Liquid Biopsy as a Primary Diagnostic Triage for EGFR-Mutated NSCLC in Resource-Limited Settings: A Systematic Review

Ahmad Baihaqi Ahnaf[1], Muhammad Yusuf Al Fatih[1], Titus Nanda Pratama[1], Rokhmatul Asiyah[1*]

[1]Malang State University, Semarang Street 5, Malang, 65145, Indonesia
*Corresponding author, email: rokhmatul.asiyah.fk@um.ac.id

Keywords
Circulating Tumor DNA,
Diagnostic Concordance,
Liquid Biopsy,
Non-Small Cell Lung Cancer

Abstract
Background of study: Lung cancer remains a leading cause of cancer-related mortality in Indonesia, where geographic and infrastructural constraints frequently delay tissue-based molecular diagnosis. Although tissue biopsy is the gold standard for detecting epidermal growth factor receptor (EGFR) mutations in non-small cell lung cancer (NSCLC), it is invasive and often limited by inadequate samples and tumor heterogeneity.

Aims or objectives: This systematic review evaluates the diagnostic concordance between liquid biopsy using circulating tumor DNA (ctDNA) and tissue biopsy for EGFR mutation detection and assesses its feasibility as a primary diagnostic triage modality in resource-limited settings.

Methods: A systematic search of PubMed, Wiley Online Library, and SAGE Journals was conducted for paired diagnostic studies published between 2020 and 2026. Ten eligible studies were included, and methodological quality was assessed using the QUADAS-2 tool.

Result: A total of 1,458 patients were analyzed. Diagnostic concordance between plasma ctDNA and tissue biopsy ranged from 56.1% to 100%. High-sensitivity platforms, including next-generation sequencing and droplet digital polymerase chain reaction, demonstrated superior performance. Specificity was consistently high (>90%), whereas sensitivity varied widely (34.6%–100%) and was influenced by tumor stage and metastatic burden.

Conclusion: Liquid biopsy demonstrates high diagnostic validity and logistical feasibility as an initial screening approach. A liquid-first diagnostic algorithm, with reflex tissue biopsy in negative cases, may improve access to precision oncology while preserving diagnostic safety in resource-limited healthcare systems.

1. Introduction

Lung cancer remains the leading cause of cancer related mortality worldwide and poses a significant health burden in developing regions. In Southeast Asia, the incidence continues to rise. According to recent data from 2022, lung cancer accounted for 16.7% of all new cancer cases in males (1). This burden is particularly pronounced in Indonesia, which recorded an estimated 42,382 lung cancer deaths in 2022, corresponding to a mortality rate of 15.2 per 100,000 population (2). Histologically, Non-Small Cell Lung Cancer (NSCLC) comprises approximately 85% of all lung cancer cases, with the majority of patients being diagnosed at advanced stages (Stage III or IV), where surgical intervention is often no longer feasible (3).

In the era of precision medicine the management of advanced NSCLC has shifted from empirical cytotoxic chemotherapy to targeted therapies based on molecular profiling. The most critical biomarker particularly in the Asian context, is the mutation of the Epidermal Growth Factor Receptor (EGFR) gene (4). Epidemiological studies indicate that EGFR mutations are present in 40–60% of NSCLC adenocarcinomas in Asian populations including Indonesia compared to only 10–15% in Caucasian populations (5,6). Consequently, accurate identification of EGFR mutation status is mandatory to guide the administration of EGFR-Tyrosine Kinase Inhibitors (TKIs), such as gefitinib, erlotinib, or osimertinib, which have demonstrated superior progression-free survival compared to standard chemotherapy (7).

Currently, tissue biopsy remains the gold standard for diagnosis and molecular analysis. However, tissue acquisition presents significant clinical limitations. Procedures such as bronchoscopy, transthoracic needle aspiration (TTNA), or surgical biopsy are invasive and carry risks of complications, including pneumothorax, hemoptysis, and infection (8). Furthermore, in clinical practice obtaining adequate tissue is often challenging, approximately 20–30% of biopsies yield insufficient samples for molecular testing. Additionally, single-site tissue biopsies may fail to capture spatial tumor heterogeneity which can lead to incomplete mutational profiling (9).

ISSN:

To address these limitations, liquid biopsy has emerged as a minimally invasive alternative. This technique detects circulating tumor DNA (ctDNA) shed by 2 apoptotic or necrotic tumor cells into the peripheral blood circulation (10). Previous studies, including recent meta-analyses and data from Indonesian cohorts, have demonstrated that liquid biopsy can identify EGFR mutations with high specificity. However, reports on sensitivity vary significantly across different detection platforms and tumor stages, creating a gap in clinical consensus (10,11). Furthermore, in archipelagic nations like Indonesia, unequal access to advanced interventional pulmonology centers further complicates tissue acquisition that can delay diagnosis. Therefore, this systematic review aims not only to evaluate the diagnostic accuracy of liquid biopsy but also to assess its feasibility as a primary screening tool to overcome these logistical barriers.

2. Method

Study Design: This study was conducted as a systematic review of paired diagnostic accuracy studies comparing plasma-based liquid biopsy with tissue biopsy for EGFR mutation detection in patients with NSCLC.

Literature Search: A comprehensive literature search was performed using PubMed, Wiley Online Library, and SAGE Journals. The search was restricted to studies published between 2020 and 2026. Search terms were developed using the PICO framework and combined with Boolean operators to identify studies evaluating concordance, sensitivity, and specificity between liquid biopsy and tissue biopsy.

Eligibility Criteria: Eligible studies included observational studies, cohort studies, or clinical trials involving patients with NSCLC that directly compared EGFR mutation detection using plasma ctDNA and tissue biopsy in paired samples. Review articles, case reports, conference abstracts, in vitro or animal studies, and studies without paired sampling were excluded.

Data Extraction: Data extraction was performed independently by two reviewers using a standardized form. Extracted variables included study characteristics, patient demographics, cancer stage, liquid biopsy and tissue biopsy methodologies, and diagnostic outcomes, including concordance, sensitivity, specificity, positive predictive value, and negative predictive value.

Quality Assessment: Methodological quality and risk of bias were assessed using the QUADAS-2 tool across four domains: patient selection, index test, reference standard, and flow and timing. Discrepancies were resolved through consensus.

Research Procedures and Timeline (if applicable): Detail the sequence of research activities, including data collection phases, interventions (if any), and other key procedural steps. If relevant, include a timeline or duration of each phase, especially in longitudinal or multi-stage studies.

Data Analysis: Diagnostic performance measures were summarized descriptively. Given heterogeneity in study design, populations, and detection platforms, a qualitative synthesis was prioritized.

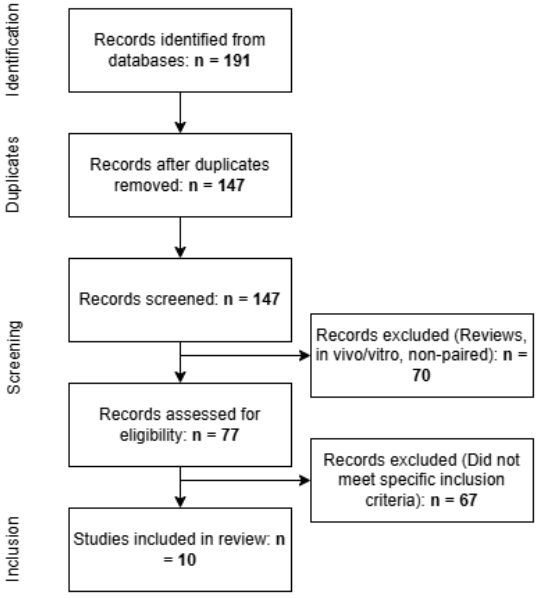

Figure 1. Flowchart of the Literature Selection

ISSN:

Table 1. Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
Primary studies (Observational, Cohort, or Clinical Trials) involving patients with Non-Small Cell Lung Cancer (NSCLC)	Review articles, case reports, editorials, and conference abstracts.
Studies providing a direct, head-to-head comparison of EGFR mutation detection between Liquid Biopsy (plasma ctDNA) and Tissue Biopsy (Gold Standard)	In vivo (animal models) or in vitro (cell culture) studies
Studies reporting diagnostic outcomes such as concordance, sensitivity, or specificity	Studies without paired samples (i.e., not testing both blood and tissue in the same patient)
Full-text articles available in English	Full-text articles not available in English

Table 2. Quality Assessment

Study	Risk of Bias			
	Patient Selection	Index Test	Reference Standard	Flow and Timing
Mirikar et al. (2025) (12)				
Zwierenga et al. (2025) (13)				
Malapelle et al. (2026) (14)				
Kang et al. (2025) (15)				
Zhang et al. (2022) (16)				
Ho et al. (2022) (17)				
Prabhash et al. (2022) (18)				
Soeroso et al. (2022) (11)				
Vendrell et al. (2020) (19)				
Fu et al. (2021) (20)				

Red: high risk; Yellow: unclear; Green: low risk

3. Results and Discussion

This section presents the findings of the study and interprets them in relation to the research questions, relevant literature, and broader educational implications. It should demonstrate both analytical depth and scholarly engagement. The results and discussion section must include the following key elements:

Results: The initial search identified 191 records. After removing 44 duplicates, 147 unique records were screened. Seventy records were excluded for not meeting the study type criteria, and an additional 67 were excluded after full-text assessment. Ultimately, 10 primary studies fully met the inclusion criteria. The publication years ranged from 2020 to 2026, reflecting the rapid evolution of liquid biopsy technology. Geographically, the studies predominantly originated from Asian populations (including Indonesia, China, India, South Korea, and Taiwan), providing high contextual relevance for EGFR mutation prevalence in this region. The total sample size across all studies comprised 1,458 patients.

Based on the QUADAS-2 assessment, the risk of bias was lowest for the reference standard domain, marked as low risk in all 10 studies. Patient selection raised the most concern (high risk in 4/10, unclear in 6/10), reflecting limitations in sampling strategies. Flow and timing also showed mixed quality, implying potential bias from clinically meaningful time gaps between plasma and tissue testing.

ISSN:

Diagnostic accuracy demonstrated high overall agreement between liquid biopsy and tissue biopsy. The overall concordance ranged from 56.1% to 100%. Notably, a study conducted in Indonesia reported a concordance rate of 83.0%, demonstrating local feasibility. Specificity was consistently robust, ranging from 70.0% to 98.7%, indicating low false-positive rates across platforms. Conversely, sensitivity exhibited significant variability (34.6% to 100%). Studies utilizing high-sensitivity platforms, such as Next-Generation Sequencing (NGS) and Droplet Digital PCR (ddPCR), generally reported superior sensitivity compared to earlier PCR-based methods due to improved limits of detection.

Discussion: The synthesized evidence strongly supports utilizing liquid biopsy as the initial diagnostic triage in advanced NSCLC to accelerate access to actionable biomarkers. Across studies, plasma assays frequently demonstrate high specificity for actionable variants, meaning that a detected EGFR sensitizing mutation is typically clinically actionable and justifies the prompt initiation of an EGFR-TKI. This is particularly crucial when tissue is limited or turnaround time is a barrier.

However, concordance and discordance metrics must be interpreted carefully. A Plasma-positive/Tissue-negative (Plasma+/Tissue-) pattern can often be consistent with tumor spatial heterogeneity or tissue sampling limitations (i.e., a tissue false-negative due to a non-representative biopsy). At the same time, this discordance can arise from pre-analytical variables or assay sensitivity differences. Therefore, Plasma+/Tissue- results may reveal clinically relevant alterations missed by limited tissue sampling, but histopathologic confirmation and tissue-based profiling remain necessary whenever feasible.

Implications: This study aligns directly with Sustainable Development Goal (SDG) 10 (Reduced Inequalities) by demonstrating how a "liquid-first" diagnostic pathway can democratize access to precision oncology. In archipelagic and developing settings like Indonesia, severe inequities in access to advanced interventional pulmonology and thoracic surgery can critically delay molecular stratification. Implementing a concurrent testing model drawing plasma ctDNA upfront when advanced NSCLC is suspected acts as a health-equity accelerator. It standardizes and expedites access to targeted therapies across geographically remote referral networks, translating academic molecular oncology into equitable clinical practice.

Limitations: Despite its high specificity, the sensitivity of liquid biopsy is variable and not yet 100%. False-negative results remain a significant challenge, particularly in patients with intrathoracic-only disease (M0/M1a) or low tumor shedding. Furthermore, this review is limited by the heterogeneity of the included studies specifically concerning detection platforms and patient stages which precluded a quantitative meta-analysis. Incomplete reporting of blinding procedures in some primary studies also introduces a potential risk of bias that could distort sensitivity estimates.

4. Conclusion

Liquid biopsy using plasma ctDNA offers a high-specificity, minimally invasive approach that directly addresses the limitations of tissue biopsy, particularly for patients with insufficient tissue samples. While it cannot entirely replace tissue biopsy due to variable sensitivity, we propose a "liquid-first" diagnostic algorithm prioritizing liquid biopsy as the primary triage tool, with reflex tissue biopsy reserved as a mandatory confirmatory step only when plasma results are negative. This strategy is scientifically robust and pragmatically vital for resource-limited and geographically dispersed healthcare systems, ensuring equitable access to precision oncology while maintaining diagnostic safety.

Author Contributions

ABA, TNP, and MYAF contributed equally to the conceptualization, methodology, data extraction, analysis, and manuscript preparation. All authors have read and approved the final manuscript.

Funding

No funding support was received for the conduct of this research or the preparation of this article.

Declaration of Conflicting Interests

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data Availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

ISSN:

Ethical Clearance

This study is a systematic review and meta-analysis of previously published literature. It did not involve any direct intervention, interaction, or data collection from human participants or animals by the authors. Therefore, formal ethical approval from an Institutional Review Board (IRB) or ethics committee was not required.

Acknowledgement

The authors acknowledge the Faculty of Medicine, Universitas Negeri Malang, for their academic environment and support.

References

Statista. SEA: share of new male cancer cases by type. 2022. Available from: https://www.statista.com/statistics/1112481/southeast-asia-share-of-cancer-cases-in-males-by-type/

Statista. Lung cancer mortality rates by region worldwide 2022. 2022. Available from: https://www.statista.com/statistics/1286286/lung-cancer-mortality-rates-worldwide-region/

Siddiqui F, Vaqar S, Siddiqui AH. Lung Cancer. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025.

Izumi M, Suzumura T, Ogawa K, Matsumoto Y, Sawa K, Yoshimoto N, et al. Differences in molecular epidemiology of lung cancer among ethnicities (Asian vs. Caucasian). J Thorac Dis. 2020;12(7):3776-84.

Midha A, Dearden S, McCormack R. EGFR mutation incidence in non-small-cell lung cancer of adenocarcinoma histology: a systematic review and global map by ethnicity (mutMapII). Am J Cancer Res. 2015;5(9):2892–911.

Heriyanto DS, Trisnawati I, Rachmadi L, Tenggara JB, Lau V, Gunawan AN, et al. Spectrum of rare EGFR mutations in Indonesian lung adenocarcinoma: Findings from an 8-year analysis of 4,778 cases highlighting the need for advanced targeted therapies. Narra J. 2025;5(2):e1721.

Pakkala S, Ramalingam SS. Personalized therapy for lung cancer: striking a moving target. JCI Insight. 2018;3(15).

McLean AEB, Barnes DJ, Troy LK. Diagnosing Lung Cancer: The Complexities of Obtaining a Tissue Diagnosis in the Era of Minimally Invasive and Personalised Medicine. J Clin Med. 2018;7(7):163.

Tajarernmuang P, Ofiara L, Beaudoin S, Gonzalez AV. Bronchoscopic tissue yield for advanced molecular testing: are we getting enough? J Thorac Dis. 2020;12(6):3287–95.

Wang N, Zhang X, Wang F, Zhang M, Sun B, Yin W, et al. The Diagnostic Accuracy of Liquid Biopsy in EGFR-Mutated NSCLC: A Systematic Review and Meta-Analysis of 40 Studies. SLAS Technol. 2021;26(1):42–54.

Soeroso NN, Taufik H, Tarigan SP, Mutiara E. Concordance of Epidermal Growth Factor Receptor Mutation from Tissue Biopsy and Plasma Circulating Tumor DNA in Treatment-Naïve Lung Adenocarcinoma Patients. Open Access Maced J Med Sci. 2022;10(T7):164–9.

Mirikar D, Banerjee N, Prabhash K, Kaushal RK, Naronha V, Pramesh CS, et al. Comparative analysis of EGFR mutations in circulating tumor DNA and primary tumor tissues from lung cancer patients using BEAMing PCR. Sci Rep. 2025;15(1):1252.

Zwierenga F, Muntinghe-Wagenaar MB, Rozendal P, De Langen AJ, Hendriks LEL, Van Den Heuvel M, et al. Circulating Tumor DNA in Advanced EGFRex20+ NSCLC: Concordance with Tissue Biopsy, Monitoring of Response, and Resistance to High-Dose Osimertinib. Target Oncol. 2025;20(4):663–77.

Malapelle U, Nasirova F, Wang A, Cooper M, Salomonsen R, Baser E, et al. Liquid biopsy and tissue biopsy for the detection of EGFR mutations in patients with stage III non-small-cell lung cancer: an observational real-world study. ESMO Open. 2026;11(1):106029.

Kang YK, Shin DH, Park JY, Hwang CS, Lee HJ, Lee JH, et al. Comparison of tissue-based and plasma-based testing for EGFR mutation in non–small cell lung cancer patients. J Pathol Transl Med. 2025;59(1):60–7.

Zhang M, Feng Y, Qu C, Meng M, Li W, Ye M, et al. Comparison of the somatic mutations between circulating tumor DNA and tissue DNA in Chinese patients with non-small cell lung cancer. Int J Biol Markers. 2022;37(4):386–94.

Ho HL, Wang FY, Chiang CL, Tsai CM, Chiu CH, Chou TY. Dynamic Assessment of Tissue and Plasma EGFR-Activating and T790M Mutations with Droplet Digital PCR Assays for Monitoring Response and Resistance in Non-Small Cell Lung Cancers Treated with EGFR-TKIs. Int J Mol Sci. 2022;23(19):11353.

ISSN:

Appendix

Table 3. The Characteristics of NSCLC Patients in the Included Studies.

Study	Country	Design	Sample Size (n)	Median Age (Years)	Gender (Male/Female)	Cancer Stage
Mirikar et al. (2025) (12)	India	Prospective	100	54	67 / 33	NG
Zwierenga et al. (2025) (13)	Netherland	Retrospective	25	67	8 / 17	NG
Malapelle et al. (2026) (14)	Italy	Retrospective	425	67	218 / 207	IIIA - IIIC
Kang et al. (2025) (15)	Korea	Retrospective	248	67	106 / 142	I - IV
Zhang et al. (2022) (16)	China	Retrospective	125	62	78 / 47	I - IV
Ho et al. (2022) (17)	Taiwan	Prospective	137	64	61 / 76	IIIB - IV
Prabhash et al. (2022) (18)	India	Prospective	245	58	158 / 87	IV

ISSN:

Study	Country	Design	Sample Size (n)	Median Age (Years)	Gender (Male/Female)	Cancer Stage
Soeroso et al. (2022) (11)	Indonesia	Cross-Sectional	100	60	71 / 29	I - IV
Vendrell et al. (2020) (19)	France	Observational	3	71	1 / 2	IV
Fu et al. (2021) (20)	Canada	Retrospective	50	65	27 / 23	IIIB - IV

NG: not given

ISSN:

Table 4. Technical Methodologies for Liquid and Tissue Biopsy

Study	Liquid Biopsy Details			Tissue Biopsy Details	
	Sample (Vol)	**DNA Extraction**	**Detection Platform**	**Sampling Method**	**Analysis Method**
Mirikar et al. (2025) (12)	Plasma (10 mL)	DNA Micro Kit	BEAMing PCR	FFPE tumor tissue	qPCR
Zwierenga et al. (2025) (13)	Plasma	Guardant Health	NGS	Histological & Cytological	NGS
Malapelle et al. (2026) (14)	Plasma	NG	NGS, PCR, IHC, Others	NG	NGS, PCR, IHC, Others
Kang et al. (2025) (15)	Plasma (10 mL)	Cobas EGFR Mutation Test v2	Real-time PCR	Biopsy, Resection	Real-time PCR
Zhang et al. (2022) (16)	Plasma (10 mL)	QIAamp Circulating Nucleic Acid Kit	NGS	FFPE tumor tissue	NGS
Ho et al. (2022) (17)	Plasma (10 ml)	Cobas cfDNA Sample Preparation Kit	ddPCR	Tumor Biopsy, Macrodissection	ddPCR, Cobas EGFR Mutation Test
Prabhash et al. (2022) (18)	Plasma	NG	NGS	NG	Histopathology, EGFR Mutation Testing
Soeroso et al. (2022) (11)	Plasma (8 - 10 ml)	QIAamp DNA Micro Kit	ddPCR	Bronchoscopy, Core Biopsy	PCR HRM
Vendrell et al. (2020) (19)	Plasma	QIAamp Circulating Nucleic Acid Kit	NGS, ddPCR	Surgical Resection, Bronchoscopy	Histopathology & IHC, NGS

ISSN:

Fu et al. (2021) (20)	Plasma (8 ml)	QIAamp Circulating Nucleic Acid kit	NGS, ddPCR	NG	NGS, Cobas EGFR Mutation Test

BEAMing: beads, emulsion, amplification, magnetics; PCR: polymerase chain reaction; FFPE: formalin-fixed paraffin-embedded; qPCR: quantitative real-time PCR; NGS: next generation sequencing; IHC: immunohistochemistry; ddPCR: droplet digital polymerase chain reaction; EGFR: epidermal growth factor receptor; HRM: high-resolution melting; DNA: deoxyribonucleic acid; cfDNA: cell-free DNA; NG: not given

ISSN:

Table 5. Diagnostic Performance of Liquid Biopsy for EGFR Mutation

Study	Primary Outcome	Secondary Outcome				Raw Data (TP / FP / FN / TN)
	Concordance Rate	Sensitivity	Specificity	PPV	NPV	
Mirikar et al. (2025) (12)	Exon 19: 98.8% Exon 21: 95.5%	Exon 19: 100% Exon 21: 72.7%	Exon 19: 98.5% Exon 21: 98.7%	Exon 19: 95.5% Exon 21: 88.9%	Exon 19: 100% Exon 21: 96.2%	Exon 19: 21 / 1 / 0 / 65 Exon 21: 8 / 1 / 3 / 75
Zwierenga et al. (2025) (13)	65%	65%	N/A	100%	0%	13 / 0 / 7 / 0
Malapelle et al. (2026) (14)	93%	45%	98%	67%	95%	24 / 12 / 29 / 518
Kang et al. (2025) (15)	56.1%	34.6%	70.0%	42.9%	62.2%	9 / 12 / 17 / 28
Zhang et al. (2022) (16)	80.0%	63.8%	89.7%	78.9%	80.3%	30 / 8 / 17 / 70
Ho et al. (2022) (17)	71.4%	53.3%	85.0%	72.7%	70.8%	8 / 3 / 7 / 17
Prabhash et al. (2022) (18)	82.9%	68.4%	90.1%	77.1%	85.3%	54 / 16 / 25 / 145
Soeroso et al. (2022) (11)	83.0%	45.0%	92.5%	60.0%	87.0%	9 / 6 / 11 / 74
Vendrell et al. (2020) (19)	100%	100%	N/A	100%	N/A	3 / 0 / 0 / 0

ISSN:

Fu et al. (2021) (20)	78.3%	N/A	N/A	N/A	N/A	N/A

ISSN: