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REVOLUTIONIZING LUNG CANCER MANAGEMENT: AI-POWERED LIQUID BIOPSY–IMMUNOTHERAPY SYNERGY FOR EARLY INTERNIST-LED INTERVENTIONS IN HIGH-RISK POPULATIONS

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ABSTRAK

Abstract:
Lung cancer continues to be a predominant global cause of death. Clinical outcomes are significantly influenced by the timely identification of high-risk populations, accurate diagnosis, and appropriate therapy selection. Progress in artificial intelligence (AI), liquid biopsy, and immunotherapy has opened new avenues for improving diagnostic accuracy and individualized treatment. Therefore, this review aimed to summarize the current evidence regarding the integration of artificial intelligence, liquid biopsy, and immunotherapy in improving lung cancer diagnosis, treatment selection, and personalized management. structured literature search was conducted in PubMed using keywords related to AI, liquid biopsy, immunotherapy, and lung cancer, with a focus on publications from the past 10 years. Of 18,169 records, 45 studies were selected after screening. AI-driven deep learning and radiomics enhance the precision of early detection, distinguish between benign and malignant nodules, and predict molecular changes, including EGFR, ALK, and PD-L1 expression. Liquid biopsy facilitates the non-invasive identification of biomarkers, such as ctDNA, CTCs, and exosomes, while AI enhances the interpretation of biomarkers and the characterization of cancer. AI models, such as CNN and multiomics methodologies, accurately predict treatment response and prognosis, thereby facilitating informed decision-making for immunotherapy. The combination of AI, liquid biopsy, and immunotherapy has significant potential to improve lung cancer management by enabling earlier diagnosis, personalized treatment, and improved response prediction.

***Abstrak*:**
Kanker paru-paru tetap menjadi penyebab utama kematian di seluruh dunia. Hasil klinis sangat dipengaruhi oleh identifikasi tepat waktu terhadap populasi berisiko tinggi, diagnosis yang akurat, dan pemilihan terapi yang tepat. Kemajuan dalam bidang kecerdasan buatan (AI), biopsi cair, dan imunoterapi telah membuka jalan baru untuk meningkatkan akurasi diagnosis dan pengobatan yang disesuaikan secara individual. Oleh karena itu, tinjauan ini bertujuan untuk merangkum bukti terkini mengenai integrasi kecerdasan buatan, biopsi cair, dan imunoterapi dalam meningkatkan diagnosis kanker paru, pemilihan pengobatan, serta pengelolaan yang dipersonalisasi. Pencarian literatur terstruktur dilakukan di PubMed menggunakan kata kunci terkait AI, biopsi cair, imunoterapi, dan kanker paru, dengan fokus pada publikasi dari 10 tahun terakhir. Dari 18.169 catatan, 45 studi dipilih setelah proses penyaringan. Pembelajaran mendalam (deep learning) berbasis AI dan radiomik meningkatkan ketepatan deteksi dini, membedakan nodul jinak dan ganas, serta memprediksi perubahan molekuler, termasuk ekspresi EGFR, ALK, dan PD-L1. Biopsi cair memfasilitasi identifikasi biomarker secara non-invasif, seperti ctDNA, CTCs, dan eksosom, sementara AI meningkatkan interpretasi biomarker dan karakterisasi kanker. Model AI, seperti CNN dan metodologi multiomik, secara akurat memprediksi respons pengobatan dan prognosis, sehingga memfasilitasi pengambilan keputusan yang terinformasi untuk imunoterapi. Kombinasi AI, biopsi cair, dan imunoterapi memiliki potensi signifikan untuk meningkatkan pengelolaan kanker paru-paru dengan memungkinkan diagnosis lebih dini, pengobatan yang dipersonalisasi, dan prediksi respons yang lebih baik.

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INTRODUCTION

While the World Health Organization (WHO) reported approximately 1.8 million global deaths in 2019 from tracheal, bronchial, and lung cancer—ranking sixth among all causes of death overall—lung cancer specifically remains the second leading cause of cancer death in women worldwide, accounting for 13.8% of female cancer mortality [1], [2]. Accurate early diagnosis can improve patient prognosis. The varying gene expression in lung cancer and the complex tumor microenvironment pose challenges in achieving an accurate diagnosis [3]. Recently, liquid biopsy has been developed as a non-invasive diagnostic tool for lung cancer due to its significant potential. Liquid biopsy can detect biomarkers such as circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), and exosomes or extracellular vesicles (EVs) using blood, urine, or saliva samples [4]. The latest breakthrough in lung cancer diagnosis using a combination of liquid biopsy and artificial intelligence (AI) is the most influential innovation of the past decade [5]. AI can assist various lung cancer diagnostic modalities, such as bronchoscopy, endobronchial ultrasound (EBUS), fine needle aspiration biopsy (FNAB), and pathology or cytology results, to determine lung cancer staging [6], [7], [8]. The potential of liquid biopsy combined with AI offers high sensitivity and specificity across various aspects comprehensively, such as prevention, screening, clinical manifestations, treatment, and prognosis [3].

In patients with NSCLC without positive driver mutations, immunotherapy in the form of immune checkpoint inhibitors (ICIs) has become an integral part of lung cancer therapy [9]. Recent advances in artificial intelligence demonstrate that radiomics can serve as promising non-invasive biomarkers for predicting responses to ICIs. Radiomics has been shown to predict CD8 T cell infiltration and its response to ICIs or radiotherapy, and some studies have also attempted to determine PD-L1 expression [10]. Given the complexity of the immune system's response to the tumor microenvironment, managing such large datasets can be addressed using AI frameworks, such as machine learning (ML) techniques, which offer efficient, pioneering, and theoretical approaches to decision-making for individual patient predictions. To date, in NSCLC, PD-L1 remains the sole biomarker for identifying candidates for immunotherapy [11]. Deep learning can be used to accurately predict PD-L1 status from hematoxylin and eosin staining in NSCLC tumor samples [12]. This review is based on the increasing number of journals and literature discussing the application of AI in lung cancer over the past five years. Although many reviews have focused on specific aspects of AI in lung cancer, few have addressed the integration of AI with liquid biopsy and immunotherapy.

Therefore, this review aims to comprehensively summarize current evidence regarding the synergistic role of artificial intelligence, liquid biopsy, and immunotherapy in improving early detection, biomarker identification, treatment selection, and personalized management of lung cancer, particularly in high-risk populations.

RESEARCH METHOD

A structured literature search was conducted using the PubMed database to identify peer-reviewed articles relevant to the integration of artificial intelligence (AI), liquid biopsy, and immunotherapy in lung cancer management. The search strategy used the keywords “artificial intelligence” OR “machine learning” OR “liquid biopsy” OR “immunotherapy” OR “prevention” AND “lung cancer”, with the search limited to articles published within the last 10 years. The 10-year timeframe was selected to ensure that the review captured contemporary evidence reflecting the rapid evolution of artificial intelligence, liquid biopsy technologies, and

immunotherapy, while maintaining the clinical relevance of the included studies.

Eligible studies included original research articles published in English within the last 10 years that investigated the application of artificial intelligence, liquid biopsy, and immunotherapy in lung cancer. Review articles, conference abstracts, editorials, letters to the editor, duplicate records, non-English publications, and studies unrelated to the objectives of this review were excluded.

The literature search was performed using predefined Boolean operators to combine the search terms. The keywords "artificial intelligence" OR "machine learning" were combined with "liquid biopsy" OR "immunotherapy" OR "prevention" using the operator AND "lung cancer". Titles and abstracts were initially screened for relevance, followed by full-text assessment of potentially eligible articles according to the predefined eligibility criteria. Duplicate records were removed prior to study selection.

PubMed was selected as the primary database because it provides comprehensive coverage of peer-reviewed biomedical and clinical literature, including studies related to artificial intelligence, liquid biopsy, immunotherapy, and lung cancer. As this review aimed to summarize current evidence from biomedical research, PubMed was considered an appropriate and reliable source for identifying relevant publications.

The retrieved records were initially screened based on their titles and abstracts to assess their relevance to the objectives of this review. Studies that met the predefined eligibility criteria underwent full-text assessment before final inclusion. The eligible studies were subsequently categorized into three thematic sections: immunotherapy, liquid biopsy, and high-risk prevention.

This journal search yielded 18,169 results, 11 of which were duplicates and had to be excluded before screening. Additionally, 147 articles could not be accessed, leaving 18,011 articles. During the journal screening process, 17,875 articles were excluded for not being relevant to the research theme, leaving 136. The 136 articles were divided into three subchapters: 'IMMUNOTHERAPY' (42 articles), 'LIQUID BIOPSY' (80 articles), and 'HIGH RISK PREVENTION' (14 articles). After reviewing the abstracts, the final number of journals was 18 in the 'IMMUNOTHERAPY' subchapter, 21 in the 'LIQUID BIOPSY' subchapter, and 6 in the 'HIGH RISK PREVENTION' subchapter. The flow diagram of the research methods in this study selection is shown in Figure 1.

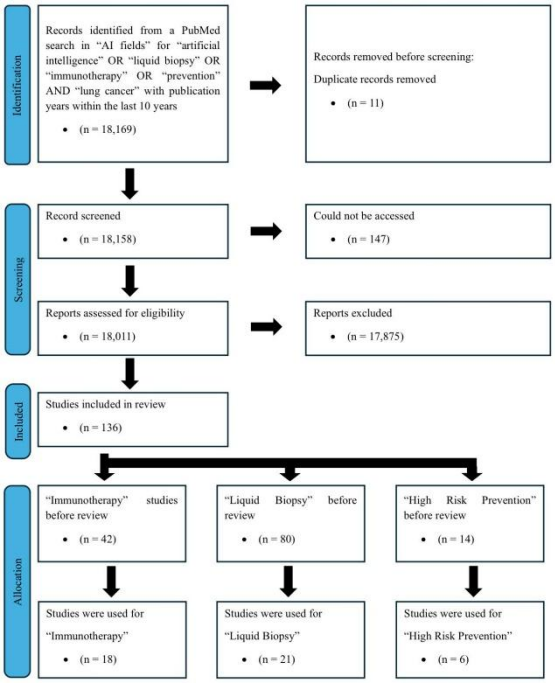

Figure 1. The flow diagram illustrating the literature search and study selection process.

RESULT AND ANALYSIS

A total of 45 articles were included in this review following the screening and eligibility assessment process. The included studies were published between 2020 and 2024 and represented diverse study designs conducted predominantly in Asia, Europe, and North America. Based on their primary focus, the studies were categorized into three thematic areas: high-risk population prevention (n = 6), liquid biopsy (n = 21),

and immunotherapy (n = 18). An overview of the characteristics of the included studies is presented in Table 1. Detailed summaries of the studies within each thematic category are subsequently presented in Tables 2–4.

Table 1.
General Characteristics of the Included Studies

Characteristic	Summary
Number of included studies	45
Publication period	2020-2024
Geographic distribution	Asia, Europe, and North America
Study design	Benchmarking studies, laboratory studies, retrospective observational studies, cohort studies, clinical trial protocols, and case reports
Thematic categories	High-risk population prevention (n = 6); Liquid biopsy (n = 21); Immunotherapy (n = 18

Table 2.
Studies in the sector of high-risk population prevention.

References	Study	Sensitivity	Specificity	AUC	AI Model	Patients	Conclusion
Uthoff JM, et al., 2022	Benchmarking study			0.80	LASSO	278 Patients with pulmonary nodules	Automated quantitative computed tomography (qCT) can provide information between individuals regarding malignant and benign pulmonary nodules as comorbidities in lung cancer in patients who have a history of smoking.
Yang R, et al., 2022	Benchmarking study			0.771	Artificial intelligence-based MLA	7413 patients with lung adenocarcinoma	EGFR mutation by an AI-based MLAs prediction model (AUC = 0.771) showed better results than traditional models, with five main influencing factors such as smoking, gender, age, and albumin-globulin ratio.
Ye M, et al., 2022	Benchmarking study	89.52%	81.31%	0.880	AI algorithm with three-stage end-to-end deep conventional neural networks (DCNNs)	728 patients	The use of AI for individual prediction of high-risk lung cancer integrates clinical characteristics, radiological characteristics, AI-based LDCT analysis, and liquid biopsy. With the

References	Study	Sensitivity	Specificity	AUC	AI Model	Patients	Conclusion
							result of improving early diagnosis for lung cancer better.
Daneshkhah A, et al., 2023	Laboratory study				combination of csPWS with AI software	96 lung cancer patients and 83 LDCT negative patients	This research, in addition to detecting high risk, can also screen lung cancer stages with an AUC = 0.82
Liu D, et al., 2021	Benchmarking study			0.916	deep learning convolutional neural networks (CNN)	4644 patients with small pulmonary nodules (SPN)	Lung cancer screening using AI shows significant efficacy; in addition, CNN combined with Asian lung cancer epidemiology can improve accuracy in classifying lung cancer epidemiology, especially in Asians.
Gauthier MP, et al., 2022	Retrospective observational study				natural language processing (NLP), DARWEN	333 lung cancer patients	Data collection and identification using DARWEN is faster and more specific, with an accuracy level of 78%-94%

Table 3.
Studies in the sector of liquid biopsy

Reference	Study	Sensitivity	Specificity	AUC	AI Model	Patients	Conclusion
Ye M, et al., 2022	Benchmarking study	89.52%	81.31%	0.880	AI algorithm with three-stage end-to-end deep conventional neural networks (DCNNs)	728 patients	The use of AI for individual lung cancer risk prediction integrates clinical characteristics, radiological characteristics, AI-based LDCT analysis, and liquid biopsy. With the results of improving early diagnosis for lung cancer, better and liquid biopsy is getting the best performance for diagnostics in the training cohort.
Kirienko M, et al., 2021	Retrospective single-center observational study			0.87	Generalized Linear Model (GLM) and Machine Learning (ML)	151 NSCLC patients who have undergone	Several radiomics features have been identified as successfully predicting histotype using ML. These dadiogenomic data can be clinically helpful in providing information on

Reference	Study	Sensitivity	Specificity	AUC	AI Model	Patients	Conclusion
						surgery	NSCLC patients, and gene expression analysis also reveals potential new biomarkers.
Lococo F, et al., 2023	Protocol of a multi-center observational clinical trial				Multiple multivariate models advanced machine learning	600 lung cancer patients	Establishment of AI models to create predictive models for lung cancer diagnosis, establishment of predictive models for the specific management of each patient, and feedback for preventive strategies in health.
Cheng G, et al., 2022	Benchmarking study			0.602	AI-powered scoring algorithm	1288 lung cancer patients	An AI diagnostic model to analyze PD-L1 expression that identifies more samples compared to manual scoring. It also has the potential to implement digital pathology methods to help identify patients for immuno-oncology therapy.
WangX, et al., 2021	Benchmarking Study	1.0	0.9		Dual-scale Category (DSC)	110 patients with NSCLC	The use of DSC-based methods that can evaluate PD-L1
MahmoudAM, et al.,2023	Benchmarking study			Correlation coefficient 0.88	AI algorithm of immunoreactive scoring on PRMT6	33 lung cancer networks	Optimal use of AI to determine the PRMT6 expression determination algorithm in lung cancer that is in accordance with the pathologist's scoring degree.
Ishii S, et al., 2022	Benchmarking study			accuracy = 0.945 and precision = 0.991	CNN1 & CNN2	106 and 32 positive and negative cancer samples	Implementation of the use of AI to predict gene changes in cytological speci-mens containing lung cancer cells, with an accuracy and precision of 0.945 and 0.991 in cancer-positive cells.
Al Jabbar M, et al., 2023	Benchmarking study	0.99	1	0.99	ANN with a combination of GoogleNET, VGG-19, and additional features, manually	Histology images from the LC25000 dataset	The combination of AI ANN with Google Net, VGG-19, and additional features can accurately diagnose lung cancer and colon cancer.

Reference	Study	Sensitivity	Specificity	AUC	AI Model	Patients	Conclusion
Kanavati F, et al., 2020	Benchmarking study			0.975	Convolution Neural Network (CNN) based on Efficient Net-B3 architecture	3354 slide images	The use of AI for diagnosis through pulmonary lesions with an EfficientNet-B3-based CNN.
Kriegsmann M, et al., 2020	Benchmarking study			Result classification = 95% and 100%	Multiple CNN architectures (VGG16, Inception V3, and Inception ResNetV2)	270 specimens	AI CNN to classify lung cancer from images, with results reaching 95% and 100%.
Cao L, et al.,2023	Benchmarking study	0.97	0.87	0.95 - 0.97	HELLO AI	2607 slide images	AI methods for end-to-end learning for morphological feature extraction and histomorphological pattern identification
Sakamoto T, et al., 2022	Benchmarking study				convolutional neural networks (CNNs) synergize with HALO image analysis	201 cases of lung cancer	Detect tumor segmentation and nucleus recognition with sensitivity and specificity in detecting tumor segmentation of 97% and 87% and accuracy in detecting nuclei recognition of 99%
Zhao Y, et al., 2023	Benchmarking study			> 0.80	DeepLab v3 with ResNet-5	523 whole-slide sample images	able to predict both major and minor subtypes of invasive non-mucin LUAD, although with small lesions, this AI is still sensitive, with an AUC > 0.80
Choi S, et al., 2022	Benchmarking study			0.902	Lunit SCOPE PD-L1	802 sample whole-slide images NSCLC	A detects lung cancer pathology using PD-L1 TPS expression accurately, without using AI, AUC = 0.814
Hondelink LM, et al., 2022	Benchmarking study				convolutional neural networks (CNNs) in synergy	199 whole-slide image samples and 60	This journal presents a new deep learning model for detecting PD-L1 using TPS.

Reference	Study	Sensitivity	Specificity	AUC	AI Model	Patients	Conclusion
					with HAIL annotations	NSCLC cases	
Huang Z, et al., 2022	Benchmarking study			0.791	Aitrox AI Model	222 cases of lung cancer	AItrox can detect PD-L1 expression by assessing TPS expression (pathologically), in conditions of low TPS expression, AItrox can still detect PD-L1 with AUC = 0.852
Li J, et al., 2022	Benchmarking study			0.822	molecular signaling map (MSM) and metabolic network (MCPM)	139 patients with pulmonary nodules	using an AI model combined with the IM-index to classify malignant lung cancer subtypes, in addition to prediction, the IM-index can also predict with an AUC = 0.883
Waissengrin B, et al., 2023	Case report				Real-time imageneaarificial intelligences (AI's).	1 NSCLC patient	Using AI-based molecular analysis tools to quickly determine treatment continuation
Tan X, et al., 2022	Benchmarking study			AUC deep learning = 0.747 AUC DRF = 0.972 AUC GBM = 0.934 AUC GLM = 0.737 AUC XGBoost = 0.790 AUC XRF = 0.974	1 deep learning and 5 machine learning (GBM, XGBoost, XRT, DRF, and GLM)	2553 NSCLC patients	The combination of 6 AI models achieved AUCs of 0.897 and 0.883 for detecting EGFR mutations and 0.921 for ALK rearrangement status.
Sorin M, et al., 2023	Laboratory study				deep learning (deep residual networks (Resnet50)	416 patient samples with lung adenocarcinoma	Can predict lung cancer progression with an accuracy rate of 95.9% from tumors measuring 1mm squared
Keller A, et al.,	Laboratory study			0.816	self-organizin	210 serum	The liquid biopsy results will be analyzed using

Reference	Study	Sensitivity	Specificity	AUC	AI Model	Patients	Conclusion
2020					g map (SOM)	samples from cancer patients (lung, colon, mammary)	AI (SOM) to detect early disease before clinical manifestations appear in patients.

Table 4.
Studies in the sector of immunotherapy

References	Study	Sensitivity	Specificity	AUC	AI Model	Patients	Conclusion
Zhou H, et al., 2021	Prospective, single-arm, multi-centre, phase II trial				AI multi-omics system	40 patients with lung cancer	The efficacy of ICIs is influenced by many factors, such as smoking and genes, indicating that the use of multiomics AI provides a valid strategy for predicting the effects of neoadjuvant therapy.
Tong H, et al., 2022	Retrospective multi-cohort study			0.932	F-FDG PET/CT radiomics	1405 patients with NSCLC	The F-FDG PET/CT radiomics combined model can perform well in predicting the TIME profile in NSCLC. In the DPH Cohort, the radiomic model outperformed the CT model with an AUC of 0.907. Moreover, in the combined model of PET/CT radiomics, the AUC was obtained: 0.932
Wang C et al., 2022	Benchmarking Study			AUC of EGFR prediction = 0.805 and PD-L1 prediction = 0.799	A multitask AI system includes DL, radiomics, and joint modules.	9136 patients with NSCLC	Multitask AI delivers promising performance in detecting EGFR and PD-L1 mutation gene expression
Dora D, et al.,	Cohort	Positive predictio			Shotgun metagenomi	129 patients	Establishment of a prediction model with

References	Study	Sensitivity	Specificity	AUC	AI Model	Patients	Conclusion
2022		n rate = 90%			cs (MG) and ITS	with NSCLC	AI based on QTA parameters and gut microbiome that can predict OS, therapy response, PD-L1 expression, and toxicity in NSCLC patients treated with ICIs.
Tonneau M, et al., 2022	Benchmarking Study			0.66	PyRadiomics and DeepRadiomics	642 patients with NSCLC	AI radiomics followed by CT scan harmonization showed similar performance to clinical practice + PD-L1 with AUC 0.66
Trebeschi S, et al., 2022	Benchmarking Study			0.83	Characterization of AI based on lesions before management via CT imaging	1055 primary and meta-lesions from 465 patients with NSCLC	Radiographic characteristics identified by AI can serve as a noninvasive biomarker of response to immunotherapy in NSCLC lesions, leading to a 24% increase in the 1-year survival difference.
Jin W, et al., 2022	Benchmarking Study			0.91	Deep learning (DL) radiomics	143 primary lung cancer patients	Dynamic hybrid models show promise as tools for predicting lesion response to PD-1 blockade.
Deng K, et al., 2022	Retrospective study	hazard ratio: 0.33, 95% CI: 0.18−0.55, p<0.0001			EfficientNet V2	570 patients with stage 4 NSCLC with EGFR mutation	Development of an AI model based on pre-operative CT imaging to predict patient survival from EGFR-TKI and ICIs therapy
Trebeschi S, et al., 2022	Benchmarking Study			0.69	An AI neural network trained to identify morphological changes in chest CT	152 patients with stage 4 NSCLC	Deep larynx can detect morphological changes in tumors and non-tumors, which are important for prognostication via imaging.
Park C, et al., 2022	Benchmarking Study	[95% CI 2.2–5.7]			AI-powered TIL analysis	512 patients with NSCLC	A CT radiomics model can significantly predict TILs associated with ICI outcome in NSCLC patients
Ventura D, et al., 2023	Benchmarking Study			0.75	F-FDG PET/CT radiomics	44 patients with	Use of radiomic-based models to predict the response of patients

References	Study	Sensitivity	Specificity	AUC	AI Model	Patients	Conclusion
					feature (RF)	NSCLC	with NSCLC given CKI.
Su Z, et al., 2023	laboratory study			0.8701 and 0.9110	LDAenDL	Two human IncRNA diseases	CCDC26 and IFNG-AS1, which may be new biomarkers for lung cancer through identification from AI
Wang X, et al., 2021	Benchmarking Study	1.0	0.9		Dual-scale Categorization (DSC)	110 patients with NSCLC	The use of DSC-based methods that can evaluate PD-L1
Prelaj A, et al., 2023	Multi-center, retrospective and prospective, observational study					15 study references	An AI assistant to guide immunotherapy administration in NSCLC patients, ensuring easy access and cost-effectiveness
Prelaj A, et al., 2022	Prospective observational study			LR, AUC = 0.83 KFNN, AUC = 0.80 K-NN, AUC = 0.81SVM, AUC = 0.83RF, AUC = 0.82	feedforward neural network (FFNN), logistic regression (LR), K-nearest neighbors (K-NN), support vector machines (SVM), and random forest (RF)	164 NSCLC patients	AI algorithms in multifactorial data integration have become one of the methods for planning immunotherapy treatments
Prelaj A, et al., 2023	Retrospective observational study			0.82	Xplainable AI (XAI) Machine Learning (ML)	480 lung cancer patients (73 patients combined with chemotherapy)	Neutrophil-to-lymphocyte ratio (NLR), Eastern Cooperative Oncology Group performance status (ECOG-PS), PD-L1 expression, immunotherapy treatment line, and chemotherapy-immunotherapy combination were the most important factors in immunotherapy outcomes, with accuracy rates ranging

References	Study	Sensitivity	Specificity	AUC	AI Model	Patients	Conclusion
							from 0.73 to 0.83; immunotherapy is a major focus in lung cancer treatment and prognosis.
Li S, et al., 2022	Retrospective observational study			0.704 - 0.9526	Dense Neural Network (DNN)	289 lung cancer patients	The AUC values for a number of AI models predicting different outcomes, including disease control rate (DCR), objective response rate (ORR), PFS, and OS, ranged from 0.704 to 0.9526; patients may benefit more from neoadjuvant and adjuvant immunotherapy.
Guo H, et al., 2021	Cohort			0.80-0.87	single-plex chromogenic IHC	121 NSCLC patients and recruited 30 external patients	Overall survival (OS) and relapse-free survival (RFS) were significantly influenced by galectin-9, OX40, OX40L, KIR2D, and KIR3D features in the internal cohort; the integrated score had the highest AUC for OS and RFS, reaching 0.9 and 0.85 in the internal testing cohort; in the external cohort, the AUC ranged between 0.80 and 0.87 for OS and between 0.83 and 0.94 for RFS; in the external cohort, the neutrophil-to-lymphocyte ratio (NLR) together with the PD-1/PD-L1 signature were predictors of RFS.

DISCUSSION

1. High-Risk Population

Lung cancer has various risk factors, with smoking being one of the most common causes of lung cancer. It is estimated that 90% of lung cancer cases are related to smoking. The risk is significantly more complex when exposed to other carcinogens, such as asbestos.

Additionally, chronic obstructive pulmonary disease (COPD) is a common comorbidity for lung cancer, independent of smoking risk. The performance of the Least Absolute Shrinkage and Selection Operator (LASSO) and Ensemble of Neural Networks (ENN) was evaluated

using 183 qCT images to assess lung cancer risk associated with COPD. LASSO, with the highest performance, achieved an AUC of 0.80, which automatically measures nodule diameter, which can be highly informative in distinguishing between individuals with malignant and benign pulmonary nodules without requiring segmentation and analysis [13]. EGFR mutation prediction may also be possible in lung cancer using machine learning algorithms (MLAs), including logistic regression (LR), random forest (RF), lightGBM, support vector machine (SVM), multi-layer perceptron (MLP), extreme gradient boosting (XGBoost), and decision tree (DT) in 7,413 patients. RF achieved the best performance in predicting EGFR mutations with an AUC of [0.771, 95% confidence interval (CI): 0.770, 0.772]. Five highly influential factors included smoking, gender, cholesterol, age, and albumin-globulin ratio [14].

Lung cancer screening can also be performed using low-dose computed tomography and can reduce mortality, but it may increase the incidence of undetected pulmonary nodules. AI prediction models can identify individuals with high-risk factors for lung cancer development. The model's results integrate clinical characteristics (age and smoking history), radiological characteristics of pulmonary nodules (nodule diameter, number, location, malignant signs, and subsolid status), AI analysis of LDCT, and liquid biopsy, achieving the best diagnostic performance with a sensitivity of 89.53%, specificity of 81. 31%, and AUC = 0.880. These results are significantly better at predicting cancer status than radiological findings and AI risk scores alone [15].

Identifying cancer before symptoms appear can improve treatment outcomes and reduce mortality. Optical spectro-scopic statistical nanosensing AI techniques can be used for early-stage lung cancer detection by detecting molecular abnormalities in cells of the buccal mucosa, a phenomenon known as field carcinogenesis [16]. In another study, a risk-prediction nomogram for lung cancer was developed using a CNN. This screening demonstrated significant efficacy, and its combination with lung cancer epidemiology can enhance classification ability, particularly in Asia [17]. Automatic extraction using natural language processing (NLP) can also help extract patient clinical data more quickly. NLP is calculated to take less than one day compared to manual extraction using electronic health records (EHRs) in collecting demographic data (gender, age, diagnosis) with an accuracy of 99%–94% compared to manual extraction with an accuracy of 78%–94% [18]. Table 1 lists studies related to high-risk population prevention.

2. Liquid Biopsy

Lung cancer is one of the leading causes of death worldwide, with approximately 2.48 million cases globally. Early diagnosis and accurate staging are critical components in improving the prognosis for lung cancer patients. Several modalities can be used for diagnosis, such as CT and PET-CT, but their accuracy in detecting small lesions is very low. Tissue biopsy is currently the gold standard because it allows for histological analysis and can classify tumors based on the molecular characteristics present in the sample [3]. Advances in medical technology now offer a non-invasive procedure for detecting lung cancer, namely, liquid biopsy. Liquid biopsy is a promising diagnostic tool because it can analyze biomarkers in cancer cells, such as circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), and exosomes or extracellular vesicles (EVs) found in blood, urine, or saliva. Recently, the development of artificial intelligence (AI) has accelerated and can be applied in medicine, including in lung cancer. The potential of AI can be leveraged to detect lung cancer in synergy with liquid biopsy, thereby achieving high detection accuracy.

Detection using liquid biopsy in synergy with AI provides high accuracy in diagnosing lung cancer. In cohort studies, the use of AI algorithms in the early diagnosis of lung cancer has shown excellent performance [15]. AI models can be developed to predict lung cancer diagnoses, aiming to predict individual patient management as a preventive health strategy [19]. Early diagnosis of lung cancer using histological images from the Lung-Colon (LC25000 dataset) in synergy with AI features (ANN and CNN) can provide high-dimensional histological images by enhancing area contrast, thereby achieving high accuracy, specificity, and AUC, with a sensitivity of 99.85%, precision of 100%, accuracy of 99.64%, specificity of 100%, and AUC of 99.86% [20].

AI Convolutional Neural Network (CNN) models based on HALO, ResNet, or EfficientNet-B3 can detect histopathological lung cancer lesions by extracting morphological features, achieving an AUC of 95%–97%. Additionally, the HALO-based model can accurately detect lung cancer through tumor segmentation and nuclear recognition, achieving 99% accuracy, 97% sensitivity, and 87% specificity [21], [22], [23]. Deep learning based on ResNet-5 also provides accuracy and precision in predicting lung cancer. This method, using 523 whole-slide image samples, can predict invasive non-mucin LUAD in both major and minor subtypes with an AUC >80% [24]. In another study, the use of deep learning based on ResNet-5 was able to accurately predict the progression of lung cancer originating from a 1mm² tumor with an accuracy of 95.9% [25]. Molecular signaling maps (MSM) and metabolic networks (MCPM) are types of AI that, when combined with the IM-index, can classify lung cancer subtypes with an AUC of 82% [26]. Additionally, self-organizing maps (SOM), another type of AI, can detect cancer lesions early, before clinical manifestations appear, with an AUC of 81% [27]. This detection or diagnosis is based on the expression of biomarkers that are overexpressed by cancer lesions in the lungs.

One of the important biomarkers in the diagnosis of lung cancer is programmed cell death ligand 1 (PD-L1). Traditional quantitative evaluation of PD-L1 expression using immune-histochemistry staining remains challenging for pathologists. The use of deep learning (DL) based on artificial intelligence (AI) can automatically analyze PD-L1 expressions in lung cancer patients. The diagnostic capabilities of three different AI models (M1, M2, and M3) were evaluated using the PD-L1 (22C3) and PD-L1 (SP263) assays. M2 and M3 demonstrated improved performance in evaluating PD-L1 expression (22C3) and PD-L1 (SP263), with accuracy and specificity up to 96.4% and 96.8%. This makes AI-assisted diagnostic models for PD-L1 expression highly promising for enhancing clinical pathological efficiency [28]. Additionally, Dual-scale Categorization (DSC) based on deep learning methods was tested on a cohort of 110 patients diagnosed with NSCLC to analyze PD-L1 expression. This AI method showed agreement of up to 88% with pathology, which is higher than the baseline method's 83% [29]. The use of four convolutional neural networks (CNNs) with 199 whole slide images (WSIs) from routine diagnosis of stage 4 NSCLC histology samples to analyze PD-L1 expression also showed 79% similarity with the reference score by pathology [30]. Furthermore, Aitrox AI segmentation on WSIs was also used to train, validate, and test datasets for PD-L1 scoring analysis. This AI model strongly correlates with the TPS gold standard and can be compared to the performance of experienced pathologists. Aitrox AI performs better than inexperienced pathologists [31].

Understanding genetic changes in lung cancer is crucial for diagnosis and determining treatment strategies. The neural network model developed to analyze

positive cancer images achieved accuracies of 0.945 and 0.991, and precisions of 0.991 and 0.991, respectively. Prediction accuracy for EGFR and KRAS with data validation is around 0.95 [32]. In addition to PD-L1, PRMT6 expression is associated with poor prognosis in lung cancer. However, manual analysis of PRMT6 expression is time-consuming. The use of AI algorithms to replicate pathologists' PRMT6 immunoreactive scores showed agreement, with a correlation coefficient of 0.88, an intraclass correlation of 0.95, and a reliability coefficient of 0.96. This makes the AI algorithm optimal for determining PRMT6 expression scores in lung cancer [33]. Epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) mutations in NSCLC are important for the administration of tyrosine kinase inhibitors (TKIs) and lung cancer diagnosis. A single deep learning model and five modified machine learning models were combined into a final AI learning model to predict EGFR mutations, rare EGFR mutations, and ALK rearrangements. This AI provides optimal diagnostic performance with AUC values of 0.897 and 0.883 for predicting EGFR mutations and 0.995 and 0.921 for predicting ALK rearrangements [34]. In lung cancer patients, tumor features identified through imaging such as CT and PET can be used as biomarkers for diagnosis, prediction, and prognosis. Generalized linear models (GLMs) and machine learning (ML) algorithms can utilize data from both imaging modalities, whereas genomic analysis includes genetic variants, transcript fusions, and gene expression. The best radiogenomic ML model for predicting outcomes had an AUC of 0.87. This data can provide relevant information for NSCLC patients regardless of histotype, aggressiveness, and progression. Gene expression analysis also shows the potential for new biomarkers for patient management [35]. Table 2 lists studies related to the field of liquid biopsy.

3. Immunotherapy

Immune checkpoint inhibitors (ICIs) targeting PD-1 have become an advanced management option for NSCLC. ICIs are used as neoadjuvant therapy in NSCLC patients undergoing resection. The efficacy of ICIs is influenced by several factors, such as smoking history and patient genetics. The use of multi-omics AI can help predict the efficacy of neoadjuvant therapy and support decision-making [36].

Although immunotherapy has revolutionized the management of NSCLC, only approximately 30%–50% of patients experience long-term benefit from IO. Furthermore, identifying this 30%–50% is challenging, as PD-L1 remains the sole biomarker for predicting IO outcomes in NSCLC patients. Given the complexity of the immune system-tumor micro-environment (TME) and its interactions with the host and patient behaviour, it is highly challenging for a single biomarker to accurately predict patient outcomes. Here, the role of AI and machine learning becomes crucial in establishing a data repository and analysis framework to guide the administration of IO in NSCLC patients, ensuring ease of access and cost-effectiveness for healthcare providers [37]. The use of AI feedforward neural networks (FFNN), logistic regression (LR), K-nearest neighbour (K-NN), support vector machines (SVM), and random forest (RF) in 164 patients with NSCLC can be used to improve response prediction and efficacy in NSCLC patients managed with IO [11]. Prediction models using R/NR in patients achieved an accuracy (ACC) of 0.756 and an AUC of 0.82, indicating that integrating multifactorial data via ML is useful for selecting NSCLC patients as candidates for IO [38].

Gene expression in lung cancer can also be detected by analyzing the tumor microenvironment (TIME). In a study using F-FDG PET/CT radiomics, NSCLC prediction using the TIME profile yielded an AUC of 0.932 [39]. Analysis of PD-L1

and EGFR biomarkers in 9,136 NSCLC patients using an AI radiomics system yielded an AUC of 0.799 for PD-L1 and 0.805 for EGFR. Another study analyzing PD-L1 in 624 NSCLC patients reported an AUC of 0.66 [10], [40]. Additionally, shotgun metagenomics (MG) and ITS can predict OS, treatment response, PD-L1 expression, and ICI toxicity in 129 NSCLC patients. This demonstrates that AI systems can enhance immunotherapy efficacy by analyzing biomarkers (positive predictive value of 90%) [41]. The role of deep learning combined with chest CT imaging can calculate morphological changes, both tumor-related and non-tumor-related, in 152 stage 4 NSCLC patients with an AUC of 0.69, thereby improving patient prognosis [42]. Additionally, AI has shown that Small Nucleolar RNA Host Gene 3 (SNHG3) may be associated with PD-L1, and that new biomarkers such as CCDC26 and interferon gamma antisense RNA 1 (IFNG-AS1) may be associated with lung cancer [29], [43]. Various AI models have improved outcomes by increasing pathologist agreement rates to 90.2% regarding PD-L1 status and predicting response to immunotherapy with AUC values ranging from 0.82 to 0.91 and accuracy between 0.756 and 0.839 [37]. Additionally, with AUC values ranging from 0.934 to 0.950, AI successfully identified various PD-L1 expression levels (<1%, 1–49%, and ≥50%) and, on average, produced more accurate PD-L1 expression measurements than manual assessment for various cutoff points [39].

In IO therapy response planning for lung cancer patients, AI algorithms can automatically calculate associated radiographic characteristics and serve as a noninvasive radiomic biomarker for immunotherapy response. In 203 patients with NSCLC undergoing anti-PD1 therapy, AI was used to analyze the characteristics of metastatic lesions before treatment from CT images to establish and validate a biomarker capable of discriminating against immunotherapy response. This study identified a biomarker that demonstrated significant performance in NSCLC lesions (AUC = 0.83), resulting in a 1-year survival difference of up to 23% (P = 0.02). These results indicate that radiographic characteristics of lesions on imaging can serve as noninvasive biomarkers of IO response and have utility for improving patient stratification in both neoadjuvant and palliative settings [42]. Major pathologic remission (MPR; residual tumor <10%) is a promising clinical endpoint for prognostic analysis in lung cancer patients receiving PD-1 blockade before surgery. However, current biomarkers for predicting MPR, such as PD-L1 and tumor mutation burden (TMB), require invasive techniques. Radiomics and AI are practical tools for non-invasive, data-driven analysis of tumor structures during follow-up. The optimized model can predict MPR with cross-validation AUC = 0.91. This model can be a promising tool for predicting the response to PD-1 blockade lesions [44]. In clinical decision-making, it is important to identify patients with stage IV NSCLC who may benefit from TKIs and ICIs. EfficientNetV2-based survival benefit prognosis (ESBP) was developed through CT images before therapy, ESBP was able to provide positive prediction rates of 80.4%, 75.4%, and 77.43%/ A high ESBP score (>0/2) indicating a better prognosis for progression-free survival (hazard ratio: 0.36, 95% CI: 0.19-0.68, p<0.0001) in patients with external datasets. Assistance from ESBP improved the diagnostic accuracy of clinicians with 2 years of experience from 47.91% to 66.32% and those with 5 years of experience from 53.12% to 61.41% [45].

Tumor-infiltrating lymphocytes (TILs) in the TME are biomarkers that can be used to guide ICI in NSCLC patients. AI powered by hematoxylin and eosin (H&E) analysis of TILs through images and their analysis related to quantitative features of radiomic features (RFs), with a total of 220 NSCLC samples in the training cohort with

two features, gray level variance (coefficient 1.71 x 10-3) and large gray area (coefficient-2.48 x 10-5). In the validation cohort, patients with high predicted TIL (>median) had significantly longer cancer-free progression than those with low predicted TIL (median 4.0 months [95% CI 2.2-5.7] versus 2.1 months [95% CI 1.6-3.1], p = 0.002). Patients who experienced ICI response had higher predicted TILs, indicating that predicted TILs were significantly associated with cancer-free progression regardless of PD-L1 status [46]. In addition, F-FDG-PET-CT (PET-CT) radiomic features (RFs) for CKI in lung cancer patients were tested in 44 NSCLC patients, in terms of cancer-free progression analysis, patients with low PET-Skewness (threshold < 0.2014; hazard ratio (HR) 0.17, 95% CI 0.06-0.46; p < 0.001) and high values of PET-Median (threshold > 0.5233; HR 0.23, 95% CI 0.11-0.49; p < 0.001) had a significantly lower probability of cancer progression or death. The use of this radiomics-based model can help predict the response of NSCLC patients given CKIs as first-line [47]. A cohort-trained neural network model to examine the efficacy and outcomes of immunotherapy in lung carcinoma based on clinical information with primary outcomes of disease control rate (DCR), objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). From a total of 289 patients, DCR had an AUC = 0.9526 (95%CI, 0.9088-0.9879) in internal validation and 0.9491 95%CI, 0.8704 1.0000) in external validation. ORR had an AUC of 0.8030 (95% CI, 0.7437-0.8545) for internal validity and 0.7040 (95% CI, 0.5457-0.8379) for external validity. PFS had an AUC of 0.8531 (95% CI, 0.8024-0.8975) for internal validity and 0.7602 (95% CI, 0.6236-0.8733) for external validity. OS had an AUC of 0.8006 (95% CI, 0.7995-0.8017) for internal validity and 0.7382 (95% CI, 0.7366-0.7398) for external validity. This neural network model shows the advantages of efficacy evaluation in immunotherapy patients, especially in DCR and ORR models [48]. Finally, localization analysis of immune checkpoints in NSCLC can be performed using EfficientUnet applied to tumor cell segments (TCs) and TILs, while ResNet is used for feature extraction from IHC images. Features of galectin-9, OX40, KIR2D, and KIR3D contributed to OS and RFS in the internal cohort, and IC score and Res-Score served as predictive models. Integrated scores were obtained with AUC 0.9 and 0.85, and Res-Score with external validity AUC = 0.80-0.87 for OS and 0.83-0.94 for RFS [49]. Table 3 lists studies related to the immunotherapy sector.

Despite the promising findings summarized in this review, several limitations should be acknowledged. First, the literature search was conducted using only the PubMed database, which may have resulted in the omission of relevant studies indexed in other databases. Second, only English-language publications from the last 10 years were included, potentially introducing language and publication time bias. Third, the included studies were heterogeneous in terms of study design, AI models, biomarkers, and clinical outcomes, which precluded direct quantitative comparison. Despite these limitations, this review provides a comprehensive synthesis of current evidence regarding the integration of artificial intelligence, liquid biopsy, and immunotherapy in lung cancer management and highlights potential directions for future research

CONCLUSION

This review demonstrates that current evidence supports the complementary integration of artificial intelligence, liquid biopsy, and immunotherapy to improve early detection, biomarker identification, treatment.

REFERENCES

[1] F. Bray *et al.*, “Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for

36 cancers in 185 countries," *CA Cancer J Clin*, vol. 74, no. 3, pp. 229–263, 2024, doi: 10.3322/caac.21834.

[2] L. P. Wulandari, R. W. Triningsih, and H. R. Aryani, "Risk Factors For Breast Cancer Incidence In The Malang City Hospital Area," *Indonesian Journal for Health Sciences*, vol. 9, no. 2, pp. 79–89, Sep. 2025, doi: 10.24269/ijhs.v9i2.11651.

[3] W. Qi, L. Tian, J. Xu, Z. Li, and T. Wang, "Multimodal Framework in Lung Cancer Management: Integrating Liquid Biopsy with Traditional Diagnostic Techniques," *Cancer Manag Res*, vol. 17, pp. 461–481, Mar. 2025, doi: 10.2147/CMAR.S506630.

[4] K. L. Reckamp *et al.*, "A Highly Sensitive and Quantitative Test Platform for Detection of NSCLC *EGFR* Mutations in Urine and Plasma," *Journal of Thoracic Oncology*, vol. 11, no. 10, pp. 1690–1700, Oct. 2016, doi: 10.1016/j.jtho.2016.05.035.

[5] H. Zhang *et al.*, "The application of artificial intelligence in lung cancer: a narrative review," *Transl Cancer Res*, vol. 10, no. 5, pp. 2478–2487, May 2021, doi: 10.21037/tcr-20-3398.

[6] O. Kalchiem-Dekel *et al.*, "Shape-Sensing Robotic-Assisted Bronchoscopy in the Diagnosis of Pulmonary Parenchymal Lesions," *Chest*, vol. 161, no. 2, pp. 572–582, Feb. 2022, doi: 10.1016/j.chest.2021.07.2169.

[7] N. Ozcelik, A. E. Ozcelik, Y. Bulbul, F. Oztuna, and T. Ozlu, "Can artificial intelligence distinguish between malignant and benign mediastinal lymph nodes using sonographic features on EBUS images?," *Curr Med Res Opin*, vol. 36, no. 12, pp. 2019–2024, Dec. 2020, doi: 10.1080/03007995.2020.1837763.

[8] N. Coudray *et al.*, "Classification and mutation prediction from non-small cell lung cancer histopathology images using deep learning," *Nat Med*, vol. 24, no. 10, pp. 1559–1567, Oct. 2018, doi: 10.1038/s41591-018-0177-5.

[9] H. Mamdani, S. Matosevic, A. B. Khalid, G. Durm, and S. I. Jalal, "Immunotherapy in Lung Cancer: Current Landscape and Future Directions," *Front Immunol*, vol. 13, p. 823618, 2022, doi: 10.3389/fimmu.2022.823618.

[10] M. Tonneau *et al.*, "Generalization optimizing machine learning to improve CT scan radiomics and assess immune checkpoint inhibitors' response in non-small cell lung cancer: a multicenter cohort study," *Front. Oncol.*, vol. 13, Jul. 2023, doi: 10.3389/fonc.2023.1196414.

[11] A. Prelaj *et al.*, "Machine Learning Using Real-World and Translational Data to Improve Treatment Selection for NSCLC Patients Treated with Immunotherapy," *Cancers (Basel)*, vol. 14, no. 2, p. 435, Jan. 2022, doi: 10.3390/cancers14020435.

[12] L. Sha *et al.*, "Multi-Field-of-View Deep Learning Model Predicts Nonsmall Cell Lung Cancer Programmed Death-Ligand 1 Status from Whole-Slide Hematoxylin and Eosin Images," *J Pathol Inform*, vol. 10, p. 24, 2019, doi: 10.4103/jpi.jpi_24_19.

[13] J. M. Uthoff *et al.*, "Computed Tomography Features of Lung Structure Have Utility for Differentiating Malignant and Benign Pulmonary Nodules," *Chronic Obstr Pulm Dis*, vol. 9, no. 2, pp. 154–164, Apr. 2022, doi: 10.15326/jcopdf.2021.0271.

[14] R. Yang, X. Xiong, H. Wang, and W. Li, "Explainable Machine Learning Model to Prediction EGFR Mutation in Lung Cancer," *Front. Oncol.*, vol. 12, Jun. 2022, doi: 10.3389/fonc.2022.924144.

[15] M. Ye *et al.*, "A Classifier for Improving Early Lung Cancer Diagnosis Incorporating Artificial Intelligence and Liquid Biopsy,"

Front. Oncol., vol. 12, Mar. 2022, doi: 10.3389/fonc.2022.853801.

[16] A. Daneshkhah *et al.*, "Early detection of lung cancer using artificial intelligence-enhanced optical nanosensing of chromatin alterations in field carcinogenesis," *Sci Rep*, vol. 13, no. 1, p. 13702, Aug. 2023, doi: 10.1038/s41598-023-40550-6.

[17] D. Liu *et al.*, "Predictive value of a novel Asian lung cancer screening nomogram based on artificial intelligence and epidemiological characteristics," *Thorac Cancer*, vol. 12, no. 23, pp. 3130–3140, Dec. 2021, doi: 10.1111/1759-7714.14140.

[18] M.-P. Gauthier *et al.*, "Automating Access to Real-World Evidence," *JTO Clinical and Research Reports*, vol. 3, no. 6, Jun. 2022, doi: 10.1016/j.jtocrr.2022.100340.

[19] F. Lococo *et al.*, "Lung cancer multi-omics digital human avatars for integrating precision medicine into clinical practice: the LANTERN study," *BMC Cancer*, vol. 23, no. 1, p. 540, Jun. 2023, doi: 10.1186/s12885-023-10997-x.

[20] M. Al-Jabbar, M. Alshahrani, E. M. Senan, and I. A. Ahmed, "Histopathological Analysis for Detecting Lung and Colon Cancer Malignancies Using Hybrid Systems with Fused Features," *Bioengineering (Basel)*, vol. 10, no. 3, p. 383, Mar. 2023, doi: 10.3390/bioengineering10030383.

[21] F. Kanavati *et al.*, "Weakly-supervised learning for lung carcinoma classification using deep learning," *Sci Rep*, vol. 10, p. 9297, Jun. 2020, doi: 10.1038/s41598-020-66333-x.

[22] L. Cao *et al.*, "E2EFP-MIL: End-to-end and high-generalizability weakly supervised deep convolutional network for lung cancer classification from whole slide image," *Med Image Anal*, vol. 88, p. 102837, Aug. 2023, doi: 10.1016/j.media.2023.102837.

[23] T. Sakamoto *et al.*, "A collaborative workflow between pathologists and deep learning for the evaluation of tumour cellularity in lung adenocarcinoma," *Histopathology*, vol. 81, no. 6, pp. 758–769, Dec. 2022, doi: 10.1111/his.14779.

[24] Y. Zhao *et al.*, "Deep learning-based diagnosis of histopathological patterns for invasive non-mucinous lung adenocarcinoma using semantic segmentation," *BMJ Open*, vol. 13, no. 7, p. e069181, Jul. 2023, doi: 10.1136/bmjopen-2022-069181.

[25] M. Sorin *et al.*, "Single-cell spatial landscapes of the lung tumour immune microenvironment," *Nature*, vol. 614, no. 7948, pp. 548–554, Feb. 2023, doi: 10.1038/s41586-022-05672-3.

[26] J. Li *et al.*, "Differential early diagnosis of benign versus malignant lung cancer using systematic pathway flux analysis of peripheral blood leukocytes," *Sci Rep*, vol. 12, no. 1, p. 5070, Mar. 2022, doi: 10.1038/s41598-022-08890-x.

[27] A. Keller *et al.*, "Competitive learning suggests circulating miRNA profiles for cancers decades prior to diagnosis," *RNA Biol*, vol. 17, no. 10, pp. 1416–1426, Oct. 2020, doi: 10.1080/15476286.2020.1771945.

[28] G. Cheng *et al.*, "Artificial Intelligence-Assisted Score Analysis for Predicting the Expression of the Immunotherapy Biomarker PD-L1 in Lung Cancer," *Front. Immunol.*, vol. 13, Jul. 2022, doi: 10.3389/fimmu.2022.893198.

[29] X. Wang *et al.*, "Dual-scale categorization based deep learning to evaluate programmed cell death ligand 1 expression in non-small cell lung cancer," *Medicine (Baltimore)*, vol. 100, no. 20, p. e25994, May 2021, doi: 10.1097/MD.0000000000025994.

[30] L. M. Hondelink *et al.*, "Development and validation of a supervised deep learning algorithm for automated whole-slide programmed death-ligand

1 tumour proportion score assessment in non-small cell lung cancer," *Histopathology*, vol. 80, no. 4, pp. 635–647, Mar. 2022, doi: 10.1111/his.14571.

[31] Z. Huang *et al.*, "A new AI-assisted scoring system for PD-L1 expression in NSCLC," *Computer Methods and Programs in Biomedicine*, vol. 221, p. 106829, Jun. 2022, doi: 10.1016/j.cmpb.2022.106829.

[32] S. Ishii *et al.*, "Machine learning-based gene alteration prediction model for primary lung cancer using cytologic images," *Cancer Cytopathol*, vol. 130, no. 10, pp. 812–823, Oct. 2022, doi: 10.1002/cncy.22609.

[33] A. M. Mahmoud *et al.*, "Machine Learning for Digital Scoring of PRMT6 in Immunohistochemical Labeled Lung Cancer," *Cancers (Basel)*, vol. 15, no. 18, p. 4582, Sep. 2023, doi: 10.3390/cancers15184582.

[34] X. Tan *et al.*, "Predicting EGFR mutation, ALK rearrangement, and uncommon EGFR mutation in NSCLC patients by driverless artificial intelligence: a cohort study," *Respiratory Research*, vol. 23, no. 1, p. 132, May 2022, doi: 10.1186/s12931-022-02053-2.

[35] M. Kirienko *et al.*, "Radiomics and gene expression profile to characterise the disease and predict outcome in patients with lung cancer," *Eur J Nucl Med Mol Imaging*, vol. 48, no. 11, pp. 3643–3655, Oct. 2021, doi: 10.1007/s00259-021-05371-7.

[36] Y. Zhang *et al.*, "The co-mutation of EGFR and tumor-related genes leads to a worse prognosis and a higher level of tumor mutational burden in Chinese non-small cell lung cancer patients," *J Thorac Dis*, vol. 14, no. 1, pp. 185–193, Jan. 2022, doi: 10.21037/jtd-21-1921.

[37] A. Prelaj *et al.*, "The EU-funded I3LUNG Project: Integrative Science, Intelligent Data Platform for Individualized LUNG Cancer Care With Immunotherapy," *Clinical Lung Cancer*, vol. 24, no. 4, pp. 381–387, Jun. 2023, doi: 10.1016/j.cllc.2023.02.005.

[38] A. Prelaj *et al.*, "Real-world data to build explainable trustworthy artificial intelligence models for prediction of immunotherapy efficacy in NSCLC patients," *Front Oncol*, vol. 12, p. 1078822, Jan. 2023, doi: 10.3389/fonc.2022.1078822.

[39] H. Tong *et al.*, "A Machine Learning Model Based on PET/CT Radiomics and Clinical Characteristics Predicts Tumor Immune Profiles in Non-Small Cell Lung Cancer: A Retrospective Multicohort Study," *Front Immunol*, vol. 13, p. 859323, 2022, doi: 10.3389/fimmu.2022.859323.

[40] C. Wang *et al.*, "Predicting EGFR and PD-L1 Status in NSCLC Patients Using Multitask AI System Based on CT Images," *Front Immunol*, vol. 13, p. 813072, 2022, doi: 10.3389/fimmu.2022.813072.

[41] D. Dora *et al.*, "Computed Tomography-Based Quantitative Texture Analysis and Gut Microbial Community Signatures Predict Survival in Non-Small Cell Lung Cancer," *Cancers (Basel)*, vol. 15, no. 20, p. 5091, Oct. 2023, doi: 10.3390/cancers15205091.

[42] S. Trebeschi *et al.*, "Predicting response to cancer immunotherapy using noninvasive radiomic biomarkers," *Ann Oncol*, vol. 30, no. 6, pp. 998–1004, Jun. 2019, doi: 10.1093/annonc/mdz108.

[43] Z. Su, H. Lu, Y. Wu, Z. Li, and L. Duan, "Predicting potential lncRNA biomarkers for lung cancer and neuroblastoma based on an ensemble of a deep neural network and LightGBM," *Front Genet*, vol. 14, p. 1238095, 2023, doi: 10.3389/fgene.2023.1238095.

[44] W. Jin *et al.*, "Non-linear modifications enhance prediction of pathological response to pre-operative

PD-1 blockade in lung cancer: A longitudinal hybrid radiological model," *Pharmacol Res*, vol. 198, p. 106992, Dec. 2023, doi: 10.1016/j.phrs.2023.106992.

[45] K. Deng *et al.*, "A deep learning-based system for survival benefit prediction of tyrosine kinase inhibitors and immune checkpoint inhibitors in stage IV non-small cell lung cancer patients: A multicenter, prognostic study," *EClinicalMedicine*, vol. 51, p. 101541, Sep. 2022, doi: 10.1016/j.eclinm.2022.101541.

[46] C. Park *et al.*, "Tumor-infiltrating lymphocyte enrichment predicted by CT radiomics analysis is associated with clinical outcomes of non-small cell lung cancer patients receiving immune checkpoint inhibitors," *Front. Immunol.*, vol. 13, Jan. 2023, doi: 10.3389/fimmu.2022.1038089.

[47] D. Ventura *et al.*, "Radiomics of Tumor Heterogeneity in 18F-FDG-PET-CT for Predicting Response to Immune Checkpoint Inhibition in Therapy-Naïve Patients with Advanced Non-Small-Cell Lung Cancer," *Cancers (Basel)*, vol. 15, no. 8, p. 2297, Apr. 2023, doi: 10.3390/cancers15082297.

[48] S. Li *et al.*, "Assessing the efficacy of immunotherapy in lung squamous carcinoma using artificial intelligence neural network," *Front. Immunol.*, vol. 13, Nov. 2022, doi: 10.3389/fimmu.2022.1024707.

[49] H. Guo *et al.*, "Artificial intelligence-based analysis for immunohistochemistry staining of immune checkpoints to predict resected non-small cell lung cancer survival and relapse," *Transl Lung Cancer Res*, vol. 10, no. 6, pp. 2452–2474, Jun. 2021, doi: 10.21037/tlcr-21-96.