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Review

Artificial intelligence in clinical trials of lung cancer: Current and future prospects

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ABSTRACT

Lung cancer remains a leading cause of mortality globally, with particularly high incidence rates in China. This review investigates the pivotal role of artificial intelligence (AI) in the clinical trials of lung cancer drugs, aiming to address the challenges of drug development and clinical research processes. The objective is to explore how AI technologies, including machine learning and deep learning, enhance clinical trials' efficiency, accuracy, and personalization in this context. Our methodology involved a comprehensive literature search and analysis, focusing on integrating AI into various stages of clinical trials, namely, preclinical drug discovery, trial design, participant recruitment, and data analysis. The results indicate that AI demonstrates proficiency in integrating and analyzing extensive datasets, facilitating the identification of novel drug targets, and repurposing existing drugs. This capability enhances insights crucial for drug development, optimizes trial designs, streamlines participant recruitment, and conducts precise data analyses of trial outcomes. In conclusion, this review highlights the transformative potential of AI in lung cancer clinical trials and emphasizes the need for high-quality data collection and interpretability improvement to realize its benefits fully. Future research could focus on integrating multimodal approaches and multi-omics data into the entire process of clinical trials on lung cancer drugs to improve patient treatment outcomes and alleviate the global burden of lung cancer.

1. Introduction

Cancer incidence and mortality rates are increasing globally, with lung cancer currently holding the highest incidence among cancers. Due to its high mortality rate, lung cancer ranks as the leading cause of cancer-related deaths worldwide.[1] It is estimated that in 2024, the most common cause of cancer deaths in the United States will be lung cancer.[2] In China, lung cancer is both the most frequently diagnosed and deadliest of all tumors.[3] Lung cancer originates from respiratory epithelial cells and is primarily classified into two histological types: non-small cell lung cancer (NSCLC), which constitutes 80–85 % of cases, and small cell lung cancer (SCLC), comprising 10–15 % of cases.[4] According to the 2021 WHO classification of lung cancer,[5] common types include

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adenocarcinoma, squamous cell carcinoma, and neuroendocrine tumors. Key risk factors include smoking, environmental pollutants, and genetic predispositions,[6] which significantly contribute to lung cancer development.

Treatment strategies and overall survival (OS) rates vary widely among different histological types of lung cancer. NSCLC, characterized by biological heterogeneity, can be effectively treated with targeted therapies, resulting in a five-year survival rate of approximately 18 % across all stages. In contrast, the aggressive nature of SCLC necessitates primary treatment with platinum-based chemotherapy, yielding a five-year survival rate of about 6 % for both limited and extensive stages.[7] The high cost of treating both NSCLC and SCLC imposes substantial financial burdens on patients and society, underscoring lung cancer's significant public health impact and the impediment it represents to human progress and socioeconomic development.[3]

In the era of precision medicine, personalized treatment strategies have shown efficacy in combating lung cancer. Extensive evidence indicates that genomic alterations often underlie cancer, providing a basis for genomic and immunotherapeutic approaches. However, these alterations vary among individuals, necessitating tailored treatment plans.[8] Developing novel targeted drugs forms the cornerstone of personalized therapy.[9] Traditional lung cancer drug development typically follows a phased clinical trial design, including Phase I, II, and III trials, where patients are assigned to different treatment groups through randomized controlled trials (RCTs). Phase I primarily evaluates the drug's safety and optimal dosage, Phase II focuses on the drug's efficacy, and Phase III involves large-scale trials comparing the new drug with standard treatments. These trials often use OS and progression-free survival as primary endpoints, with strict patient selection criteria to ensure data reliability. Despite the scientific rigor of this approach, several limitations exist. First, clinical trials are lengthy and expensive. Second, strict patient inclusion criteria limit the generalizability of the results. Although innovative designs such as basket and umbrella trials can improve trial efficiency,[10] the development process for a new drug from discovery to market approval typically requires over a decade and costs more than $1 billion. This complex process, along with the high costs and uncertainties, challenges traditional drug development. Furthermore, focusing solely on the efficacy of a single aspect while neglecting potential treatments for other diseases is a limitation of conventional methods. Addressing the challenges posed by lung cancer and other cancers requires novel technologies to aid in drug development and clinical research and predict the efficacy of existing lung cancer drugs, thereby reducing development costs and increasing productivity.

Artificial intelligence (AI), encompassing technologies such as machine learning (ML), deep learning, and natural language processing (NLP), aims to simulate, extend, and enhance human intelligence by constructing theoretical frameworks, developing methodologies, innovating technical tools, and designing application systems.[11] One key application of AI is creating mathematical models that establish connections among diverse types of information. AI can expedite problem detection, improve diagnostic accuracy, and provide personalized treatment plans in healthcare. Core AI technologies, including algorithm optimization and logical reasoning, play integral roles throughout drug development. Compared to traditional drug discovery methods, AI strengthens efficiency in predicting compound bioactivity,[12] ensuring high-standard analysis and significantly reducing economic and time investments in research and development. This technology offers a swift and effective pathway for new drug creation. AI not only assists in efficiently processing large datasets, such as patient radiomics and clinical data, but also plays a critical role in addressing the complexities of lung cancer, which has various subtypes and highly intricate genomic profiles. Over the past two decades, treatments have become increasingly sophisticated, with continual advancements in targeted immunotherapies.[13] Even subtle differences among patients can lead to marked variations in gene mutations and treatment response.[14] The application of AI facilitates the identification of these nuanced distinctions and aids in developing treatment plans. Additionally, with numerous clinical studies on lung cancer underway, leveraging AI's efficiency in problem identification and resolution within clinical research, such as target prediction in multi-target umbrella studies and Bayesian designs in multi-stage clinical trial designs, can further promote the development of lung cancer drugs.[10] AI can also support cancer vaccine development and protein antigen-based drug design while addressing challenges in clinical trials for rare mutations and optimizing strategy formulation.[15] As lung cancer remains a global concern, its management and research increasingly demand a shift from regional to global collaboration. The effective application of AI can facilitate better categorization and management of lung cancer clinical trials, increasing trial diversity and representativeness.

To the best of our knowledge, this is one of the first reviews to summarize the application of AI in lung cancer clinical trials. This review provides a forward-looking perspective on the prospects of AI in lung cancer drug trials, identifying emerging trends and potential breakthroughs that can shape the future of cancer treatment.

The literature search was conducted in October 2024 using PubMed and ScienceDirect databases, focusing on English-language publications. Search terms included "lung cancer," "artificial intelligence," and "clinical trials," and the timeframe encompassed studies from January 2000 to October 2024. The inclusion criteria targeted clinical trials, meta-analyses, RCTs, systematic reviews, case series, and guidelines. Studies such as single case reports were excluded. The study selection process was performed independently by H. Y. Z, Y. H. Z, and P. M. Y, who screened titles and abstracts, followed by a full-text review. Discrepancies were resolved through discussion until a consensus was reached. We synthesized findings qualitatively, focusing on study designs, AI methodologies, and clinical applications specific to lung cancer trials.

This review systematically introduces and explores the application of AI in supporting clinical research for lung cancer drugs, focusing on preclinical drug discovery, clinical trial design, and participant recruitment. We also discuss the handling of missing data and multimodal data analysis (Figure 1). Finally, we offer insights into the future directions and potential advancements of AI in lung cancer drug trials. We have summarized the key literature in Table 1.

2. Preclinical drug discovery

The application of AI in drug development, particularly in the preclinical research of lung cancer drugs, demonstrates great potential and prospects. By emulating human intelligence, AI reduces the human and material resources required for drug discovery and development, lowering costs and increasing efficiency. The application of AI in the preclinical development of lung cancer drugs is illustrated in Figure 2.

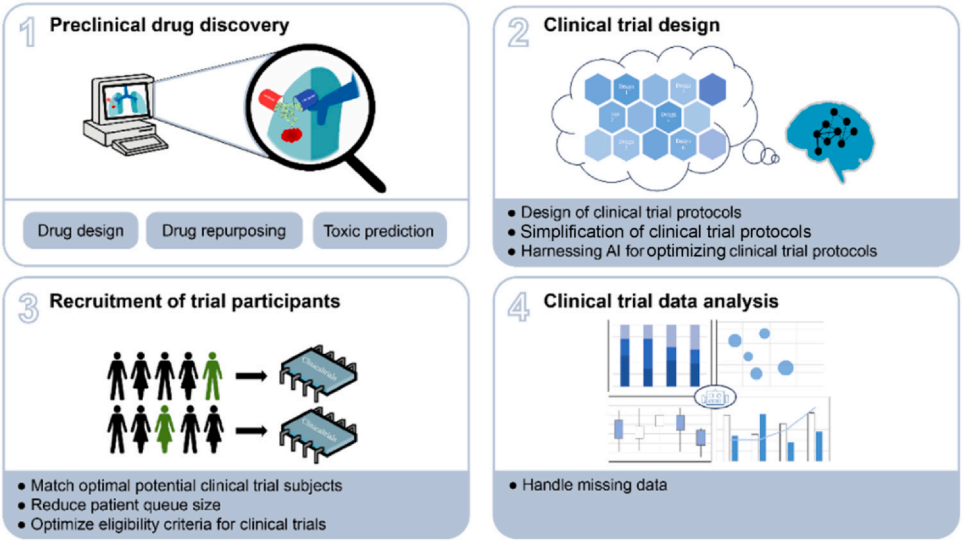


Fig. 1. Main roles of AI-Assisted lung cancer drug clinical trials.

2.1. Drug design

Traditional drug discovery methods, also known as forward pharmacology, rely on the repeated testing of various compounds in cultured cells or animal models to identify candidate drugs by matching compound structures with their pharmacological activities (structure–activity relationship). Ideally, candidate drug compounds should also meet "ADME-related drug-likeness" criteria, which include oral bioavailability, chemical stability, metabolic stability, and sufficiently low toxicity. However, drug design is associated with a high failure rate, particularly during the clinical development stages, especially in Phase II clinical trials.[55] The process from new drug development to market launch is complex and often takes 12–15 years and costs over $1 billion.[56] AI-designed precision-engineered drugs have advanced to Phase I clinical trials for treating obsessive-compulsive disorder patients. This project progressed from target identification to candidate drug selection in less than 12 months, a significant reduction compared to the average four to five years required using traditional development methods.

The application of AI in drug design for lung cancer is revolutionizing traditional paradigms. Advanced AI models leverage immense computational power and sophisticated analytical techniques to predict drug targets, protein–ligand interactions, PPIs, and toxicological properties with unprecedented speed and accuracy. Through ML and deep learning, AI can analyze extensive biological datasets and chemical information, providing researchers with innovative approaches and methodologies in drug design.

2.1.1. Identification of drug target

The computational drug discovery process typically begins with the identification and evaluation of drug targets followed by the search for suitable candidate compounds. The primary goals are to identify target proteins implicated in the pathophysiology of disease and establish a coherent research framework. Thus, target selection is crucial in understanding disease mechanisms. In oncology research, however, experimental target identification is both labor-intensive and resource-draining. Drug target identification is pivotal in early-stage drug development, as selecting precise targets impacts a drug's progression into clinical phases and trial success. AI can be used to streamline the growing amount of histology data to identify previously unknown gene pathways and drug targets.

Target deconvolution is a vital initial step in preclinical drug development to determine research focus and strategy.[57] In this respect, computational target prediction is used to identify the most probable targets of an orphan ligand or the most similar targets to a protein under investigation. However, due to the heterogeneity of lung cancer as well as limitations such as drug tolerance and a small range of applications, single-target drugs have limited success. He et al. utilized AI to expedite drug development with CODE-AE, predicting therapeutic targets in squamous cell lung cancer and streamlining treatment selection processes.[16]

ML models such as Kronecker regularized least squares (KronRLS) and SimBoost are employed for predicting drug-small molecule binding affinities, providing valuable insights for aptamer affinity prediction. KronRLS addresses the complexity of drug-target prediction realistically, surpassing simpler clustering methods in practical applications.[58] Hakami et al. recently utilized AI-driven molecular docking rather than ML to screen a drug library against key lung cancer proteins such as heat shock protein 5 (BIP/GRP78) ATPase.[17] Their findings identify 3–1-BenCarMethInYlPro-Phosphonic Acid as a promising multi-target candidate that demonstrates strong binding affinities supported by hydrogen bonds and other interactions. This approach highlights the compound's potential to inhibit lung cancer-related proteins effectively.

Another team used AI to predict neoantigens generated by post-transcriptional regulation to provide an untapped library of common immunogenic targets for targeted therapies.[18] To comprehensively define tumor-specific and potentially immunogenic

Table 1
Published applications of AI in lung cancer clinical trials.

Authors	Application Stage	AI Technology and Statistical Methods	Data Modality
He et al.[16]	Identifying drug targets	Pre-trained and fine-tuned CODE-AE.	Cancer cell line and patient tissue gene expression data
Hakami et al.[17]	Identifying drug targets	Molecular docking using HTVS, SP, XP, MM/GBSA, and QM-DFT	Drug Bank compounds and lung cancer-related protein structures
Li et al.[18]	Identifying drug targets	Workflow for splicing quantification and neoantigen prediction	RNA-Seq data from cancer patients and healthy tissues
Xuan et al.[19]	Identifying drug targets	GCNLDA using graph and convolutional neural networks	lncRNA-disease-miRNA association data
Aamri et al.[20]	Identifying drug targets	Co-occurrence network construction for rare-event classification	PubMed abstracts and OMIM data
Chen et al.[21]	Identifying drug targets	PPI network construction and topological analysis	Proteomics data of prostate cancer
Choi et al.[22]	Identifying drug targets	Transfer learning using a recurrent neural network based on long short-term memory (LSTM) networks	ChEMBL for ligand selection, PDBbind for binding data
Dhakal et al.[23]	Identifying drug targets	ML methods review for protein–ligand interaction prediction	Multiple databases for training and validation
Ashtawy et al.[24]	Identifying drug targets	ML regression techniques for scoring functions	PDBbind for complex data and feature extraction
Wang et al.[25]	Identifying drug targets	A3C-based reinforced learning for docking	PDBbind for protein-ligand complex data
Chen et al.[26]	PPI	SAM for data analysis, PPI network with shortest path search, permutation test, and centrality measures	TCGA data for gene expression, miRNA, methylation and mutation
Mayr et al.[27]	Prediction of toxicity	DeepTox pipeline with DNNs, multi-task learning, and dropout techniques	Tox21 dataset (12,000 compounds, 12 toxicity assays)
Hu et al.[28]	Prediction of toxicity	ML, deep learning (Chemprop with D-MPNN), and transfer learning	Human organ-level toxicity, acute toxicity, and in-vitro toxicity data
Xu et al.[29]	Prediction of toxicity	Deep learning with UG-RNN for molecular encoding	Four datasets including FDA-related and Liew's data
Ivanov et al.[30]	Prediction of toxicity	ML using molecular fingerprints and descriptors	FDA-approved chemicals and LTKB DILI cases
Mohanan et al.[31]	Drug repurposing	Structure-based approach with MEP for docking	EGFR structure, FDA drugs
Li et al.[32]	Drug repurposing	DNN for classification and similarity comparison	LINCS data, KEGG pathways
Thirunavukkarasu et.al[33]	Drug repurposing	MLSF.	DrugBank data
Zhao et al.[34]	Design of clinical trial protocols	Q-learning (ML method) for censored data handling	Simulated data on patient disease and treatment
Bajard et al.[35]	Design of clinical trial protocols	Computer simulations with various models for trial design	Virtual patient data with diverse parameters
Liu et al.[36]	Design of clinical trial protocols	Trial Pathfinder using real-world EHR data	EHR data of NSCLC patients
Huang et al.[37]	Design of clinical trial protocols	Multi-stakeholder recruitment planning methods	From multiple sources
Trebeschi et al.[38]	Optimizing clinical trial protocols	Employed ML to develop biomarkers from radiomic features in pretreatment contrast-enhanced CT images	Pretreatment contrast-enhanced CT
Wu et al.[39]	Optimizing clinical trial protocols	AI-based extraction of 51 radiomic features from tumor and peritumor volumes on pretreatment CT images	Pretreatment CT
Chaunzwa et al.[40]	Optimizing clinical trial protocols	Implemented an AI-assisted workflow consisting of two deep-learning models	Baseline and follow-up CT
Zhao et al.[41]	Optimizing clinical trial protocols	AI-based extraction of radiomic features from ROI on pretreatment chest CT images	Pretreatment chest CT
Park et al.[42]	Optimizing clinical trial protocols	Deep learning-based whole-slide image analyzer	H&E-stained WSI and immunohistochemistry (IHC) for PD-L1
Jiang et al.[43]	Optimizing clinical trial protocols	Designed a multi-task deep convolutional neural network model	Diagnostic CT images and IHC data for TME biomarkers
Whitty et al.[44a]	Recruitment of participants	Mendel.ai uses NLP and text recognition for medical records and clinical reasoning	Oncology patient clinical data (structured and unstructured)
Alexander et al.[45]	Recruitment of participants	NLP and ML for unstructured data processing and patient–trial matching benchmarked against clinician consensus	Clinical data of 102 lung cancer patients and 10 trial eligibility criteria
Armeni et al.[46]	Recruitment of participants	Generative AI for DTs development and natural history prediction	Patient characteristics, clinical variables, and prognosis data
Lee et al.[47]	Recruitment of participants		Drug concentration, tumor volume change, and patient TTP data

(*continued on next page*)

Table 1 (*continued*)

Authors	Application Stage	AI Technology and Statistical Methods	Data Modality
		ISELA-V2: Combines biological and clinical data from multiple sources for training and validation	
Darré et al.[48]	Recruitment of participants	ISELA-V2: Data integration for drug effect prediction	Drug pharmacokinetics and mechanism of action data
Kim et al.[49]	Recruitment of participants	Eligibility criteria evaluation for oncology trials via literature review, polling, and auditing	ClinicalTrials.gov and industry-sponsored trial data
Liu et al.[50]	Recruitment of participants	Trial Pathfinder: Real-world data and propensity score weighting for eligibility criteria evaluation	EHR data from 61,094 aNSCLC patients (structured and unstructured)
Li et al.[51]	Reanalysis of missing data	Evaluation of eight methods, including KNN and RF	Queue research datasets
Caruso et al.[52]	Outcome assessment	Based on Transformer architecture and related methods	NSCLC clinical data
Austin et al.[53]	Reanalysis of missing data	Introduced MI techniques	Patient hospitalization data for heart failure
Baron et al.[54]	Outcome assessment	Developed an AI-based "meta-model"	EHR data

[a] **Abbreviations**: 1. CODE-AE: context-aware deconfounding autoencoder 2. HTVS: high throughput virtual screening 3. SP: standard precision 4. XP: extra precision 5. MM/GBSA: molecular mechanics with generalized Born and surface area solvation 6. QM-DFT: quantum mechanics-density functional theory 7. GCNLDA: graph convolution and convolution neural network 8. OMIM: Online Mendelian Inheritance in Man 9. PPI: protein–protein interaction 10. PC: prostate cancer 11. SAM: significance analysis of microarrays 12. TCGA: The Cancer Genome Atlas 13. DNNs: deep neural networks 14. D-MPNN: directed message passing neural network 15. UG-RNN: undirected graph recursive neural networks 16. LTKB: liver toxicity knowledge base 17. DILI: drug-induced liver injury 18. MEP: molecular electrostatic potential 19. EGFR: epidermal growth factor receptor 20. LINCS: Library of Integrated Network-Based Cellular Signatures 21. KEGG: Kyoto Encyclopedia of Gene Genomics 22. MLSF: machine-learning-based scoring functions 23. EHR: electronic health record 24. ROI: regions of interest 25. WSI: whole slide imaging 26. PD-L1: programmed death-ligand 1 27. TME: tumor microenvironment 28. DTs: digital twins 29. aNSCLC: advanced non-small cell lung cancer 30. KNN: K-nearest neighbor 31. RF: random forest 32. MI: multiple imputation

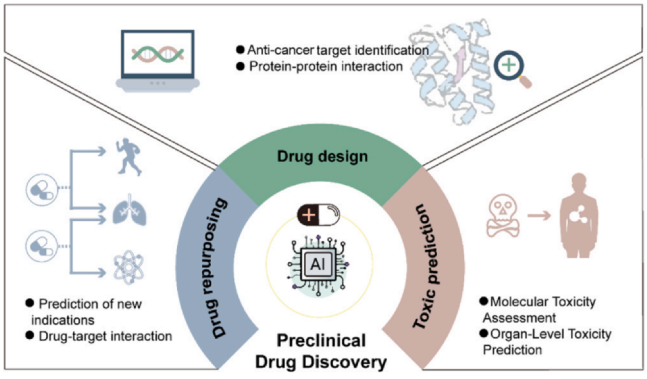


Fig. 2. Applications of AI in the preclinical discovery of lung cancer drugs.

neoantigens from patient RNA-Seq, the team developed the Splice Neoantigen Finder, an easy-to-use, open-source computational workflow for predicting splicing-derived MHC-binding peptides that are immunogenic (T-cell antigens) and unannotated transmembrane proteins with altered extracellular epitopes (B-cell antigens) and revealing potential common therapeutic targets for heterogeneous cancers.

Moreover, Xuan et al. introduced the GCNLDA method, which notably improved the linkage between targets and tumors, thus aiding in drug development.[19] By leveraging the strengths of graph convolutional networks and convolutional neural networks, GCNLDA effectively integrated diverse biological data. In studies of diseases such as gastric cancer, osteosarcoma, and lung cancer, in particular, this approach successfully identified potential associations between long non-coding RNAs and diseases.

In addition, many researchers employ module detection algorithms to identify potential therapeutic targets intelligently. Aamri et al. constructed a gene–gene interaction network of the entire human genome, then ranked central genes in the network using centrality measures such as betweenness, closeness, eigenvector, and degree centrality[20] to evaluate and identify the top 15 candidate cancer-related genes across different cancer types (prostate, breast, and lung cancers). The results indicated that the average precision in identifying breast, prostate, and lung cancer genes is in the range of 80–100 %. These findings demonstrated the system's potential to enhance the accuracy of predicting gene–gene interactions and disease–gene associations, thereby facilitating the development of predictive drug targets. Chen et al. constructed a PPI network based on differentially expressed proteins in prostate cancer, ultimately identifying SLC2A4 and TUB2C as crucial proteins regulating cancer pathogenesis.[21] They suggested that proteins involved in biological processes and pathways represent potential targets for diagnosing and treating prostate cancer.

These findings provide valuable leads and theoretical foundations for developing targeted therapeutics, promising significant contributions to future drug development. To accurately identify anticancer targets, single-omics studies are insufficient. Instead, integrating multi-omics data—encompassing epigenetics, genomics, proteomics, and metabolomics—using AI biological analysis is essential.[59] This approach addresses the intricate interactions between genes and their products that underpin cancer complexity and enhances our understanding of carcinogenesis. In the future, research must focus on refining AI algorithms to effectively integrate multi-omics data, aiming to uncover novel anticancer targets. This strategic direction promises to advance oncological research significantly.

2.1.2. Prediction of protein–ligand interactions

The potential exists to enhance the exploration and development of highly precise ML-based prediction strategies to investigate protein–ligand interactions. In response to the well-documented resistance posed by EGFR mutations (L858R/T790M/C797S) in NSCLC, Choi et al. concentrated on the development of next-generation EGFR tyrosine kinase inhibitors (TKIs).[22] This study used AI to extract 139 TKI-related ligands from 1.96 million compounds in ChEMBL. A deep learning model based on LSTM generated 10,316 TKI-like SMILES sequences. After rigorous filtering, 6,283 drug-like ligands showed an affinity for EGFR mutations (L858R/T790M/C797S), with scaffold analysis and affinity predictions using DeepDTA to validate their potential. Further evaluations identified 360 promising candidate ligands suitable for potential advancement in NSCLC therapy.

Recently, data-driven ML has diverged from classical virtual screening approaches. Many research teams now integrate traditionally separate tasks—predicting binding site, binding affinity, and binding pose—into unified deep learning systems using multitask learning.[23] Ashtawy and Mahapatra employed various ML approaches to estimate root mean square deviation, aiming to select the optimal ligand pose within a protein's binding site.[24]

Moreover, powerful deep learning methods have spurred the development of more accurate scoring functions. Wang and colleagues introduced a reinforcement learning-based approach to predicting ligand pose scores.[25] In this method, an agent optimized ligand poses and could be trained to identify binding sites, leveraging atomic, spatial, and molecular features to achieve optimized poses in target protein binding sites adopted.

2.1.3. PPI

In predicting PPIs, network-based biological analysis algorithms were utilized to identify therapeutic targets for cancer treatment and discover new drugs.[60]

Chen et al. developed a computational approach to identify potential novel lung cancer driver genes.[26] Using the network-based biological analysis method SAM, they analyzed multi-omics data and identified 153 differentially methylated CpG sites and differentially expressed molecules. Initially, the authors constructed a PPI network of differentially expressed genes using the STRING database. They then explored all the shortest paths connecting functionally dysregulated genes to determine potential cancer driver genes. Subsequently, genes were ranked using permutation tests and their network properties. The analysis suggests that some identified genes may drive lung adenocarcinoma at multiple differentiation levels.

2.2. Prediction of toxicity

Testing the toxicity of drug molecules is crucial for developing anticancer drugs. Conventionally, this involves initial studies through in-vitro cell tests followed by animal experiments to assess toxicity.[61] However, these conventional methods are time-consuming and costly and raise additional safety and ethical concerns. Clinical trial analysis has revealed that 30 % of drug development failures stem from uncontrollable toxicity.[62] Causal ML offers flexible, data-driven methods for predicting treatment outcomes, including efficacy and toxicity, thereby supporting the assessment and safety of drugs.[63] In this context, computational toxicity prediction proves beneficial during initial drug discovery phases, helping to screen out molecules with a high likelihood of clinical trial failure.

AI approaches typically predict potential toxicity by comparing the EGFR similarity of drug molecules or inputting specific characteristics of the molecules. Mayr et al. utilized deep learning techniques to develop a predictive model named DeepTox, which effectively forecast the toxicity of drug molecules by identifying their static and dynamic molecular properties, such as relative molecular mass and van der Waals forces.[27] This advancement allowed for efficient toxicity prediction in drug development. Hu et al. developed comprehensive computational prediction models using ML, deep learning, and transfer learning algorithms for eight critical human organ-level toxicity endpoints.[28] The results demonstrated that the deep learning-based D-MPNN method outperformed traditional ML models, showing robust performance across most human organ-level toxicity endpoints evaluated in the study. This model thus provided valuable guidance for rapidly identifying compounds with huMman organ-level toxicity for drug discovery purposes.

Hepatotoxicity is one of the common side effects of targeted therapies for lung cancer. DILI poses a significant challenge in drug development, historically contributing to clinical trial failures and drug recalls.[64] With over 700 drugs implicated in hepatotoxicity, there is a critical need for in-silico models to predict DILI potential early in the drug development process. Lai et al. introduced a deep learning model based on graph recurrent neural networks to predict DILI, achieving high sensitivity and specificity.[29] Ivanov et al. developed binary classification models using ML techniques trained on data from Food and Drug Administration (FDA)-approved chemicals and human DILI cases from the LTKB.[30] They demonstrated that the support vector machine algorithm and Molecular Access System keys provided exceptional predictive accuracy.

In the future, as technology advances and data accumulate, computational methods will continue to play a pivotal role in toxicity prediction. New algorithms and models are anticipated to enhance predictive accuracy further and extend to a broader range of organ

toxicities and adverse reactions. Moreover, interdisciplinary collaboration and data sharing will accelerate the application and dissemination of these technologies, ultimately facilitating a safer and more efficient process for developing anticancer drugs.

2.3. Drug repurposing

Drug repurposing strategies represent a methodology for discovering novel applications for existing medications, with an emphasis on their use in oncology. Such strategies hold significant value in drug development, as they can markedly reduce the costs and timelines associated with developing new pharmaceuticals. Moreover, repurposed drugs have typically undergone extensive safety assessments, mitigating the risks of uncovering unforeseen adverse effects during clinical trials.[65]

Reports indicate that a high-throughput virtual screening campaign targeting the MEK kinase within the RAS-RAF-MEK-ERK signaling pathway of NSCLC was conducted using computer-aided drug design and drug repurposing strategies.[33] Employing the Glide docking, MM/GBSA calculations, and MLSF, lead compounds with high affinity for the MEK receptor were identified from the DrugBank database. The study's findings suggest that these compounds exhibit significant inhibitory effects on MEK and demonstrate favorable binding capabilities with the co-target PIM1. Further stability validation through molecular dynamics simulations has underscored their potential as novel therapeutic agents to combat tumor drug resistance.

Another team introduced an innovative drug repurposing strategy leveraging transcriptomic data and chemical structures through a deep neural network (DNN) model. This approach successfully repositioned pimozide, previously an anti-dyskinesia medication, as a potential anti-NSCLC drug, a claim substantiated by in-vitro experimental evidence. Integrating chemical structures with pathway activation scores in the drug redirection process has been validated as an efficacious method for drug repurposing.[32]

In addition, the overexpression, mutation, or activation of EGFR leads to dysregulation of its downstream signaling pathways, contributing to the development of various cancers, including breast and lung cancers. Identifying EGFR as a critical target for anticancer drug development, Mohanan et al. proposed a novel ML strategy to identify drug molecules capable of potentially binding to and inhibiting EGFR dimerization.[31] They employed a structure-based drug repurposing approach to repurpose existing FDA-approved drugs to block EGFR domain II-mediated dimerization. Through various ML techniques, they identified five optimal repurposed drug molecules that exhibited strong binding affinity to critical arm-pocket dimer interface residues. This technology demonstrated the potential of small molecule inhibitors as future candidates for drug repurposing in anti-EGFR therapy.

In summary, the application of AI in drug repurposing offers new impetus to accelerate the drug development cycle and reduce associated costs. Given the extensive clinical and toxicological information amassed for existing drugs, AI's advanced computational capabilities and ML algorithms can play pivotal roles in exploring new therapeutic uses of drugs and discovering potential drug combinations.

3. Clinical trial design

Clinical trials typically require the use of marketed drugs or placebos as control groups to compare the effects of a drug or other medical treatments on participants. Conventional methods usually involve a series of standardized steps, including defining research objectives, selecting appropriate study designs, calculating sample sizes, implementing randomization and blinding, and collecting and analyzing data.[66] These methods rely on statistical principles and clinical expertise and aim to ensure the scientific validity and reliability of trial results. The application of AI in optimizing clinical trial design offers a new, data-driven approach that can provide more personalized and optimized trial designs than traditional experience- and statistics-based methods. Additionally, AI has the potential to further promote the efficiency and effectiveness of clinical trials by streamlining their planning processes.

3.1. Design of clinical trial protocols

In the clinical trials design phase, ML leverages simulation techniques to experiment with large datasets from previous trials, optimizing the selection of test treatment regimens. For instance, Zhao et al. applied a reinforcement learning approach known as Q-learning in a clinical study targeting aNSCLC patients who had not previously undergone systemic therapy.[34] This method effectively learned from patient data generated through clinical reinforcement trials, successfully identifying personalized optimal strategies tailored to appropriate patient subgroups.

Bajard et al. explored using computer simulations to optimize RCT designs.[35] The study compared designs based on statistical power, treatment effect accuracy, and patient outcomes. Simulated patient groups were randomized across various trial setups, with treatment effects modeled using dose–response relationships. The results show that each design has unique benefits: shorter treatment duration for parallel and early escape, higher power for crossover, and more patients receiving effective treatment for play the winner and drop the loser designs. This approach is coducive to selecting optimal trial designs, patient cohorts, and outcomes, which is particularly useful in developing targeted therapies for rare types of lung cancer and personalized medicine.

Reasonable patient cohort selection and recruiting criteria are further key factors in whether a clinical trial will be successful. For example, 86 % of clinical trials fail to reach recruitment goals within their proposed time frame.[37] To overcome this dilemma, AI models are deployed to evaluate and modify the criteria of clinical trials. Liu et al. applied the computational framework for emulating clinical trials with 61,094 advanced NSCLC patients, revealing that many common criteria, especially laboratory tests, greatly restricted recruitment.[36] While the AI approach relaxes the thresholds of laboratory tests, the pool of eligible patients is doubled with a decreased hazard ratio of OS.

A scoping review of RCTs of AI in clinical practice revealed a growing interest in AI among clinical professionals and institutions.[67] The majority of trials reported positive primary endpoints. Despite these encouraging findings, considering the potential for publication bias, it is crucial to carry out more comprehensive clinical research designs, including multicenter trials and the use of diverse outcome measures, and to improve reporting standards.

3.2. Simplification of clinical trial protocols

Large language models (LLMs), trained on extensive textual data, excel in predicting and generating coherent, contextually relevant text. Through carefully designed prompts and fine-tuning, they demonstrated robust multitask learning and contextual comprehension abilities.[68] Consequently, LLMs can streamline clinical trial planning. By parsing and processing vast amounts of textual data from clinical research, they train comprehensive corpora of clinical trial documents, presenting these files quickly in standardized and normalized formats.

This capability facilitates the efficient handling and presentation of clinical trial documents, significantly advancing toward a more streamlined and standardized approach to trial planning and execution. Beyond trial planning, LLMs can also address the patient–trial matching problem. Jin et al. utilized an LLM to aid physicians in pre-screening patients who met the inclusion criteria for various trials, thereby reducing both the time and financial costs associated with initial screening.[69] Leveraging the significant generative capabilities of LLMs enabled the matching process rationale to be made comprehensible to physicians, facilitating the practical deployment of LLMs in real-world settings.

3.3. Harnessing AI for optimizing clinical trial protocols

The integration of AI into clinical trial design is particularly transformative, enabling better prediction of treatment efficacy, identification of biomarkers, and optimization of patient stratification.[70] AI is now integral to clinical trial design, enabling both the assessment of new therapies and the personalization of treatments based on patient-specific molecular profiles and tumor characteristics. Single-modality approaches (radiomics, genomics, pathology, and clinical data) and multi-temporal, multimodal data fusion offer new possibilities for refining clinical trial design and improving patient screening, treatment stratification, and personalized medicine (Figure 3). AI-driven approaches are fundamentally reshaping the design of clinical trials for lung cancer therapies. AI models can predict which patients are most likely to benefit from specific therapies based on genetic and molecular profiles, improving the precision of patient selection. These AI tools also assist in identifying the most promising biomarkers for response prediction, allowing for more targeted clinical trials that reflect real-world patient heterogeneity.

AI is transforming clinical trial design by enhancing predictions of treatment efficacy. Kureshi et al. developed a system using real-world data to predict responses to EGFR-targeted therapies in aNSCLC.[71] Their approach represented a significant step toward personalized treatment strategies. In the field of radiomics, Sun et al. pioneered an algorithm predicting tumor-infiltrating immune

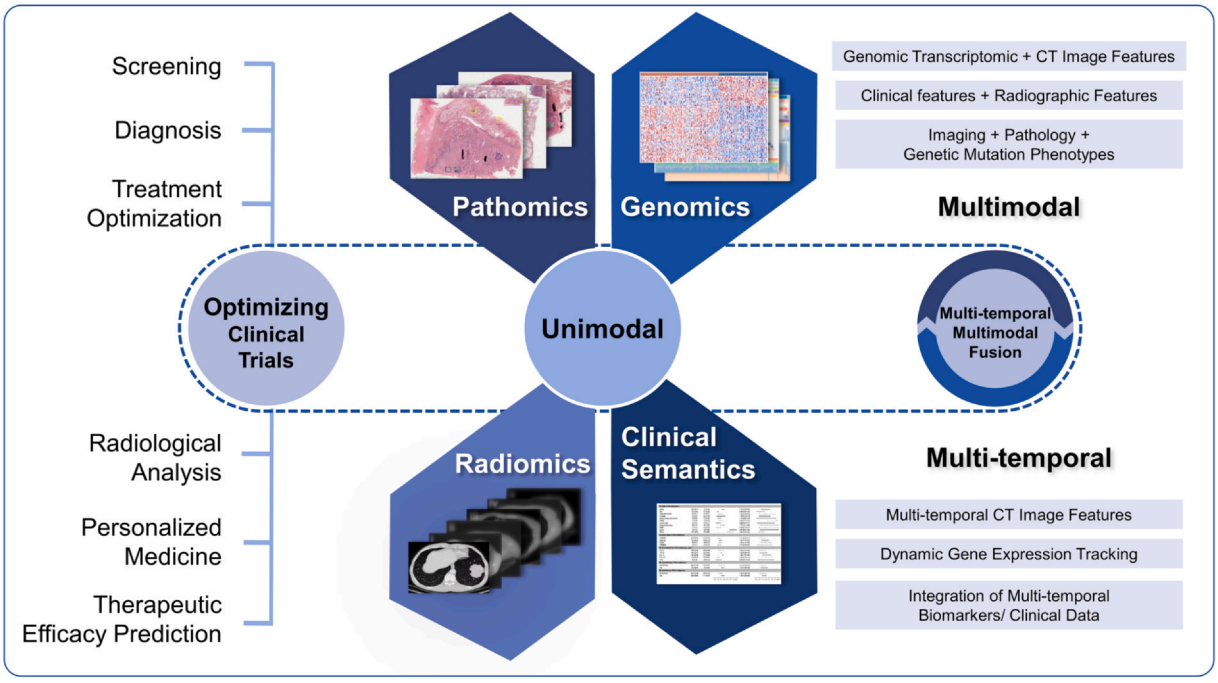


Fig. 3. AI optimizes clinical trial design for lung cancer drugs through single-modality and multi-temporal multimodal approaches.

cells using radiomic biomarkers extracted from imaging data.[70] Their work is crucial for evaluating responses to immunotherapies across various solid tumors, beneficial to treatment efficacy predictions. Trebeschi et al. applied AI to quantify radiological features predicting immunotherapy responses in melanoma and NSCLC, enhancing treatment efficacy predictions and patient outcomes.[38] Wang et al. developed a CT-based AI system to predict responses to EGFR-targeted therapies, enabling personalized treatment decisions from detailed imaging data.[72] Wu et al. developed non-invasive biomarkers to stratify the survival outcomes of NSCLC patients undergoing immune checkpoint inhibitor (ICI) therapy, improving patient stratification for tailored medicine approaches.[39] These innovations facilitate personalized treatment, shorten trial durations, and improve outcome prediction accuracy.

Chen et al. introduced LCI-RPV, a radiomic feature combining tumor characteristics and PD-L1 expression, to predict suitability for immunotherapy in NSCLC, thereby improving trial patient selection and refining personalized therapy strategies.[73] Zhao et al. integrated clinical and radiomic data to predict outcomes and resistance to chemo-immunotherapy in SCLC, offering critical insights that can inform trial design and patient stratification.[41] To enhance model interpretability, Jiang et al. proposed a biology-guided framework for predicting tumor microenvironment features and treatment responses using CT imaging, advancing clinical decision-making and facilitating more adaptive trial protocols.[43] Chaunzwa et al. developed a deep learning model for body composition analysis from CT scans, correlating body composition changes with treatment responses in advanced NSCLC, which can optimize trial monitoring and prognosis assessment.[40] She et al. incorporated 274 patients from four centers undergoing neoadjuvant immunotherapy for NSCLC.[74] They utilized the ShuffleNet neural network to extract baseline CT image tumor region features, constructing a primary pathological response prediction model. Additionally, they analyzed correlations between deep learning image features and molecular characteristics of the tumor microenvironment, thus supporting more precise outcome prediction in clinical trials.

In pathomics, AI technologies have been integrated into clinical trials to analyze subvisual morphological features from digital pathology-based whole slide imaging (WSI), enabling the precise quantification of NSCLC tissue morphology and the development of predictive models for immunotherapy efficacy. Rakaee et al. developed ML models to assess tumor-infiltrating lymphocyte (TIL) densities in late-stage NSCLC pathology slides, which correlate with immunotherapy outcomes and can inform patient stratification in clinical trials.[75] Park et al. employed ML analysis of NSCLC digital pathology to quantify TIL densities and spatial distributions, proposing immune phenotyping as a predictive biomarker for immunotherapy efficacy, which has implications for trial design and patient targeting.[42]

In genomics, AI is facilitating the identification of critical biomarkers for clinical trials. For example, Lu et al. used whole-exome sequencing data to identify mutations in lung cancer patients that predict responses to neoadjuvant immunotherapy.[76] Integrating these genomic insights with imaging data has enabled the construction of predictive models that guide trial design and inform treatment strategies.[77] These AI-driven models are critical for identifying the patient populations most likely to benefit from specific therapies, thus raising the efficiency and precision of clinical trials.

Tumor spatiotemporal heterogeneity (TSTH) remains a critical challenge in clinical trials, as it shapes the temporal dynamics of tumor responses to therapy. Recent advances in AI now allow for the precise quantification of TSTH by integrating multimodal data from imaging, pathology, and genomics.[78] This approach boost the accuracy of treatment response predictions, allowing real-time monitoring of tumor evolution. AI-driven analysis of dynamic tumor features throughout treatment provides critical insights into patient outcomes, supporting more granular patient stratification and the development of adaptive trial designs. These capabilities hold significant promise for personalizing treatment regimens in clinical trials, thereby improving the likelihood of favorable outcomes in lung cancer therapy.

Tumor heterogeneity remains a significant challenge in evaluating treatment responses, particularly during ICI therapy. Spatiotemporal changes in tumor lesions during neoadjuvant immune therapy can be difficult to capture with standard imaging techniques, complicating clinical trial assessments.[79] AI-driven models, using baseline and follow-up CT images, offer a powerful tool for predicting therapeutic efficacy and refining patient stratification in clinical trials.[80] Modeling based on multi-temporal CT image features of advanced NSCLC further enables the precise prediction of immune therapy efficacy, enabling better trial design and outcome forecasting.[81] Jin et al. applied deep learning and handcrafted features to track dynamic tumor changes over time, improving the predictive accuracy of efficacy models and supporting more adaptive trial designs.[82] These innovations are pivotal for designing personalized treatment protocols and optimizing clinical trial strategies, ensuring more accurate outcomes in lung cancer research.

Recent global clinical research on lung cancer has increasingly incorporated AI to integrate multimodal data from digital pathology, radiology, and genomics. A review of clinical studies registered on ClinicalTrials.gov (Table 2) highlights AI's potential in lung cancer treatment, including screening, diagnosis, and personalized medicine. These studies demonstrate how AI is transforming clinical trial designs and guiding future research in this area. Trials registered in the Chinese Clinical Trial Registry also heavily leverage deep learning models (Table 3), focusing on single-omic and multiomic approaches to diagnose and treat lung cancer, underscoring AI's crucial role in optimizing clinical trial protocols and patient stratification in lung cancer research.

In summary, AI-driven advancements in radiomics, pathomics, genomics, and clinical data integration are reshaping the clinical research landscape in lung cancer. By synthesizing multimodal data from imaging, genomics, and pathology, AI models enable the development of dynamic trial designs that better reflect patient heterogeneity, enhance outcome prediction, and reduce trial duration. These capabilities optimize clinical trial protocols by improving patient recruitment, refining treatment predictions, and identifying novel biomarkers. Ultimately, AI-driven innovations not only increase the efficiency of clinical trials but also pave the way for more personalized, targeted therapies, thereby improving patient outcomes and accelerating the progression of lung cancer treatments.

Table 2
Evaluating completed clinical trials of AI in lung cancer.

Study Type	Study Description	Identifier	Detailed Description
INTERVENTIONAL	AI-EBUS-Elastography for lymph node staging	NCT04816981	EBUS-Elastography for lymph node imaging, followed by computer algorithm analysis
OBSERVATIONAL	AI in lung cancer screening	NCT06444373	AI program for optimizing lung cancer screening on a web platform
OBSERVATIONAL	IDEAL: AI and big data for early lung cancer diagnosis	NCT03753724	Novel CT image analysis techniques for better characterization of small pulmonary nodules
OBSERVATIONAL	Prediction of cancerous lymph nodes for lung cancer staging during ultrasound imaging	NCT03849040	Testing NeuralSeg DNN for assigning the Canada Lymph Node Score in EBUS-TBNA
OBSERVATIONAL	Optimizing cancer therapy and identifying causes of pneumonitis (COVID − 19)	NCT04721444	ML model to distinguish parenchymal lung changes in radiotherapy vs. immunotherapy patients
OBSERVATIONAL	Evaluation of Contextflow DETECT lung CT nodule detection Software in chest CT scans	NCT05481762	Evaluating the impact of Contextflow DETECT lung CT on lung nodule detection effectiveness
OBSERVATIONAL	Comprehensive digital archive of cancer imaging-radiation oncology (CHAVI-RO)	NCT04249895	Creating an annotated image database of cancer patients with flexible query options and filter design via a GUI
OBSERVATIONAL	Retrospective study of Carebot AI CXR performance in preclinical practice	NCT05594485	Testing whether Carebot AI CXR software aids radiologists in interpreting postero-anterior or anterior-posterior chest radiographs
OBSERVATIONAL	D-Lung: An analytics platform for lung cancer based on deep learning technology	NCT04036903	Testing the D-Lung platform for improved primary lung cancer screening, diagnosis, and management using deep learning
OBSERVATIONAL	Accuracy of deep-learning algorithm for detection and risk stratification of lung nodules	NCT04022512	Determining the accuracy and sensitivity of a deep-learning AI system for detecting and stratifying lung nodules in osteosarcoma patients
OBSERVATIONAL	Predicting response to PD − 1 checkpoint blockade using deep learning analysis of imaging and clinical data	NCT05711914	Developing a multiomic classifier to predict PD − 1/PD-L1 blockade response in mutation-negative NSCLC; using ML to analyze treatable lesions
OBSERVATIONAL	Multi-reader retrospective study examining Carebot AI CXR 2.0.21-v2.01 implementation	NCT05963945	Evaluating the performance of DLAD (Carebot AI CXR) compared to individual radiologists in standard clinical practice
OBSERVATIONAL	Detection of lung cancer by plasma lipids	NCT04287712	Developing an accurate method for early-stage lung cancer detection using ML and metabolomics
OBSERVATIONAL	Interstitial lung disease detection based on the patient data from digital devices in unresectable stage III NSCLC patients receiving durvalumab	NCT04884269	Evaluating a ML model to predict Grade 2 + interstitial lung disease progression in unresectable Stage III NSCLC patients treated with durvalumab

4. Recruitment of trial participants

Recruiting clinical trial participants, particularly cancer patients, has long been a significant challenge for researchers. It has been reported that subject recruitment directly impacts the success or failure of trials: 85 %–95 % of delays are attributed to the inability to recruit eligible participants on schedule, and 19 % of clinical trials are terminated due to failure to meet the target sample size.[83] As recruitment criteria become more stringent, conventional methods of subject identification, such as manually reviewing medical records within siloed systems such as hospital information systems, are inefficient and often fail to accurately pinpoint eligible candidates. This inefficiency increases the risk of missing the opportunity window for trial participation. However, with the advent of AI, intelligent matching systems have the potential to significantly broaden recruitment channels, enhancing both efficiency and accuracy in the recruitment process.

In clinical trials for lung cancer, AI plays a crucial role by accelerating patient enrollment and improving study efficiency. Mendel.ai, an AI-driven technology applied in oncology trials, has proven effective, particularly in lung cancer research. It utilizes text recognition technology and NLP to process text data from scanned documents as well as automated clinical reasoning to handle both structured and unstructured medical records. Studies demonstrate that Mendel.ai significantly enhances the identification of potentially eligible patients and drastically reduces patient screening time. Utilizing this technology has reduced the confirmation of patient eligibility from an average of 263 days based on clinical chart information to just minutes. This finding highlights the substantial improvements facilitated by AI compared to conventional methods, particularly in enhancing patient screening efficiency, evaluating research center suitability, and optimizing trial selection strategies.[44]

Alexander's team developed an AI-based clinical trial matching system and evaluated its performance in a cohort of lung cancer patients at a hospital in Australia.[45] The system employs NLP techniques to process trial and patient information from unstructured data sources and utilizes ML algorithms to match patients who may meet the trial criteria. Ten phase I to III clinical trials involving 102 patients, registered on ClinicalTrials.gov and open to lung cancer patients at the institution, were assessed. The system, targeting 11,467 trial eligibility criteria, evaluated over 7,000 patient attributes. Comparing the system's performance with a gold standard of trial eligibility established through clinician consensus, the results demonstrate high consistency with the gold standard. Notably, the

Table 3
Clinical trials evaluating AI in lung cancer.

Study Type	Study Description	Identifier
DIIAGNOSTIC	Solution and demonstration application of intelligent diagnosis products for lung cancer	ChiCTR2400084624
DIIAGNOSTIC	CT image features and AI prediction of EGFR gene type in NSCLC: a multicenter study	ChiCTR2400083082
DIIAGNOSTIC	Application research of AI model in evaluating the prognosis of early lung cancer	ChiCTR2200059642
DIIAGNOSTIC	Research on the prediction of synchronous radiotherapy and chemotherapy efficacy and related molecular signaling pathways	ChiCTR2100053175
DIIAGNOSTIC	Research and preliminary application of AI cellular pathology diagnosis system for lung cancer	ChiCTR2100046913
DIIAGNOSTIC	Related research on the differential diagnosis of pulmonary nodules based on radiomics and AI	ChiCTR2100043351
DIIAGNOSTIC	Exploring the diagnostic efficacy of blood tumor autoantibodies combined with CT for benign and malignant diagnosis of pulmonary nodules smaller than 3 cm	ChiCTR2100042605
DIIAGNOSTIC	Application research of AI-assisted system in preoperative comprehensive evaluation of early lung cancer	ChiCTR2000035689
DIIAGNOSTIC	The value of combining medical imaging AI technology with intraoperative frozen pathology	ChiCTR2000032054
DIIAGNOSTIC	Accuracy and application value of AI technology based on deep learning for the diagnosis of benign and malignant pulmonary nodules	ChiCTR2000030379
DIIAGNOSTIC	Application of AI in the interpretation of PD-L1 expression results in lung cancer	ChiCTR1900022640
DIIAGNOSTIC	Research on multiomics-assisted early screening of non-SLCL based on AI	ChiCTR1900021189
DIIAGNOSTIC	Application of deep learning in multimodal medical imaging intelligent diagnosis of peripheral lung cancer and construction of clinical decision support system	ChiCTR2300078539
DIIAGNOSTIC	Prediction of N2 metastasis in clinical stage I NSCLC using deep learning models: a multicenter prospective diagnostic trial	ChiCTR2000041310
DIIAGNOSTIC	Establishment and application research of lung tissue pathology image-assisted diagnosis system based on deep learning	ChiCTR2000037216
DIIAGNOSTIC	Diagnosis and postoperative prognosis evaluation of pulmonary subsolid nodules based on deep learning: medical imaging evidence within the model	ChiCTR2000029908
DIIAGNOSTIC	Study on the prediction of EGFR mutations in NSCLC using deep learning methods combined with CT imaging	ChiCTR1800019891
INTERVENTIONAL	Evaluation of the application effect of AI 3D virtual imaging technology	ChiCTR2400083950
INTERVENTIONAL	Prospective randomized controlled clinical study of AI technology and standard open chest surgery for N2 stage NSCLC	ChiCTRINR17012777
OBSERVATIONAL	AI combined with plasma methylation detection for predicting the growth of pulmonary subsolid nodules	ChiCTR2400085290
OBSERVATIONAL	The relationship between pathological subtypes and prognosis of early lung adenocarcinoma	ChiCTR2100043750
OBSERVATIONAL	Clinical study on automatic delineation of lung cancer radiotherapy target area and endangered organs based on 4DCT and AI	ChiCTR2000032417
OBSERVATIONAL	Symptom clusters of pain, fatigue, and sleep disorders in lung cancer patients after chemotherapy	ChiCTR2300070944
OBSERVATIONAL	Lung cancer prognosis based on clinical electronic medical records and medical imaging data	ChiCTR2300069854
OBSERVATIONAL	Research on body tumor radiotherapy technology based on ML and DNNs guided by optical surface imaging	ChiCTR2100042714
OBSERVATIONAL	Research on the predictive ability of deep learning models based on radiomics for infiltration classification of high-risk pulmonary nodules	ChiCTR2400079796

system executes queries and returns results in a median time of just 15.5 seconds, significantly reducing the time for clinical trial patient matching. This suggests efficient and reliable screening of cancer patients for clinical trials. Furthermore, the system achieves an exclusion accuracy of 95.7 % and an overall eligibility assessment accuracy of 91.6 %. Therefore, this automated system holds promise as a clinical decision support tool for pre-screening large patient cohorts to identify candidates suitable for further evaluation in clinical trials.

Generative AI also facilitates the development of DTs, digital replicas of physical objects or systems linked by bidirectional data flow.[46] DTs should closely resemble real patients in observed characteristics, such as monitored clinical variables and disease prognosis. Currently, generative DTs primarily center on simulating control arms to which significant portions of participants are allocated in clinical trials. With sufficient data, AI models can predict the natural history of each participant, potentially substituting virtual controls for conventional control arms, thereby significantly reducing recruitment targets and expediting patient enrollment.[47] It is anticipated that DTs will be applied more extensively across various aspects of clinical trials, including trial design and adverse event prediction. One study introduced a comprehensive approach, the ISELA-V2 model, to compare the efficacy of two EGFR-TKIs, osimertinib and gefitinib.[48] The model incorporated biological and clinical data modalities during both training and inference, including drug concentration data, tumor volume change data, and patient time to progression. Research data from multiple pharmacokinetic-related sources were used for model training and validation, covering various aspects from the in-vivo distribution of the drug to its therapeutic efficacy. The model successfully predicted responses to these standard treatments among patients with EGFR mutations in NSCLC. Researchers generated virtual patients representing the target trial population. Using a similar process, a virtual control group receiving standard treatment could be created. Subsequently, this virtual control group could be compared with the real patient group receiving the study treatment. Such comparisons enabled a more accurate assessment of the study treatment's efficacy, as the generated virtual control group possesses measurable characteristics similar to those of the study group. Moreover, constructing the virtual group could account for unmeasurable patient characteristics that may alter the efficacy differences between study and control treatments.

There is another aspect worth discussing regarding AI-assisted patient recruitment. Optimizing eligibility criteria for clinical trials is crucial, especially in addressing challenges posed by patients with aNSCLC.[49] It has been reported that approximately 80 % of patients failed to meet current trial enrollment standards, largely due to overly stringent criteria. Many of these standards are not based on their necessity for the trial but are, rather, inherited from previous studies with similar populations.

Currently, integrating real-world data and AI offers new opportunities for establishing more rational eligibility criteria. Liu et al. employed the advanced computational framework Trial Pathfinder, utilizing data from a national EHR database to assess the impact of different eligibility criteria on the aNSCLC patient population and trial outcomes.[50] This framework is used to simulate clinical trials and evaluate the impact of eligibility criteria. Data from the EHR of 61,094 aNSCLC patients—including structured lab results and unstructured data, such as clinical notes—were utilized to train and assess the Trial Pathfinder framework. The research team developed rules to identify eligible patient cohorts through simulation and propensity score adjustment, simulating the randomization process. The results indicated that relaxing the current eligibility criteria significantly increases the number of eligible patients while reducing patient risk, ensuring trial result stability. Furthermore, synthetic clinical trials validated that adjusting the combination of inclusive and exclusive criteria expands patient enrollment without compromising trial integrity.

As previously noted by George, it is paramount to strike a balance between having an adequately qualified study population and avoiding unnecessary complexities in trial completion and result application.[84] Predictive models and AI technologies play crucial roles in optimizing eligibility criteria and preventing the exclusion or excessive inclusion of patients due to overly strict or lenient criteria, thereby maximizing the potential benefits of research. In the future, AI technology holds promise for supporting adaptive designs in clinical trials for lung cancer medications, allowing dynamic adjustments of eligibility criteria to address recruitment challenges and respond to emerging data feedback.

5. Reanalysis of clinical data from trials

In clinical trials, data are commonly missing for various complex reasons, such as participant dropout, non-compliance, and data entry omissions. Addressing missing data is crucial, as data missingness significantly impacts the accuracy of outcome assessments. A study investigating the impact of missing death data on mortality rate estimation using a database derived from the EHR of advanced NSCLC patients revealed substantial bias.[85] This finding underscored the importance of robust methodologies to handle missing data, ensuring more reliable survival analyses in clinical research settings. The potential bias introduced by missing data depends on the mechanism underlying the missingness and the analytical methods used to address the missing values.[86] Therefore, the analysis of trial data containing missing values requires careful planning and thoughtful consideration.

In queue research, data missingness is often unavoidable and can affect study outcomes negatively. Li et al. evaluated the effectiveness of eight commonly used statistical and ML imputation methods in predicting missing data within queue research datasets.[51] The results demonstrated that KNN and RF exhibited excellent performance and were particularly effective at imputing missing data in predictive modeling within queue research datasets. Caruso et al.'s model aims to deliver accurate OS predictions for NSCLC patients, thereby addressing these substantial challenges.[52] The findings demonstrated that their model not only surpassed the performance of current state-of-the-art methods but also streamlined analysis in the context of missing data, eliminating the need to determine the optimal imputation strategy for OS prediction in NSCLC patients.

Austin et al. reported on a tutorial on MI.[53] MI is a statistical technique that enables researchers to substitute missing values with multiple plausible values of the respective variable. This approach permits the analysis of complete datasets while integrating uncertainty regarding the imputed values. By generating multiple imputed datasets, analysts can explicitly address the inherent uncertainty associated with imputation.

Baron et al. have developed a novel ML-based strategy termed the "meta-model" to address the issue of missing patient data.[54] The performance of the meta-model was significantly superior to that of more conventional methods relying on imputation. This advancement lays a foundation for enhancing clinical decision-making and predicting survival rates among cancer patients. Moreover, this approach holds promise for resolving missing data challenges encountered in clinical trials.

6. Current challenges and potential solutions

While AI plays a crucial role in clinical research on lung cancer medications, achieving widespread application in healthcare requires continuous efforts to address challenges such as data quality, model interpretability, and biases. Figure 4 illustrates the key challenges associated with the application of AI in lung cancer clinical trials and proposes corresponding solutions to overcome these obstacles. In this section, we will discuss the current challenges and potential solutions.

6.1. Quality control of training data

The performance of algorithms largely hinges on the availability of large quantities of accurately annotated data despite potential measurement errors in these data. It is crucial to reduce reliance on manual annotation by generating algorithms using more objective and higher-quality data.[47] The value of data, whether extensive or in small datasets, transcends their volume, and all data require careful attention during the training process.[87]

Moreover, there are numerous challenges to data sharing among multiple centers due to inter-institutional competition and data privacy regulations. Addressing these challenges involves employing privacy-preserving technologies such as data encryption and

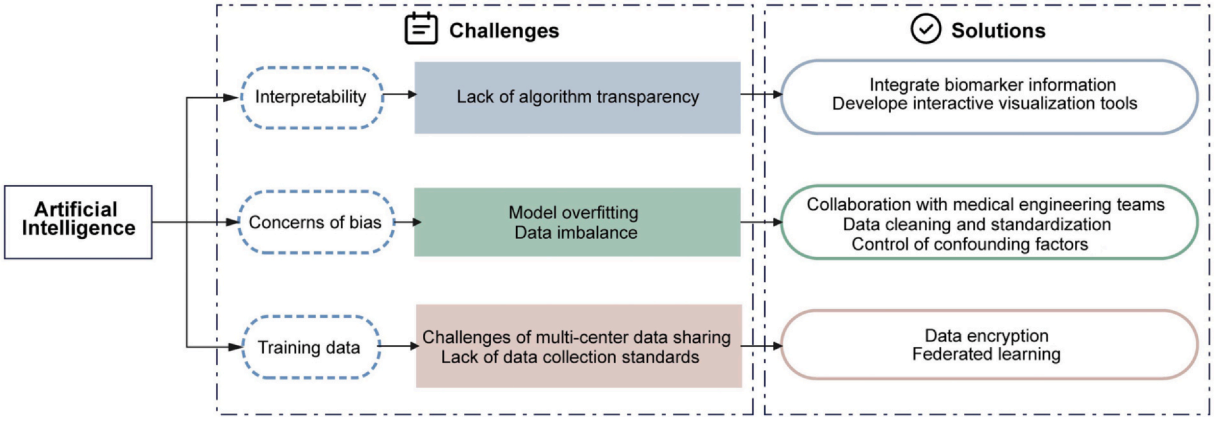


Fig. 4. Challenges and solutions in the application of AI in lung cancer clinical trials.

federated learning.[88] This enables each center to train models using its data and update a central server model without directly sharing raw data.[89]

6.2. Improvement of interpretability

Another key challenge in the use of AI is interpretability. ML models are often referred to as black-box models, and they offer limited transparency into how decisions are made.[90] Kumar and colleagues emphasized in their recent review the importance of developing reliable AI systems, noting that the complexity of AI models could diminish their interpretability, particularly in oncology drug development.[91] Therefore, establishing reliable AI systems capable of accurately interpreting outputs in cancer drug development is crucial to avoid overreliance on potentially flawed results and reduce the costs associated with erroneous pathways. Post-hoc interpretability techniques offer a solution, including generating heatmaps on inputs and clustering inputs into interpretable groups based on embeddings from the ML model.[92]

An example of embedding interpretability into clinical design is illustrated by Zhang et al., who developed an ML model that learns to generate explanations in natural language for its predictions during training.[93] Kim et al. proposed a novel foundational approach named medical concept retriever (MONET) aimed at constructing a reliable and transparent image-based AI system in healthcare.[94] MONET excels in accurately annotating concepts within images. The paper demonstrated MONET's methodology for achieving transparency in AI system development, including building inherently interpretable models, datasets, and model audits and dissecting AI clinical trial outcomes through case studies. Furthermore, associating interpretability with biomarker information can aid clinical researchers in understanding the model's decision-making process. Another approach involves developing interactive visualization tools that allow users to adjust parameters and immediately see updated visual results, enabling a deeper understanding of how the model processes parameters. Methods that explore the source of an AI decision tree, such as occlusion testing, will be key in integrating AI into clinical trials.[95]

In conclusion, as AI is increasingly integrated into clinical trials, it is vital to develop and apply interpretability techniques. Methods that delve into the basis of AI decisions will be pivotal in ensuring that these decisions are not only effective but also trustworthy and comprehensible to clinicians and researchers. This transparency will foster more informed and confident clinical decisions, ultimately benefiting patients and advancing drug clinical trials.

6.3. Concerns of bias

Biases in clinical research pose substantial challenges. AI models may encounter overfitting issues: they perform well on training data but generalize poorly to validation data. Therefore, accurately assessing overfitting and enhancing model generalization through methods such as cross-validation are crucial steps. Relying on a single dataset inevitably introduces biases. Addressing this requires not only data cleaning and standardization but also training models on more diverse and independent datasets to mitigate hidden biases.[96] Collaboration between medical and engineering teams during model development is essential. Clinical scientists can offer insights into the biases inherent in their fields, while engineering teams can tailor ML models to address specific needs and eliminate biases.[97]

7. Discussion

The treatment and care of lung cancer present complex and multifaceted challenges. Clonal evolution, driven by intra-tumor heterogeneity, drives tumor development and treatment resistance.[98] Due to this high heterogeneity, single-drug therapies often prove limited in efficacy and prone to resistance.[99] Consequently, the development of new drugs and clinical research are pivotal in addressing this challenge. Continuous exploration and innovation offer the potential for providing lung cancer patients with more

effective, safe, and cost-efficient treatment options, raising their quality of life and ultimately improving survival rates. This endeavor is not only critical at the individual patient level but also holds profound implications for societal health and economic development.

In recent years, the integration of AI technologies has revolutionized the design of drug clinical trials. AI is extensively applied in drug design, development, and clinical trial validation methods spanning the entire drug development cycle. Through ML algorithms, we can handle and analyze vast amounts of complex biomedical data, offering new perspectives for drug discovery in lung cancer treatment and the design of clinical trials. AI-driven clinical research not only increases the quality and efficiency of biomedical evidence but also provides more precise treatment plans and efficacy predictions through personalized medicine approaches. A recent study indicated that incorporating circulating tumor DNA (ctDNA) monitoring into clinical trial designs provides insights into identifying optimal beneficiary groups, treatment duration, and priority treatment modalities for NSCLC immunotherapy.[100] Consequently, future clinical trial designs may explore the potential of utilizing AI technology for real-time monitoring of ctDNA levels.

Currently, AI primarily contributes to the clinical trial design and patient recruitment stages, with limited reports on its application in managing lung cancer drug clinical trials. AI can improve clinical trial management in areas such as trial design evaluation and participant recruitment. Sun's hierarchical interaction network algorithm and sequential predictive modelling of clinical trial outcome model predict trial success and progression, aiding design adjustments.[101] NLP optimizes patient–trial matching and recruitment before trials and enables continuous, automated monitoring during trials.[102] It also accelerates data collection and analysis in oncology drug development, including dose optimization and pharmacokinetic analyses.[103] However, AI applications for monitoring patient adherence in lung cancer trials are still limited. Wang et al. used ML to quantify factors influencing patient adherence to incidental pulmonary nodule follow-up, with potential applications for improving adherence in lung cancer trials.[104] AI has shown notable applications in managing clinical trials, including monitoring patient adherence, automated data collection, and real-time trial monitoring. Given these advancements, the application of AI to these aspects of lung cancer trials is likely imminent.

Future research exploring AI technology's integration with real-time data for dynamic dose adjustments and real-time patient information monitoring holds vast potential for advancement. For example, most treatment guidelines advocate for chemotherapy at the maximum tolerated doses, which may not always achieve optimal efficacy and often results in toxicity. Addressing this challenge, Blasiak et al. developed CURATE.AI, a small-data, AI-driven platform that utilizes a patient's own longitudinally acquired data to determine personalized chemotherapy doses dynamically.[105] They applied CURATE.AI to adjust individualized chemotherapy doses in a prospective clinical trial. Another review examined a study utilizing evolutionary game theory to simulate the strategic interaction between drug dosing and cancer cell proliferation dynamics.[106] This approach aided clinicians in more accurately predicting the adaptive responses of cancer cells, thereby facilitating dynamic adjustments to treatment protocols based on these predictions. Furthermore, in the management of clinical studies on immune-related adverse events (irAEs), AI chatbots can offer a wealth of accurate and comprehensive information on irAEs, paving the way for future investigations that integrate irAEs pertinent to lung cancer.[107] These approaches are now being explored in other types of cancers and hold promise for future applications in lung cancer.

As AI-driven clinical research enhances the efficiency and quality of biomedical evidence, it becomes closely tied to the quality of life of lung cancer patients, necessitating ethical considerations.[97] Specific and detailed regulatory guidance for AI use in clinical trials needs further refinement. Novel data-driven trial designs must strike a balance between progress and safety while safeguarding patient privacy and autonomy. Additional considerations, such as data ownership and patients' access to their own data, require further exploration and discussion.[108] Given the stringent regulatory oversight and risk-averse nature of drug development and clinical trials, the industry's digital transformation is expected to progress cautiously but steadily.

Effective quality control (QC) is essential in clinical trials to ensure compliance with protocols, safeguard patient safety, and maintain data reliability. QC processes involve monitoring data recording accuracy, adherence to protocols, and equipment calibration. Such processes are typically managed by personnel following standard operating procedures and require continuous, rigorous oversight. Studies have shown that AI holds significant potential in promoting QC through automated data monitoring, anomaly detection, and consistency checks. For example, ML algorithms can detect data anomalies at the point of entry, thereby assuring data consistency and accuracy, which ultimately enhances QC efficiency.[109] NLP further supports QC by automating the review of EHR and patient reports, helping monitors identify potential issues more swiftly. Accurate outcome assessment is equally crucial for evaluating treatment efficacy, identifying adverse effects, and ensuring the generalizability of findings. This process currently requires careful analysis of diverse data points, such as patient adherence and adverse events, demanding extensive time and oversight. AI applications, such as NLP and ML, have shown broad utility in analyzing unstructured data, including patient-reported outcomes and clinician notes, to identify treatment responses and adverse events. Research has demonstrated that AI-driven analysis can provide faster and more accurate insights.[110] Additionally, AI can reduce bias in outcome assessment through data standardization across trials and by integrating diverse data sources to enhance generalizability. Together, these advancements highlight AI's potential to make clinical trials more efficient, accurate, and adaptive to the complexities of modern biomedical data.

Despite advancements in clinical trial methodologies, several challenges persist that neither conventional methods nor AI have fully addressed.[111] In both conventional and AI-assisted approaches, data missingness and heterogeneity remain key issues, impacting the accuracy and applicability of research findings. Conventional methods typically rely on complete datasets, while AI models require high-quality, comprehensive datasets to achieve reliable predictions. Additionally, safeguarding patient data privacy and security remains critical. Recruiting a diverse and representative patient cohort, particularly for specific populations, continues to be challenging for both conventional and AI-driven methods. Moreover, as novel clinical research techniques emerge, regulatory bodies often face delays in adapting standards, resulting in a lack of consistent and effective criteria for validating the safety and efficacy of new methodologies. Among the reasons is a lack of prospective studies comparing the effectiveness of AI with that of conventional methods, with clinical researchers and physicians often maintaining reservations regarding the accuracy and reliability of AI technologies. To alleviate these concerns, there is an urgent need for further prospective research to validate model effectiveness.

The accuracy and practicality of AI in designing lung cancer drug clinical trials require further evaluation. Rigorous control over factors such as data acquisition and clinical trial enrollment criteria is essential. Further clarification is needed regarding the interpretability and robustness of drug development models to ensure their safety and potential clinical benefits. However, the validation of AI for clinical trials remains a critical issue. Although the quantity of research on the accuracy and applicability of AI in clinical trials has increased, it remains insufficient. A systematic review revealed that of 11,839 articles on AI applications in clinical practice, only 39 (0.33 %) were RCTs.[112] Moreover, while most studies demonstrate that AI-assisted tools outperform conventional methods in clinical practice, the generalizability and external validity of these validation studies are constrained by small sample sizes and single-center designs. Existing research still faces limitations regarding training sample sizes, data quality, and ethical and legal considerations. Future efforts must prioritize large-scale, multi-center, interdisciplinary RCTs to thoroughly validate the accuracy and practicality of AI applications.

Precision non-invasive prediction of neoadjuvant immunotherapy efficacy in NSCLC has been a focal point in clinical research both in China and internationally. Current AI-associated studies primarily focus on single-modal data, such as CT imaging, pathology, and genetic information, to explore biomarkers and construct predictive models. Meanwhile, compared to analyses based solely on single time-point information, the potential of utilizing multimodal time-series data to quantify tumor temporal heterogeneity has not been thoroughly explored. Future efforts could involve extracting imaging features from the peritumoral region to assess spatial heterogeneity, quantifying global and local features of the tumor microenvironment at the cellular and tissue levels, and constructing quantifiable predictive models based on multi-temporal CT images and digital pathology images. These approaches have the potential to improve predictions of effectiveness, thereby reducing the number of participants needed in clinical trials and speeding up research progress. These approaches aim to comprehensively address the spatiotemporal heterogeneity of lung cancer, offering robust methodologies for designing clinical studies related to immune-based therapies.

8. Conclusions

In summary, AI opens new avenues and holds great promise in the design of clinical trials for lung cancer drugs. Interdisciplinary collaboration, clear regulatory guidance, overcoming technological challenges, and the continuous assessment and validation of AI system accuracy and practicality are necessary to fully harness the potential of clinical research. The path to personalized and precision medicine is fraught with challenges, but through concerted efforts, AI can realize its promise of enabling more effective, safe, and cost-effective clinical research innovations in revolutionizing lung cancer treatment.

Ethical statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CRediT authorship contribution statement

R. Z. L: Writing – original draft, Resources, Investigation. **Y. W. L:** Writing – original draft, Methodology, Investigation. **J. Q. L:** Writing – original draft, Methodology, Investigation. **Y. L:** Writing – original draft, Resources. **S. W. W:** Writing – review & editing, Supervision. **H. Y. Z:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Y. H. Z:** Writing – original draft, Project administration, Methodology, Investigation, Conceptualization. **P. M. Y:** Project administration, Methodology, Investigation, Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests. Haiyu Zhou reports financial support was provided by Department of Science and Technology of Guangdong Province. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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