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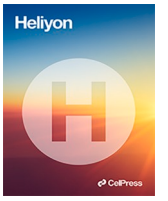

Review article

# Radiomics advances in the evaluation of pancreatic cystic neoplasms

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ABSTRACT

With the development of medical imaging, the detection rate of pancreatic cystic neoplasms (PCNs) has increased greatly. Serous cystic neoplasm, solid pseudopapillary neoplasm, intraductal papillary mucinous neoplasm and mucinous cystic neoplasm are the main subtypes of PCN, and their treatment options vary greatly due to the different biological behaviours of the tumours. Different from conventional qualitative imaging evaluation, radiomics is a promising noninvasive approach for the diagnosis, classification, and risk stratification of diseases involving high-throughput extraction of medical image features. We present a review of radiomics in the diagnosis of serous cystic neoplasm and mucinous cystic neoplasm, risk classification of intraductal papillary mucinous neoplasm and prediction of solid pseudopapillary neoplasm invasiveness compared to conventional imaging diagnosis. Radiomics is a promising tool in the field of medical imaging, providing a noninvasive, high-performance model for preoperative diagnosis and risk stratification of PCNs and improving prospects regarding management of these diseases. Further studies are warranted to investigate MRI image radiomics in connection with PCNs to improve the diagnosis and treatment strategies in the management of PCN patients.

## 1. Introduction

The incidence of pancreatic cystic neoplasms (PCNs) is approximately 2–45 % in normal adults, and its incidence is related to the age and body mass index of subjects [1–3]. The most common types of PCN are serous cystic neoplasm (SCN), solid pseudopapillary neoplasm (SPN), intraductal papillary mucinous neoplasm (IPMN), and mucinous cystic neoplasm (MCN) [4]. Among them, the malignancy rate of SCN is extremely low, and multiple guidelines recommend follow-up for patients without clinical symptoms, while MCN, IPMN and SPN have notable malignant potential and often require surgical resection. For patients with low-risk branch duct IPMN (BD-IPMN) and MCN patients with a tumour size less than 4 cm who are asymptomatic or low risk, guidelines also recommend observation follow-up [5]. The accuracy of conventional imaging diagnosis of PCN is less than 50 % [6–8]. Improvement in the

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diagnosis accuracy and risk assessment of PCNs is still a major clinical challenge, and new methods are urgently needed for the evaluation of PCNs. As a non-invasive approach of computer-aided diagnosis in the field of imaging, radiomics is a new diagnostic technology that can establish high-performance models for the diagnosis, classification, and risk stratification of diseases by extracting high throughput features from images, and it has shown promising value in PCN applications. This article presents a review of radiomics advances in the preoperative diagnosis and risk stratification of PCNs. The existing problems and directions of future development for radiomics were also addressed and proposed.

## 2. Traditional PCN diagnosis approaches

Traditional PCN diagnosis mainly relies on imaging, endoscopic ultrasonography (EUS) and biomarkers [9]. CT and MRI are the most used imaging methods for PCN diagnosis [4,5,10]. CT has a short examination time and is sensitive to calcification in tumours. The disadvantage of CT examination is the presence of ionizing radiation, and the use of iodine contrast agent may cause damage to the kidney and cause allergies. MRI has distinct advantages for evaluating the pancreaticobiliary system. The relationship between the cystic lesions and the surrounding structures can be clearly demonstrated by using MRI, which is the recommended approach for PCN patient examinations [2]. The scanning time of MRI is longer than that of CT, and MRI is also costly and not sensitive to calcification in tumours. Abdominal ultrasonography is a safe and inexpensive medical diagnosis method, but it is susceptible to intestinal gas, and the diagnostic accuracy is greatly affected by examiner experience [11]. The reported detection rate for abdominal ultrasonography is lower than that of CT and MRI [12]. For traditional imaging diagnosis based on morphological features, the experience of the radiologist is important for disease diagnosis. The reported accuracy of subtype diagnosis of PCNs is approximately 33 % with preoperative traditional imaging [4]. EUS can help to further identify PCN patients who need surgery, but EUS is less effective in the classification of PCNs, and it has the limitation of subjectivity [13]. EUS-guided fine needle aspiration (EUS-FNA) improves accuracy in the diagnosis of PCNs but may lead to complications. It is still controversial, and there is a lack of consensus regarding guidelines for PCN diagnosis with EUS-FNA.

Carcinoembryonic antigen (CEA) in patients with mucinous PCNs (MCN and IPMN) is increase in level compared with other PCNs, and the accuracy in the diagnosis of mucinous PCN is approximately 79 % using CEA analysis with a threshold of 1.92 g/L [14–17]. Measurement of serum carcinoma antigen (CA) 19.9 is commonly used in patients with pancreatic tumours, and the accuracy is approximately 73.8 % for the risk stratification of malignant IPMN [18]. Molecular genetic markers such as *KRAS* and *GNAS* mutations have potential in differentiating IPMN from MCN. Mutations of both genes provide high specificity (98 %) and sensitivity (84 %) in identifying IPMN. However, KRAS mutations are only detected in 30 % of MCN patients, and GNAS mutations do not exist in MCN patients [19,20].

The treatment of PCN requires a combination of information, including tumour types, risk factors and general patient status, and new methods should be proposed to improve the accuracy of diagnosis and risk prediction for PCNs.

## 3. Radiomics

As a computer-aided diagnosis tool, radiomics is used for disease diagnosis and risk or classification prediction [21], and the workflow of radiomics is shown in Fig. 1. Compared with traditional imaging diagnosis, radiomics allows higher accuracy for disease diagnosis and reduces the effects of subjectivity by extracting image features to build mathematical models. PubMed data retrieval showed that more than *2000* radiomics studies were reported in 2022. In the fields of intracranial tumours [22,23], lung cancer [24,25], breast cancer [26,27], gastric cancer [28,29], liver cancer [30,31], and pancreatic tumours [32,33], radiomics has shown important value.

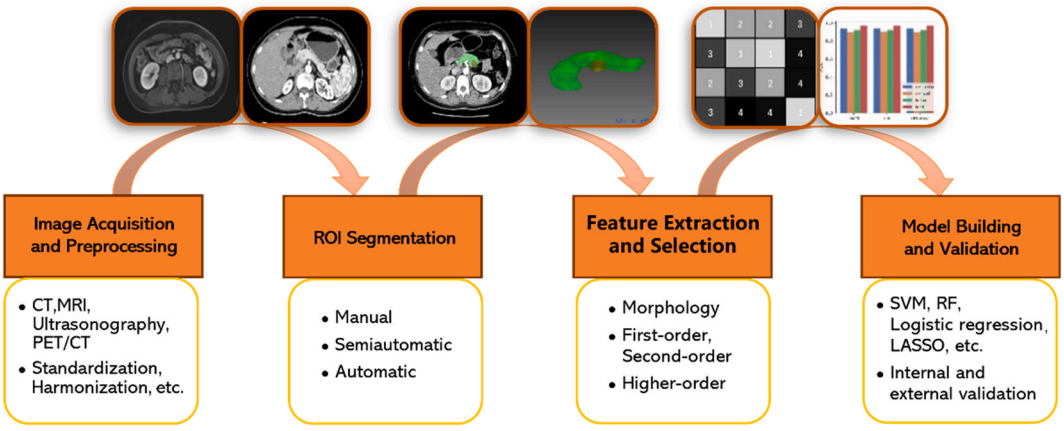


**Fig. 1.** Workflow for radiomics. LASSO: Least absolute shrinkage and selection operator; SVM: Support vector machine; RF: Random Forest.

## 4. Advances of radiomics IN PCN

### 4.1. Diagnosis of SCN and MCN

A multicentre study from Asia showed that SCN patients accounted for approximately 30.1 % of PCN patients among 2251 cases, with a malignancy rate of only 0.6 %. A European study including 2622 SCN patients from 23 countries and 71 centres found that only *3* cases were serous cystadenocarcinoma (0.2 %). The results of these studies indicated that SCN is an almost benign and inert tumour. The incidence of postoperative complications in SCN patients is approximately 50.3 %. Therefore, most guidelines recommend follow-up observations for patients with asymptomatic SCNs [4,7,15,34,35]. MCN has a high malignant potential and is recommended for surgical resection by the guidelines. Recently, European evidence-based guidelines recommended that patients with an MCN of size $<$4 cm and without clinical symptoms should be followed-up [15]. Accuracy in diagnosing SCN and MCN with preoperative imaging is approximately 13.7 % and 15.6 %, respectively [4]. As illustrated in Fig. 2 A, B, C, D, conventional imaging encounters difficulties in distinguishing between SCN and MCN due to their comparable CT findings. However, it is possible to discern the differences among these entities by employing quantitative analysis of CT images (Fig. 2 E, F, G, H). Therefore, radiomics possesses the capability to address the difficulty linked to the precise diagnosis of SCN and MCN.

The accurate diagnosis of SCN is a hot topic in the field of radiomics. Studies focused on the differential diagnosis of SCN and other PCNs with radiomics are listed in Table 1. Based on preoperative CT images, Wei et al. [36] found that SCN had a wider intensity range, higher overall density, and more homogeneously distributed local density than non-SCN. The investigators selected 22 radiomics features with the least absolute shrinkage and selection operator (LASSO) method to compose the best feature subset. The area under the curve (AUC) of the individual validation sets of the radiomics model constructed by support vector machine (SVM) was 0.837, which was higher than the performance of conventional imaging diagnosis (preoperative diagnostic accuracy of SCN, 30.4 %). Yang et al. [37] used a random forest (RF) model from the texture features of CT images with two slice thicknesses (2 mm and 5 mm) and found that both slice thicknesses provided similar performance in the differential diagnosis of SCN and MCN. In terms of consistency of feature parameters, the imaging parameters should be uniform for radiomics studies. In a further study by Yang et al. the combination of morphological features and texture features could improve diagnostic performance regarding SCN and MCN [38], and several similar findings have been reported with texture features [39,40]. Combining multiphase image features with radiologist-interpreted features or clinical features can enhance the diagnostic performance of radiomics models. Chen et al. [41] used LASSO and logistic regression methods for radiomics feature selection and model construction for identifying SCN and mucin-producing PCN (MCN and IPMN). A nomogram containing clinical features (number of cysts) and the three-phase radiomics features of plain scan, late arterial phase, and venous phase were created, and the AUC of the model in the validation cohort was 0.817, which was higher than that of the models built with single-phase or dual-phase CT features. Similar findings were also reported by Gao et al. [8], who also found that radiomics models based on the venous phase or arterial phase were more effective than those based on the plain phase. Shen et al. [42] selected five radiomics features and four clinical indicators (serum CA19-9, CEA, sex, and age) with the Boruta method and built multiclassification diagnostic models with SVM, RF, and ANN. The diagnostic accuracy in distinguishing SCN, MCN and IPMN for the three models was 71.43 %, 79.59 % and 71.43 % in the validation groups, respectively. Combining imaging features and clinical indicators could provide more accurate results for the diagnosis of PCNs. In addition, Fang et al. [43] combined four T2-weighted imaging (T2WI) features and five clinical features (gender, pancreatitis, location, tumour size, and tumour shape) to differentiate MCN and SCN by building a nomogram, which achieved AUCs of 0.93 and 0.86 in the training and validation groups, respectively.

Morphologically, SCN is usually classified into four types: microcystic, macrocystic (also known as oligocystic), mixed and solid. Macrocystic serous cystic adenoma (MaSCA) is also classified as atypical SCN (ASCN) and has imaging features similar to MCN, including independent giant cystic lesions. Preoperative identification in cases of MaSCA and MCN is still difficult [44]. CT-based

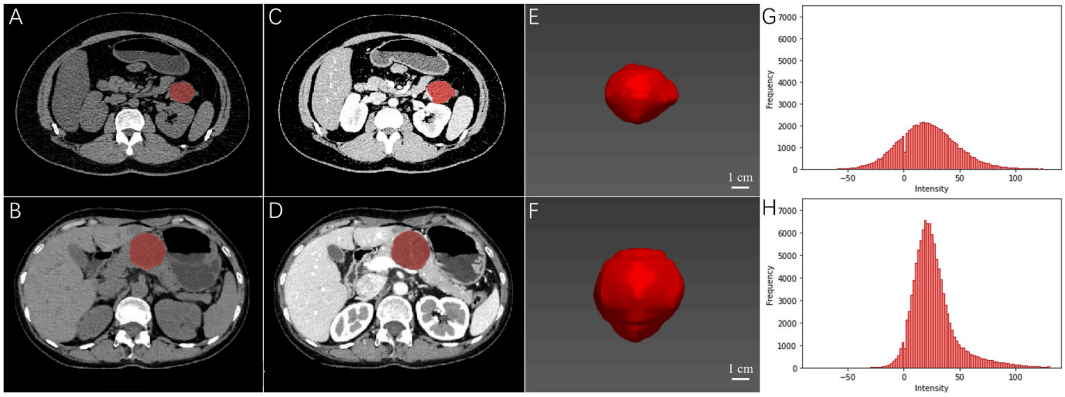


**Fig. 2.** Examples of serous cystic neoplasm (SCN) and mucinous cystic neoplasm (MCN) on CT. Pre-contrast CT for SCN (A) and MCN (B); Portal phase CT for SCN (C) and MCN (D); 3D tumours for SCN (E) and MCN (F); Intensity histograms for SCN (G) and MCN (H). CT and tumour shape analysis revealed comparable image findings for the two cases; however, a notable distinction was observed between the SCN and MCN in the histograms.

**Table 1**
Studies in differential diagnosis of SCN and other types of PCN based on radiomics.

| Author | Theme | Data Volume | Segmentation | Phase | Feature Selection | Model Building | Results |
|---|---|---|---|---|---|---|---|
| Wei R et al. | Differential diagnosis ( SCN and other PCN ) | 260 ( 102 SCN , 74 IPMN , 35 MCN , 49 SPN ) | Manual | VP | LASSO | SVM | Validation Set: AUC 0.837, SN 66.7 %, SP 81.8 % |
| Yang J et al. | Differential diagnosis (SCN and MCN) | 78 ( 53 SCA , 25 MCN ) | Manual | PP | LASSO, RF | RF | Training Set: slice thickness of 2 mm, AUC 0.77, SN 95 %, SP 83 %, ACC 85 %<br>slice thickness of 5 mm, AUC 0.72, SN 90 %, SP 84 %, ACC 86 %<br>Validation Set: slice thickness of 2 mm, AUC 0.66, SN 86 %, SP 71 %, ACC 74 %<br>slice thickness of 5 mm, AUC 0.75, SN 85 %, SP 83 %, ACC 83 % |
| Chen Hy et al. | Differential diagnosis (SCN and MCN) | 100 ( 57 SCN , 43 MCN ) | Manual | PP | LASSO, RFE_LinearSVC | logistic regression | Training Set: AUC 0.932, SN 87.5 %, SP 82.4 %<br>Validation Set: AUC 0.887, SN 90.0 %, SP 84.6 % |
| Zhang Yf et al. | Differential diagnosis (SCN and MCN) | 75 ( 46 SCN , 29 MCN ) | Semiautomatic | VP | LASSO | logistic regression | AUC 0.938, SN 93.10 %, SP 84.78 % |
| Chen S et al. | Differential diagnosis (SCN and mucin-producing PCN) | 89 ( 31 SCN , 28 MCN , 30 IPMN ) | Manual | PS, LAP, PP | LASSO | logistic regression | Training Set: AUC 0.967, SN 95.1 %, SP 86.4 %<br>Validation Set: AUC 0.869, SN 82.4 %, SP 100 % |
| Gao Jh et al. | Differential diagnosis (SCN and MCN) | 170 ( 115 SCN , 55 MCN ) | Manual | PS, AP, VP | ICCs, mRMR, LASSO | logistic regression | Training Set: AUC 0.91, SN 92 %, SP 81 %, ACC 85 %<br>Validation Set: AUC 0.90, SN 71 %, SP 90 %, ACC 78 % |
| Shen Xy et al. | Differential diagnosis (SCN, MCN and IPMN) | 164 ( 76 SCA , 40 MCN , 48 IPMN ) | Manual | AP | Boruta algorithm | SVM, RF, ANN | ACC of the training set: SVM classifier 73.04 %, RF classifier 84.35 %, ANN model 77.39 %<br>ACC of the validation set: SVM classifier 71.43 %, RF classifier 79.59 %, ANN model 71.43 % |
| Li C et al. | Differential diagnosis (SOA and MCN) | 42 ( 23 SOA , 19 MCN ) | Manual | AP , PP | Fisher score , SVM | SVM | ACC 93.02 % |
| Xie Hh et al. | Differential diagnosis (Masca and MCN) | 57 ( 26 MaSCA , 31 MCN | Manual | PP | univariate analysis , logistic regression | logistic regression | AUC 0.994, SN 96.8 %, SP 100 % |
| Xie Ts et al. | Differential diagnosis (ASCN and MCN) | 216 (113例ASCN , 103例MCN) | Semiautomatic | VP | Mann–Whitney *U* test, mRMR | RF | AUC 0.784, SN 84.7 %, SP 74.5 % |
| Fang X et al. | Differential diagnosis (SCN and MCN) | 304 ( 216 SCN , 88 MCN ) | Manual | T2WI | variance analysis, Spearman correlation analysis, LASSO | logistic regression | Training Set: AUC 0.93, SN 81.25 %, SP 92.45 %, ACC 89.24 %<br>Validation Set: AUC 0.86, SN 91.67 %, SP 78.95 %, ACC 82.72 % |

SOA: Serous oligocystic adenoma; PS: Plain scan; AP: Arterial phase; PP: Portal phase; LAP: Late arterial phase; VP: Venous phase; RFE_LinearSVC: Recursive feature elimination linear support vector machine; ANN: Artificial neural network; mRMR: Minimum redundancy and maximum relevance method; ICCs: Intra- and interclass correlation coefficients; SP: Specificity; SN: Sensitivity; ACC: Accuracy.

radiomics analysis provides a reliable scheme for the differentiation of MCN and ASCN [45–47]. Li et al. [45] combined *5* spectral CT image features and *10* conventional features (clinical and imaging features) to build an SVM model, which improved MaSCA and MCN classification accuracy from 88.37 % to 93.02 %. LongRunHighGrayLevelEmphasis is the most valuable feature for differential MCN and MaSCA [37,46]. Although radiomics has demonstrated considerable value in the diagnosis of SCN, the number of patients in reported studies is small and MRI research is relatively sparse; however, MRI is the method recommended by multiple guidelines for the examination of PCNs. Further studies should validate the usefulness of radiomics in SCN with more comprehensive data sets and multicentre trials.

### *4.2. Diagnosis and risk classification of IPMN*

IPMN accounts for approximately 21–33 % of PCNs and has the highest risk of malignancy in PCNs. There are three types: main duct IPMN (MD-IPMN), BD-IPMN and mixed-type IPMN (MT-IPMN). Among them, MD-IPMN and MT-IPMN have higher risks of malignant transformation, ranging from 38 % to 68 %, and guidelines recommend surgical resection for patients affected with them. The treatment recommendation regarding BD-IPMN is continuously updated in guidelines based on high-risk radiographic features, and further investigation is still needed because of the inability to accurately define the grade of dysplasia [1,48–50]. Chakraborty et al. [51] conducted a retrospective study of 103 patients with BD-IPMN and found that CT texture features had good predictive ability for BD-IPMN risk grading, and a combined model (AUC = 0.81) with both image features and five clinical features was superior to a model with only texture features (AUC = 0.77). Similar findings were also reported in some radiomics studies [52–55]. Small patient numbers and model overfitting for radiomics are important considerations in recent studies.

Preoperative risk classification of IPMN is critical in guiding clinical decision-making. Patients with high-risk IPMN (high-grade dysplasia to invasive carcinoma) should undergo tumour resection, while patients with low-risk IPMN (low-grade dysplasia to moderate dysplasia) should be followed-up regularly with imaging [56]. Cui et al. [57] combined MRI radiomics features and two clinical features (main pancreatic duct size and CA19-9 level) using LASSO and logistic regression analysis to build a radiomics model for IPMN risk prediction with AUCs of 0.884 and 0.876 on two external validation sets. Tobaly et al. [58] developed a radiomics model based on higher-order CT features by using logistic regression with AUCs of 0.84 and 0.71 on the training and validation sets, respectively. In both studies, most of the selected radiomics features were higher-order features, which could better reveal the heterogeneities of tumours and play an important role in IPMN grading. Li et al. [59] designed a PCN feature selection system containing *436* image features and *9* clinical features according to the findings of Sahani et al. [60] and proposed a new feature selection algorithm called BLR (Bootstrapping Repeat Lasso with Random Selections), which increased the stability of feature selection with repeated bootstrapping and reduced errors and overfitting of models. The IPMN grading model that was designed based on BLR had an AUC of 0.92 in the independent validation set.

### *4.3. SPN invasiveness prediction*

SPN, which accounts for approximately one-third of all PCNs, is a low-grade malignant tumour. Patients with SPN are mostly young women who, on imaging, present cystic solid tumours with well-defined borders and heterogeneous changes after enhancement. Guidelines recommend surgical resection for patients with SPN [4,7,14,15,48]. A multicentre study found that approximately 14.2 % of SPNs are aggressive [61], while it is difficult to differentiate the two types of SPNs with traditional imaging diagnosis. Radiomics based on CT and MRI provides a choice for predicting aggressiveness of SPNs. Huang et al. [62] built four prediction models, including 3D arterial, 3D venous, 2D arterial and 2D venous models, using *11*, *8*, *7* and *7* features based on CT images and 2D region of interest (ROI) and 3D ROI analyses. The combined arterial and venous phase 3D model had the best performance with an AUC of 0.918. Liang et al. [63] used 33 radiomics features from T1WI, enhanced T1WI, T2WI and DWI images and tumour location to build an effective radiomics model that could well predict SPN aggressiveness with an AUC, sensitivity, and specificity of 0.81, 0.75 and 0.78, respectively.

## 5. The future development trends of radiomics IN PCN

One of the critical instruments in the advancement of precision medicine is radiomics. When comparing radiomics to conventional diagnostic imaging, it is evident that the former significantly improves efficiency while simultaneously enhancing the accuracy of disease diagnosis and prediction. In contrast to deep learning, radiomics frequently yields reliable outcomes with a smaller sample size, is less reliant on hardware equipment, and provides results that are highly interpretable. We anticipate that clinical specialist groups for various diseases will establish standardized imaging scan protocols in future radiomics research in an effort to further reduce image heterogeneity. We advise conducting prospective, multicenter studies to assure the generalizability of radiomics models. Furthermore, it is recommended that research organizations transparently disclose study data and labels during the publication of their findings. This will enable subsequent studies to improve upon the results and facilitate comparisons.

The establishment of a scientific method to evaluate the quality of research is an additional critical aspect in the advancement of radiomics. The ongoing process of summarizing, formulating, and updating comprehensive assessment schemes for radiomics research is crucial for standardizing studies and optimizing experimental designs. These schemes should encompass various factors including efficiency, reproducibility, and clinical utility. A suggested approach for evaluating the quality of radiomics is the utilization of the Radiomics Quality Score (RQS), which was initially introduced by Lambin et al. [64].

The potential for further improvement in the quality of radiomics is represented by the integration of lightweight deep learning

methods for lesion segmentation and classification, which is an emerging area of research in radiomics. Radiomics comprises a multitude of fields of study, such as computer science, clinical medicine, and medical imaging. It is imperative to actively participate in interdisciplinary research collaborations. The integration of radiomics tools into the Picture Archiving and Communication System (PACS) of a hospital enables the practical implementation of research outcomes. By integrating prompt feedback from clinical practitioners, the performance of radiomics model can be enhanced and integrated more seamlessly into the clinical workflow. The overarching goal of this integration is to provide patients with personalized precision medicine.

## 6. Conclusions

Radiomics is a promising tool in the field of medical imaging and provides a non-invasive, high-performance model for preoperative diagnosis and risk stratification of PCNs, including differential diagnosis of SCN and MCN, grading and risk assessment of IPMN, and SPN aggressiveness prediction. A large sample size, good image quality, and standardized data set are the basis for radiomics studies. Combined imaging and clinical features could further improve the performance of radiomics models and help to improve PCN patient management. Guidelines for radiomics should be established in the fields of standardized image acquisition protocols, tumour segmentation, feature extraction and modelling tools. MRI image radiomics should be further investigated in connection with PCNs to improve the diagnosis and treatment strategies in the management of PCN patients.

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## Data availability statement

The research dataset for the current study is available from the corresponding author upon reasonable request.

## Ethics declarations

This study was approved by our Institutional Review Board (Shanghai Changhai Hosptial Ethics committee).

## CRediT authorship contribution statement

**Kuan-Zheng Mao:** Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Methodology, Investigation, Formal analysis, Data curation. **Chao Ma:** Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Bin Song:** Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

## Declaration of competing interest

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

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