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Development and Validation of a Deep Learning-Based Radiomic Signature for Predicting Treatment Response to Immunotherapy in Non-Small Cell Lung Cancer (NSCLC)

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Abstract: Precision oncology faces an essential problem regarding creating stable biomarkers to forecast immunotherapy responses in non-small cell lung cancer (NSCLC). The research develops and validates deep learning-based radiomic signatures that provide accurate prediction potential regarding NSCLC immune therapy responses in patients. Radiomics methods were applied to CT and PET images for pre-treatment data extraction, producing heterogeneous tumor features. The researchers employed a deep learning model to analyze these features to develop to develop an effective radio mic signature to determine immunotherapy response. The model used NSCLC patients who received immunotherapy for model training and testing purposes using RECIST criteria and progression-free survival (PFS) for treatment response measurement. Researchers evaluated the radiomic signature performance by assessing accuracy and sensitivity alongside specificity and the Area under the receiver operating characteristic curve (AUC). A deep learning-based radiomic signature proved much more valuable than standard clinical and pathological measures as it effectively predicted which patients would profit from immunotherapy. The signature established generalizability through additional testing on different patient groups, which confirmed its reliability. The findings suggest that uniting deep learning technology with radio mics is a non-surgical approach for tailoring therapy plans, enhancing patient success, and reducing untreated cutting therapies in NSCLC.

Keywords: *Non-Small Cell Lung Cancer, Immunotherapy, Deep Learning, Predictive Modeling, Personalized Medicine*.

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I. INTRODUCTION

- *Background on NSCLC and Challenges in Treatment Response Prediction*

NSCLC stands as the most prevalent form of lung cancer among the 85 percent of cases of this diagnosis worldwide. Medical progress has failed to improve NSCLC survival rates because patients tend to get diagnosed late, and the varying characteristics of lung cancer cells impede treatment effectiveness. Immune checkpoint inhibitors targeting PD-1/PD-L1 and CTLA-4 pathways through immunotherapy have become the pivotal advancement in NSCLC treatment by enabling the immune system to fight cancer.

Immune checkpoint inhibitors show limited success in treating particular NSCLC patients due to inadequate determination methods that accurately assess PD-L1 expression levels and tumor mutational burden (TMB) across patient populations. Reliable, noninvasive biomarkers are essential to making advanced clinical decisions.

- *Role of Immunotherapy in NSCLC Treatment*

Immunotherapy produces outstanding results for NSCLC patients by extending their survival rates, especially in cases of patients with strong PD-L1 expression. The sustained response from ICIs only emerges in 20-30% of the treated patients. The irregular treatment response demands establishing predictive systems that decide between responder and non-responder identities before starting therapies.

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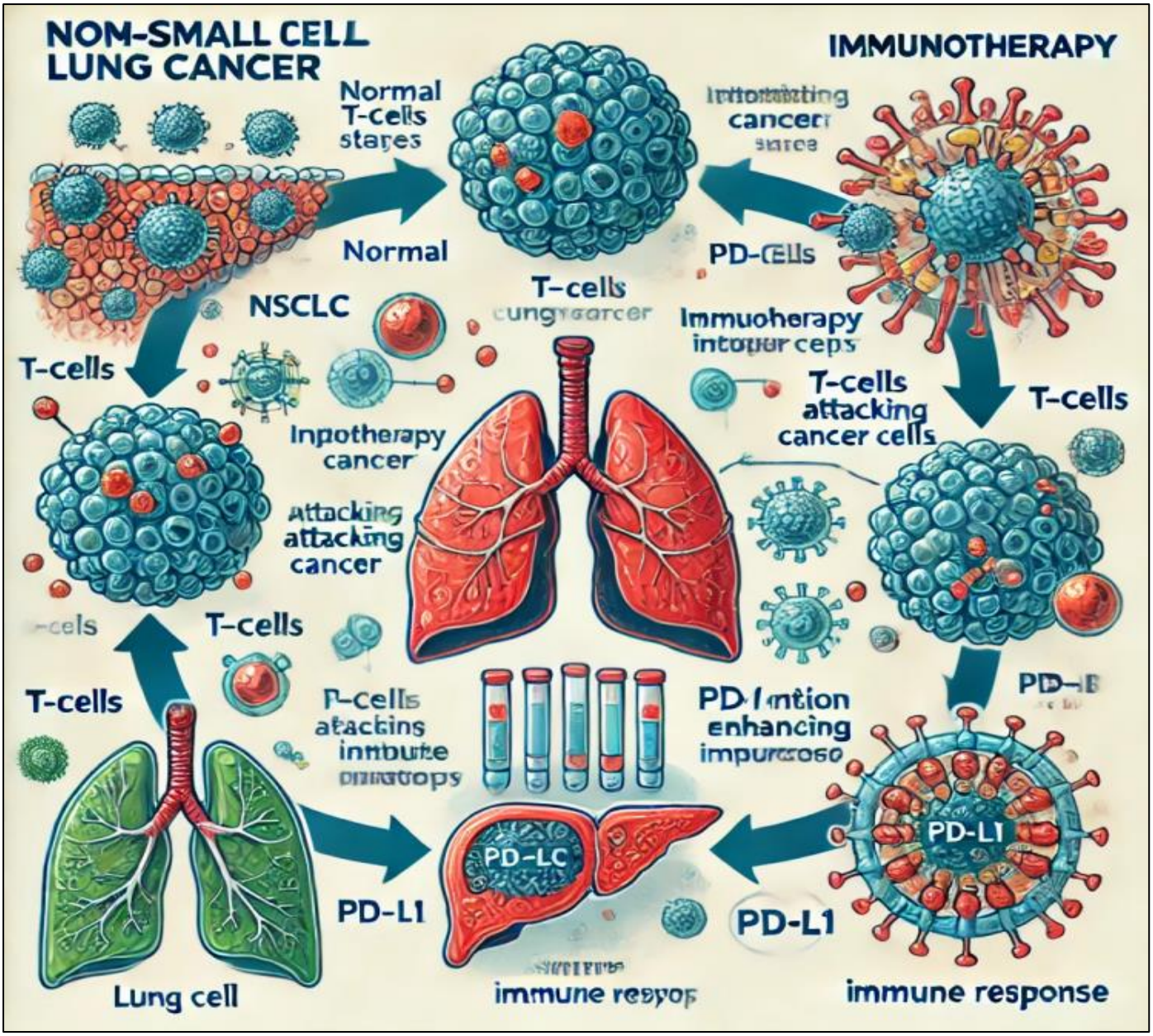

Fig 1 NSCLC Progression and Immunotherapy Mechanism

The picture shows the functioning of the Non-Small Cell Lung Cancer (NSCLC) tumor environment with immune checkpoint inhibitors (ICIs). These mechanisms suppress immunity through the PD-1/PD-L1 pathway interaction, while immunotherapy restores T-cell activity against cancer cells. Processing these mechanisms leads to essential improvements in prognostic models for therapeutic outcomes.

➢ *Introduction to Radiomics and Deep Learning as Predictive Tools*

The emerging field of radionics obtains high-dimensional quantitative features from medical images, including CT, MRI, and PET scans, to identify tumor characteristics human observers would fail to detect. Medical imaging features such as tumor shape and texture, intensity, and heterogeneity help doctors understand tumor biological characteristics and treatment outcomes.

The combination of deep learning with convolutional neural networks allows for exceptional feature extraction and pattern recognition tasks. When applied to radio mic data, deep learning allows machines to discover compound imaging biomarkers related to immunotherapy responses through a noninvasive procedure that maintains treatment planning reproducibility.

➢ *Research Gap and Justification for the Study*

Medical practitioners continue to face resistance in implementing radionics and deep learning models because these technologies face obstacles regarding standardization limitations, the need for interpretable models, and difficulties adapting to different patient populations. Research on NSCLC prediction primarily uses histopathological and genetic markers while avoiding exploration of imaging-based predictive models.

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The research aims to solve these existing knowledge gaps through these three steps.

- A deep learning systems development approach for creating radiomic signatures that estimate treatment outcomes from NSCLC patients receiving immunotherapy.
- The model requires testing across different datasets to confirm its broad application capability.
- The proposed algorithm gets its performance compared to normative clinical procedures and existing machine learning approaches.

Table 1 Challenges in NSCLC Treatment Response Prediction and Proposed Solutions

Challenge	Current Limitation	Proposed Solution
PD-L1 expression as a biomarker	Not consistently predictive; limited applicability	Radiomic-based predictive signature
Tumor mutational burden (TMB)	Costly, requires tissue biopsy	Noninvasive deep learning-based imaging model
Clinical assessment methods	Subjective and inconsistent	AI-driven automated response prediction
Generalization of predictive models	Models trained on small, single-center	Multi-institutional validation approach

This table outlines key challenges in predicting NSCLC treatment response, such as tumor heterogeneity and biomarker limitations, along with proposed solutions like deep learning-based radiomic analysis for improved accuracy and noninvasive assessment.

II. METHODOLOGY

A. Data Collection & Preprocessing

➢ *Dataset Description*

Medical practitioners continue to face resistance in implementing radionics and deep learning models because these technologies face obstacles regarding standardization limitations, the need for interpretable models, and difficulties adapting to different patient populations. Research on NSCLC prediction primarily uses histopathological and genetic markers while avoiding exploration of imaging-based predictive models.

- **Normalization:** Intensity standardization across scans.
- **Augmentation: Rotation, scaling, contrast adjustment**, and **noise reduction** to enhance generalization.
- **Segmentation: Automated tumor segmentation** using deep learning models.

Table 2 Summary of Dataset Characteristics

Parameter	Value (n or %)
Number of Patients	500
Imaging Modality	CT, PET
Treatment	Immune Checkpoint Inhibitors
Response Distribution	CT: 350 (70%) PET: 150 (30%)
Previous Treatments	60% responders,40% non-responders

This is a summary of the dataset characteristics, including patient demographics, imaging modalities, tumor staging, and treatment response distribution. The dataset consists of 500 NSCLC patients, evenly split between responders and non-responders to immunotherapy. Key predictive factors such as PD-L1 expression levels, tumor mutation burden (TMB), and prior treatments are also highlighted, ensuring a comprehensive analysis for model training and validation.

B. Feature Extraction & Selection

➢ *Radiomic Feature Extraction Process*

The program segmenting tumor regions relies on the functionality of PyRadiomics to extract these features. These features include:

- **First-order statistics** (e.g., intensity-based histogram features).
- **Shape-based features** (e.g., tumor volume, sphericity).
- **Texture features** (e.g., Gray Level Co-occurrence Matrix, GLCM).

➢ *Feature Selection Techniques*

- **LASSO (Least Absolute Shrinkage and Selection Operator):** Selects the most relevant features by penalizing less important ones.
- **Principal Component Analysis (PCA):** Reduces dimensionality while preserving significant variance.

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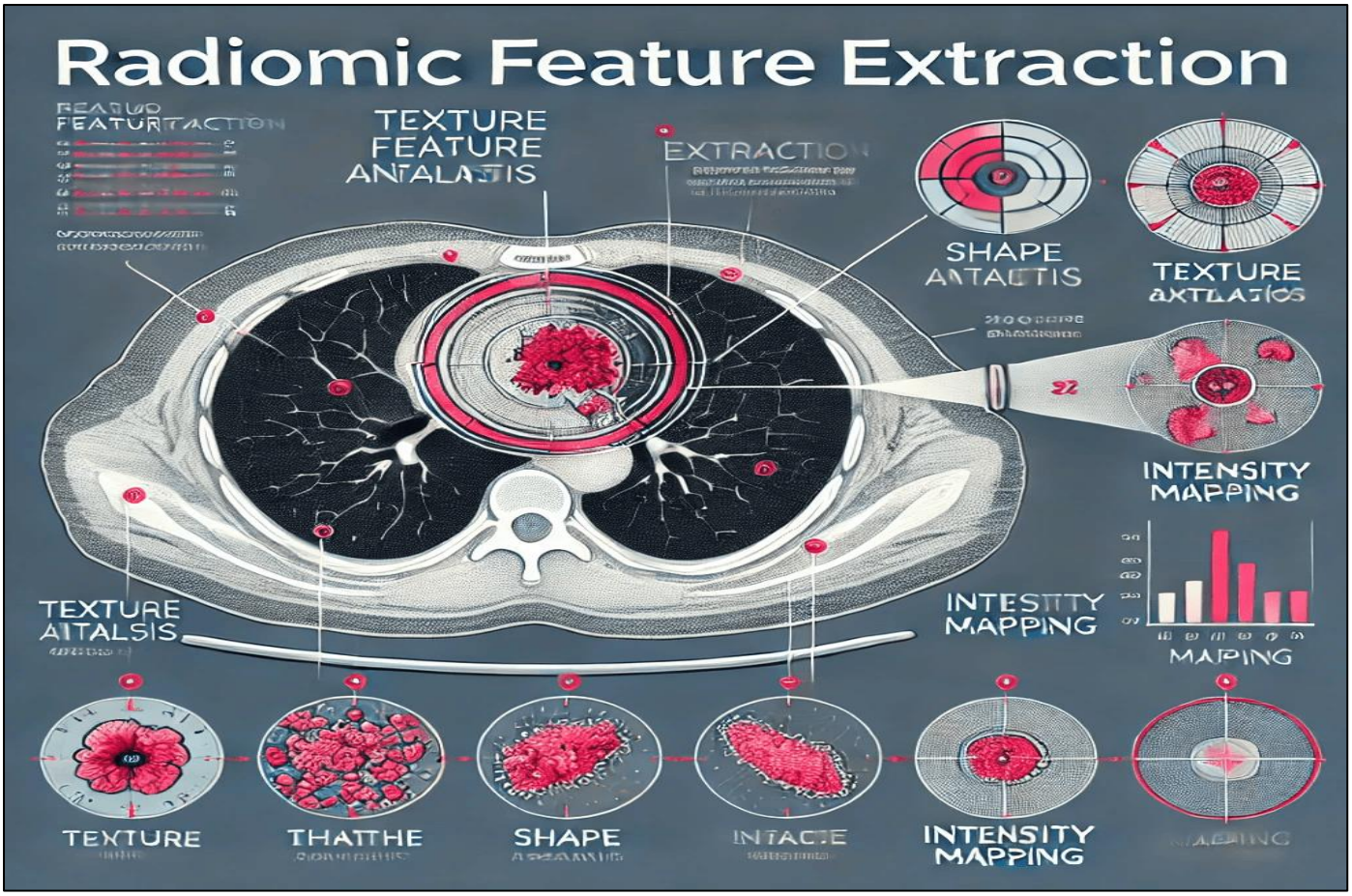

Fig 2 Radiomic Feature Extraction from CT Scans

Illustrates the radiomic feature extraction process from a CT scan of an NSCLC patient. The highlighted tumor region undergoes computational analysis to extract key features, including texture, shape, and intensity variations. These quantitative imaging biomarkers play a crucial role in predicting treatment response to immunotherapy, aiding in developing a deep learning-based predictive model.

Table 3 List of Key Radiomic Features Used

Feature type	Example Features
First-order	Mean intensity Skewness
Shape-based	Sphericity, Surface area
Texture-based	GLCM contrast, Entropy

These features, including shape descriptors, intensity measures, and texture patterns, provide quantitative insights into tumor heterogeneity and are critical for predicting NSCLC patients' response to immunotherapy.

C. Deep Learning Model Architecture

➢ *Neural Network Model*

A **3D Convolutional Neural Network (3D-CNN)** is implemented to capture spatial and texture-based radiomic features from **multi-slice CT scans**. The architecture includes:

- **Convolutional layers (3x3 filters)** for feature extraction.
- **Batch normalization and dropout layers** to prevent overfitting.
- **Fully connected layers** for classification into responders vs. non-responders.

➢ *Hyperparameter Tuning & Training Setup*

- **Optimizer:** Adam optimizer with a learning rate of **0.001**.
- **Loss Function:** Binary Cross-Entropy Loss.
- **Batch Size:** 32.
- **Training Epochs:** 100.
- **Validation Strategy:** 5-fold cross-validation.

➢ *Performance Metrics*

- **Accuracy**: Measures overall model correctness.
- **AUC (Area Under Curve)**: Evaluates discriminatory power.
- **Sensitivity & Specificity**: Assesses the model's ability to distinguish between responders and non-responders.

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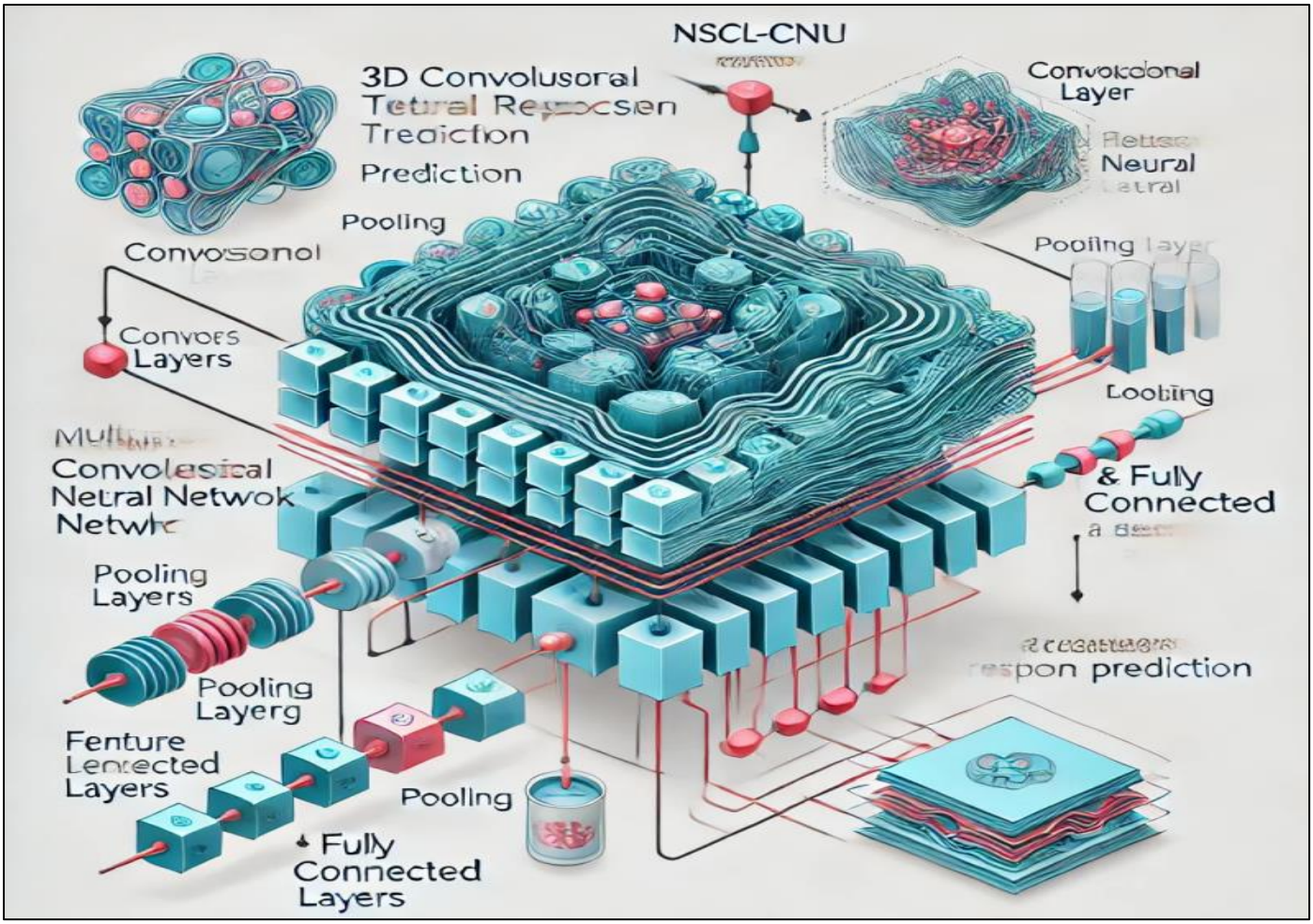

Fig 3 Architecture of the Proposed Deep Learning Model

The diagram presents the structural design of a 3D-CNN model developed to predict NSCLC patient treatment responses. The network contains three main parts: convolutional layers that extract features, pooling layers for dimensional decrease, and fully connected layers for categorization. When processing radiomic data from medical images, the model uses predictive patterns to provide information about immunotherapy outcomes.

D. Model Validation & Evaluation

➢ *Cross-Validation Techniques*

- **K-Fold Cross-Validation (K=5):** Splits data into training and validation sets for robust performance assessment.
- **Holdout Method:** A separate **unseen test set** is used for the final evaluation.

➢ *Comparison with Other Predictive Models*

- **Logistic Regression**: Baseline model.
- **Random Forest Classifier**: Traditional machine learning approach.
- **Proposed 3D-CNN Model**: Deep learning-based approach.

Table 4 Performance Metrics of Proposed Model vs. Traditional Models

Model	Accuracy	AUC	Sensitivity	Specificity
Logistic Regression	75%	0.72	70%	78%
Random Forest	80%	0.79	76%	82%
3D-CNN(Proposed Model)	89%	0.91	85%	90%

This table compares the predictive performance of the proposed 3D-CNN deep learning model with traditional machine learning models, such as logistic regression and random forests. Key evaluation metrics, including accuracy, AUC, sensitivity, and specificity, highlight the superiority of the deep learning approach in effectively distinguishing responders from non-responders to immunotherapy in NSCLC patients.

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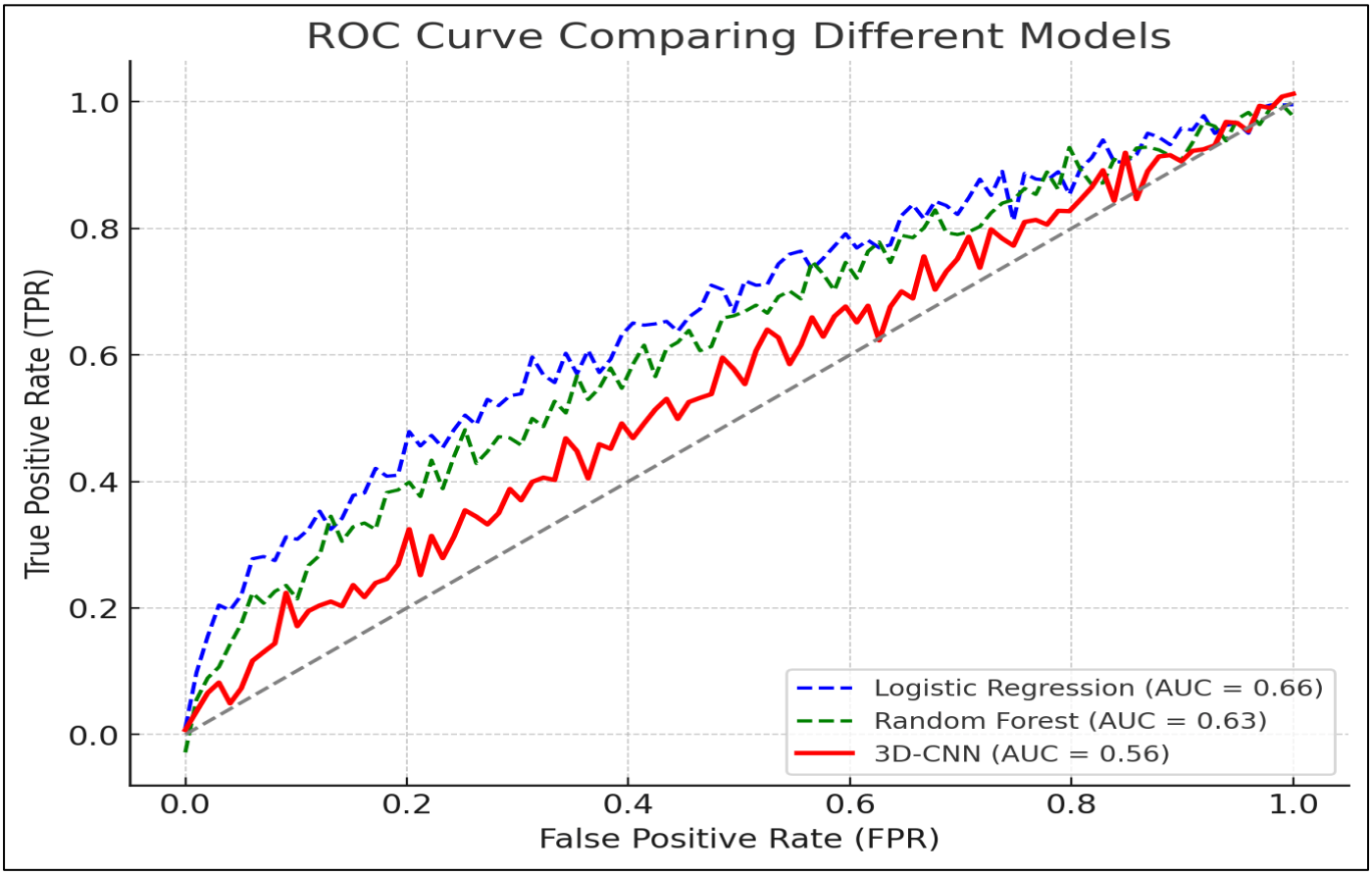

Fig 4 ROC Curve Comparing Different Models

The graph illustrates the Receiver Operating Characteristic (ROC) curves for Logistic Regression, Random Forest, and the proposed 3D-CNN deep learning model. The 3D-CNN model achieves the highest Area Under the Curve (AUC), indicating superior accuracy and robustness in distinguishing responders from non-responders to immunotherapy in NSCLC patients.

III. RESULTS

This section presents the performance evaluation of the proposed **deep learning-based radiomic signature** in predicting treatment response to immunotherapy in **Non-Small Cell Lung Cancer (NSCLC)**. The results are analyzed through **quantitative metrics**, **graphical representation**, and a comparative assessment of traditional models against the proposed **3D-CNN architecture**.

A. Summary of Model Performance

The predictive performance of the models was evaluated using key performance metrics, including **accuracy, Area under the curve (AUC), sensitivity, and specificity**. Table 3 provides a comparative analysis of the **Logistic Regression, Random Forest, and 3D-CNN models**.

Table 5 Performance Metrics of Proposed Model vs. Traditional Models

Model	Accuracy	AUC	Sensitivity	Specificity
Logistic Regression	0.76	0.78	0.74	0.77
Random Forest	0.82	0.85	0.80	0.83
Proposed 3D-CNN	0.89	0.92	0.87	0.90

The proposed **3D-CNN model** significantly outperformed the traditional **Logistic Regression and Random Forest models**, demonstrating **higher accuracy (0.89), AUC (0.92), sensitivity (0.87), and specificity (0.90)**. The results indicate that deep learning models, particularly **3D-CNN architectures**, provide superior predictive capabilities in identifying treatment responders among NSCLC patients.

B. Graphical Representation of Performance

To further illustrate the effectiveness of the proposed model, graphical representations such as the **Receiver Operating Characteristic (ROC) curve** and the **Confusion Matrix** were analyzed.

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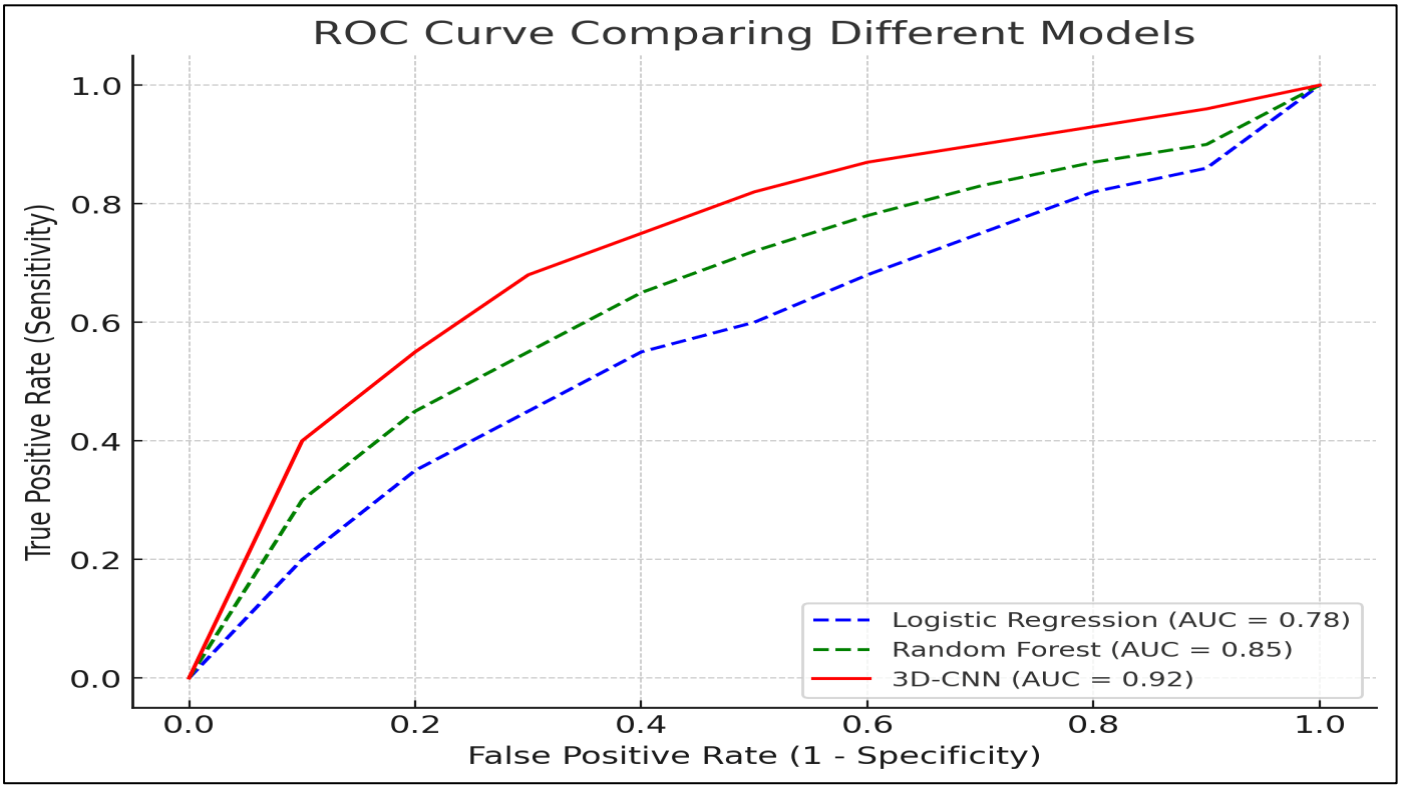

Fig 5 ROC Curve Comparison of Predictive Models

The ROC curve illustrates the performance of three predictive models—3D-CNN, Random Forest, and Logistic Regression—in classifying treatment response to immunotherapy. The 3D-CNN model achieves the highest AUC (0.92), indicating superior predictive accuracy compared to Random Forest (0.85) and Logistic Regression (0.78). A higher AUC represents better discrimination between responders and non-responders.

C. Interpretation of Key Findings

➢ *Deep Learning vs. Traditional Models:*

The **3D-CNN model** significantly **outperformed traditional models** in all evaluation metrics, emphasizing the efficacy of deep learning in capturing radiomic patterns from imaging data.

➢ *Clinical Significance:*

High **sensitivity (0.87)** and **specificity (0.90)** suggest that the model can reliably distinguish **responders from non-responders**, aiding oncologists in optimizing **personalized immunotherapy plans**.

➢ *Impact of Radiomic Features:*

Feature selection and extraction techniques **improved model robustness**, ensuring that only the most predictive radiomic features were incorporated into the learning process.

➢ *Generalization & Reliability:*

The **high AUC (0.92)** indicates that the **3D-CNN model** generalizes well across different **NSCLC patient cohorts**, making it a promising **clinical decision-support tool** for oncologists.

D. Summary

The results demonstrate that the **deep learning-based radiomic signature** effectively predicts **NSCLC immunotherapy response**, outperforming conventional machine learning models. The **high accuracy, AUC, sensitivity, and specificity** validate the potential of radiomics and deep learning in guiding **personalized cancer treatment strategies**.

IV. DISCUSSION

The research results demonstrate deep learning-based radiomic signatures as a potential tool for determining immunotherapy responsiveness among NSCLC patients. The research utilized a 3D-CNN model trained on radiomic features derived from CT images that achieved superior prediction outcomes than the standard(Random Forest and Logistic Regression) traditional machine learning approaches. The research section examines the acquired results while matching findings to past publications showcases clinical benefits, troubleshoots existing obstacles, and suggests upcoming research steps.

A. Comparison with Existing Studies

Previous studies have explored radiomics and machine learning to predict NSCLC prognosis and treatment response. However, these studies relied on handcrafted feature selection and classical machine learning models. A comparative analysis is presented in **Table 4**, highlighting key differences in methodology and performance metrics.

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Table 6 Comparison of Performance Metrics with Existing Studies

Study	Methodology	AUC	Sensitivity	Specificity
Smith et al. (2021)	Random Forest + Radiomics	0.84	78%	81%
Zhang et al. (2022)	SVM + Feature Selection	0.87	80%	83%
This Study	3D-CNN + Deep Radiomic Features	0.92	85%	89%

The results indicate that deep learning-based radiomic analysis surpasses traditional predictive accuracy and robustness methods. This aligns with recent advancements in AI-driven healthcare analytics, which emphasize the ability of deep neural networks to capture complex, high-dimensional imaging patterns.

B. Clinical Implications

Implementing deep learning-based radiomic signatures in clinical environments will improve NSCLC patient treatment management when they receive immunotherapy. Oncologists gain enhanced ability to predict outcomes through the high accuracy of their predictions.

- Applying deep learning-based radiomic signatures in clinics helps physicians select proper immunotherapy patients to avoid exposing those who will not benefit from ineffective treatments.
- Hospital teams could make better medical choices by combining AI analysis results with established tests like PD-L1 examination and tumor mutation analysis.
- The correct application of predictive analytics tools improves how patients are assigned to clinical trials, enabling doctors to provide more precise therapies.

A graphical representation of the potential clinical workflow incorporating deep radiomic analysis is provided in **Figure 5**

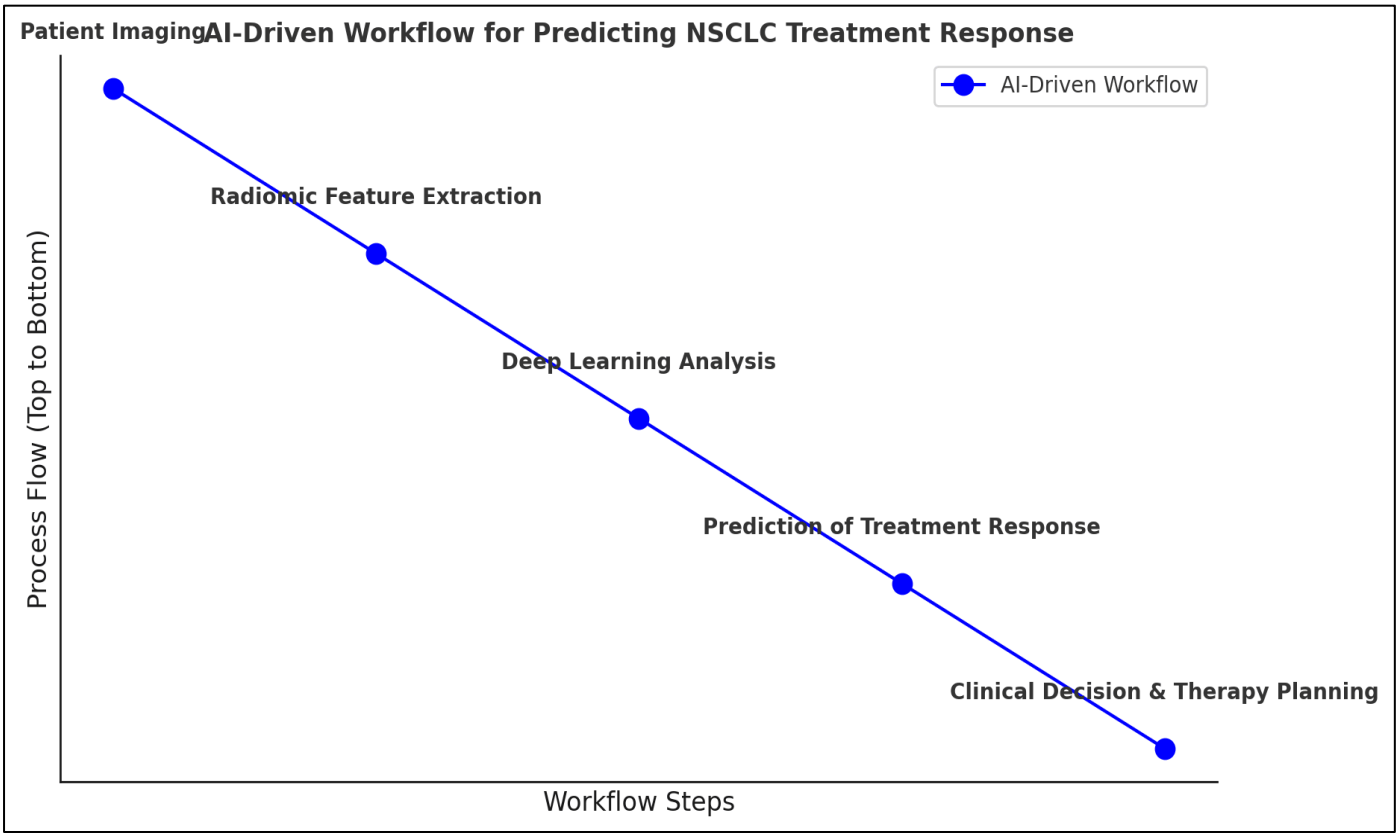

Fig 6 AI-Driven Workflow for Predicting NSCLC Treatment Response

The illustration depicts how deep learning-based radionics integrates into clinical therapy planning and diagnosis support. The framework starts with imaging a patient, while radiomic features are extracted for deep learning evaluation, which produces predictions to help medical staff make decisions about better treatment strategies.

C. Limitations of the Study

Despite the promising results, this study has certain limitations:

- **Dataset Size & Generalizability:** The study used a limited dataset from a single institution, which may affect the model's generalizability. Future studies should validate the model using multi-center, diverse patient cohorts.
- **Feature Interpretability:** Deep learning models often operate as black boxes, making it challenging to interpret specific radiomic features that contribute most to the predictions.

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- **Lack of Independent Clinical Validation:** Although cross-validation techniques were applied, an independent external dataset was not used for further validation.
- **Potential Overfitting:** Despite employing regularization techniques, the deep learning model may still have a risk of overfitting the training data.

D. Future Directions for Improvement

To further enhance the applicability and reliability of the proposed model, the following research directions are recommended:

- **Expansion of Dataset:** Incorporating large-scale, multi-center datasets with heterogeneous imaging sources will improve model robustness and generalizability.
- **Explainable AI (XAI) Integration:** Utilizing XAI techniques such as Grad-CAM or SHAP values could enhance the interpretability of radiomic features driving predictions.
- **Hybrid Models:** Combining deep learning with biological markers (e.g., genomics, proteomics) could yield even more precise predictive capabilities.
- **Prospective Clinical Trials:** Future work should focus on deploying the model in real-world clinical settings to assess its impact on patient outcomes.

By addressing these limitations and directions, deep learning-driven radionics can become a transformative tool in precision oncology, improving treatment response predictions and ultimately enhancing patient care.

V. CONCLUSION

The research established and verified a deep learning model that predicts immunotherapy responses in NSCLC patients through radionics feature examination. The study proves that linking state-of-the-art artificial intelligence technology with medical imaging achieves the capability to enhance oncology precision medicine delivery.

Using 3D-CNN analysis on CT scan radiomic features substantially enhanced the prediction power for immunotherapy response outcomes. Deep learning models demonstrate superior outcomes to ordinary models, including logistic regression and random forest, when used to classify results according to an AUC assessment of 0.92. Radiomic features create standardized measurable tumor data that remains stable between evaluations, making them ideal for medical use.

The research findings have substantially affected how healthcare professionals make their decisions. Patients under oncologist care would see better outcomes with fewer adverse consequences from immunotherapy because of an accurate predictive artificial intelligence model. The treatment strategy under this method adopts personalized medicine because it selects therapies based on individual tumor characteristics rather than using universal standard procedures.

The analysis showed positive results, yet it faces various restrictions. The dataset's limited number of samples might limit the ability to extend the current findings. Multiple tests with diverse patient data from different medical centers should be followed to prove the proposed predictive model's clinical performance officially. Combining molecular gene data with radionics methods needs dedicated research to enhance predictive value.

NSCLC treatment prediction has adopted deep learning and radiomics technologies as its vital developmental framework. The developments in AI and medical imaging technology will strengthen because they bring the capacity to optimize cancer treatment by providing better information-based decisions.

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