

Development and validation of a fusion model based on multi-phase contrast CT radiomics combined with clinical features for predicting Ki-67 expression in gastric cancer

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Abstract. The present study aimed to develop and validate a fusion model based on multi-phase contrast-enhanced computed tomography (CECT) radiomics features combined with clinical features to preoperatively predict the expression levels of Ki-67 in patients with gastric cancer (GC). A total of 164 patients with GC who underwent surgical treatment at our hospital between September 2015 and September 2023 were retrospectively included and were randomly divided into a training set (n=114) and a testing set (n=50). Using Pyradiomics, radiomics features were extracted from multi-phase CECT images and were combined with significant clinical features through various machine learning algorithms [support vector machine (SVM), random forest (RandomForest), K-nearest neighbors (KNN), LightGBM and XGBoost] to build a fusion model. Receiver operating characteristic, area under the curve (AUC), calibration curve and decision curve analysis (DCA) were used to evaluate, validate and compare the predictive performance and clinical utility of the model. Among the three single-phase models, for the arterial phase model, the SVM radiomics model had the highest AUC value in the training set, which was 0.697; and the RandomForest radiomics model had the highest AUC value in the testing set, which was 0.658. For the venous phase model, the SVM radiomics model had the highest AUC value in the training set, which was 0.783; and the LightGBM radiomics model had the highest AUC value in the testing set, which was 0.747. For the delayed phase model,

the KNN radiomics model had the highest AUC value in the training set, which was 0.772; and the SVM radiomics model had the highest AUC in the testing set, which was 0.719. The clinical feature model had the lowest AUC values in both the training set and the testing set, which were 0.614 and 0.520, respectively. Notably, the multi-phase model and the fusion model, which were constructed by combining the clinical features and the multi-phase features, demonstrated excellent discriminative performance, with the fusion model achieving AUC values of 0.933 and 0.817 in the training and testing sets, thus outperforming other models (DeLong test, both $P < 0.05$). The calibration curve showed that the fusion model had goodness of fit (Hosmer-Lemeshow test, > 0.5 in the training and validation sets). The DCA showed that the net benefit of the fusion model in identifying high expression of Ki-67 was improved compared with that of other models. Furthermore, the fusion model achieved an AUC value of 0.805 in the external validation data from The Cancer Imaging Archive. In conclusion, the fusion model established in the present study was revealed to have excellent performance and is expected to serve as a non-invasive tool for predicting Ki-67 status and guiding clinical treatment.

Introduction

Gastric cancer (GC) is one of the most common tumors worldwide, ranking fifth regarding cancer-related mortality rate (1). Particularly in East Asia, the incidence and mortality rates of GC remain high. Due to the strong pathological heterogeneity of GC, patients often already have advanced stage cancer at the time of diagnosis, and the prognosis remains poor (2). Despite advancements in diagnostic and therapeutic strategies, its heterogeneous biological behavior and poor prognosis (particularly in advanced stages) highlight the urgent need for reliable biomarkers to guide risk stratification and personalized treatment (2). Among these biomarkers, cell proliferation markers have garnered significant attention due to their direct association with tumor aggressiveness and therapeutic resistance. Therefore, identifying effective biomarkers, especially those that can reflect tumor proliferation activity, is of great significance for the development of personalized treatment strategies and the assessment of patient prognosis.

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Ki-67 is a nuclear protein closely associated with cell proliferation and is widely used to evaluate the proliferative activity of tumor cells. In gastric cancer, the expression level of Ki-67 is closely linked to tumor biological behavior, clinical prognosis, and treatment response (3). Multiple studies indicate that high Ki-67 expression correlates with poorer overall survival (OS) and progression-free survival (PFS) in gastric cancer patients (4). A high Ki-67 index may suggest a higher likelihood of lymph node metastasis and distant metastasis (5). Poorly differentiated or undifferentiated gastric cancers often exhibit higher Ki-67 indices, indicating active proliferation (6). Ki-67 is a protein marker related to cell proliferation. Research has shown that the expression levels of Ki-67 are closely related to the invasiveness, staging, prognosis and treatment response of various malignant tumors (7). In GC, high expression of Ki-67 often indicates that the tumor has stronger invasive ability and a poorer prognosis (8). Therefore, accurately assessing the expression of Ki-67 is crucial for the diagnosis, staging and personalized treatment decisions of GC.

Currently, detecting the expression levels of Ki-67 mainly relies on pathological testing of tissue biopsies or surgical resection samples. This method is not only invasive but also has sampling bias, and for patients with advanced or unresectable GC, repeated biopsies carry significant operational risks and limitations (9). Therefore, developing a non-invasive, convenient and efficient method to predict the expression levels of Ki-67 has recently garnered attention.

Existing research has shown that radiomics has high accuracy in predicting various biomarkers, including Ki-67. The rich tumor information provided by contrast-enhanced computed tomography (CT) imaging can effectively capture its potential biological characteristics (10). Therefore, the present study aimed to establish a non-invasive and feasible Ki-67 expression prediction model based on the radiomics features of multi-phase enhanced CT, to provide new imaging evidence for clinical treatment decisions for patients with GC. This model is expected to serve as a non-invasive tool for predicting Ki-67 status and guiding clinical treatment, helping doctors better assess tumor proliferation activity, and providing important references for personalized treatment and prognostic evaluation of GC.

Patients and methods

Patients. The present study was approved (approval no. KY-20243021) by the Ethics Committee of the Second Affiliated Hospital of Xuzhou Medical University, and all studies were conducted in accordance with relevant guidelines/regulations and The Declaration of Helsinki. The present study is a retrospective, and the used data collected as part of the participants' routine care. Written informed consent for participation was waived in accordance with the national legislation and the institutional requirements. The current study reviewed a total of 266 patients who were diagnosed and surgically treated for GC at The Second Affiliated Hospital of Xuzhou Medical University between September 2015 and September 2023. Inclusion criteria were enhanced CT examination was performed within 1 week before gastric resection surgery and postoperative pathology confirmed GC. Exclusion criteria were as follows: Poor gastric filling or artifacts in CT

images making it difficult to identify small GC lesions; preoperative chemotherapy or radiotherapy and no postoperative detection of Ki-67 expression levels. A total of 164 patients were finally included in the study, which were allocated into two independent cohorts in a 7:3 ratio, namely the training set (n=114 cases) and the testing set (n=50 cases). Due to the notably lower number of patients with high Ki-67 expression compared with those with low Ki-67 expression in the present study, the borderline synthetic minority over-sampling technique was used to address the imbalanced data (Fig. 1 shows the flow chart for inclusion and exclusion). Moreover, 40 cases of GC from The Cancer Imaging Archive (TCIA) (<https://www.cancerimagingarchive.net/>) were utilized as the external validation set.

Acquisition of clinical and imaging data. Clinical laboratory data and imaging results were obtained from the hospital information system, and patient preparation and imaging standards before CT image acquisition were performed in accordance with the imaging technology standards of tertiary hospitals. Re-evaluation of T staging, lymph node status and serosal invasion in enhanced CT images was performed by three radiologists with >5 years of experience in abdominal diagnosis. This evaluation process was independently performed by the three radiologists, who were blinded to the pathological information of the patients. If there were discrepancies, the majority opinion was taken as the final T staging, lymph node status and serosal invasion status.

Determination of Ki-67 expression levels. Tumor tissue samples were obtained through surgical resection or endoscopic biopsy, and immunohistochemical (IHC) staining was used to detect the expression levels of the Ki-67 protein, strictly following the staining and scoring criteria. Paraffin-embedded tissue samples (3-5) were fixed in 10% neutral buffered formalin at for 24-48 h. For blocking, 5-10% normal goat serum (cat. no. S26-100ML; MilliporeSigma) in Tris-buffered saline was used at room temperature (RT) for 30-60 min. Primary antibody [Clone: MIB-1; cat. no. M7240; Agilent; 1:50-1:200 in antibody diluent (REAL Antibody Diluent; cat. no. S2022; DAKO; Agilent Technologies, Inc.)] was incubated at 4°C overnight. 3,3'-Diaminobenzidine (DAB) (DAB + Substrate Buffer; cat. no. K3468; DAKO; Agilent Technologies, Inc.) was used as a chromogen at a concentration of 0.05% DAB (prepared with 0.03% H₂O₂ in TBS). Staining was performed at RT for 5-10 min. Light microscope for DAB-based chromogenic staining was used for observation.

The scoring criteria for Ki-67 were primarily based on the proportion of positive cells (for example, Ki-67 labeling index, LI). The typical scoring range was 0-100%, with a higher proportion of positive cells indicating stronger tumor proliferative activity. In the present study, Ki-67 LI ≤30% was considered to indicate low proliferative activity, whereas Ki-67 LI >30% was considered to indicate high proliferative activity (11).

Region of interest segmentation. To eliminate the difference in the signal intensity of the images acquired by different CT devices, all images were normalized to the signal intensity to 1-500 HU. After normalizing the images, two radiologists

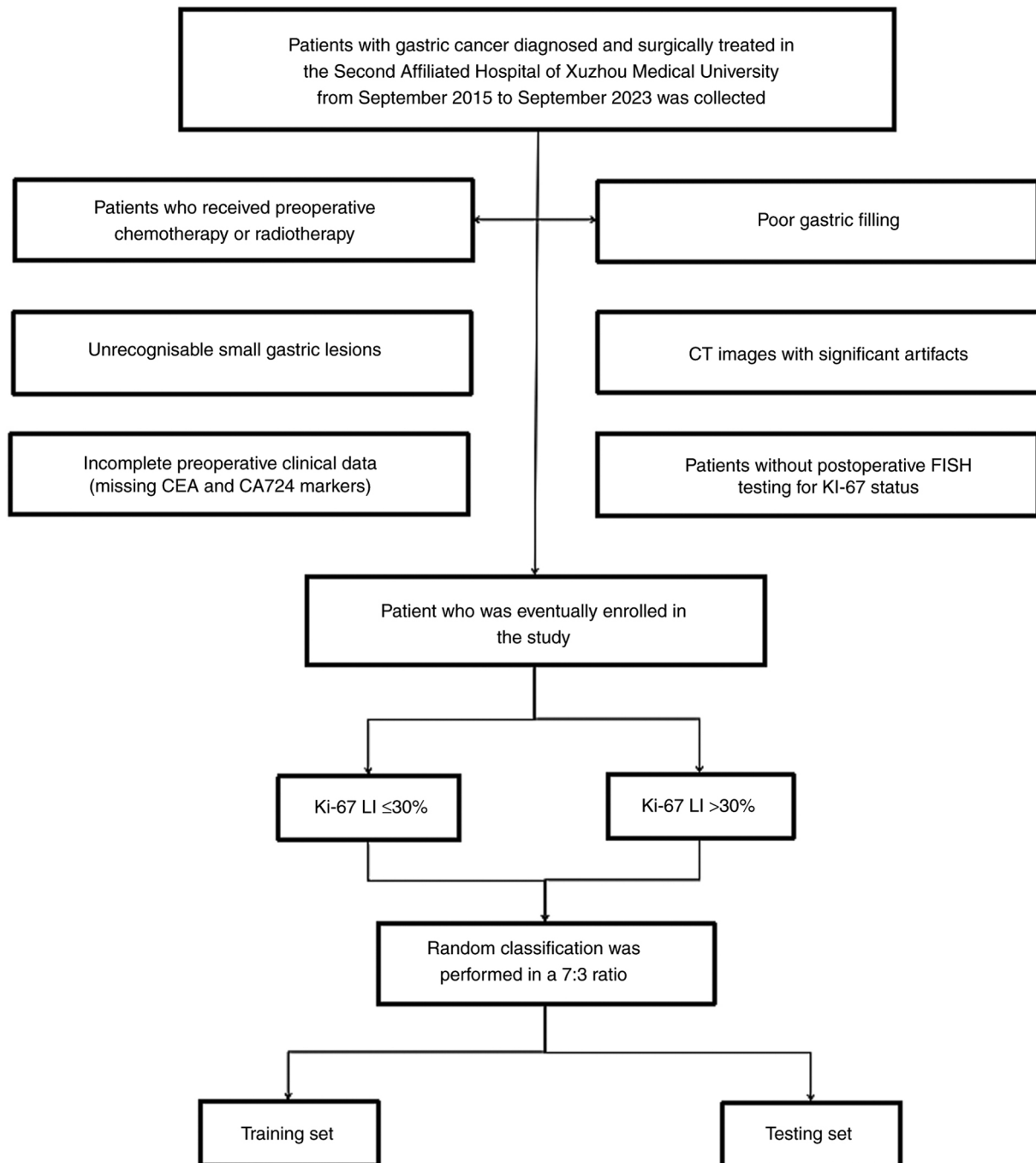


Figure 1. Flowchart illustrating participant selection process: Inclusion and exclusion criteria for the final study cohort. CEA, carcinoembryonic antigen; FISH, fluorescence *in situ* hybridization.

with >5 years of experience in abdominal CT diagnosis used ITK-SNAP software (version 3.8.0) (<http://www.itksnap.org/>) to outline the three phases of CT images in three-dimensional regions of interest (volume of interest, VOI). The three phases refer to the arterial phase, venous phase and delayed phase, which are described as follows. Arterial phase: Scanning was performed immediately after injection of the contrast agent, usually within 20-30 sec post-injection, at which point the contrast agent is primarily concentrated in the arterial vessels; this is used to observe the blood supply to the tumor. Venous phase: Conducted after the arterial phase, usually 60-70 sec post-injection, at which point the contrast agent begins to

flow from the arteries to the veins; this is used to assess the contrast between the tumor and surrounding tissues. Delayed phase: Conducted after the venous phase, usually 2-5 min post-injection, at which point the distribution of the contrast agent in the tissues is more uniform, helping to observe the late enhancement characteristics of the tumor. For different pathological types of GC, the area of maximum enhancement in the three phases was selected as the baseline for outlining, with strict adherence to the tumor edges during outlining, avoiding gas, gastric fluid, necrotic areas and adipose tissue, and then VOIs of the same shape and size were drawn in the same region of the remaining phase images, while excluding

the top and bottom image slices to reduce bias caused by partial volume effects. One doctor segmented the lesions of all subjects. Another doctor randomly selected 30 cases from all samples for outlining, calculating the intra-class correlation coefficient to assess inter-operator variability.

Feature extraction. The open-source PyRadiomics software package based on Python (version 3.0.1) (<https://pyradiomics.readthedocs.io/>) was used to extract radiomics features from the VOIs. Detailed calculations of the radiomics features are described and provided in the online documentation of PyRadiomics (<https://pyradiomics.readthedocs.io/en/latest/>). The extracted features comply with the Image Biomarker Standardization Initiative. A total of 386 candidate radiomics features were extracted from three Dynamic Contrast Enhanced (DCE)-CT phases of each patient in four major categories, including 14 shape features, 18 first-order statistical features, 75 texture features and 279 features based on the Laplacian of Gaussian. Specifically, texture features were further divided into gray-level co-occurrence matrix features, gray-level size zone matrix features, gray-level run length matrix features, neighboring gray tone difference matrix features and gray-level dependence matrix features. These features cover multiple aspects of tumor morphology, texture and signal distribution, providing rich information for subsequent model construction and analysis. Various machine learning algorithms were used to build predictive models, specifically support vector machine (SVM), random forest (RandomForest), K-nearest neighbors (KNN), LightGBM and XGBoost. The fusion model was built by multi-phase radiomics features and independent clinical risk factors for patients with high expression levels of Ki-67, and the multi-phase model was built by the three single-phase radiomics features.

Statistical analysis. For continuous variables, the Kolmogorov-Smirnov test was applied to check for normal distribution, followed by the Mann-Whitney U test or independent t-test to compare differences, whereas the χ^2 test was used to compare categorical variables. Normally distributed data were presented as the mean $\pm$ standard deviation (SD) and compared using the independent t-test. Non-normally distributed data were presented as median (interquartile range, IQR) and analyzed with the Mann-Whitney U test. The DeLong test was used to compare the statistical differences of the area under the curve (AUC) between different models, and the Hosmer-Lemeshow test was used to assess the goodness of fit of the model. All statistical analyses were performed using SPSS 26.0 (IBM Corp.) and R 4.1.0 (R Foundation for Statistical Computing, Austria), with statistical significance set at $P < 0.05$.

Results

Patient characteristics. The study cohort comprised 164 participants (male: 117, female: 47) meeting eligibility criteria, with median age of 69 years (range: 35-88). The clinical characteristics of 164 patients with GC are summarized in Table I; the training set included 114 patients and the testing set included 50 patients. The average age of patients in the training set was 68.44 years and was 67.90 years in the testing

set. There was no significant difference in the proportion of patients with high Ki-67 expression between the training set and the testing set ($P > 0.05$). In addition, there were no significant differences between the training set and the testing set in terms of age, sex, tumor location, tumor marker levels, lymph node metastasis status, T staging, Ki-67 expression and serosal invasion status, indicating that the two groups of samples had a favorable balance in baseline characteristics, thus providing a reliable foundation for subsequent model training and validation.

Clinical features screening and model establishment. Univariate analysis of clinical indicators for patients in the training set after oversampling showed that sex, CA724 levels and CT serosal invasion were associated with high expression of Ki-67 (all $P < 0.05$; Table II). Subsequently, multivariate analysis of the aforementioned indicators showed that CT serosal invasion and CA724 levels were independent risk factors for high expression of Ki-67 ($P < 0.05$). Both were used to construct a clinical prediction model using RandomForest regression and to draw the receiver operating characteristic curve, with AUC values of 0.614 and 0.520. Correlation heatmap of selected features is demonstrated in Fig. 2. The radiomics workflow for the venous model construction is revealed in Fig. 3A-E.

Imaging feature selection. Sequentially using the t-test, Spearman correlation analysis, least absolute shrinkage and selection operator regression and 10-fold cross-validation, and Random Forest feature importance ranking, the radiomics features of the three phases were screened; based on the features with the best AUC values obtained, two, 10 and five features were finally selected from the arterial phase, venous phase and delayed phase CT images, respectively.

Construction and validation of multiple models. Based on the selected imaging features, machine learning was used to apply various algorithms to construct three radiological feature signatures as independent predictors of Ki-67. For the arterial phase, the SVM model in the training set had the highest AUC value of 0.697, whereas in the validation set the RandomForest model had the highest AUC value of 0.658; for the venous phase, the SVM model in the training set had the highest AUC value of 0.783, and in the validation set the LightGBM model had the highest AUC value of 0.747; for the delayed phase, the KNN model in the training set had the highest AUC value of 0.772, whereas in the validation set the SVM model had the highest AUC value of 0.719. Subsequently, the three phase feature signatures were fused to obtain a multi-phase feature model, with the KNN model in the training set having the highest AUC value of 0.873, and in the validation set the RandomForest model had the highest AUC value of 0.752. The ROC curves of different models in the training and testing sets are demonstrated in Fig. 4. The AUC values of different models in the training and testing sets are shown in Fig. 5.

Construction and validation of the integrated model. Screened independent predictors and independent clinical risk factors for patients with high expression levels of Ki-67 were fused to build a fusion model through machine learning. The highest

Table I. Comparison of clinical characteristics between training set and test set patients.

Variable	Training set	Testing set	t/x ²	P-value
Sample size	114	50		
Average age, years	68.44	67.90	0.064	0.297
Sex			0.250	0.624
Female	32	15		
Male	82	35		
Tumor location			0.531	0.684
Cardia/Fundus	26	12		
Body	55	18		
Antrum	27	19		
Multi-location	6	1		
Carcinoembryonic antigen			-0.203	0.683
Normal	15	6		
Abnormal	99	44		
CA724			0.322	0.515
Normal	91	41		
Abnormal	23	9		
CT reported LNM			1.170	0.301
Negative	48	26		
Positive	66	24		
CT reported T stage			0.434	0.435
T1 + T2	46	22		
T3 + T4	68	28		
Ki-67			0.000	1.000
Negative	57	25		
Positive	57	25		
CT-serous membrane invasion			-0.353	0.473
Negative	28	11		
Positive	86	39		
HER2				
Negative	85	37	-0.075	0.881
Positive	29	13		

Table II. Preoperative clinical risk factors for HER2 positive.

	Univariate analysis (P-value)	Multivariate analysis (P-value)
Average age, years	0.719	
Sex	0.037	0.067
Tumor location	0.909	
Carcinoembryonic antigen	0.784	
CA724	0.002	0.001
CT reported LNM	0.259	
CT reported T stage	0.256	
CT-serous membrane invasion	0.030	0.032
HER2	0.832	

AUC value of the SVM algorithm model in the training set was 0.933, whereas in the testing set the highest AUC value of the stochastic gradient descent (SGD) algorithm model was 0.817; the Hosmer-Lemeshow test showed that the R-values in both the training set and the validation set were >0.5, indicating that the predicted values of the fusion model aligned well with the actual values, and the calibration curve had a favorable fit. Both the multi-phase model and the fusion model were shown to have favorable decision-making capabilities, and their clinical applicability was better than that of other models, with the fusion model being even more advantageous. The DCA curves of different models in the training and testing sets are demonstrated in Fig. 6. The clinical + radiomics model calibration curve is presented in Fig. 7. Furthermore, the fusion model achieved an AUC value of 0.805 in the external validation dataset from TCIA.

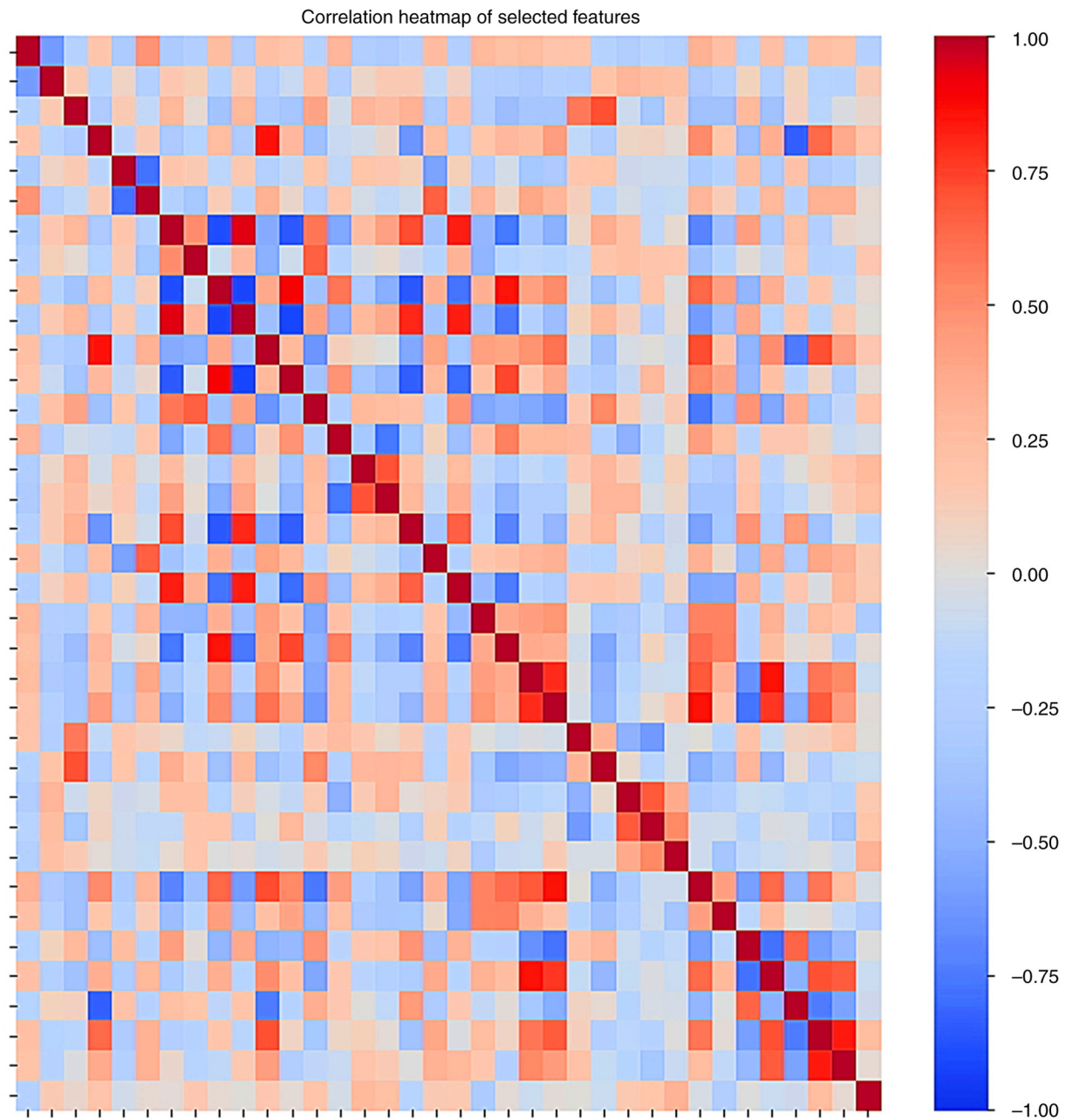


Figure 2. Radiomics feature selection, correlation heatmap of selected features for the venous model construction, and 34 radiomics features with the highest correlation were selected through Spearman's correlation test.

Discussion

GC is one of the most common types of cancer worldwide, and early GC may not have obvious symptoms, leading to a high mortality rate (12). Ki-67 is a nuclear antigen associated with cell proliferation, and its expression is higher in numerous malignant tumors compared with in normal tissues, reflecting the proliferation status of these tumors. In GC, high expression of Ki-67 is usually closely related to the proliferative activity of the tumor (13). Studies have shown that Ki-67 serves an important role in the occurrence of GC, and its expression is related to the degree of tumor differentiation and depth of invasion. The positive expression rate of Ki-67 significantly increases in gastritis, low-grade atypical hyperplasia, high-grade atypical hyperplasia and GC, and with the worsening of lesion

severity, strong positive expression significantly increases (14). By detecting the expression of Ki-67, it can help assess the biological behavior of GC and provide important information for clinical treatment decisions (15). The detection of Ki-67 protein expression usually requires pathological analysis of samples obtained through a tissue biopsy or surgery, which is an invasive method and may lead to biased results due to sampling limitations. For patients with advanced or surgically unresectable GC, repeated biopsies not only carry higher risks but also have certain limitations (16). Chen *et al* (17) conducted a retrospective analysis of 167 patients with gastrointestinal stromal tumor (GIST) who preoperatively underwent enhanced CT; the results showed that a higher necrotic volume ratio combined with lobulated/irregular shapes may predict high expression of Ki-67 in gastric GIST.

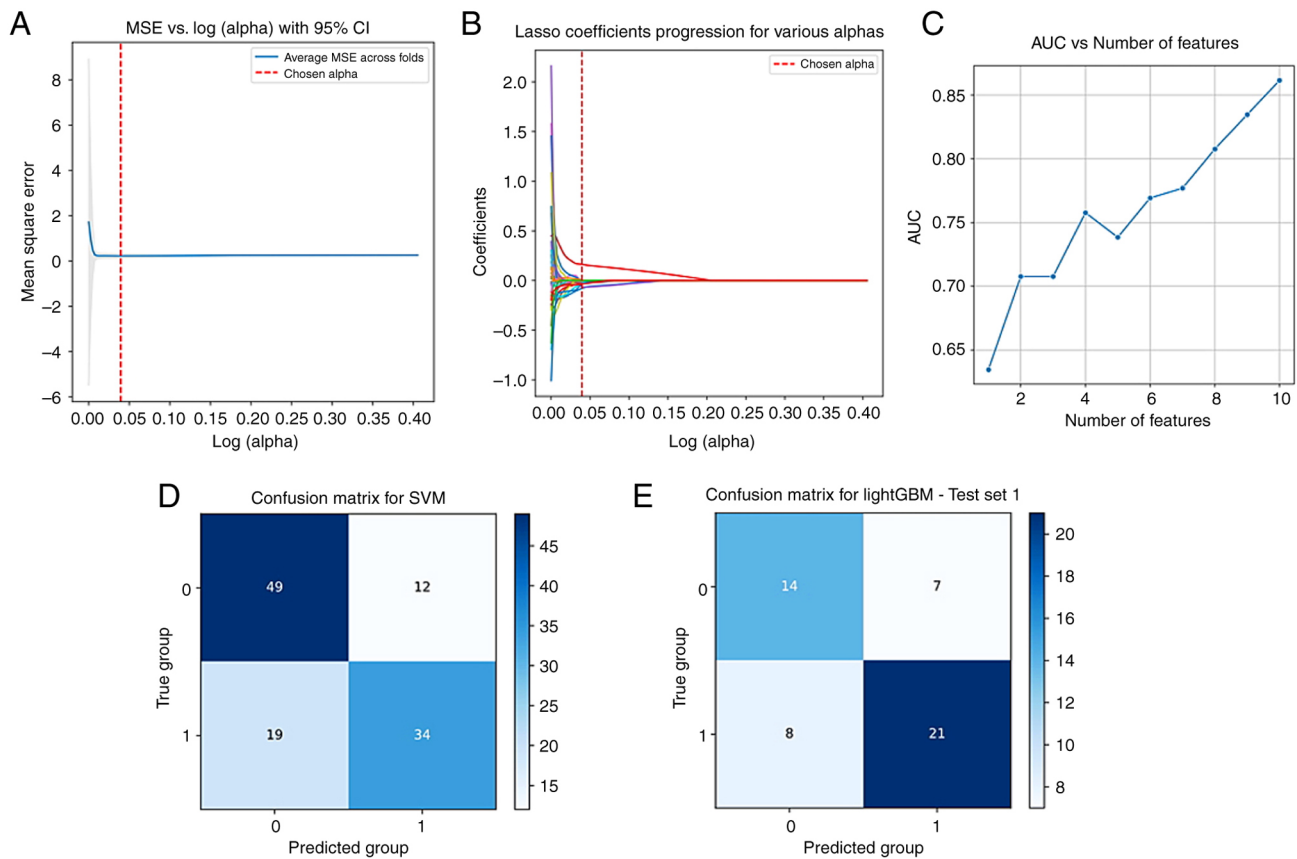


Figure 3. Radiomics workflow for the venous model construction (Predictor selection using the LASSO regression analysis with five-fold cross validation). (A) Alpha selection in the LASSO regression based on the mean square error. (B) A coefficient profile plot was created against the log (Alpha) sequence. (C) AUC vs. Features, 10 radiomics features with the highest AUC value were selected through the feature importance sorting. (D) Confusion matrix in the training set. (E) Confusion matrix in the testing set. LASSO, least absolute shrinkage and selection operator; AUC, area under the curve; CI, confidence interval.

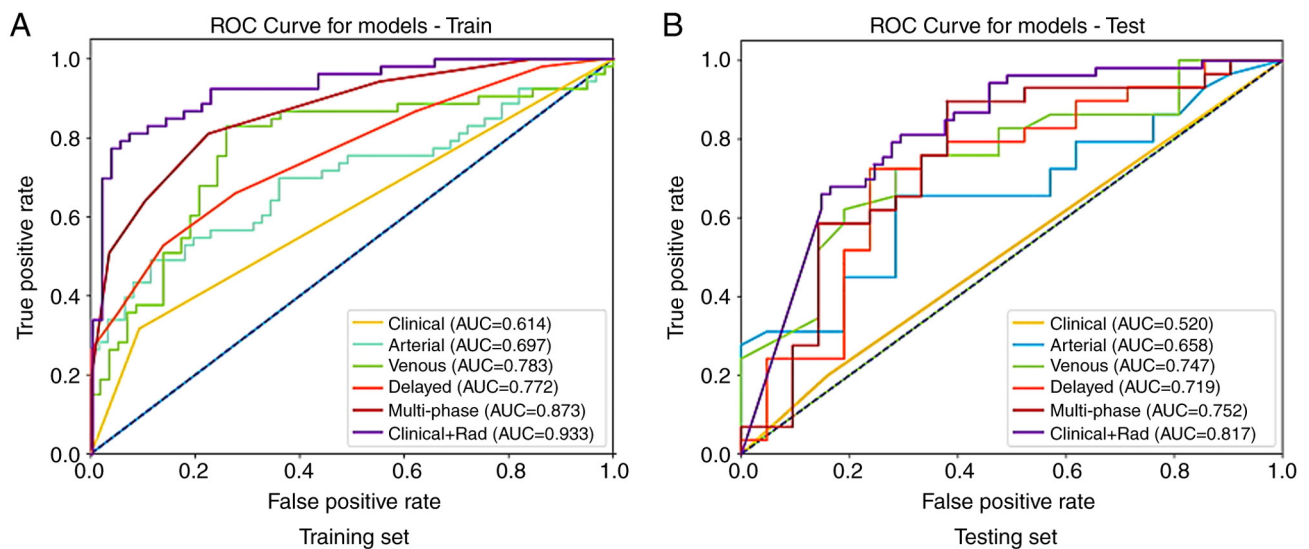


Figure 4. ROC curves of different models in the training and testing sets, in the present study, the fusion model's ROC curve show the highest predictive accuracy rate. (A) Training set. (B) Testing set. Roc, receiver operating characteristic.

The present study adopted a late fusion strategy, training random forest models to process radiomics features and logistic regression models to process clinical data, and finally fusing the results through weighted average probability. The

principle is to independently mine information from different data sources, reduce inter modal interference, and highlight important features through weight adjustment. The advantages include: (1) Comprehensively utilizing the complementarity of

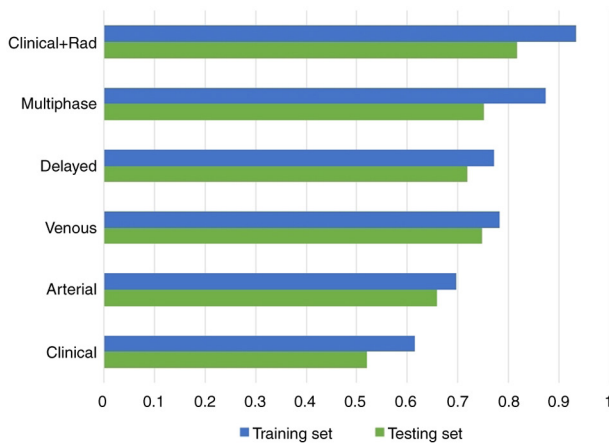


Figure 5. AUC values of different models in the training and testing sets (the fusion model show the highest AUC value, with 0.933 in the training set and 0.817 in the testing set, respectively). AUC, area under the curve.

imaging and clinical information to improve diagnostic accuracy; (2) Reduce the risk of over-fitting in high-dimensional radiomics data; (3) The weighting mechanism can flexibly adapt to different clinical scenarios.

The present study adopts a hierarchical cross validation strategy, first dividing the data into a training set and an independent testing set in a 7:3 ratio. During the training phase, hyper-parameters such as tree depth and feature subset size of random forests are optimized through 5-fold cross validation, and early stopping is used to prevent over-fitting. During the validation phase, the optimal weight fusion ratio (radiomics vs. clinical model) is determined through grid search. The final evaluation on the test set showed that the AUC of the fusion model reached 0.817, significantly improved compared with that of the single modal model ($P < 0.05$).

Compared with models that rely solely on radiomics or clinical features, fusion models bring significant performance improvements. The primary reasons for these results are as follows: First, radiomics features and clinical features are complementary (rather than being highly redundant); Second, the fusion methodology in the model is well-designed and has undergone rigorous statistical validation.

The present study developed and validated various omics models and conducted comparative evaluations. The results revealed that the clinical model alone had the lowest ability to differentiate Ki-67 expression levels, whereas the other radiomics models (except for the arterial phase model) were significantly different from it ($P < 0.05$). Among the three single-phase radiomics models, the arterial phase model had poor predictive ability; however, there were no significant differences in these three models in distinguishing Ki-67 expression levels. Among them, the performance of the multi-phase radiomics model was slightly improved, but there was only a significant difference between the clinical and arterial phase models, and no significant difference between the venous and delayed phase models in distinguishing Ki-67 expression levels. At the same time, data analysis found that the predictive performance of the fusion model was the best, and there were significant differences between other models; it was thus obtained that the addition of radiomics signatures

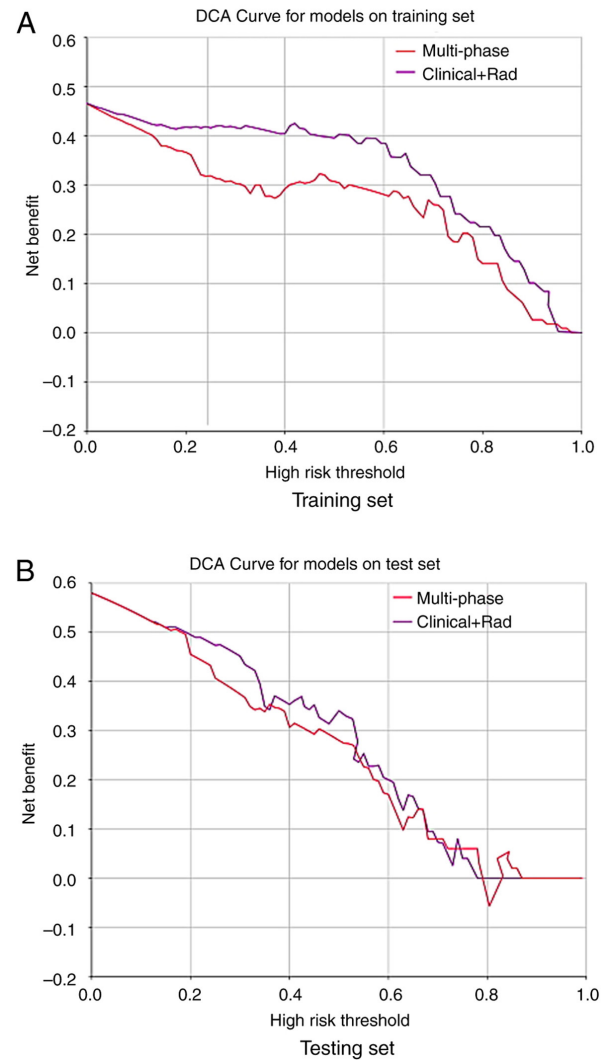


Figure 6. DCA curves of different models in the training and testing sets (The x-axis represents the high-risk threshold, and the y-axis represents the net benefit). (A) Training set. (B) Testing set. DCA, decision curve analysis.

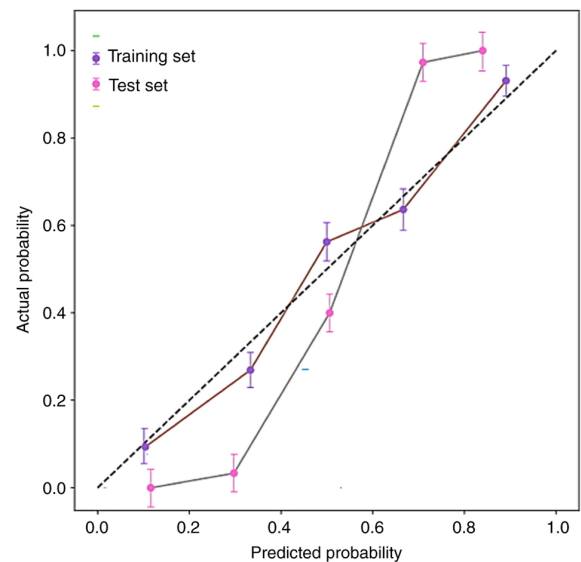


Figure 7. Calibration curves of the fusion model in the training and testing sets (The x-axis represents the predicted probability risk, and the y-axis represents the actual diagnosed probability; the diagonal dotted line represents a perfect prediction by an ideal model).

Table III. Significance comparison of the differences in AUC values across the different models in the training and testing sets.

	Training set		Testing set	
	AUC difference	P-value	AUC difference	P-value
Clinic + Rad-Clinical	0.319	<0.0001	0.297	0.003
Clinical + Rad-Arterial	0.236	<0.0001	0.159	0.009
Clinical + Rad-Venous	0.150	0.015	0.070	0.210
Clinical + Rad-Delayed	0.161	0.009	0.098	0.104
Clinical + Rad-Multiphase	0.060	0.363	0.065	0.273
Clinical-Arterial	-0.083	0.088	-0.138	0.067
Clinical-Venous	-0.169	0.006	-0.227	0.008
Clinical-Delayed	-0.158	0.010	-0.199	0.024
Clinical-Multiphase	-0.259	0.000	-0.232	0.006
Arterial-Venous	-0.086	0.068	-0.089	0.169
Arterial-Delayed	-0.075	0.198	-0.061	0.307
Arterial-Multiphase	-0.176	0.001	-0.094	0.184
Venous-Delayed	0.011	0.863	-0.028	0.712
Venous-Multiphase	-0.095	0.108	-0.005	0.978
Delayed-Multiphase	-0.101	0.058	-0.033	0.641

could significantly improve the discriminative ability of the clinical models, and the inclusion of the clinical models may also enhance the predictive ability of the multi-phase radiomics model for Ki-67 expression (Table III). A decision analysis comparing the clinical model, multi-phase radiomics model and fusion model showed that within a certain threshold, all two models had a net benefit advantage over the 'full treatment or no treatment' scheme, with the multi-phase radiomics model only having a net benefit advantage within a narrow threshold range. In addition, the predictive ability of the clinical model was far lower than that of the multi-phase radiomics model and the fusion model, thus its applicability may be limited. The net benefit advantage of the fusion model was higher than that of the multi-phase radiomics model in both the training and testing sets. Ultimately, it was concluded that the fusion model incorporating radiomics signatures based on three-phase CT enhancement, CT showing serosal invasion and CA724 levels had improved discriminative ability and clinical applicability, demonstrating certain clinical application potential.

Multi-phase enhanced CT can provide information on the hemodynamic changes and tissue perfusion of tumors at different time points, thereby capturing the biological characteristics and microenvironment of tumors more comprehensively (18,19). Compared with biopsies that require tissue samples, multi-phase enhanced CT is a non-invasive examination that reduces patient suffering and the risk of complications (20). Due to the potential heterogeneity within tumors, a single-point biopsy may not fully represent the entire tumor. Multi-phase enhanced CT can provide information about the entire tumor region, thus reducing sampling bias (21). Du *et al* (22) used novel spectral CT-derived parameters to predict the histological types of GC and Ki-67 expression, with results showing significant differences in values between the mucinous and non-mucinous cancer groups during both

the arterial and venous phases, and quantitative spectral parameters were shown to distinguish between low and high Ki-67 expression, as well as different histological types in GC.

The current study indicated that the multi-phase enhanced CT radiomics model could effectively predict the expression levels of Ki-67. By analyzing CT imaging data from multiple phases, including plain scan, arterial phase, venous phase and delayed phase, a large number of radiomics features related to Ki-67 expression were extracted, capturing important information such as tumor heterogeneity, hemodynamic changes and tumor microenvironment. Compared with single-phase imaging data, multi-phase enhanced CT provides more information on tumor dynamic changes, allowing the multi-phase model to more accurately assess the biological behavior of tumors and thus predict the expression level of Ki-67.

Radiomics, as an emerging imaging analysis method, is gradually being applied in the diagnosis and prognostic assessment of tumors (23,24). Chen *et al* (25) evaluated the relationship between the radiomics features of visceral adipose tissue (VAT) from 18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET)/CT imaging, and the positive expression of Her-2 and Ki-67 in GC. The results indicated that the VAT radiomics model based on 18F-FDG PET/CT performed well in predicting the expression status of Her2 and Ki-67 in patients with GC. These findings indicated that radiomics features can serve as imaging biomarkers for GC. The results of the present study suggested that radiomics methods cannot only assist in assessing Ki-67 expression but also support personalized treatment decisions. Patients with high Ki-67 expression typically have a poorer prognosis and may require more aggressive treatment strategies. By predicting Ki-67 expression through CT radiomics models, clinicians can quickly assess the proliferation status of the tumor at the time of diagnosis and adjust treatment plans in a timely manner. Furthermore, radiomics models can

continuously and dynamically monitor changes in Ki-67, providing data support for post-treatment efficacy evaluation and recurrence risk prediction. Compared with traditional tissue biopsies, the non-invasive nature of radiomics makes it more suitable for long-term follow-up and multiple assessments, especially in cases of high tumor heterogeneity, multiple tumors or when patients are unsuitable for multiple biopsies. By accurately assessing Ki-67 expression, doctors can improve formulation of personalized treatment plans, thereby improving patient survival rates and quality of life. Additionally, the application of this model helps reduce reliance on traditional tissue biopsies, lowering the risk of invasive procedures for patients, and enhancing the efficiency and accuracy of clinical decision-making. The promotion of this radiomics approach may provide novel insights for the early diagnosis and treatment of GC, demonstrating significant clinical application potential.

Radiomics features are high-dimensional quantitative features (such as texture, shape and intensity heterogeneity) extracted from medical images (CT and MRI), capturing microscopic heterogeneity information that the human eye cannot recognize. For example, the radiomics features of tumors may reflect their invasiveness, gene expression, or treatment response. Clinical features are the integration of demographic information (age, sex), medical history (complications, staging), laboratory indicators (such as blood markers) or treatment records of patients, providing disease background and clinical interpretability. Radiomics compensates for the lack of microscopic information in clinical features, while clinical features assist in interpreting the biological significance of imaging results (26-28).

Recent studies (6,29) have shown that the fusion model based on CT/MRI radiomics combined with clinical features has an accuracy of 83-89%, sensitivity of ~80-85%, specificity of ~78-84%, and AUC of 0.85-0.91 for predicting Ki-67 expression in GC. These models significantly outperform single data source prediction by quantifying the synergistic effect of tumor heterogeneity and clinical parameters such as CEA levels and Borrmann classification. Despite its excellent performance, current clinical applications still face the following challenges: Firstly, the corresponding mechanism between imaging features and the spatial distribution of Ki-67 protein needs further exploration; Secondly, it is necessary to develop real-time analysis tools that are compatible with the DICOM standard; Furthermore, it has not been validated through large-scale prospective clinical trials.

The present study demonstrated the potential of radiomics models in predicting Ki-67 expression; however, there are certain limitations. First, as a retrospective study, although the images were normalized, there may still be some differences in the quality and consistency of the imaging data, and future research should include more prospective data for validation. Second, the sample size of the study was relatively small, and single-center data may not fully represent the situation of patients from other institutions or different regions. Therefore, subsequent research should expand the sample size and conduct multi-center validation to improve the generalizability of the model. In addition, although CT imaging data were included from multiple phases, the image acquisition at different phases may be affected by

factors such as patient positioning, breathing and heartbeat. Future studies could consider applying more refined image registration techniques to further enhance the predictive performance of the model.

In summary, the present study constructed various CT radiomics models and successfully predicted the expression levels of Ki-67 in patients with GC. The fusion model demonstrated high accuracy and reliability in predicting high and low expression levels of Ki-67, showcasing the potential of radiomics in non-invasive assessment of GC. Future research should aim to further optimize the models and validate their applicability in different clinical settings, providing more support for precision medicine and personalized treatment.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

TS and BX performed data acquisition and drafted the manuscript. TS and LC were in charge of statistical analyses and data interpretation. TS and ML was responsible for recruiting patients. PD made substantial contributions to the study design. PD and AC made substantial contributions to conception and design of the study and provided professional guidance. All authors read and approved the final version of the manuscript and confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of The Second Affiliated Hospital of Xuzhou Medical University (approval no. KY-20243021; Xuzhou, China), and all studies were conducted in accordance with relevant guidelines/regulations, and all studies were conducted in accordance with the Declaration of Helsinki. This study is retrospective, and the used data collected as part of the participants' routine care. Written informed consent for participation was waived in accordance with the national legislation and the institutional requirements.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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