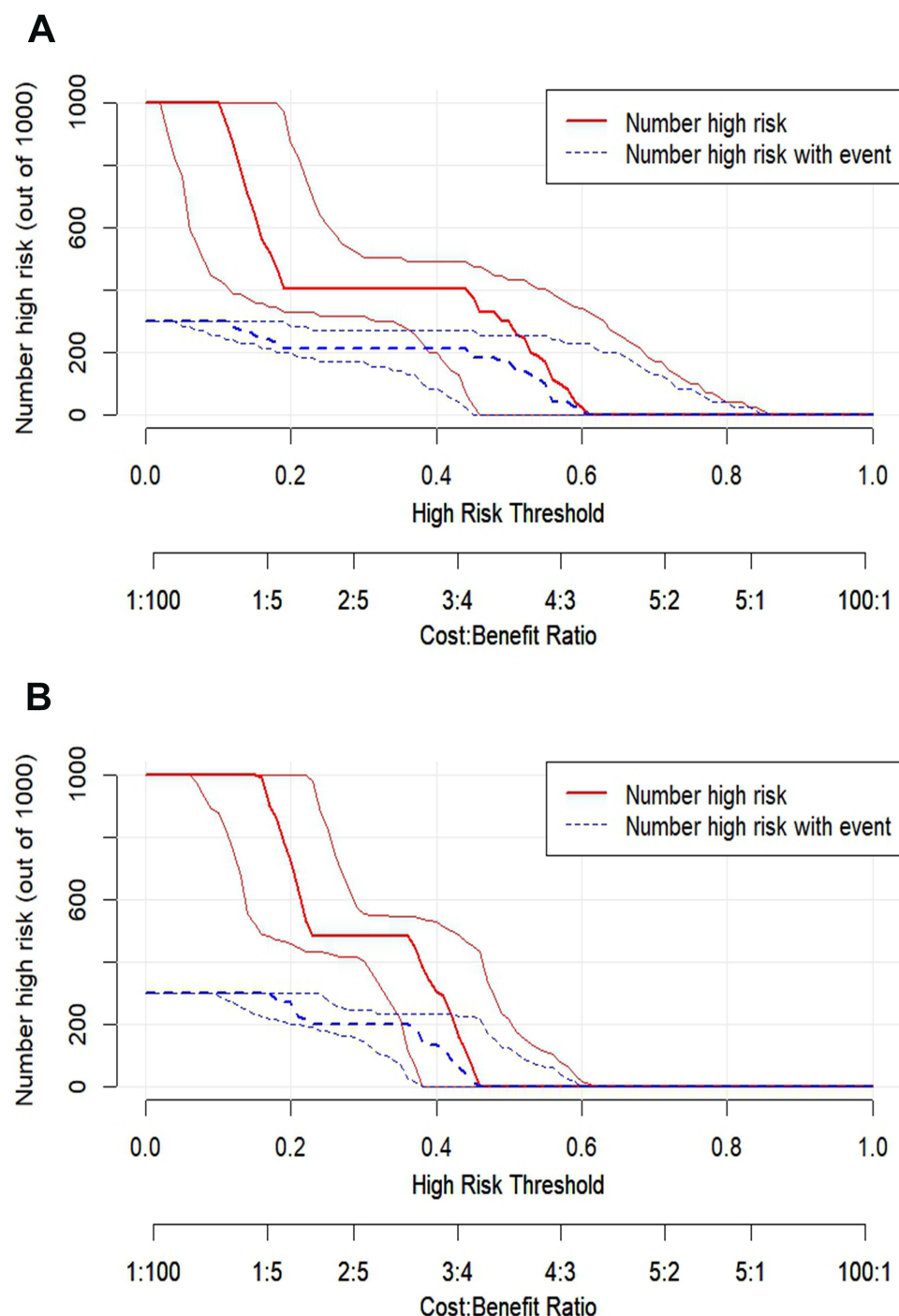
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Figure 6 Differentiation performance of random forest prediction models based on CIC evaluation. **(A)** Training set; **(B)** Validation set.

Conclusion

In conclusion, radiation pneumonitis occurs in patients with esophageal cancer, which is related to the severity of the condition and the parameters of radiation dose volume. The combination of radiomics features and dosimetric parameters of the affected lung has good predictive value for radiation pneumonitis in esophageal cancer patients after radiotherapy. Especially with the combination of imaging and lung dosimetry parameters, the random forest prediction model has the optimal predictive performance, which can help medical personnel develop personalized prevention and intervention strategies.

Disclosure

The authors report no conflicts of interest in this work.

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