



MS-ResNet: disease-specific survival prediction using longitudinal CT images and clinical data

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Abstract

Purpose Medical imaging data of lung cancer in different stages contain a large amount of time information related to its evolution (emergence, development, or extinction). We try to explore the evolution process of lung images in time dimension to improve the prediction of lung cancer survival by using longitudinal CT images and clinical data jointly.

Methods In this paper, we propose an innovative multi-branch spatiotemporal residual network (MS-ResNet) for disease-specific survival (DSS) prediction by integrating the longitudinal computed tomography (CT) images at different times and clinical data. Specifically, we first extract the deep features from the multi-period CT images by an improved residual network. Then, the feature selection algorithm is used to select the most relevant feature subset from the clinical data. Finally, we integrate the deep features and feature subsets to take full advantage of the complementarity between the two types of data to generate the final prediction results.

Results The experimental results demonstrate that our MS-ResNet model is superior to other methods, achieving a promising 86.78% accuracy in the classification of short-survivor, med-survivor, and long-survivor.

Conclusion In computer-aided prognostic analysis of cancer, the time dimension features of the course of disease and the integration of patient clinical data and CT data can effectively improve the prediction accuracy.

Keywords Disease-specific survival prediction · Deep learning · Longitudinal CT images · Clinical data · Attention mechanism

Introduction

Nowadays, cancer is one of the major diseases affecting human health, especially lung cancer, which is currently the leading cause of cancer death [1–4]. According to cell morphology, lung cancer is divided into small cell lung cancer and non-small cell lung cancer (NSCLC), the latter accounting for about 80 to 90%. NSCLC can be divided into adenocarcinoma, squamous cell carcinoma, and large cell according to different tissue subtypes [5], lung cancer, most of which are squamous cell carcinoma and adenocarcinoma. Therefore, further exploration of NSCLC predictive analysis is also of great clinical significance. Survival prediction has become a research hotspot of cancer research. An individualized and

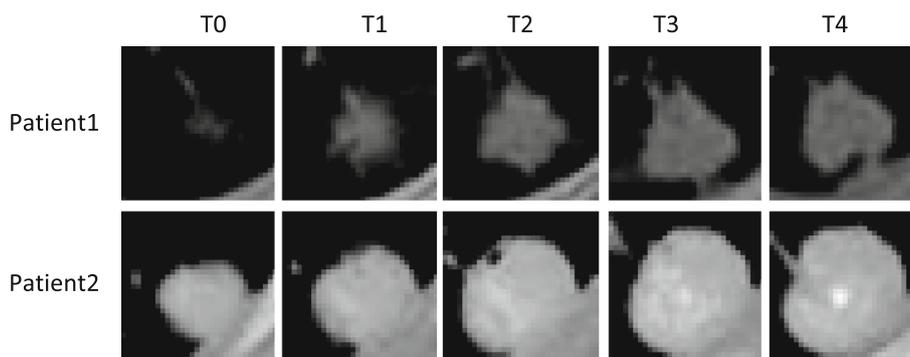
accurate survival prediction model is important for prognosis assessment, treatment plan selection, and clinical decision support for lung cancer patients [6,7]. Disease-specific survival (DSS) prediction is used as a common prognostic assessment tool. Compared to other types of survival (e.g., overall survival), the improvement in DSS is more responsive to the clinical benefit of a specific disease. The greatest significance of accurate DSS survival prediction lies in that it can lead to guideline coordinate treatments which optimizes survival and effectively avoid excessive treatment and waste of medical resources [8].

At present, there are three major problems in computer aided diagnosis (CAD) and survival prediction of lung cancer. The first problem is that conventional methods for predicting the survival of lung cancer patients are mainly based on tumor stage [9]. However, in clinical practice, even if patients in the same stage have the same treatment plan, the difference in patients' response to treatment and survival remains substantial [10]. Therefore, there is an urgent clinical

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Fig. 1 CT imaging data of the same pulmonary nodules in two patients at five different stages



need to incorporate further features to more accurately assess the prognosis and thus rationalize the treatment options. And CAD measures are necessary to systematically extract deep features from digital medical images to provide decision support for cancer prognosis [11,12].

The second problem is that most of the existing CAD methods for lung lesions are studied for images of a single period, especially for the automatic identification and diagnosis of images of the middle and late stages of lung cancer [13–15]. The medical imaging data of lung cancer lesions in different periods are shown in Fig. 1, which contains a large amount of time-related evolutionary information (such as the formation and growth of tumor, including its diameter, shape, gray distribution, texture, and calcification). Exploring the evolution of serial images of lung lesions in the temporal dimension and studying the mechanism of all-stage evolution of lung cancer images can play a key guiding role in early lung cancer screening and identification [16,17]. However, existing methods ignore the impact of the progressive evolution of lesion characteristics on survival and do not consider the correlation between multi-period computed tomography (CT) images.

The third problem is that multiple types of medical data are not yet integrated or insufficiently integrated. Multi-modal fusion techniques are bringing profound changes to prediction research in computer vision, communication, biomedicine, and other related fields and are a research trend in many research areas. Many computational models for predicting cancer survival have been proposed, but most of them use only imaging data to generate prediction models, and clinical information of patients (e.g., age, smoking history, family history, etc.) is not considered [8,18,19]. To address the above problems, we propose a DSS prediction model for lung cancer based on multi-period CT images and clinical information. The main contributions of this paper can be summarized as the following three points:

- A novel multi-branch network based on residual convolutional neural network model is proposed for the prediction of lung cancer disease-specific survival.

- The designed spatiotemporal attention mechanism can assign appropriate weights to features in different periods.
- The deep features from the deep network combine with the key clinical attributes of the patients for training, which can effectively improve the accuracy of survival prediction.

Methodology

In this study, we effectively exploit the correlations among multi-period CT images as well as integrate some key clinical attributes for improving the DSS prediction performance. The proposed framework is illustrated in Fig. 2. Our work mainly includes the following parts: data preprocessing, feature selection, feature extraction, feature fusion, and survival prediction.

Data preprocessing

The data preprocessing section includes preprocessing of both the CT images and clinical data.

In this study, we apply rotation and flip to augment our training set. These methods facilitate the ability of the proposed model to view the same image from different geometric perspectives. Inspired by several recent SSL studies [20,21], we chose the angle setting 90° and 180° to rotate the training data. The preprocessing of clinical raw data includes the following three aspects: clarifying the distribution status of the data, data cleaning, and data transformation. Specifically, first use SPSS software to analyze the distribution of the original data to understand the mean, median, missing number, etc., of each variable, which can effectively understand its central tendency and degree of dispersion, and judge whether there are outliers. Data cleaning refers to discovering and correcting identifiable errors in data, including checking data consistency, processing invalid, missing, and duplicate values. For attributes that are missing more than 50% of the data, we will delete them directly. Data transformation means that

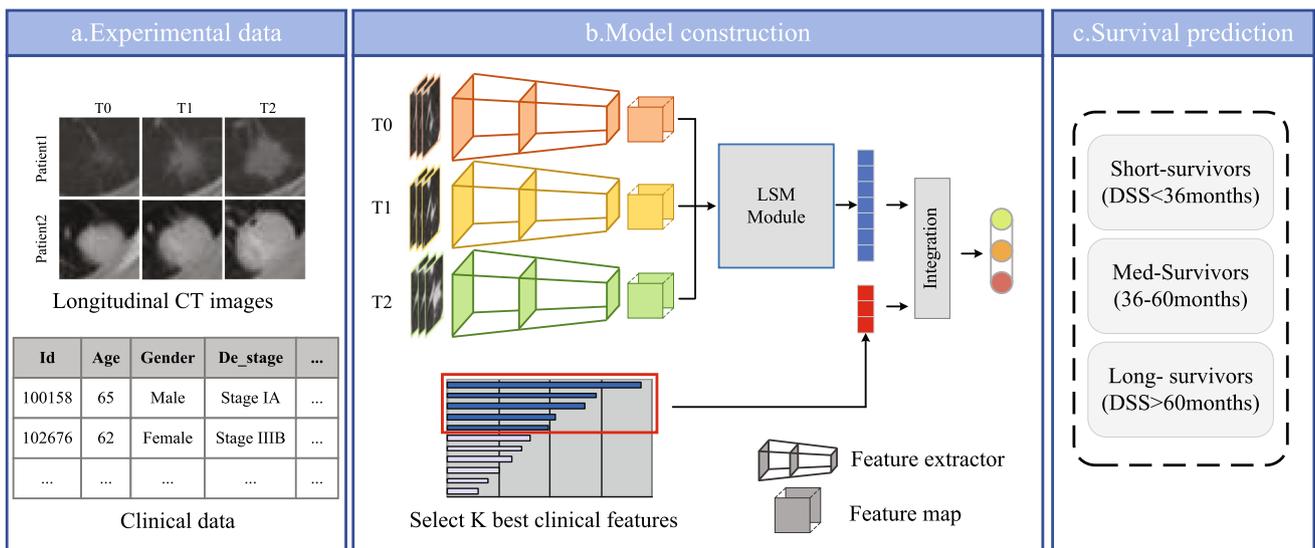


Fig. 2 The architecture of the proposed model: **a** The experimental dataset uses information on 198 patients from the NLST dataset, and each patient data includes follow-up CT image data and clinical record data for 3 periods. **b** The core part of the proposed model consists of a 3-branch residual network for extracting deep features of CT images,

a longitudinal self-attention mechanism (LSM) module for capturing time-related evolutionary information, and an integration module for integrating deep features and clinical attributes. **c** The model survival prediction results will be classified into three categories: short survivor, medium survivor, and long survivor

Table 1 The seven clinical information variables most related to DSS are screened out and their descriptions

Variable	Label	Format text
Can_type	Cancer cell type	0=“non-small cell lung cancer” 1=“small cell lung cancer”
De_stag	Lung cancer Stage	0=“Stage IA” 1=“Stage IB” 2=“Stage IIA” 3=“Stage IIB” 4=“Stage IIIA” 5=“Stage IIIB” 6=“Stage IV” 7=“other”
Can_scr	Result of the screen associated with the first confirmed lung cancer diagnosis	0=“No Cancer” 1=“Positive Screen” 2=“Negative Screen” 3=“Missed Screen” 4=“Post Screening”
Age	Age at randomization	In years; whole number.
Treatlc	Status of treatment data	1=“Confirmed treatment” 0=“Confirmed no treatment”
Locmed	Cancer in Mediastinum	0=“No” 1=“Yes”
Educat	Level of education completed	1=“8th grade or less” 2=“9th-11th grade” 3=“High school graduate/GED” 4=Associate degree/ some college 5=“Other”

the original data cannot meet the requirements of all aspects of statistical analysis. In order to facilitate the training of machine learning models, it is necessary to convert the categorized attribute values into numerical values. The unified representation of the clinical variables used in the experiment is listed in Table 1.

Feature selection

A total of 140 attributes are used to describe participants in the downloaded clinical data, including basic information, smoking and alcohol use, disease diagnosis, family genetic history, follow-up records, etc. Many of these attributes are redundant or irrelevant to survival prediction. With the grad-

ual application of artificial intelligence technology in medical image and big data processing, feature selection algorithm is also used by more and more researchers for clinical information processing [22–24]. To improve the performance and reduce overfitting, we use the feature selection method to select a feature subset with the greatest predictive power. First, the filter method is used to calculate the correlation between each clinical attribute and DSS label by the ANOVA method [25]. Each clinical feature is scored, that is, each dimension of clinical features is given a weight, which represents the importance of the feature. Then the top *K* clinical attributes with the highest feature scores are selected for feature fusion in the later stage.

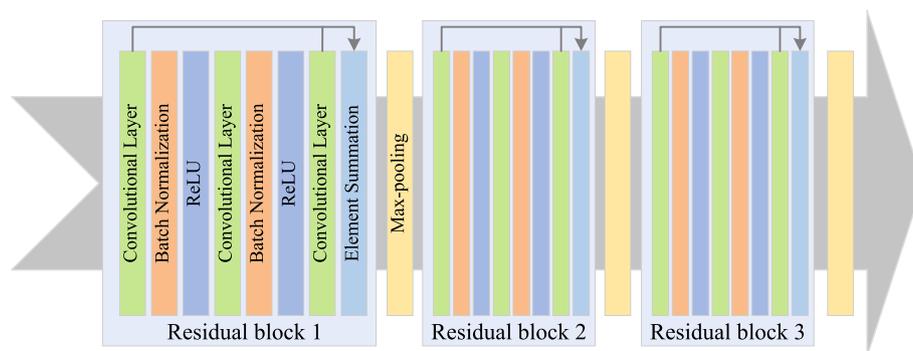


Fig. 3 Residual network architecture is adopted in the feature extractor. The network consists of three residual blocks. Each block consists of three convolution layers, two batch normalization layers, two ReLU layers, and one element addition operation unit, followed by a max-

imum pooling layer. Because of the shortcut connection, the shallow features jump to the deep layer, and the deep network can get a result that is no worse than the shallow network

Feature extraction

Feature extraction is the most important step of the survival prediction task. Recently, deep learning methods have been widely applied to feature extraction in various image classification tasks. However, for medical image processing tasks, the limited availability of images makes it very difficult to fully train a novel convolutional neural network (CNN) model from scratch.

Several studies have demonstrated that a pre-trained convolutional neural network model can be used as a feature extractor for any image [26]. Besides, Li et al. reported that the residual convolutional neural network (ResNet) has a better diagnosis and classification performance than other models, and it has a broad application prospect in the classification of CT images [27]. Because of the shortcut connection, the shallow features jump to the deep layer, and the deep network can get a result that is no worse than the shallow network. The shallow features are added to the deep features, which ensures that the deep network has the same performance as the shallow one, even if the features obtained from the intermediate operations do not have any effect. Up to now, ResNet has been widely used for its simplicity and practicality [28,29]. Therefore, we employ ResNet as the backbone model to extract deep features in our work.

To effectively exploit the correlations among multi-period CT images, as well as preserve specific features for each period, we propose a multi-branch spatiotemporal residual network (MS-ResNet). As shown in Fig. 2b, specifically, MS-ResNet adopts three complementary branches to simulate the radiologist's level of attention and learn multi-period deep characteristics from different periods. The structure of our multi-branch CNN is shown in Fig. 3, where subnetworks in all branches have the same structure but with different parameters. A 64×64 pixels tumor image is input to each branch of the model, and the feature extraction network is

mainly composed of three residual blocks. Each block consists of three convolution layers, two batch normalization layers, two ReLU layers, and one element addition operation unit, followed by a maximum pooling layer.

Spatiotemporal attention module

The attention mechanism in deep learning is essentially similar to the human selective visual attention mechanism, and the core goal is also to select the information that is more critical to the current task goal from a large amount of information [30].

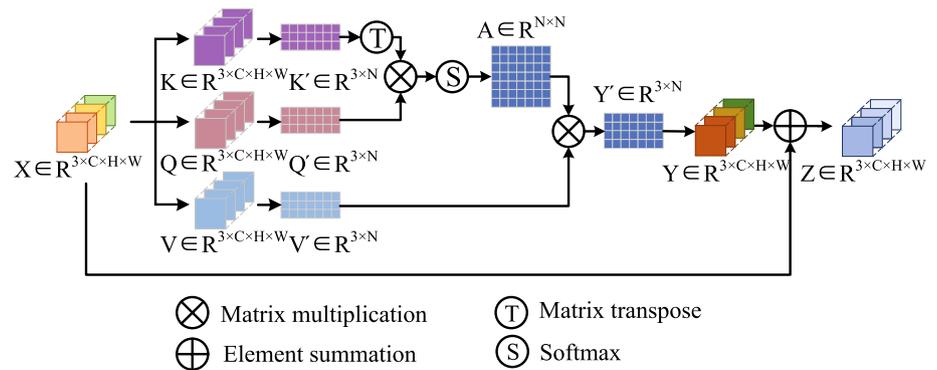
Images from different periods contain different characteristics. To discover the distinctions and relationships between tumors from each period, an attention mechanism is needed to focus on the salient features of tumors. Self-attention is an effective mechanism to simulate longitudinal spatiotemporal dependence [31]. Motivated by the mechanism, we design a longitudinal self-attention mechanism (LSM), which can capture the rich global spatial-temporal relationships between pixels in the whole space-time, so as to obtain more discriminative features. The details of the LSM are shown in Fig. 4.

As can be seen from Z, the features at each position of the output tensor fuse the features at all positions with the original features. Therefore, it has a global contextual view and selectively aggregates contexts according to the spatiotemporal attention map. Similar semantic features achieve mutual benefit, thus improving intraclass compactness and semantic consistency [32].

Feature fusion and survival prediction

Clinical patient information, such as age, disease history, diagnostic records, and work environment, is critical to obtaining the correct diagnosis. The clinician's diagnosis

Fig. 4 Longitudinal self-attention mechanism. The module takes the stacked multi-period deep features as input and implements the weight distribution of the characteristics of different periods and different channels through matrix transformation measures



often relies on the integration of both medical images and clinical information. To enable the computer to fully simulate the clinician’s diagnostic process, we effectively integrate the CT images and some key clinical data for improving the DSS prediction performance. By using the fused features as the input of the softmax classifier, the probability values of the final classification of different patients as long-survivor, med-survivor, and short-survivor can be obtained.

Experiments

Dataset and evaluation metrics

The sources of longitudinal lung cancer CT images and clinical data from the National Lung Screening Trial (NLST) datasets are available upon request [33,34]. The authority of the data and record comprehensiveness in a certain extent to ensure the credibility of the forecasting model. Our datasets contain a total of 198 cases. For the longitudinal CT images, the time to study in NLST is often described in “study years” using the notation $T[X]$, as in T_0 , T_1 , T_2 , etc. To eliminate the background area on the image of the study, this article invited an experienced physician to manually segment the pulmonary nodule interest area as the basis of the study. For the labeling of the same nodule in the longitudinal image, it is first necessary to register the longitudinal image at different times using multi-atlas image registration method. Then, the physician will segment and label the image containing the nodule after the registration. All pulmonary nodules ROI are manually segmented by a partner physician using 3D Slicer (version 4.11.20210226; <https://download.slicer.org/>). In clinical data, the collection of data records including the serial number of patients, diagnosis, age, race, primary lesion location, tumor size, but also including the patient’s follow-up records and survival state, etc. Five years and 3 years were taken as thresholds to divide patients with lung cancer [6]. Taking into account the clinical significance between the groups and the distribution of our data, the samples are divided into long-survival (greater than 60 months)

med-survival (between 36 and 60 months), and short-survival (less than 36 months) patients according to the thresholds. We employ Accuracy, macroF1, and microF1 to evaluate the classification performance of DSS survival for lung cancer patients.

Moreover, the confusion matrix is a standard format for accuracy evaluation, which is often used to visually evaluate the performance of supervised learning algorithms [35].

Results of feature selection

The top ten most influential clinical information variables for DSS are illustrated in Fig. 5. The figure shows that information such as cancer cell type, cancer stage, cancer location, patient age, and education has a great influence on the prediction of survival. However, the performance of the model usually decreases as the number of selected features increases. In this issue, a trade-off is made between test set accuracy and model complexity by comparing experiments. Figure 6 shows that the highest accuracy is achieved when we select 7 features for training. Therefore, in this experimental study, the top seven clinical attributes (including cancer type, stage, initial diagnosis result, age, the status of treatment, tumor location, and level of education) ranked in importance to the DSS are selected for fusion with the deep features from CT images, and the selected clinical information variables are listed in Table 1.

Results of survival prediction

In this section, we depict the classification results of our proposed model in detail and provide a brief discussion and analysis of the results. The confusion matrix is used as an important tool to evaluate the error of the classification problem. We construct the confusion matrix of the proposed model, as shown in Fig. 7. As can be seen from the figure, our proposed model can successfully classify the test sample into three categories: short survivors, medium survivors, and long survivors. Among them, the long-survivor has the highest percentage of correct predictions with 88.63%, followed by

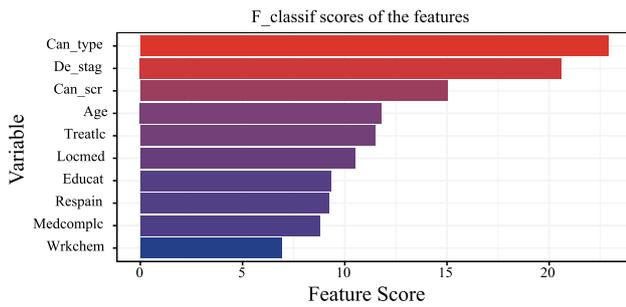


Fig. 5 Rank the importance of attributes to DSS in all clinical information. Variables with higher feature scores indicate a greater influence on DSS. Can_type, De_stag, Can_scr, Age, Treatlc, Locmed, Educat, Respain, Medcomple and Wrkchem represent the cancer cell type, lung cancer stage, result of the screen, age at randomization, status of treatment data, cancer in mediastinum, level of education completed, whether engaged in paint work, earlier complications related to lung cancer and whether engaged in chemical/plastic manufacturing

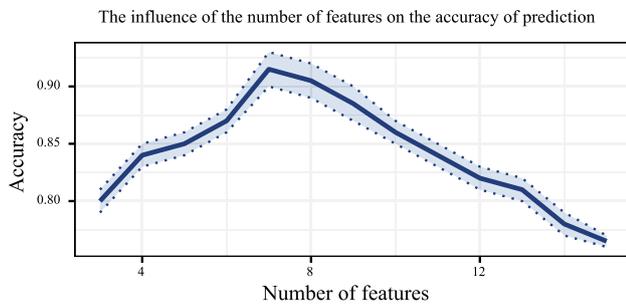


Fig. 6 The influence of the variation of the number of features on the prediction accuracy. The highest accuracy of the model prediction is achieved when the number of features is chosen to be 7

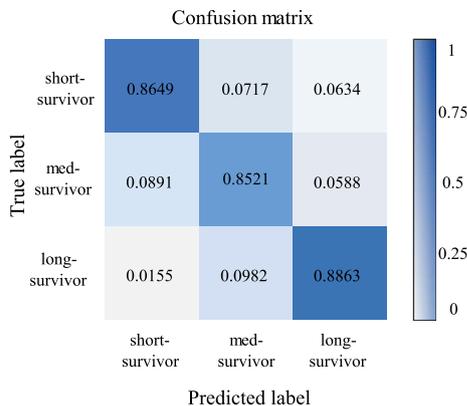


Fig. 7 Confusion matrix for the proposed model

the short-survivor with 86.49%, and finally the med-survivor with 85.21%. This result ensures that the classification of the three categories is performed correctly.

To verify the effectiveness of multi-period deep feature fusion, we also adopt the same single-branch residual neural network to perform DSS prediction for CT image data of each period. The detailed classification results are listed in Table 2. Where the first three rows indicate the images of

periods T_0 , T_1 , and T_2 , respectively as inputs for prediction using ResNet alone, and mean indicates the average classification accuracy of the three periods. MR-Net represents the use of multi-branch ResNet, where images from three periods are simultaneously served as inputs to the network, and the extracted multiple deep features are directly integrated for prediction. MR-Net + LSM indicates the addition of a longitudinal self-attention mechanism module to the model. MS-ResNet represents our proposed complete model, which adds the LSM module to MR-Net and further fuses the filtered clinical attributes.

In order to further analyze the prediction effect of NSCLC in MS-ResNet model, we divided the experimental dataset into four types according to cell morphology: small cell carcinoma, adenocarcinoma, squamous cell carcinoma and large cell carcinoma. These four types of data were input into the proposed network model for training and testing. The experimental results are shown in Table 3.

Finally, we further compare the methods and performance of the proposed model with those of the state-of-the-art research results. Table 4 summarizes the methods and performance of these advanced models. Doppalapudi et al. used only single-period images for lung cancer survival classification in their study [8]. The artificial neural network, recurrent neural network, and convolutional neural network are used to extract deep features for prediction, respectively. An accuracy of 71.18% was achieved. Wang et al. proposed a model for prognostic analysis using radiological features to make predictions based on CT images of 173 non-small cell lung cancer (NSCLC) patients [36].

The results indicate that our model has the advantage of being able to cleverly combine CT images from multiple periods compared to the most advanced models currently used in the same field. The process of diagnosis is more similar to that of clinicians, and its accuracy of survival prediction is significantly better than that of other single-period studies.

The proposed model is validated using the NLST dataset. To validate the effectiveness of multi-period CT image data integration for DSS prediction, we have compared the proposed network with the model using only single-period CT data alone. To verify that the fusion of CT images and clinical attributes can improve the predictive performance of lung cancer-specific survival, we complete a comparison experiment before and after the fusion of the two types of data. The results in Table 2 provide ample evidence of the effectiveness of survival classification using the temporal information contained in multi-phase CT images. This also suggests that multi-temporal information (MTI) must be considered in similar medical aid diagnostics. Comparing the experimental results, we can also draw the following points:

- When only one period image is used for prediction, the image from T_2 has the highest accuracy, while the

Table 2 Comparison of accuracy resulting from various fusion approaches

Longitudinal information	Approach	Accuracy (%)	MacroF1 (%)	MicroF1 (%)
Non-fusion	T0	78.52	77.65	78.52
	T1	79.93	78.84	79.93
	T2	81.30	80.47	81.30
	Mean	79.92	78.99	79.92
	Clinical data	80.34	79.90	80.34
Fusion	MR-Net	82.54	81.67	82.54
	MR-Net + LSM	85.94	84.84	85.94
	MS-ResNet	86.78	85.82	86.78

Table 3 The experimental results of different subtypes of lung cancer in this model

Histology classes	No. of patients(%)	Accuracy (%)	MacroF1 (%)	MicroF1 (%)
Adenocarcinoma	41.9	88.02	87.78	88.02
Squamous cell carcinoma	34.3	86.83	86.33	86.83
Large cell carcinoma	9.1	80.92	80.34	80.92
Small cell carcinoma	14.7	85.44	85.16	85.44

Table 4 Comparison of the methodology and performance of our proposed model with the state-of-the-art studies

	Methodology	Performance
Doppalapudi et al. [8]	The artificial neural network, recurrent neural network, and convolutional neural network are used to extract deep features for prediction, respectively.	The prediction accuracy was 71.18%
Wang et al. [36]	Using radiological features to make predictions.	The prediction accuracy was 79.6%
Proposed	Deep spatiotemporal features and clinical information extracted from CT image data of multiple periods are combined for DSS prediction.	The accuracy rate is up to 86.78%

image from T0 has the lowest accuracy. The experimental results show that our model can capture more deep features related to survival from the images of the third stage.

- Direct integration of the deep features of the three periods using MR-Net can improve the classification accuracy to some extent, but the effect is not particularly obvious.
- With the addition of the LSM module, the fusion network can allocate appropriate weights to the features in different periods, which can effectively improve the accuracy of prediction.
- The integration of CT deep features and clinical information can improve the predictive ability of the model.

In addition, we also conduct a series of comparisons between the model and current related studies in the similar field, and the experimental results are shown in Table 4. Our model achieves the best results in several indicators and is able to accurately classify lung cancer patients into long survivors, medium survivors, and short survivors, and the accuracy rate could reach 86.78%. The necessity and feasibility of combining longitudinal data with clinical data for research and the great significance of DSS prediction are fully demonstrated.

Conclusion

In conclusion, we propose a survival prediction method based on multi-branch residual convolutional neural networks. CT image data from multiple periods of patients are used as input to fully exploit the deep features of lesion region of interest (ROI) images. By adding a temporal attention mechanism, the deep features of different periods are given different weights. The potential shared information among different disease processes and time points is exploited to explore the heterogeneity and complementarity of information among multiple features, to comprehensively represent the evolutionary information of lesions. Since the patient case information has an important influence and role in the diagnosis and analysis of the final condition, the temporal information of multi-period CT image data is innovatively utilized, while clinical information is effectively combined. The model can more accurately predict the DSS of lung cancer patients and is used to accurately perform prognosis assessment of lung cancer patients. By narrowing the scope and further distinguishing the experimental dataset according to cell morphology, using this model can achieve more accurate results for adenocarcinoma and squamous cell

carcinoma. The low prediction accuracy of large cell carcinoma is mainly due to the small amount of data. In the follow-up work, we will obtain more datasets from the cooperative hospitals to train our MS-ResNet model to continue to improve the accuracy. It has promising application prospects and can be extended to corresponding clinical studies to provide treatment decision support, improve patient satisfaction, and achieve individualized treatment.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

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