Prediction of High-Risk Gastrointestinal Stromal Tumor Recurrence Based on Delta-CT Radiomics Modeling: A 3-Year Follow-up Study After Surgery

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ABSTRACT

BACKGROUND: Medium- to high-risk classification-gastrointestinal stromal tumors (MH-GIST) have a high recurrence rate and are difficult to treat. This study aims to predict the recurrence of MH-GIST within 3 years after surgery based on clinical data and preoperative Delta-CT Radiomics modeling.

METHODS: A retrospective analysis was conducted on clinical imaging data of 242 cases confirmed to have MH-GIST after surgery, including 92 cases of recurrence and 150 cases of normal. The training set and test set were established using a 7:3 ratio and time cutoff point. In the training set, multiple prediction models were established based on clinical data of MH-GIST and the changes in radiomics texture of enhanced computed tomography (CT) at different time periods (Delta-CT radiomics). The area under curve (AUC) values of each model were compared using the Delong test, and the clinical net benefit of the model was tested using decision curve analysis (DCA). Then, the model was externally validated in the test set, and a novel nomogram predicting the recurrence of MH-GIST was finally created.

RESULTS: Univariate analysis confirmed that tumor volume, tumor location, neutrophil-lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), diabetes, spicy hot pot, CT enhancement mode, and Radscore 1/2 were predictive factors for MH-GIST recurrence ($P < .05$). The combined model based on these above factors had significantly higher predictive performance (AUC = 0.895, 95% confidence interval [CI] = [0.839-0.937]) than the clinical data model (AUC = 0.735, 95% CI = [0.6 62-0.800]) and radiomics model (AUC = 0.842, 95% CI = [0.779-0.894]). Decision curve analysis also confirmed the higher clinical net benefit of the combined model, and the same results were validated in the test set. The novel nomogram developed based on the combined model helps predict the recurrence of MH-GIST.

CONCLUSIONS: The nomogram of clinical and Delta-CT radiomics has important clinical value in predicting the recurrence of MH-GIST, providing reliable data reference for its diagnosis, treatment, and clinical decision-making.

KEYWORDS: Prediction model, nomogram, decision curve, computed tomography, Delta-CT Radiomics, neutrophil-lymphocyte ratio, platelet lymphocyte ratio

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Introduction

Gastrointestinal stromal tumor (GIST) is a common mesenchymal tumor of the digestive tract that was first proposed by Mazur et al in 1983. The histology of GIST mainly consists of spindle cells (70%) and epithelial cells (20%). Gastrointestinal stromal tumor mostly occurs in the stomach, intestines, esophagus, and retroperitoneum, with gastric GIST accounting for 60% to 70% and having a higher malignant potential.[1,2] With the deterioration of food environmental pollution, alcohol abuse, and misuse of traditional Chinese medicine, etc in China, the incidence of GIST has been increasing year by year, reaching 3.5 per 100,000. Due to China's total population of

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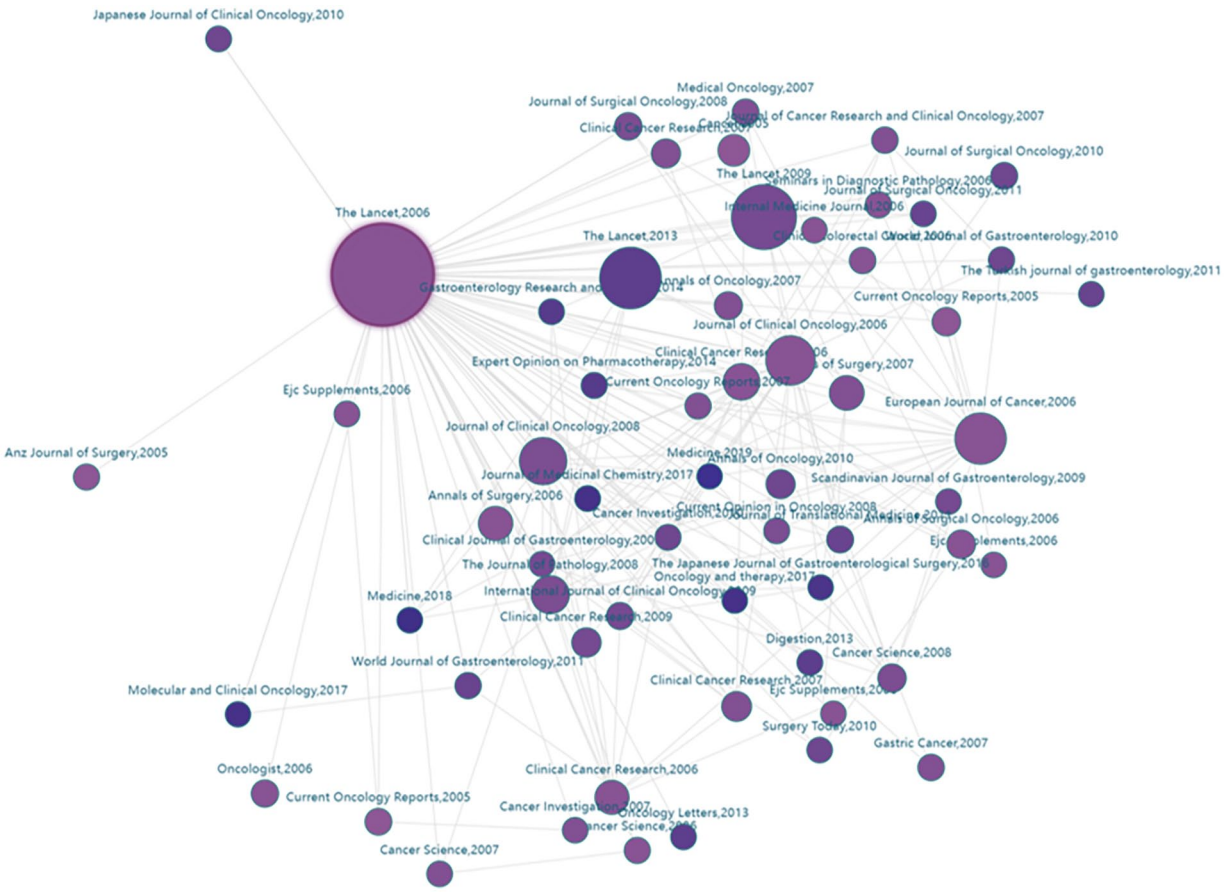

Figure 1. The results of quantitative reference analysis using key word "MH-GIST" indicate that rare study was conducted on radiomics model for predicting recurrence of MH-GIST since 2004, but most studies have focused on the molecular mechanisms of GIST and chemotherapy, but clinical imaging radiomics prediction models have not been reported before.

1.4 billion, the number of existing GIST cases in China is much higher than the world average. It has been reported that the malignancy of GIST varies greatly, but the cause and molecular mechanisms of the disease are still unclear, and it is still not possible to accurately predict the invasiveness and prognosis of GIST. The National Institutes of Health (NIH) has made significant contributions to the treatment of GIST by classifying it into very low risk, low risk, intermediate risk, and high risk based on tumor size, mitotic index, primary site, and rupture. Currently, surgery is still the preferred treatment for GIST, but due to the difficulty in predicting its biological behavior and the lack of adjuvant treatment options, the postoperative recurrence rate is high. According to statistics, approximately 26% to 35% of GIST cases experience recurrence after surgery, and the median survival period after recurrence for medium- to high-risk classification-gastrointestinal stromal tumor (MH-GIST) is only 25 months, with the recurrence rate being difficult to accurately predict. It has been reported that quantitative analysis of the imaging characteristics of locally advanced or advanced solid tumors can improve the surgical resection rate, reduce the recurrence rate, and even bring survival benefits. Radiomics is an emerging tool for tumor diagnosis and prognosis prediction in recent years, playing an important role in the prognosis analysis of known lung nodules, liver, and kidney tumors.[3-6] Delta Radiomics is a comprehensive evaluation of the changes in imaging texture parameters of enhanced computed tomography (CT)/ magnetic resonance (MR) or post-neoadjuvant radiotherapy and chemotherapy, which plays an important role in the treatment of ovarian, brain, and lung tumors. Therefore, in the prediction of recurrence in MH-GIST, we have also introduced the relatively novel Delta Radiomics, which improves the efficiency of the prediction model by analyzing the differences in radiographic texture associated with enhanced CT over time-region, providing strong data support for the screening and decision-making of high-risk populations for MH-GIST recurrence. No related research content has been reported on PubMed[7,8] (Figure 1).

Materials and Methods

Clinical data

Retrospective analysis of clinical and CT data of 282 cases confirmed as MH-GIST in Xiangyang No. 1 People's Hospital from January 2014 to May 2021. Inclusion criteria were as follows: pathological diagnosis of MH-GIST cases; preoperative abdominal enhanced CT examination within 2 weeks; and primary GIST. Exclusion criteria as follows: cases of GIST recurrence;

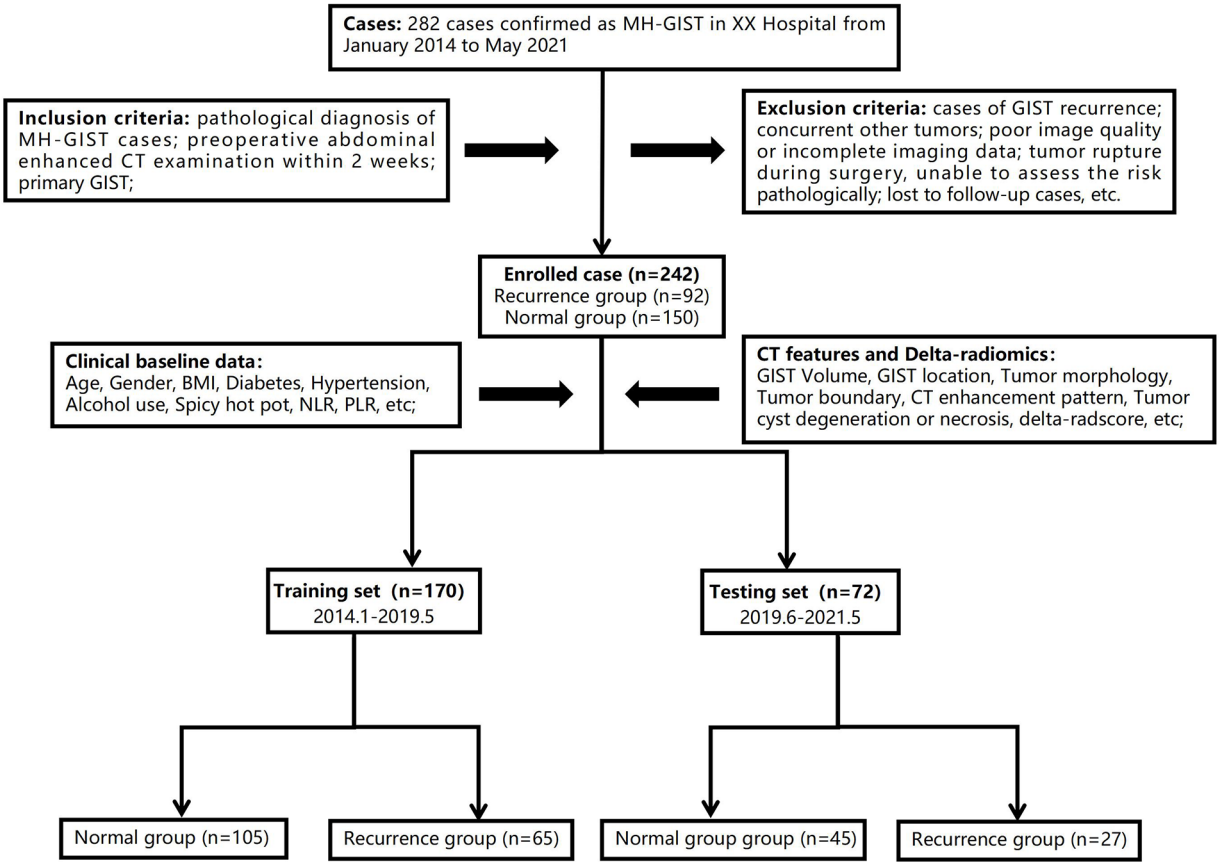

Figure 2. The enrolled inclusion and exclusion criteria and case grouping method of this research.

concurrent other tumors; poor image quality or incomplete imaging data; tumor rupture during surgery, unable to assess the risk pathologically; lost to follow-up cases, etc. Clinical baseline data include age, sex, body mass index (BMI), diabetes, hypertension, alcohol use, spicy hot pot, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), GIST Volume, GIST location, Tumor morphology, Tumor boundary, CT enhancement pattern, Tumor cyst degeneration, or necrosis[9,10] (Figure 2).

This is an exploratory, single-center, and retrospective study. This study was approved by the Xiangyang No. 1 People's Hospital Institutional Review (Issue No. XYYYE20210020.0390) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from individual or guardian participants. The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[11] We have de-identified patient details such that the identity of any person may not be ascertained in any way.

Inspection method

We used GE Revolution CT and Philips Brilliance iCT spiral CT scanners to perform whole abdominal axial CT scans and multiphase enhanced scans within 14 days before surgery. All patients were instructed to fast for 4 to 6 hours before the examination and were given 1000 to 1500 mL of warm water orally 45 to 60 minutes before the scan to ensure gastrointestinal tract filling. The patients were positioned supine, and the scan was performed from the diaphragm to the lower margin of the pubic symphysis, with plain scans followed by enhanced scans. Lead shields were used to cover important body parts that did not need to be scanned, to reduce the potential damage from radiation. The parameters for the plain scans were as follows: slice thickness and spacing of 5 mm, voltage of 120 kV, current of 350 mA, pitch of 1.375, table feed speed of 27.5 mm/rotation, and scan speed of 0.85 s/rotation. Patients were instructed to hold their breath during the scan to avoid diaphragmatic motion affecting image quality. After the routine plain scans, contrast-enhanced scans were performed using a high-pressure injector, with 60 to 100 mL of non-ionic contrast agent (calculated at a rate of 3-3.5 mL/s) injected through the patient's elbow vein. Dynamic arterial and venous phase scans and delayed phase scans were performed at 25 to 30, 60 to 75, and 150 to 180 seconds after contrast agent injection. Lesions and the relationship with surrounding tissues were analyzed using GE post-processing software for multiplanar reconstruction and volume rendering, among other methods.[12,13]

Computed tomography routine feature analysis

Two radiologists with more than 10 years of working experience independently reviewed the films using a blind method and reached a consensus. Computed tomography findings include tumor location (stomach, small intestine, or other);

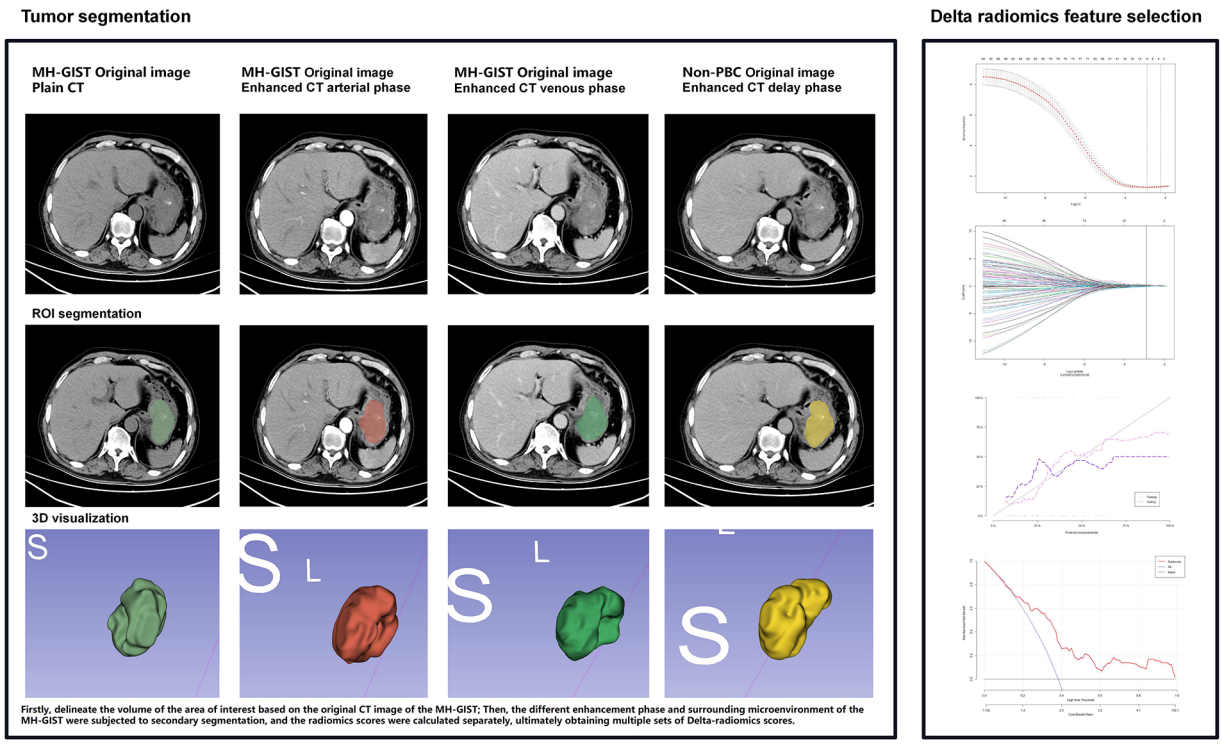

Figure 3. The simple technology roadmap of MH-GIST lesion delineation and radiomics extraction using enhanced CT in this research.

tumor morphology (regular or lobulated); tumor volume; growth pattern (intraluminal, extraluminal, or intraluminal and extraluminal); cystic degeneration, ulceration, bleeding, calcification, gas-containing; intestinal obstruction, intestinal perforation; infiltrative metastasis; degree and pattern of enhancement (inflow, plateau, or outflow).[2,13]

Computed tomography image segmentation and radiomics feature extraction

Export all enhanced CT images (plain scan, arterial and venous phase) of GIST as DICOM files and import them into 3Dslicer software for volume of interest (VOI) delineation and feature extraction. Volume of interest delineation was independently performed manually by 2 experienced radiological technologists (with 10 and 12 years of experience), who were blinded to the pathological results and did not consult each other. Volume of interest was outlined in the maximum axial image along the edge of GIST, away from surrounding blood vessels, fascia, and adipose tissue. Texture parameters were extracted using the control module (Slicer Radiomics) in 3Dslicer, and the original data were resampled with the Nearest Neighbor method for interpolation, adjusting the resampling interval to $1 \times 1 \times 1$. All images were normalized. In the feature extraction process, the first step involved selecting features (NLRGM, NGTLM, etc), and the second step involved selecting filters: LoG, Wavelet, and LBP. The consistency between 2 repeated VOIs was evaluated by the intraclass correlation coefficient (ICC) within the group ($ICC \geqslant 0.7$ indicates good consistency, and this study required $ICC > 0.75$). A total of 859 features were obtained for each scanning period, resulting in a total of 859×3 sets of radiomics features. These features were then imported into the Imaging Research Software version 3.0 (python3.7.7 + Mysql 5.7 + uni + HBuilder X + list-pip + Navicat 11 + Django + nodejs based) from United Imaging Corporation for Delta Radiomics calculation using the Lasso algorithm with 10-fold cross-validation: Delta feature value = CT Radiomics feature value after enhancement − CT Radiomics feature value before enhancement. Valuable texture parameters were selected using the Lasso algorithm and 10-fold cross-validation to generate 3 sets of Delta Radiomics Radscores (Radscore 1: arterial phase scan-plain scan; Radscore 2: arterial phase scan-venous phase scan; Radscore 3: venous phase scan-plain scan)[7,14] (Figure 3).

Gastrointestinal stromal tumor danger level classification

The risk classification of GISTs in this study was based on the 2008 NIH-GIST modified version and the revised version of the GIST China Expert Consensus in 2017. It was evaluated based on tumor size, mitotic count, primary site, and whether the tumor was ruptured. The pathologist-imaging physician classified the included GIST cases into extremely low risk, low risk, moderate risk, and high risk.[15-17]

Statistical analysis

All experimental data in this study are analyzed using R 4.3.2 version (https://cloud.r-project.org/) from Bell Laboratories

(formerly AT&T, now Lucent Technologies) by John Chambers and colleagues and imaging research platform (https://www.uii-ai.com/) from United Imaging Corporation; all continuous variables are subjected to normal distribution and homogeneity of variance tests. Quantitative data that conform to normal distribution are represented by X ± S, and compared by intergroup using *t*-tests; non normally distributed econometric data are represented by median values (25%-75%), and rank sum tests are used for intergroup comparisons. The categorical variables are represented as the number of cases (percentage) (%), and intergroup comparisons are conducted using the chi-square test or the Fisher exact probability test. The training and testing sets are established by a 7/3 ratio and time cutoff. In the training set, the differences in clinical data and Delta Radiomics features between the 2 groups are analyzed using logistic regression, and then multiple predictive models are established. The receiver operating characteristic (ROC) area under curve (AUC) is used to compare the predictive performance of all models by the Delong test method, and it is verified on the test set. Then, the clinical net benefit of the model is evaluated using decision curve analysis (DCA), and finally, a nomogram and calibration curve is created using R. $P < .05$ indicates a significant difference.[13,14]

Result

Comparison of clinical data and conventional computed tomography image features

There were 242 cases of MH-GIST, with 102 cases in women and 140 cases in men, with an average age of 56.61 years (56.5 ± 16.8 years). A total of 205 cases had tumors growing in the stomach, whereas 37 cases had tumors growing outside of the stomach (2 cases in the duodenum, 33 cases in the small intestine, and 2 cases in the esophagus). There is no significant difference in baseline data (age, sex, BMI, hypertension, alcohol use, smoking, education background, family histories of cancer) between the 2 groups using *t*-tests, rank sum tests, or chi-square test ($P > .05$) (Table 1). There were statistically significant differences in Diabetes, Spicy hot pot, NLR, PLR, GIST Volume, GIST location, and CT enhancement pattern between the 2 groups ($P < .05$), whereas age, sex, BMI, hypertension, alcohol use, tumor morphology, tumor boundary, tumor cyst degeneration, or necrosis showed no statistically significant differences between the 2 groups ($P > .05$) and then proceeded with logistic regression (Table 1).

Delta Radiomics feature selection and establishment of multiple models

Radscore 3 showed no significant difference between the 2 groups and was therefore discarded ($P > .05$), whereas Radscore 1/2 showed statistical differences in both groups ($P < .05$). Using the discrepant clinical data and Delta Radiomics Radscore, clinical models, radiomics models, and combination models were established in the training set. The combination model showed higher predictive performance (AUC = 0.895, 95% confidence interval [CI] = [0.839-0.937]) than the clinical model (AUC = 0.735, 95% CI = [0.662-0.800]) and radiomics model (AUC = 0.842, 95% CI = [0.779-0.894]) in the training set, and this result was also validated in the testing set (combined model-AUC = 0.849, 95% CI = [0.745-0.922] vs Radiomics model-AUC = 0.805, 95% CI = [0.695-0.889] vs Clinical model-AUC = 0.700, 95% CI = [0.581-0.803]). Decision curve analysis confirmed that the combination model had higher clinical net benefit, and the nomogram and calibration curve generated based on the combination model received better clinical application evaluation (Figures 4 to 6 and Tables 2 and 3). We selected 4 eligible recurrent patients from other centers for prediction using newly established nomogram and achieved good predictive results (single scoring of every risk factor in the nomogram and calculating the final risk value).

Discussion

Gastrointestinal stromal tumor is the most common mesenchymal tumor, often originating independently from the gastrointestinal wall and exhibiting non-directional differentiated features. Gastrointestinal stromal tumor usually originates from the interstitial cells of Cajal or their precursor cells in the gastrointestinal tract. The global incidence rate of GIST is approximately 10 to 15 cases per million, but due to factors such as gene mutation, food contamination, Chinese medicine and drug abuse, etc, the incidence rate of GIST in China is much higher than the global average. When GIST is small in size, it often has no obvious clinical symptoms and is difficult to diagnose preoperatively. As the tumor grows, symptoms such as abdominal pain, abdominal mass, and gastrointestinal bleeding may occur. However, all GISTs have a certain malignant potential and can metastasize to the liver and abdominal cavity at an early stage. Due to the lower level of medical care and health checkup in China, about 35% to 42% of GIST cases are already classified as intermediate to high risk and difficult to treat at the time of diagnosis. Currently, surgery is still the preferred treatment for GIST, but MH-GIST has a high risk of recurrence and metastasis and poor prognosis.[17-20] It has been reported that early detection of recurrence after surgery can effectively improve the survival rate of GIST patients. Long-term postoperative use of imatinib, sunitinib, and adjuvant chemotherapy can effectively inhibit GIST mutations and recurrence, but this requires frequent CT appointments and radiation exposure, which can cause significant medical triage and economic pressure. Indiscriminate drug abuse can cause harm to the population and drug resistance, so it is extremely important to identify sensitive populations for predicting MH-GIST recurrence. Medium- to high-risk classification-gastrointestinal stromal tumor recurrence is a clinically important issue that directly determines the formulation of clinical treatment plans and patient prognosis. In clinical practice, noninvasive medical imaging techniques play an

Table 1. Logistic regression analysis results of clinical model based on clinical characteristics for predicting the MH-GIST prognosis (*$P < .05$).

CLINICAL MODEL	UNIVARIATE ANALYSIS		MULTIVARIATE ANALYSIS	
FACTORS	*P*	HAZARD RATIO	*P*	HAZARD RATIO
Age	.95	0.99 (0.95-1.05)		
Sex	.74	1.13 (0.60-2.11)		
BMI	.45	1.03 (0.96-1.09)		
Hypertension	.50	0.81 (0.44-1.50)		
Alcohol use	.55	0.83 (0.45-1.54)		
Smoking	.07	0.53 (0.27-1.05)		
Education Background	.12	1.26 (0.94-1.68)		
Family histories of cancer	.53	1.23 (0.65-2.32)		
Diabetes	.01*	2.39 (1.23-4.69)		
Spicy hot pot	.02*	2.23 (1.19-4.35)	0.03*	2.18 (1.06-4.69)
NLR	.03*	1.45 (1.05-2.01)		
PLR	.03*	1.26 (1.03-1.54)		
GIST Volume	.02*	1.01 (1.00-1.02)	0.03*	1.01 (1.01-1.04)
GIST location	.04*	1.52 (1.02-2.27)		
Tumor morphology	.69	1.08 (0.79-1.41)		
Tumor boundary	.23	1.47 (0.78-2.75)		
CT enhancement pattern	.01*	1.49 (1.09-2.04)		
Tumor cyst degeneration or necrosis	.81	1.08 (0.58-2.03)		
AFP	.14	1.04 (0.98-1.10)		
Preoperative CEA	.51	1.09 (0.84-1.41)		
Preoperative CA19-9	.86	1.01 (0.96-1.04)		

*There were statistically significant differences in Diabetes, Spicy hot pot, NLR, PLR, GIST Volume, GIST location, and CT enhancement pattern between the 2 groups using logistic regression ($P < .05$).

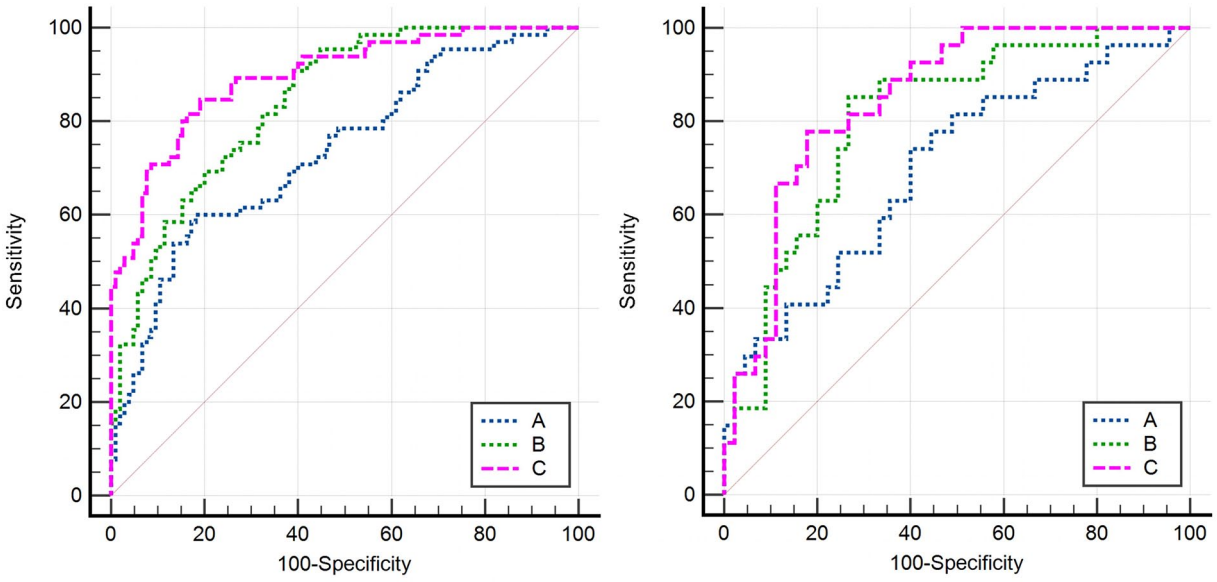

Figure 4. Delong nonparametric curves of the training set (left) and the test set (right). The area under the ROC curve of the combined model of the 2 groups is the largest, which confirms that the combined model has the best predictive performance. Clinical data model (A); imaging model (B); combined model (C).

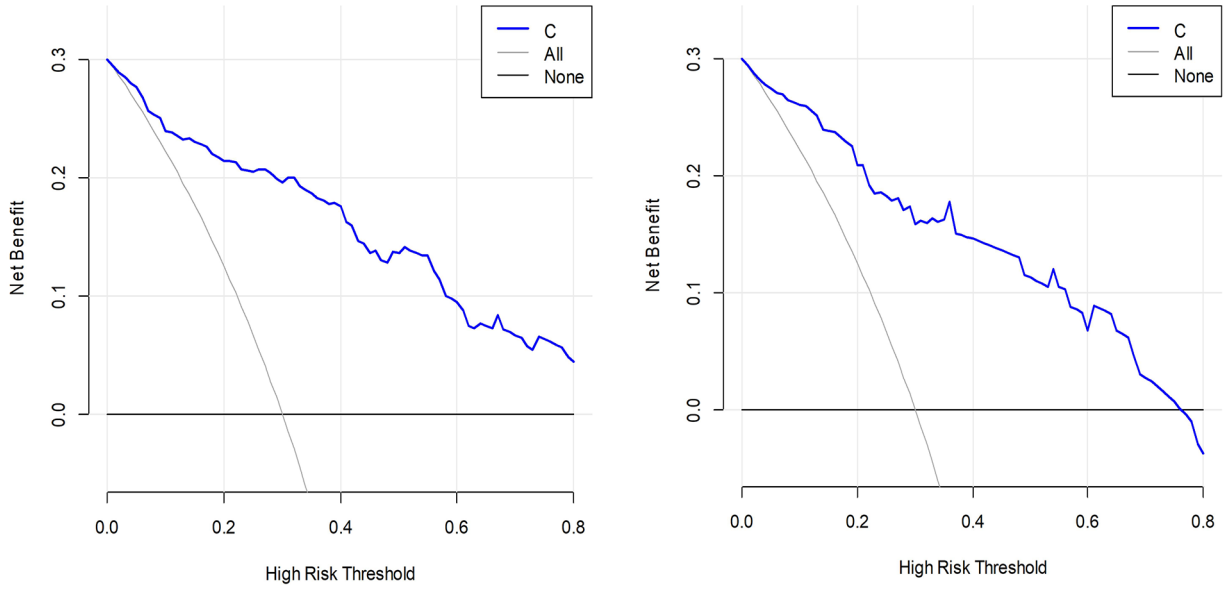

Figure 5. The higher clinical net benefits of the combined model was confirmed in the 2 groups by DCA of training set (left) and test set (right) using R software.

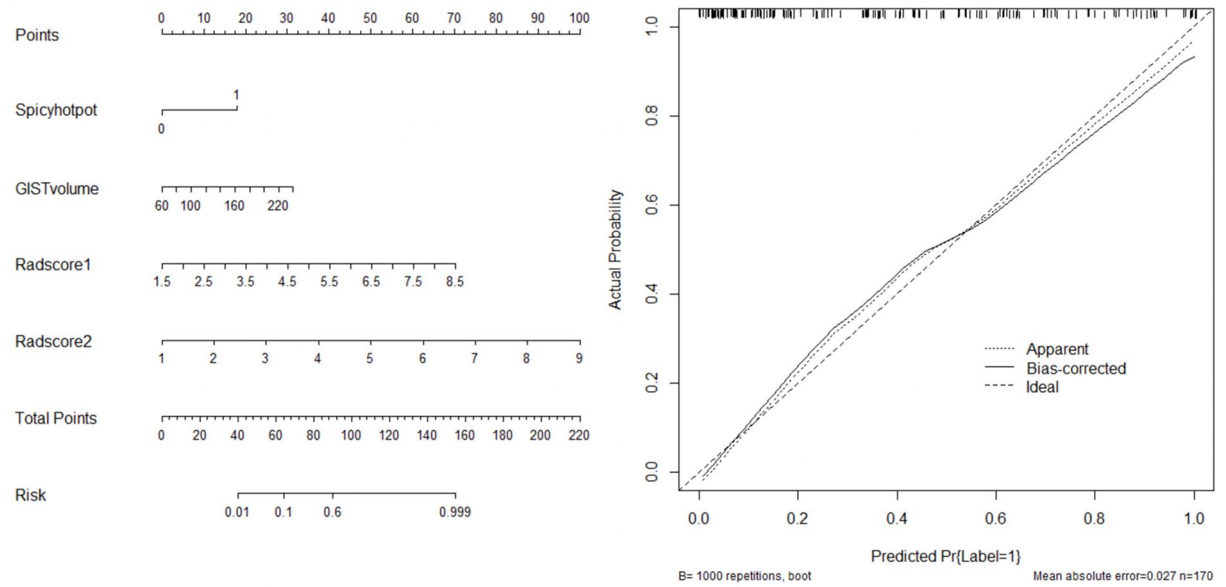

Figure 6. The nomogram prediction tool based on the risk factors of the combined model was used clinically (left: nomogram, right: calibration). Namely, each risk factor is scored, added together, and the final risk value is calculated.

Table 2. Logistic regression analysis results of imaging model based on CT characteristics for predicting the MH-GIST prognosis (*$P < .05$).

IMAGING MODEL	UNIVARIATE ANALYSIS		MULTIVARIATE ANALYSIS	
FACTORS	*P*	HAZARD RATIO	*P*	HAZARD RATIO
Radscore 1	<.05*	3.08 (1.93-4.92)	<.05*	2.72 (1.60-4.63)
Radscore 2	<.05*	2.77 (1.91-4.01)	<.05*	2.57 (1.71-3.85)

*There were statistically significant differences in Radscore 1 and Radscore 2, between the 2 groups using multivariate logistic regression ($P < .05$).

important role in the diagnosis and risk stratification of liver and kidney malignancies. Computed tomography is the most commonly used technique for screening gastrointestinal tumors and evaluating the malignancy of tumors, and its scan results can help predict the malignant potential and prognosis of GIST. Delta Radiomics can obtain high-quality enhanced CT texture

Table 3. Logistic regression analysis results of combined model based on valuable factors mentioned above for predicting the MH-GIST prognosis (*$P < .05$).

COMBINED MODEL	UNIVARIATE ANALYSIS		MULTIVARIATE ANALYSIS	
FACTORS	*P*	HAZARD RATIO	*P*	HAZARD RATIO
Diabetes	.01*	2.39 (1.23-4.69)		
Spicy hot pot	.02*	2.23 (1.19-4.35)	<.05*	6.25 (2.22-17.57)
NLR	.03*	1.45 (1.05-2.01)		
PLR	.03*	1.26 (1.03-1.54)		
GIST Volume	.02*	1.01 (1.00-1.02)	.02*	1.02 (1.00-1.03)
GIST location	.04*	1.52 (1.02-2.27)		
CT enhancement pattern	.01*	1.49 (1.09-2.04)		
Radscore 1	<.05*	3.08 (1.93-4.92)	<.05*	2.59 (1.37-4.93)
Radscore 2	<.05*	2.77 (1.91-4.01)	<.05*	4.03 (2.31-7.03)

*There were statistically significant differences in Spicy hot pot, GIST Volume, and Radscore 1/2, between the 2 groups using multivariate logistic regression ($P < .05$).

change data, indirectly reflecting the malignancy and recurrence potential of tumors, and providing strong data support for the diagnosis and treatment of MH-GIST after surgery.[18,20,21]

Unlike previous studies, this study has found that tumor volume, tumor location, spicy hot pot, NLR, PLR, diabetes, CT enhancement pattern, and Delta Radscore 1/2 are factors that influence the recurrence of MH-GIST within 3 years after surgery. Tumor volume is a classic factor for evaluating its malignant potential, with larger tumors having a higher probability of positive margins, greater surgical difficulty, and higher rates of metastasis and recurrence. Gastrointestinal stromal tumor usually occurs in the stomach and has a better prognosis. However, it has been reported that GIST in the esophagus, retroperitoneum, colon, and small intestine usually have a poorer prognosis, with early metastasis often occurring in esophageal GIST. Hot pot is a common cuisine in China, but to enhance the taste, it often contains a large amount of stimulating substances such as chili peppers and Sichuan peppercorns. Some hot pot broths even contain addictive ingredients such as poppy shells. Prolonged use at high temperatures will inevitably cause damage to the gastric and intestinal mucosa, promoting the deterioration and mutation of GIST. Neutrophil-lymphocyte ratio and PLR are classic inflammatory indicators, and in MH-GIST patients, these inflammatory indicators not only affect postoperative recovery but also represent the tumor's development toward a pro-inflammatory direction, indicating a strong tumor immunity and difficult treatment. Diabetes is a factor that affects the poor prognosis of various tumors. Elevated blood glucose levels not only damage the elasticity of blood vessel walls, leading to atherosclerosis, but also damage the nerves and immune system. A decrease in the body's immune response to tumor cells indicates a poor prognosis.[14,22-24] In this study, CT enhancement mode also had a high feature weight coefficient. Medium- to high-risk classification-gastrointestinal stromal tumor generally has a larger volume, uneven density, and is prone to cystic degeneration and necrosis. The internal blood supply is extensive and uneven, often presenting as uneven outflow-type enhancement, which usually indicates a higher malignant potential and affects prognosis. Delta Radscore 1/2 is a predictive factor for the malignant potential of GIST that we have discovered for the first time. This high-quality data based on the grayscale changes in enhanced CT helps analyze more details of the tumor and enhances tumor heterogeneity. It has been reported that dynamic time-enhanced curves (TCs) of enhanced CT help study the malignant potential of tumors, but the selection of enhancement time points is difficult and there is inevitably some error in the visual interpretation of TC. Delta Radiomics has unique diagnostic advantages. It uses the differences in radiomics features before and after enhancement to provide rich information for quantifying tumor blood perfusion and identifying changes in tumor components, further revealing the malignant potential of the tumor and guiding clinical decisions. Currently, Delta-CT or MR Radiomics can efficiently predict the prognosis of head and neck squamous cell carcinoma, which is significantly better than the predictive effect of static radiomics. Similarly, in this study, using Delta-CT Radscore to model the prognosis of MH-GIST significantly improved the predictive efficiency, surpassing previous predictive models. This is not only because enhanced CT provides richer underlying imaging information for MH-GIST, but more importantly, Delta Radscore quantifies its radiographic texture differences and reflects the essence of the tumor.[25-28]

Limitation

The follow-up time of this study was relatively short and failed to evaluate the longer-term (5-10 years) prognosis of MH-GIST. In the future, it is necessary to expand the

follow-up time to improve the accuracy of the study. This study is a single-center study, with limited case data and possible selection bias in the results. More prospective data (such as pathological subtypes, ki67, etc) are needed to further validate the predictive model's effectiveness externally. In addition, this study will require multicenter participation and multiple machine validation models in the future to verify the accuracy of the results.[29-31] This study pays tribute to publicly available integration software.[32]

Conclusions

In conclusion, the clinical-radiomics of nomogram based on Delta-CT Radscore has high clinical value in predicting prognosis in MH-GIST, and it has certain significance in changing subsequent clinical decisions and improving survival rates.

Author Contributions

YS, XJ, YH, JL, and PA conceived and drafted the manuscript. LS, JZ, YY, and LT contributed to the literature review. YY, HZ, and JW is responsible for the quality control of article statistics. PS, YY, and PA revised the manuscript critically for important intellectual content. TP and PA approved the final version to be published and agreed to act as guarantors of the work. XJ, YS, and LT contributed equally to this work.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

Consent for Publication

Written informed consent was obtained from individual or guardian participants. Authors all agree.

Ethical Approval and Consent to participate

The experimental protocol was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the Human Ethics Committee of Xiangyang No. 1 People's Hospital affiliated to Hubei University of Medicine (Issue No. XYYYE20210020.0390). Written informed consent was obtained from individual or guardian participants.

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