



Original Research

Preoperative recurrence prediction in pancreatic ductal adenocarcinoma after radical resection using radiomics of diagnostic computed tomography

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ABSTRACT

Background: The high recurrence rate after radical resection of pancreatic ductal adenocarcinoma (PDAC) leads to its poor prognosis. We aimed to develop a model to preoperatively predict the risk of recurrence based on computed tomography (CT) radiomics and multiple clinical parameters.

Methods: Datasets were retrospectively collected and analysed of 220 PDAC patients who underwent contrast-enhanced computed tomography (CE-CT) and received radical resection at 3 institutions in China between 2013 and 2017, with 153 from one institution as a training set, the remaining 67 as a validation set. For each patient, CT radiomics features were extracted from intratumoral and peritumoral regions to establish intratumoral, peritumoral and combined radiomics models using artificial neural network (ANN) algorithm. By incorporating clinical factors, radiomics-clinical nomograms were finally built by multivariable logistic regression analysis to predict 1- and 2-year recurrence risk.

Findings: The developed radiomics model integrating intratumoral and peritumoral radiomics features was superior to the conventionally constructed model merely using intratumoral radiomics features. Further, radiomics-clinical nomograms outperformed other models in predicting 1-year recurrence with an area under the receiver operating characteristic curve (AUROC) of 0.916 (95%CI, 0.860-0.955) in the training set and 0.764 (95%CI, 0.644-0.859) in the validation set, and 2-year recurrence with an AUROC of 0.872 (95%CI: 0.809-0.921) in the training set and 0.773 (95%CI, 0.654-0.866) in the validation set.

Interpretation: This study has developed and externally validated a radiomics-clinical nomogram integrating intra- and peritumoral CT radiomics signature as well as clinical factors to predict the recurrence risk of PDAC after radical resection, which will facilitate optimized and individualized treatment strategies.

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Research in context

Evidence before this study

So far, due to lack of effective preoperative assessment, the proneness for early recurrence after radical resection still remains one of the major barriers to curing patients with PDAC. Prior studies involving pancreatic CT radiomics mainly focused on the features from intratumoral area to predict survival and treatment response with only poor to moderate performance.

Added value of this study

This is the first study to build and validate clinical-radiomics models that preoperatively predict recurrence risk of PDAC using not only intratumoral, but also peritumoral CT radiomics features together with clinical factors in patients eligible for radical resection from multi-institutional datasets.

Implications of all the available evidence

PDAC is distinct from other solid tumors due to its dense stroma. CT radiomics features from peritumoral volume could add additional value to predict its tumor behaviour.

1. Introduction

With the lowest 5-year survival rate of any epithelial carcinoma at approximately 8%, pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignancies worldwide and expected to be the second leading cause of cancer-related mortality [1, 2]. Only 10–20% of patients were identified at an early stage and able to potentially get cured through radical surgery, due to lack of early clinical symptoms and effective screening approaches [3]. However, up to 80% of them will experience recurrence of the disease after curative resection, resulting in a 5-year survival of less than 20% [4–9]. Therefore, there is an urgent need to construct efficient predictive models to stratify patients preoperatively and further optimize individualized treatment decision-making.

Currently, development of non-invasive approaches to accurately predict treatment outcomes and prognosis is imperative to improving personalized medicine [10]. Several studies have achieved comparable performance in predicting the recurrence of resectable PDAC by building conventional regression-based models merely based on multiple clinicopathological factors [11–13]. In recent years, radiomics, as an emerging radiology analogue of “genomics” and “proteomics”, has attracted extensive interest in developing clinical predictive tools for diagnosis, prognosis and therapeutic response of various malignancies [14–17]. By using high-throughput mining of intratumoral medical imaging data to extract hidden information, it has also been applied for predicting tumor behavior of PDAC [18–23]. While most studies mainly focused on the primary tumor, previous reports have illustrated the unique value of peritumoral region for clinical assessment of cancerous heterogeneity [24–26]. So far, it remains unclear whether CT radiomics features from intra- and peritumoral volume could add additional predictive value to traditional clinical models for recurrence risk assessment of PDAC after radical surgery.

Hence, this study intended to develop and validate clinical-radiomics models that preoperatively predict 1- and 2-year recurrence of PDAC using intratumoral/peritumoral CT radiomics features and clinical factors in patients eligible for radical resection. Predicting the risk of recurrence before surgery could help distinguish high-risk patients and select optimal surgical candidates for surgeons, which will further facilitate individualized treatment strategies [27].

2. Materials and Methods

2.1. Study design

This study was conducted through four parts as shown in [Figure 1](#). Firstly, we preprocessed CE-CT and extracted radiomics features from intratumoral volume (ITV) and peritumoral volume (PTV). Secondly, we used feature selection method to obtain the optimal features. Then, these selected radiomics features were employed to develop ITV model, PTV model, combined model, clinical model and radiomics-clinical model. Finally, we made a comparison among all models.

2.2. Study Population

Data of PDAC patients who underwent radical resection at 3 institutions between January 2013 and December 2017 were obtained. This retrospective analysis was approved by the institutional ethical review boards of three centers including the Second Affiliated Hospital (Institution I), the Forth Affiliated Hospital (Institution II), Zhejiang University school of Medicine and the Zhejiang Cancer Hospital (Institution III). The signed informed consent forms were waived. This study was conducted according to the Declaration of Helsinki. The inclusion and exclusion details of patients were as follows: Inclusion criteria: PDAC patients who preoperatively underwent CE-CT and received radical resection at 3 institutions. Exclusion criteria: 1. Patients who had initially borderline resectable/unresectable cancers according to the NCCN guideline [28]; 2. Patients who received neoadjuvant therapy; 3. Patients who did not receive a contrast-enhanced CT scan within two weeks before surgery; 4. Patients lacking complete clinical data or follow-up data; 5. Patients who died from surgical complications within 30 days after surgery; 6. Patients who received consecutive surgical operations.

The final study population consisted of 220 patients (173 patients from the Second Affiliated Hospital, Zhejiang University school of Medicine, 7 patients from the Forth Affiliated Hospital, Zhejiang University school of Medicine, 40 patients from the Zhejiang Cancer Hospital). The training set included the first 153 patients since January 2013 from the first institution and the independent validation set included the last 20 patients from the first institution, 7 patients from the second institution and 40 patients from the third institution (training: validation=7:3). The details of profile and information of patients were presented in [Table 1](#).

2.3. Data Collection

Preoperative blood biomarkers including carcinoembryonic antigen (CEA), cancer antigen (CA) 19-9, CA125, white blood cell (WBC) count, platelet count, neutrophil count, lymphocyte count, monocyte count, albumin, globulin, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), total bilirubin (TB) and direct bilirubin (DB) were collected using the measurements that were closest to the operation and within at least 1 week before the surgery.

The follow-up of patients after surgery was initially conducted every 3 months in the first two years, every 6 months during years 3 and 4, and then annually. The surveillance protocol included physical examination, serum cancer antigens and abdominoperineal CE-CT. Magnetic resonance imaging (MRI) scan and/or fluorodeoxyglucose positron emission tomography (PET) would be implemented to further clarify ambiguous CT findings every time imaging features were consistent with a potential cancer recurrence.

2.4. Image acquisition and volume of interest (VOI) delineation

The patients in our study underwent an abdominal CE-CT preoperatively. CE-CT scan in Institution I was performed on five CT scanners including a 16-slice CT (Sensation 16, Siemens), a 16-slice CT

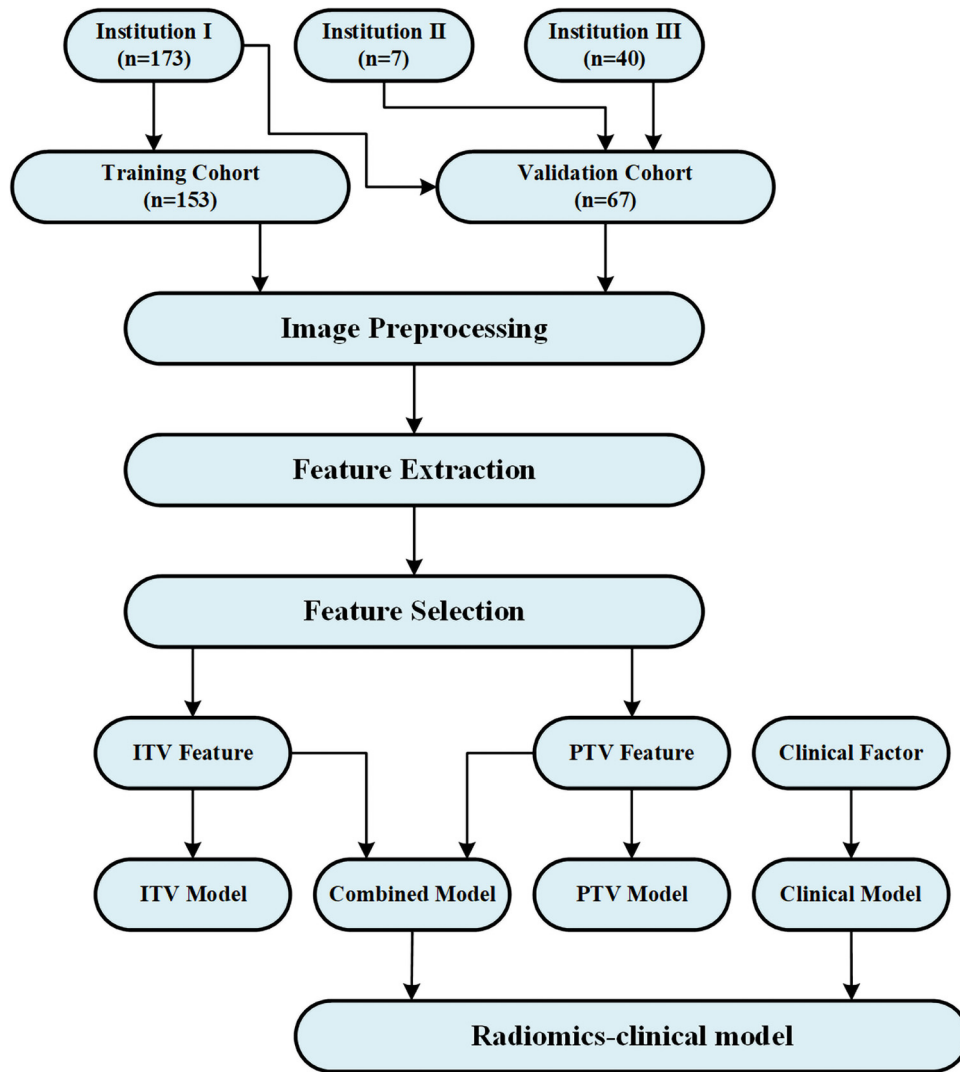


Figure 1. The workflow of this study

(BrightSpeed, GE MEDICAL SYSTEMS), a 64-slice CT (SOMATOM Definition AS, GE MEDICAL SYSTEMS), a 320-slice CT (Aquilion ONE, TOSHIBA), an 800-slice CT (SOMATOM Definition Flash, GE MEDICAL SYSTEMS). The CE-CT scan in Institution II was undertaken on two scanners, including a 16-slice CT (BrightSpeed, GE MEDICAL SYSTEMS), a 64-slice CT (SOMATOM Definition AS, GE MEDICAL SYSTEMS). The CE-CT scan in Institution III was undertaken on three scanners, including a 16-slice CT (BrightSpeed, GE MEDICAL SYSTEMS), a 64-slice CT (SOMATOM Definition AS, GE MEDICAL SYSTEMS), a 320-slice CT (Aquilion ONE, TOSHIBA). The scanning voltage of 100 kVp to 120 kVp, tube currents were 240 to 1287 mAs. The slice thickness ranged from 3 to 7.5 mm.

The 3D tumor VOI was manually segmented and validated using the ITK-SNAP open source software (<http://www.itk-snap.org/pmwiki/pmwiki.php>) by two experienced oncologists, respectively. The VOI regions were also agreed by both two oncologists. To explore the predictive value of PTV, We also expanded the segmented mask by 3mm to 7mm outward automatically according to the previous study [29] in MATLAB (MathWorks, Natick, MA, USA). The ITV and PTV area of one of the patients was shown in Figure 2.

2.5. Feature extraction

To reduce the variation in different scanners, a two-step method of the image preprocessing was conducted before radiomics features

extraction. Firstly, due to different pixel sizes and slice thicknesses of various CE-CT scanners, all the CT slices were resampled to $1 \times 1 \times 1 \text{ mm}^3$ using the bicubic interpolation [30]. Secondly, the images were normalized to 64 grey levels to compensate for the variation of CE-CT scanners. For each ITV and PTV area, 547 radiomics features were extracted covering 7 shape features, 7 histogram features, 22 gray-level co-occurrence matrix (GLCM) features, 13 gray-level run-length matrix (GLRLM) features, 13 gray-level size zone matrix (GLSZM) features, 5 neighborhood gray-tone difference matrix features, and 480 wavelet-based features. Therefore, we could obtain 1094 radiomics features for each patient. Radiomics features extraction process was conducted using the radiomics tools available in MATLAB. More details about the feature extraction methods could be found in the study by Vallières *et al.* [31]

2.6. Feature selection and model construction

Before the process of feature selection, the extracted features were normalized using the Z-score, with the mean and standard deviation of the features in the training set utilized to normalize the corresponding features in the validation set. To reduce the dimension of radiomics features, we conducted a two-step feature selection approach in the training set. Initially, each significant feature calculated by the Wilcoxon test ($p\text{-value} < 0.05$) was maintained. Afterwards, the minimum redundancy maximum relevance (mRMR)

Table 1
Characteristics of patients in the training and validation sets

Characteristic	Training set (n=153)	Validation set (n=67)	p-value
Age (years)	64 (35-90)	63 (45-83)	0.6461
Sex (Male/Female)	94/59	62/25	0.1635
BMI (kg/m ²)	22.1 (10.52-34.6)	22.35 (17.07-27.99)	0.9410
CEA (ng/mL)	3.1 (0.7-258.5)	3.8 (1.01-45.83)	0.5705
CA19-9 (U/mL)	240.4 (2-12000)	253.5 (2.2-12000)	0.2648
CA125 (U/mL)	15.2 (2.1-145.6)	19.2 (5.5-656.2)	0.1476
WBC (*10 ⁹)	5.8 (2.3-14.5)	5.8 (1.8-13.2)	0.5025
Platelet (*10 ⁹)	185 (67-401)	201 (61-335)	0.2750
Neutrophil (*10 ⁹)	3.7 (1-11.68)	3.6 (0.9-10.8)	0.3332
Lymphocyte (*10 ⁹)	1.37 (0.44-19.1)	1.48 (0.5-3.7)	0.7810
Monocyte (*10 ⁹)	0.46 (0.07-1.32)	0.4 (0.1-12.6)	0.2245
Albumin (g/L)	39.6 (23.9-65.4)	40.4 (27.7-47.3)	0.7273
Globulin (g/L)	26.5 (14.9-42.4)	28.1 (18.4-41.4)	0.0565
AST (U/L)	42 (9-524)	44 (1.6-596)	0.9382
ALT (U/L)	47 (7-743)	51 (8-910)	0.6633
ALP (U/L)	147 (6-1197)	168 (16-1178)	0.9587
GGT (U/L)	159 (9-2839)	201 (10-2298)	0.4435
TB (U/L)	23 (4.4-358.3)	21.3 (4-408.3)	0.5572
DB (U/L)	6.8 (1-260.2)	7.8 (1-263.6)	0.8784
AGR	1.49 (0.83-2.61)	1.41 (0.74-2.18)	0.1757
NLR	2.72 (0.13-11.90)	2.5 (0.67-15.43)	0.7617
LMR	2.92 (0.63-44.42)	3.20 (0.06-17)	0.6848
PLR	134.92 (10.10-616.92)	141.54 (60-343.33)	0.6960

Note: CEA: carcinoembryonic antigen; CA19-9: serum carbohydrate antigen 19-9; WBC: white blood cell; AST: aspartate transaminase; ALT: alanine transaminase; ALP: alkaline phosphatase; GGT: gamma-glutamyl transferase; TB: total bilirubin; DB: direct bilirubin; AGR: albumin-globulin ratio; NLR: neutrophil-lymphocyte ratio; LMR: lymphocyte-monocyte ratio; PLR: platelet-lymphocyte ratio.

feature selection algorithm was used to select the features most relevant to the status of 1-year recurrence and 2-year recurrence, and the selected features had minimal redundancy among each other [32]. In this study, the artificial neural network (ANN) algorithm (parameter: hidden layer = 3, initial random weight = 0.01, weight decay = 5e-3, maximum number of iterations = 100) was used to construct the prediction model. The area under the receiver operating characteristic (ROC) curve (AUC) value was the scoring criterion to obtain the optimal tumor radiomics features. The ITV model, PTV model and combined model were developed, respectively. A radiomics score was calculated to reflect the risk of tumor recurrence for each patient using the proposed radiomics model. To evaluate the capability of predicting the status of recurrence, the constructed model from the training set was verified in the independent validation set. To obtain the best prediction performance of PTV classifier, we also explored the capability of different PTV models, with the length of edge ranged from 3mm to 7mm.

2.7. Clinical-based model and combined radiomics-clinical model construction and evaluation

In addition to the radiomics model, we also constructed clinical model and radiomics-clinical model. The clinical model and radiomics-clinical model were developed by multivariate logistic regression method. The backward step-wise search method with lowest Akaike Information Criterion (AIC) score was used to selected the optimal clinical factors [33]. Then, we used the univariate analysis to select the clinical factors to combine with radiomics score to establish the radiomics-clinical model. The performances of all models were reported using the AUC in the training set and validation set. A Hosmer-Lemeshow (H-L) test was used to evaluate the goodness-of-fit of the radiomics-clinical model. The clinical utility of the models was evaluated with a decision curve analysis (DCA) in two sets [14]. DeLong test was used to measure the differences in ROC curves among all models. The comparison of all the models were carried out in the validation cohorts.

2.8. Statistical Analysis

Statistical analysis was conducted in R v3.4.1 (www.Rproject.org) and MedCalc v15.2.2 (www.medcalc.org). mRMR analysis, plotting of nomograms and calibration curves, H-L test, ROC and AUC, and DCA were performed on the packages "mRMR", "rms", "generalhoslem", "pROC", and "dca.R", respectively. The reported significance levels were two-sided and set at 0.05.

This manuscript is compliant with STrengthening the Reporting of Observational studies in Epidemiology (STROBE). A checklist is provided as an online supplement.

2.9. Role of Funding Source

All funding sources played no role in the design of the study; collection, analysis and interpretation of data; in writing the manuscript, and in the decision to submit the paper for publication.

3. Results

3.1. Basic Characteristics

Baseline clinical characteristics in the training and validation sets were summarized in the **Table 1**. The median follow-up of the entire population was 18.0 months (95% CI 16.0-20.5). The 1-year recurrence rate was 58.17% and 59.70% for the training set and validation

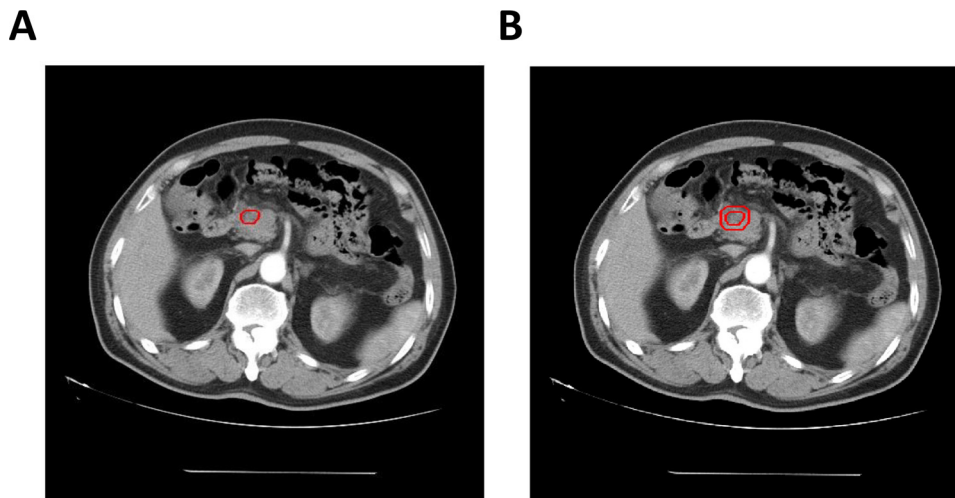


Figure 2. VOIs of ITV and PTV (7mm) for radiomics analysis. A: ITV area; B: PTV (7 mm) area.

set, respectively. The 2-year recurrence rate was 73.20% and 71.64% for the training and validation set, respectively. No significant difference was observed in the baseline patient characteristics between the groups, indicating a good consistency of the two datasets. Univariate analysis for the 1-year and 2-year recurrence was performed and only CA19-9 showed statistical significance between recurrence group and non-recurrence group in training and validation sets. Therefore, CA19-9 factor was identified as an independent predictive factor in predicting the risk of recurrence of PDAC after radical resection.

3.2. Feature selection and model construction for 1-year recurrence

In this study, three types of prediction models were developed and compared including radiomics model, clinical model and clinical-radiomics model. For the radiomics one, we constructed three sub-models including ITV model, PTV model and the combined model. By univariate analysis, 295 intratumoral radiomics features were found to be significant different between patients with 1-year recurrence and non-recurrence in the training set, 9 of which were finally selected by the mRMR algorithm to build the ITV model with an AUC of 0.851 (95%CI, 0.784-0.903) in the training set and 0.713 (95%CI, 0.589-0.817) in the validation set. In order to construct a PTV model with the best predictive performance, different regions of peritumoral parenchyma ranging from 3mm to 7mm were explored. A total of 270, 230, 229, 214, 209 radiomics features of five separate PTV models (3mm, 4mm, 5mm, 6mm and 7mm), respectively, were selected using univariate analysis. Then, 8, 10, 10, 6, 6 optimal features were accordingly picked up by mRMR method to develop the models using the ANN algorithm. Among them, the PTV_{7mm} presented the best performance in predicting the different status of 1-year recurrence with an AUC of 0.786 (95%CI, 0.713-0.848) for the training set and 0.654 (95%CI, 0.528-0.766) for the validation set. To further improve the prediction capability, the intratumoral and peritumoral features were combined to yield higher AUCs in both training (AUC= 0.901 (95%CI, 0.842-0.943)) and validation set (AUC = 0.732 (95%CI, 0.610-0.833)). The rank of mRMR score and univariate analysis for the selected top 15 radiomics features were shown in **Figure S1**.

Similarly, considering the potential effectiveness of clinical factors, we also constructed the clinical model and radiomics-clinical model. The performance of the clinical factors-based model was inferior to the radiomics models in both two datasets (training set: 0.630 (95%CI, 0.648-0.707); validation set: 0.644 (95%CI, 0.517-0.757)). However, the radiomics-clinical model combined ITV, PTV_{7mm} and CA19-9 levels presented the optimal performance in predicting the 1-year recurrence with an AUC of 0.916 (95%CI, 0.860-0.955) in the training set and an AUC of 0.764 (95%CI, 0.644-0.859) in the validation set. The ROC curves for each model were pictured in the **Figure 3A and 3B**. The H-L test showed a satisfying accuracy of the nomogram for predicting the status of 1-year recurrence both in the training set (p -value=0.7191) and validation set (p -value=0.5929).

By the Delong test, although the radiomics-clinical model was preferred, there was no significant difference in the predictive performance compared with other predictive models in the validation set. The detailed value of p -values among all models were listed in **Table S1**. Furthermore, the nomogram was visualized in **Figure 3E**. The DCA showed that the nomogram model (black) presented more area than the model merely developed by clinical factors in two sets which demonstrated the promising clinical decision utility of nomogram. The DCA curves for the two datasets were separately shown in **Figure 3C and Figure 3D**.

3.3. Feature selection and model construction for 2-year recurrence

To further explore the generalization of radiomics model in predicting the recurrence status of pancreatic cancer after radical

resection. We employed the similar method to construct radiomics model, clinical model and radiomics-clinical model to evaluate the prediction performance for 2-year recurrence. Compared with the other two radiomics models, the combined model also showed the best prediction capability in the validation set (combined model, AUC=0.709 (95%CI, 0.585-0.814); ITV model, AUC=0.648 (95%CI, 0.521-0.701); PTV_{7mm} model, AUC=0.658 (95%CI, 0.532-0.769)). In accordance with the study of 1-year recurrence, the clinical model for 2-year recurrence also achieved the worst prediction performance with a poor AUC of 0.723 (95%CI, 0.645-0.793) in the training set and an AUC of 0.541 (95%CI, 0.415-0.663) in the validation set. Finally, we integrated the CA19-9 level and radiomics scores to establish the radiomics-clinical model, which outperformed others in predicting the status of 2-year recurrence (training set: AUC=0.872 (95%CI: 0.809-0.921); validation set: AUC=0.773 (95%CI, 0.654-0.866)). The ROC curves for each model were pictured in the **Figure 4A and 4B**. The nomogram and DCA curves for 2-year recurrence models could be seen in **Figure 4C, 4D and 4E**. The H-L test showed that non-significant difference was observed between true calibration curves and ideal curves both in the training set (p -value=0.2543) and validation set (p -value=0.2678).

4. Discussion

Robust assessment tools with satisfying accuracy for individual risk of recurrence after multimodal therapy would minimize unnecessary treatments and thus serve as a decision aid for clinical decision-making [34]. In this study, we have constructed and validated nomograms integrating CT radiomics features and clinical characteristics to predict the recurrence risk of PDAC after curative surgery. It turned out that the combined clinical-radiological models were superior to conventional clinical factors-based ones in predictive capability. Moreover, incorporating additional features from peritumoral regions into the models could further improve their power.

In this study, to ensure the generalizability of the promoted model, only most commonly measured lab test results in various medical centers including cancer antigens, blood routine and biochemical indicators were used in clinical models. Inflammation-based prognostic scores, including albumin-globulin ratio (AGR) [35], lymphocyte-monocyte ratio (LMR) [36], neutrophil-lymphocyte ratio (NLR) [37] and platelet-lymphocyte ratio (PLR) [38], were calculated as well but with no statistical significance. Other clinical features like nutritional status could be reflected by patients' BMI, which also showed no statistical significance between recurrence group and non-recurrence group by univariate analysis. In fact, the study population we focused on in this study tended to have similar pre-operative nutritional status and Eastern Cooperative Oncology Group (ECOG) performance as they could withstand radical surgery and subsequent adjuvant therapy. Additionally, in alignment with various studies investigating the predictive early recurrence parameters of PDAC [6, 39-41], CA19-9 is independently associated with both 1-year and 2-year recurrence risk. To be clear, histopathologic data was not included in this study for the purpose of guiding preoperative decision-making.

So far, due to the paucity of comprehensive and in-depth preoperative assessment, the proneness for early recurrence after radical resection still remains one of the major barriers to curing patients with PDAC [42]. It has been reported that early recurrence within 12 months occur in 50% to 60% of patients considered eligible for surgical resection [43], and in this study, the number was 58.17% and 59.70% for the training and validation set, respectively. Timely and accurate prediction of recurrence risk is urgently needed to identify patients at high risk, among whom more detailed examination, the use of neoadjuvant therapy, or even the inclusion of these patients into clinical trials could be considered.

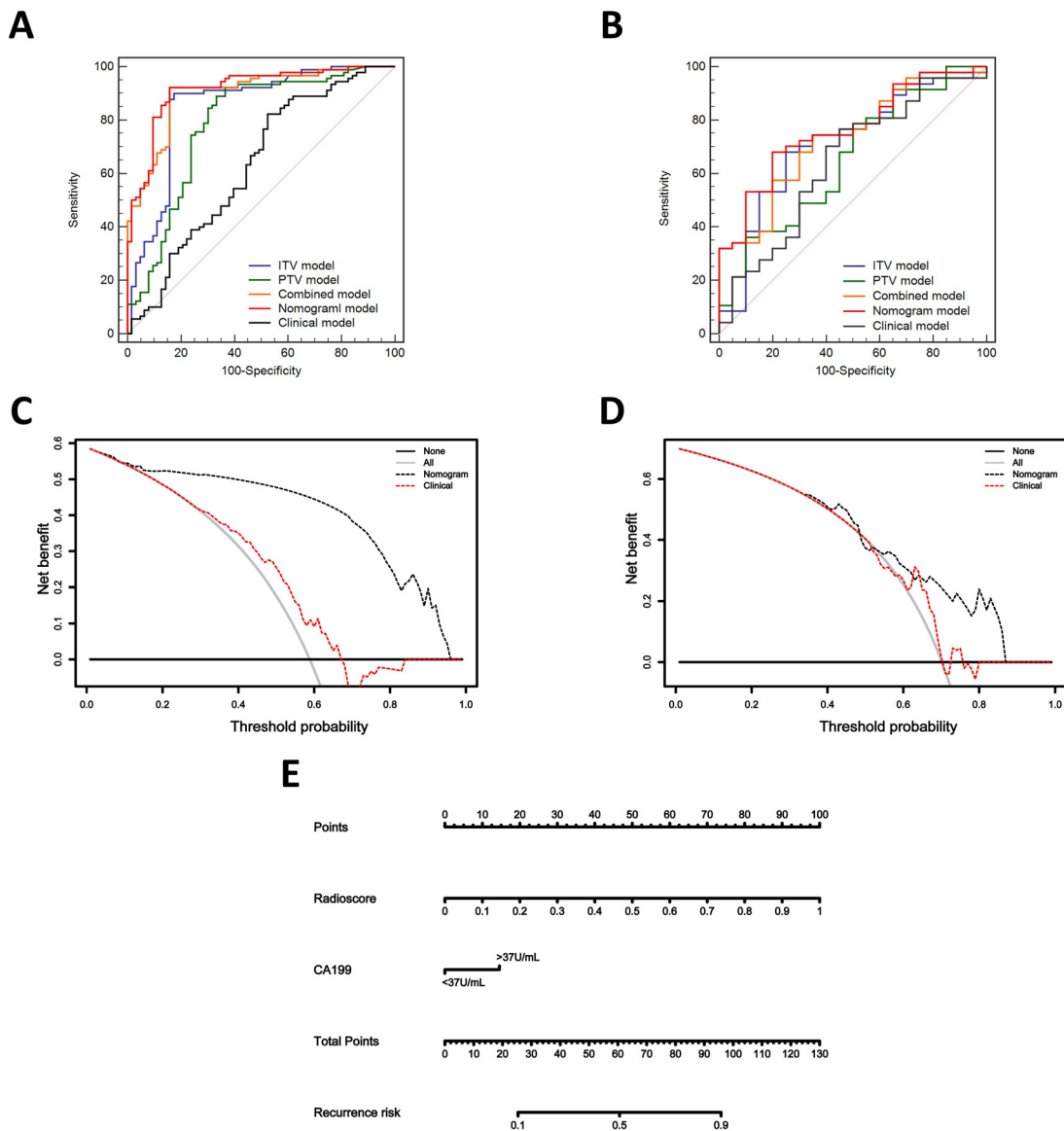


Figure 3. The ROC curve, DCA curve and nomogram for the 1-year recurrence target. A, B: the ROC curve for training and validation set. C, D: the DCA curve for training and validation set. E: the nomogram for 1-year recurrence

Nowadays, radiomics research in oncology is accelerating rapidly, with potential applications in almost every aspect of cancer management [44]. In patients with pancreatic cancer, preoperative CE-CT is the preferred primary imaging modality for the initial evaluation [45]. As is routinely used for screening, staging and monitoring the progression of PDAC, CT scan is relatively faster and more inexpensive compared to MRI, making it more easily available for use [46]. Previous studies involving CT radiomics mainly focused on the features from intratumoral area to predict survival [2, 21, 23, 47, 48] and treatment response [22, 49] with only poor to moderate performance. However, characterized by its dense desmoplastic stroma composed of stromal cells and extracellular matrix, PDAC is distinct from other solid tumors [50]. Recent radiomics reports have revealed the links between cancer behavior and peritumoral features in various malignant neoplasms including esophageal carcinoma [17], hepatocellular carcinoma [24], breast cancer [25] and lung adenocarcinoma [26], etc. Imaging characteristics of surrounding areas outside tumor itself were found to be able to reflect the subtle change of surrounding microenvironments and provide complementary information on tumor heterogeneity. To date, similar researches regarding PDAC have rarely been reported.

To the best of our knowledge, this is the first study to build and validate clinical-radiomics nomograms that preoperatively predict recurrence risk of PDAC using not only intratumoral, but also peritumoral CT radiomics features in addition to clinical parameters in patients eligible for radical resection from multi-institutional datasets. Although the concept of “radiomics” has been raised for almost a decade since 2012 by Lambin et al [51], there has never been an article investigating the relationship between CT features and recurrence risk of PDAC after radical resection. We speculate that the unsatisfying predictive capability of models merely based on intratumoral information might account for this delayed progress. Therefore, the great clinical potential of peritumoral radiomics needs to be further exploited in the future. As for the previously reported models simply based on clinicopathological factors regarding this topic, each of them has their own specific drawbacks with either a poor predictive performance (AUROC=0.655) [11], or a lack of external validation [12], or a very small sample size of less than 40 [34], respectively.

Several limitations of our work deserve to be acknowledged. First, given the retrospective nature of this study, some selection bias might be introduced, and the findings reported herein need to be confirmed in prospective trials. Second, due to the low incidence of

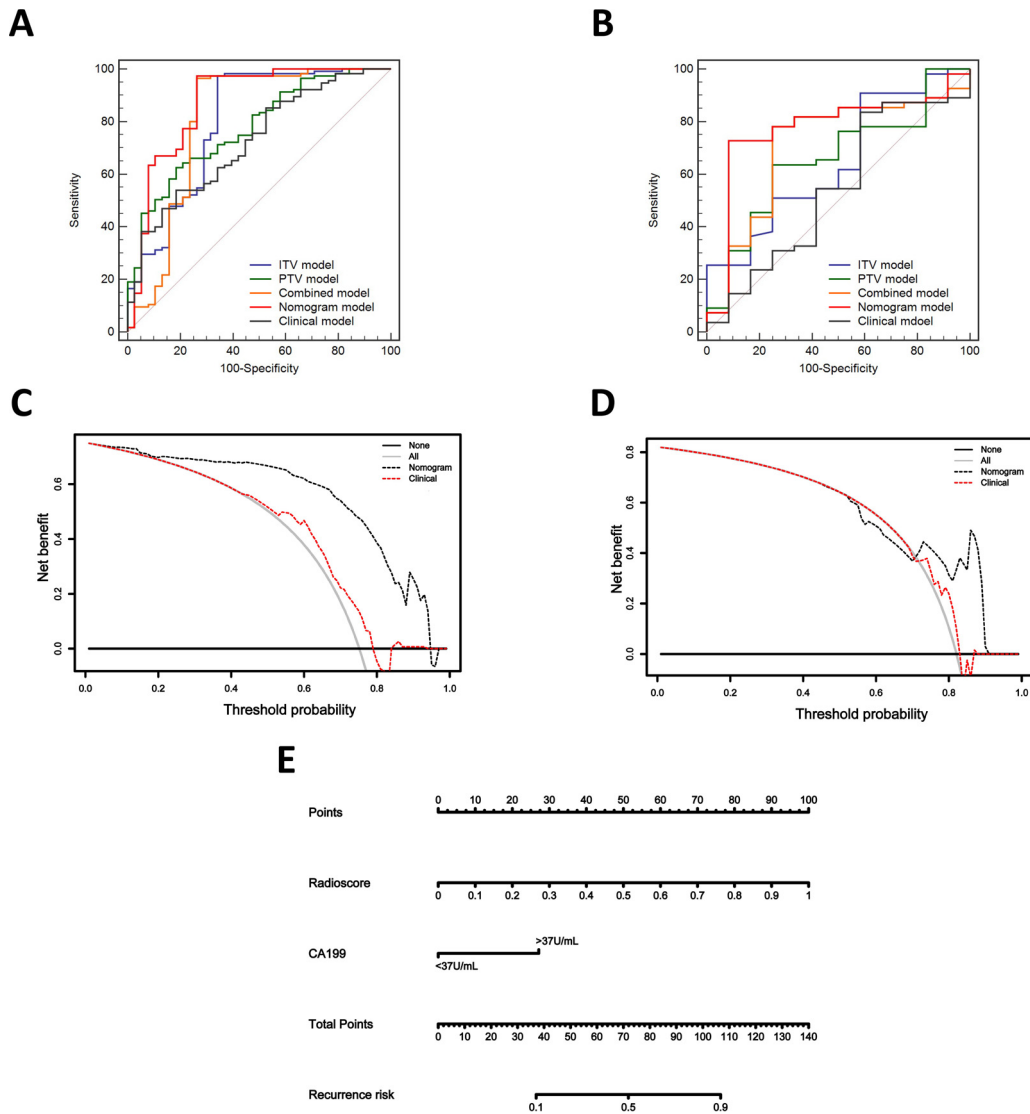


Figure 4. The ROC curve, DCA curve and nomogram for the 2-year recurrence target. A, B: the ROC curve for training and validation set. C, D: the DCA curve for training and validation set. E: the nomogram for 2-year recurrence

PDAC, the relatively limited sample size included might restrict the statistical power for quantifying interpatient variability effects. Additional studies on large-scale datasets from multiple medical institutions are required to further establish the robustness of the proposed nomogram. Notably, although the sample size might be not large compared with other tumors, it was at least not small considering the strict inclusion criteria and was actually larger than most radiomic studies regarding PDAC [2,21-23,47,48]. Third, the time-consuming and labor-intensive work of manual contouring of region of interests (ROIs) still poses a major bottleneck for implementing cutting-edge radiomics techniques in clinical practice at present. It is worthy looking forward to some novel automatic volumetric segmentation algorithms in PDAC radiomics analysis to simplify the process in the near future [52, 53].

To conclude, we have developed and validated a comprehensive radiomics-clinical nomogram integrating intra- and peritumoral radiomics signature as well as clinical characteristics to preoperatively predict the recurrence risk of PDAC after radical resection. Radiomics features extracted from CT scan can provide additional prognostic prediction value for patients before surgery, facilitating the non-invasive burgeon of individualized regimens in early treatment course.

Declaration of Competing Interest

The authors declare no potential conflicts of interest.

Data sharing statement

The datasets generated during and analysed during the current study are available by the corresponding author, upon reasonable request.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2021.101215.

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