

CCL7 as an Emerging Diagnostic Biomarker in Lung Cancer: Integrating Clinical Utility with Established Serum Markers and Risk Factors

Zena M. Kadhm¹^{*}, Farah A. Rashid¹ and Dheaa S. Zageer¹

¹Al-Nahrain University, Baghdad, Iraq.

*Corresponding Author: Zena M. Kadhm

DOI: <https://doi.org/10.55145/ajbms.2026.05.02.001>

Received 14 April 2026; Accepted 14 May 2026; Available online August 2026

ABSTRACT: Most lung cancer patients are diagnosed late, making it one of the deadliest diseases worldwide. Thus, early diagnosis and clinical decision-making need reliable circulating biomarkers, and this review evaluates the diagnostic potential of blood biomarkers, including CEA, CYFRA 21-1, and the novel immune-related biomarker CCL7 (MCP-3), and evaluates biomarker sensitivity, diagnostic thresholds, and clinical application, over fifty peer-reviewed clinical trials and meta-analyses. The diagnostic sensitivity of CEA is 40% to 65% (AUC: 0.72-0.84), notably in lung adenocarcinoma, whereas CYFRA 21-1's is nearing 60% (AUC: 0.82-0.91), in squamous cell carcinoma, and is frequently utilized in tumor staging and treatment monitoring. Combining CEA and CYFRA 21-1 increased diagnostic sensitivity to 80% (AUC: 0.88-0.94) in many trials, demonstrating the potential of multi-marker diagnostic panels, and CCL7 is associated with tumor progression, metastasis, and immune cell recruitment in the tumor microenvironment, according to recent research. Thus, immune-functional indicators may enhance tumor diagnosis when combined with conventional markers. These findings suggest that multi-biomarker methods, particularly those incorporating chemokine-based markers like CCL7, may enhance lung cancer diagnosis and treatment. The finding highlights that CCL7 and other serum markers serve as effective early warning indicators and monitoring tools rather than static indicator, providing critical utility in tracking disease progression and treatment response in lung cancer patients.



Keywords: Lung Cancer, Risk factors, CEA, MCP-3 (CCL7), Tumor Microenvironment

1. INTRODUCTION

Annually, 2.2 million new lung cancer cases strain public health infrastructures due to its genetic and clinical [1, 2]. Figure 1 shows the type of lung cancer its divided into two type 15% Small Cell Carcinoma (SCLC) and 85% non-small cell carcinoma (NSCLC), which is subdivided into 40% adenocarcinoma, 25% squamous cell carcinoma and 15% large cell carcinoma. Tumor progression or basal membrane rupture causes prolonged cough, hemoptysis, and sudden dyspnea [3].

Low-Dose Computed Tomography (LDCT) screening technologies have improved, but high operational costs, radiation concerns, and false-positive rates that may surpass 20% contribute to unneeded invasive treatments [4,5]. Clinically, liquid biopsies and AI-augmented panels are required for the disease early detection [6,7]. It was found that Carcinoembryonic Antigen (CEA) and Cytokeratin 19 fragment (CYFRA 21-1) are promising clinical markers [8,9,10,11]. Recently, it was shown that chemokine CCL7 (MCP-3), a crucial mediator in tumor-immune dynamics, is providing a novel viewpoint on the tumor microenvironment. Thus, understanding multi-phasic etiology and the multiple risk factors that cause disease is essential for developing better diagnostic methods.

The article critically evaluates the main blood biomarkers used to identify lung cancer, focusing on carcinoembryonic antigen (CEA) and cytokeratin-19 fragment (CYFRA 21-1), and explores the rising relevance of immune-related biomarker CCL7. This study explores biomarkers' effects on tumor development, immune-tumor

interactions, and clinical staging. integrate tumor markers with immune mediators may enhance lung cancer diagnosis, early detection, and care by providing more precise and tailored diagnostic techniques.

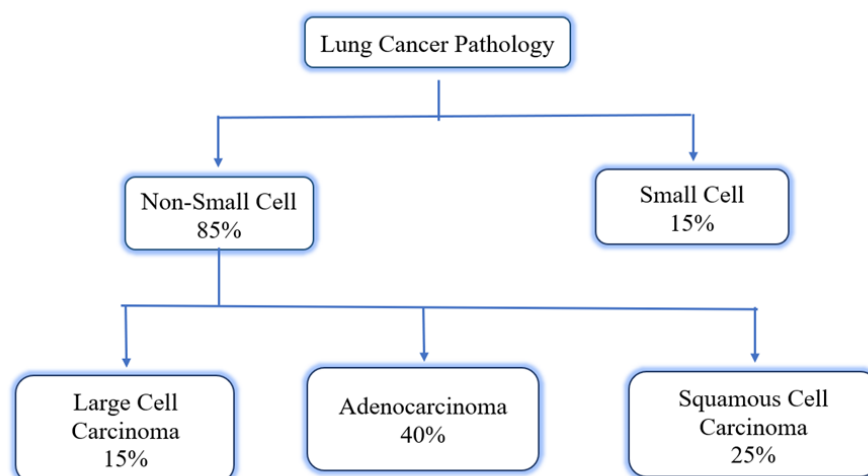


FIGURE 1. - Histologic classification of lung cancer. The two major lung cancer histologic categories (NSCLC and small cell lung carcinoma) and the most common histologic subtypes among NSCLC (adenocarcinoma, squamous cell carcinoma, and large cell carcinoma)[12]

Traditional tumor markers and immune-related biomarkers may enhance early detection and clinical decision-making in the future, and the CEA and CYFRA 21-1 are blood indicators for disease progression and therapy response, but their limited sensitivity in early-stage lung cancer suggests the need for more sensitive biomarkers.

Recent study suggests next-generation panels may use CCL7 as a biomarker. Instead of measuring tumor burden, CCL7 depicts the dynamic interaction between tumor cells and the immune environment. Therefore, future research should verify CCL7 in multi-marker diagnostic models that combine structural tumor markers with immune signaling mediators. More comprehensive molecular signature models may increase diagnostic sensitivity and minimize false-negatives.

2. METHODOLOGY

In this review, we used Google Scholar to comprehensive literature search to identify multiple studies such as the role of CCL7 as diagnosis marker in lung cancer. The search strategy employed specific keywords, including Lung Cancer, Risk factors, CEA, MCP-3 (CCL7), Tumor Microenvironment. We focus on provide a balanced historical and contemporary perspective on the review. The literature search was conducted from December 2025 to April 2026. A total of 62 peer – reviewed studies were initially identified; 52 studies were selected for final review. The selection criteria focused on peer-reviewed articles, clinical trials, and previous meta-analyses published in English, ensuring the reliability and scientific integrity of the gathered data. No primary statistical analysis was performed; data (sensitivities, specificities and Area Under the Roc (AUC)) were extracted from published meta-analyses.

3. PATHOGENESIS AND MULTIFACTORIAL RISK PROFILES

Chronic environmental stresses and innate genetic fragility cause normal pulmonary cells to become malignant [6,13]. A dangerous mistake containing 7,000 compounds is produced by smoking its considered the main reason .At least 70 carcinogens produce DNA adducts, causing cancer [3,14]. Tobacco-specific nitrosamines (TSNAs) such Nicotin-Derived Nitrosamine Ketone (NNK) and polycyclic aromatic hydrocarbons are crucial to cellular malignancy. Lung cancer is more common among non-smokers, proving that alternative environmental pressures kill. Figure 2 illustrates the risk factors that include radon, asbestos, mental stress ,aging, life style and PM2.5 [1,15]. PM2.5 particles, 30 times smaller than a hair, may enter deep alveoli [16].

Genetic variants in xenobiotic-metabolizing enzymes and DNA repair pathways and newly found susceptibility loci greatly affect [6,13,17]. Chronic Obstructive Pulmonary Disease (COPD)- related chronic pulmonary inflammation

causes oxidative stress, hypoxia-induced metabolic adaption, and rapid cytokine turnover, creating a pro-tumorigenic milieu [3,18]. These risk profiles alter serum biomarker baseline concentrations and diagnostic efficiency in subsequent making them clinically important [6,19]. Based on multiple studies

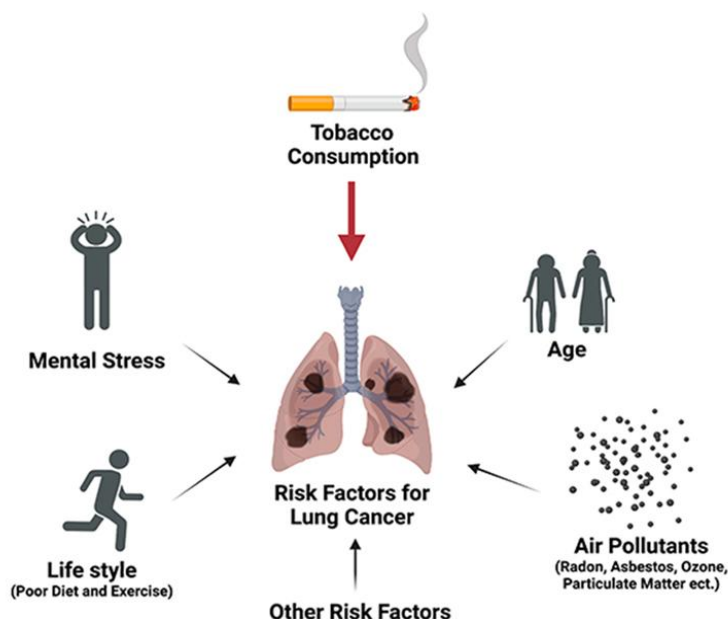


FIGURE 2. - Shows how environmental carcinogens (tobacco, PM2.5, radon), genetic susceptibility (DNA repair gene polymorphisms), and the pro-tumorigenic microenvironment combine to cause multi-phasic lung cancer Adapted from [20]

4. CLINICAL AND DIAGNOSTIC IMPORTANCE OF CARCINOEMBRYONIC ANTIGEN (CEA)

CEA is a diagnostic for thoracic oncology. The ectopic expression of this conjugate, high-molecular-weight glycoprotein in adult blood constitutes a biochemical marker for malignancy (especially in glandular epithelial tissues), [21,10] thus providing the basis for continued monitoring of serum CA-125 levels as part of clinical follow-up. The histology marker was notably better with AUC:0.72-0.84 for squamous cell diagnoses when CEA values are at a higher-than-normal level, with sensitivity from 40%-65%. Besides that, CEA is one of the liquid biopsies that can perform in a non-invasive nature with service related to its response to therapy. A CEA decline > 50% at six weeks following therapy predicts survival and prognosis. Rising CEA values >5.0 ng/mL following surgery could be indicative of residual tumor activity or relapse, particularly in the setting of early recurrence [22,23]. Although it is used and helpful clinically, interpreting claims for CEA levels is inherently difficult. For example, this marker predicts post treatment recurrence with 70% accuracy in symptomatic patients but much less so in stage I, II oncogenesis. This limitation occasionally requires a multi-marker panel to avoid false-negative results. Similar to the previously discussed levels of CEA, Figure 3 demonstrates how levels can ever increase from smoking and inflammatory diseases such as cirrhosis and pneumonia [19] indicating that CEA could also be elevated in non-malignant disease (benign) at anywhere between 10-20 ng/ml with malignant being high over 20ng/ml. Among the 277 advanced NSCLC patients, before treatment, 55.9% of them had a baseline CEA levels >5ng/mL as reported in included studies at the diagnosis time point. High CEA subgroup exhibited dramatically shorter median progression-free survival (5.3months vs 7.4 months) and median overall survival (10.0 months vs 14.0 months) than the normal serum CEA level group ($P < 0.04 - 0.0001$) [41]. A meta-analysis showed that serum CEA levels in NSCLC patients were 4.21ng/mL vs.1.50ng/mL in healthy controls ($P < 0.001$), supporting its significant elevation and role as a complementary lung cancer diagnostic alongside other markers [42]. In a separate study, baseline CEA >10 ng/mL was associated with a significantly higher risk of disease progression in NSCLC (hazard ratio 1.83, $P = 0.012$), suggesting that higher cut-off values may more strongly predict aggressive disease [43].

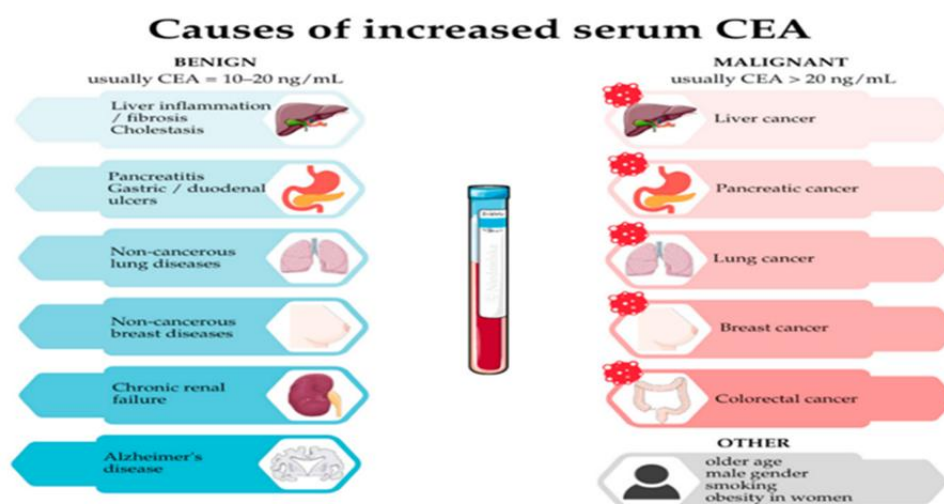


FIGURE 3. - Malignant (adenocarcinoma), non-malignant (cirrhosis, pneumonia), and lifestyle variables (smoking) affecting serum CEA levels, with clinical cutoffs Amended from [1,24]

5. CYTOKERATIN-19 FRAGMENT (CYFRA 21-1)

CYFRA21-1 is a cytokeratin showed in simple epithelium, including the bronchial epithelium, and in cancerous tumor generated from these cells [41]. Cytokeratin-19 fragment (CYFRA 21-1) is the primary blood biomarker for SCC and a strong indication of surgical resect ability. In malignant epithelial growth, soluble cytokeratin-19 fragments reach the systemic circulation as CYFRA 21-1 due to rapid cellular turnover [8,11]. In SCC cohorts, it is shown that CYFRA 21-1 has 60% sensitivity (AUC:0.82-0.91), compared to CEA 15% to 20% in the same histological subtype. The stage and tumor burden of malignant influence CYFRA 21-1 therapeutic value. Serum levels exceeding 3.3 ng/mL indicate advanced disease (TNM Stages III and IV) and vascular invasion at baseline clinical examination, providing a prognostic signal [5,25] These markers differentiate primary lung malignancies from COPD and pulmonary fibrosis, where blood levels seldom meet pathological requirements [5,3].

It was found that CYFRA 21-1 kinetic could be used to monitoring therapeutic effectiveness and staging. After early treatment cycles, marker levels decline >50% from baseline, indicating partial remission response [26]. Moreover, it was shown that early responders had a median of 8.4 months, twice as long as non-responders [27]. The diagnostic accuracy and sensitivity of serum CYFRA 21-1 for the detection of lung cancer were highest [46]. The serum CYFRA 21-1 levels were most highly elevated in lung carcinoma patients (in particular UICC Stage IV patients) across different histologic types and attained 85.1% sensitivity when using a threshold of 3.5 ng/mL. The diagnostic sensitivity for detecting lung carcinoma was substantially enhanced by means of combined assays of CYFRA 21-1 with CEA overall for lung cancer, with SCC for squamous cell carcinoma, and with CEA for adenocarcinoma [46]. previous studies have demonstrated that CYFRA 21-1 is a reliable tumor biomarker in non-small cell lung cancer (NSCLC). The serum level of CYFRA 21-1 in NSCLC was significantly higher than that in healthy control individuals ($p < 0.001$), indicating high diagnostic accuracy of the tumor marker. In addition, higher concentrations of CYFRA 21-1 were observed in advanced stage disease with poor clinicopathological behavior [47]. Karnak et al. Lung cancer patients had much higher odds of positive CYFRA 21-1 levels than controls ($p < 0.05$), and upon treatment, it decreased ($p < 0.01$) [48].

6. CHEMOKINE (C-C MOTIF) LIGAND 7(CCL7), MONOCYTE CHEMOATTRACTANT PROTEIN-3 (MCP-3) IN IMMUNE-BASED DIAGNOSTICS

And chemokine is a small cell signaling protein and gene and acts as the traffic agents of the body. They also bind to certain receptors on the cell surface and are involved in directing cells to specific locations, where they perform essential roles in embryonic development, tissue maintenance and immune responses [44,45]. By anchoring gradients to the tissue matrix or dissolving them in solution to direct cells. It plays an important role in guiding immune cells to locations of infection, regulating their movement pattern and as a navigational system for another class of mobile cells - stem cells. Graphical Abstract Chemokine (C-C motif) ligand 7(CCL7), formerly Monocyte Chemo attractant Protein-3 MCP-3, is a new paradigm in focusing from tumor mass markers to immune-driven cancer diagnostics. CCL7, a CC chemokine (11 kDa) and high-affinity ligand with complex oligomerization that acts mechanistically more as a key regulator instead of a soluble beacon in lung tumor microenvironment [28,29]. It is located on chromosome 17q11 in humans (see CCL7). 2q12, near a group of monocyte-recruiting proteins. The chemokine receptor CCR1, CCR2, and

CCR3 are chemoattractant for T lymphocytes eosinophil, monocytes as a result of genetic and structural disposition of CCL7 [30]. In contrast to biomarkers such as CEA and CYFRA 21-1 which correlate merely with tumor volume, the dynamic chemokine CCL7 can be a reflection of this complex interaction between cancerous growth and host immune system. The aforementioned characteristics of this biosensor for tumor-associated inflammation and metastatic evolution is unsurprising in its offering as a potential clinical diagnostic. Our recent findings demonstrated that high levels of blood CCL7 and a higher correct rate for advanced clinical staging as well as lymphatic metastasis are indicators for lung cancer [13]. Its expression levels correspond with tumor grade and TNM stage and enhance metastasis via CCR3 signaling [31,32].

The CCL7 accurately detects early oncogenes is cellular alterations. By attracting tumor-associated macrophages (TAMs), furthermore, research indicates that systemic concentration of CCL7 triples the risk of distant metastasis in NSCLC patients [32]. It was found that CCL7 is a notable clinical biomarker for lung cancer bone metastases, with high expression levels indicating poor prognosis [33]. The "molecular lens" of CCL7 into tumor aggressiveness and vascular regulation may reveal a biological [34]. The metabolic regulation of immune cell migration and the interactions between cancer-associated fibroblasts substantially change CCL7 signaling, therapy-mediated diagnostic sensitivity in intricate microenvironments [35,36]. The CCL7 serum level variations are being investigated as "real-time" biomarkers of immunotherapy responsiveness and the arrival of conventional type 1 dendritic cells (cDC1) [37]. Further, characteristics of immune checkpoint drug treatment suggest an initial increase and subsequent decline in CCL7 is associated with improved Objective Response Rate (ORR). Dempe et al. Such a paradigm shift in the diagnostic framework can help bridge detection and diagnosis, advancing beyond basic anatomic detection towards organized synergistic integration into personalized cancer therapy through triaging of real-time release of biological biomarkers predicted by CCL7 [38]. Several recent studies have highlighted the significant role of CCL7 (MCP-3) in the progression of lung cancer. showing levels of CCL7 have been observed in lung cancer patients compared with control group, showing a significant distribution increase ($p < 0.05$), which reflects its involvement in tumor development and immune cell recruitment. Additionally, CCL7 has been reported to contribute to tumor microenvironment modulation by enhancing inflammatory responses and promoting tumor growth. Deregulated expression of CCL7 was also associated with increased tumor invasion and metastasis, further supporting its role in cancer progression. Moreover, chemokine including CCL7 have been linked to immune cell in tumor tissues, which plays a role in disease development and patient prognosis.[49,50,51,52].

Table 1 analyzes lung cancer blood biomarkers' biological features, sensitivity ranges, and therapeutic usage.

Table 1. - Comparative diagnostic characteristics of biomarkers used in lung cancer

Biomarker	Biological nature	Major associated lung cancer subtype	Reported sensitivity	Clinical diagnostic threshold	Clinical applications	Key references
Carcinoembryonic Antigen (CEA)	Glycoprotein tumor marker involved in cell adhesion	Mainly adenocarcinoma of NSCLC	~40-65%	>5 ng/mL	Diagnosis support, monitoring therapeutic response, detection of recurrence	Grunnet & Sorensen, 2012
CYFRA 21-1	Fragment of cytokeratin-19 released during epithelial cell turnover	Squamous cell carcinoma (SCC) of NSCLC	~55–65%	>3.3 ng/mL	Tumor staging, prognosis assessment, monitoring treatment response	Pang et al., 2013
CCL7 (MCP-3)	CC-chemokine involved in immune cell recruitment and tumor microenvironment regulation	Associated with metastatic progression in NSCLC	Emerging biomarker (not fully standardized)	Not yet standardized	Indicator of tumor-immune interaction, metastasis prediction, immunotherapy monitoring	Wu et al., 2018

7. EARLY LUNG CANCER BIOMARKERS HAVE LIMITED SENSITIVITY AND SPECIFICITY

Integrated biomarker panels with several molecular indications are being developed to increase diagnosis accuracy. As lung cancer is varied, biomarkers show tumor load, epithelial cell turnover, and immune microenvironment activity. CYFRA 21-1 and CEA are common oncology blood indicators. CEA tracks adenocarcinoma burden and therapy, whereas CYFRA 21-1 tracks squamous cell carcinoma stages and prognoses. Early-stage lung cancer diagnosis is largely unsuccessful with these biomarkers

Novel immune-related indications and established biomarkers may improve diagnosis. The tumor microenvironment (TME) is more complicated because of the interactions between tumors and the immune system which can be illustrated by a chemokine like CCL7. On the other hand, incorporating the CEA, CYFRA 21-1 and immune mediator multi-marker panels increases diagnostic sensitivity while decreasing false-negatives. Integrating diagnostic models might help precision oncology and early molecular detection of lung cancer.

8. CHALLENGES AND ETHICAL CONSIDERATIONS IN BIOMARKER CLINICAL APPLICATION

The CEA, CYFRA 21-1 and CCL7 are of great diagnostic value, but in oncology we also have a challenge [39,40] as some biological interferences by non-malignant whole illnesses and the reduction on lymphocyte-mediated cytotoxicity for the diagnosis. Chronic inflammation, tobacco smoking and benign pulmonary disorders may also account for false-positives [14,1]. Genetic heterogeneity may prevent a uniform biomarker signature from being effective for lung neoplasms, with DNA repair gene polymorphisms such as ERCC1 and hOGG1 varying so widely among cohorts of patients that they potentially create major differences in lung cancer susceptibility. Advanced "Liquid Biopsy" and multi-marker testing panels pose medical fairness and global accessibility ethical concerns, and advanced chemokine detection tests, such as CCL7, are pricey and only available at university institutions, and in resource-limited places, geographic and financial concentration may promote oncological inequalities [16,2].

Early oncogenesis molecular alterations must be clinically validated to avoid over diagnosis and ethical issues with therapeutic use; these biomarkers must balance early detection with premium non nosier to prevent clinical over – diagnosis and avoid subjecting patients to unnecessary invasive procedure (first, do no harm). Patients should not undergo invasive therapies or psychological suffering before a cancer diagnosis [21,5,4].

9. FUTURE PERSPECTIVES AND STRATEGIC RECOMMENDATIONS

Integrative Diagnostic Intelligence is replacing biomarker testing in lung cancer diagnosis These strategy efforts should address clinical gaps:

- Use CCL7 immune-functional insights and CEA/CYFRA 21-1 structural data to develop Diagnostic Scores in future research, and early detection and diagnostic sensitivity range 75–85% (0.82-0.88) depending on study need synergistic panels, maybe with AI-augmented exosomal detection.
- For CCL7, longitudinal studies have to be performed on the variances in Chemokine Kinetics during immunotherapy and these kinetic patterns should consist of especially those related to recruitment of cDC1 dendritic cells. This marker that can be utilized to real-time detection of disease biomarkers consistent with CCL7 could become a true molecular sensor for treatment optimization by monitoring ORR and resistance, in order to personalize therapy regimens. Have affordable POC [1] diagnostic solutions progressed from simple biochemical tests to complex multiplex tests, aimed at reducing the burden and increasing accessibility? Do they democratize access for basic (i.e. even rudimentary care) healthcare screening where relevant especially in vulnerable populations living in areas where radon and asbestos represent environmental exposures PM2 [1,3,16]? A full Diagnostic Signature from genomic and biochemical studies, both serum protein concentrations as well as some patterns of genetic architecture may focus tightly on DNA repair efficiency and metabolic control of immunological migration. This full-spectrum approach compensates for biological heterogeneity (including hypoxia-induced metabolic adaptation) for optimal clinic outcomes [6,13,18,40].
- Combining biomarkers with chemokine is the next precision oncology frontier. Clinicians may reduce lung cancer mortality by identifying it earlier, better, and less invasively [19].

10. LIMITATIONS OF CURRENT BIOMARKER STUDIES

The CEA and CYFRA 21-1 clinical trials are variable and restrict lung cancer blood biomarker usage despite advancements, and due to study design, patient demographics, tumor histological subtypes, and laboratory detection methods, the sensitivity and specificity of these markers vary substantially across publications. Another biomarker issue is variable cutoff thresholds, as assays and platforms may alter biomarker quantification, complicating lab clinical

comparisons, such as chronic lung, liver, and smoking-related inflammation, which may raise tumor markers. Biological interference may lower diagnostic accuracy and increase false positives, and the CCL7 and other novel markers are clinically examined. Given that most research is based upon small patient cohorts or experimental models, generalizability is limited; large prospective clinical trials will be needed to demonstrate diagnostic efficacy and establish thresholds [9].

11. CONCLUSION

Lung cancer biomarker-based detection can only be feasible if those obstacles are also overcome. Conclusion we show how CEA, CYFRA 21-1, and CCL7 integration presents a combination that offers a more effective single frame work than any of the markers independently provide for lung cancer management. CEA and CYFRA 21-1 are the reference standard for tissue subtype identification (e.g., adenocarcinoma versus squamous cell carcinoma), but they fail to include one of the essential components by ED Honn et al. CCL7 (MCP-3) immune profiling data is a much-needed missing piece. This composite helps in accurate assessment of the tumor microenvironment and subsequently the risk of metastasis by researchers. However, its clinical implementation also faces a series of analytical challenges such as inter-laboratory inconsistency and biological variability among patients. To overcome such limitations, standardized biomarker panels will also help improve diagnostic sensitivity and specificity. This will subsequently enable clinical laboratories to track the synergistic kinetic profiles of these markers which will mean-focused therapy regimens and real-time monitoring of treatment response. Moving towards this integrative style of practice will reduce the number of invasive procedures and drive precision medicine, resulting in better patient outcomes and quality of life. These biomarkers can still be useful for diagnostic support data but mostly for long-term monitoring and prognostic value. Since CEA, CYFRA 21-1, and CCL7 are noninvasive biomarkers, monitoring tumor adaptability can be obtained by simply repeating blood sampling compared to obtaining tumor biopsies that are invasive. By combining these markers in a synergistic panel, we can optimize the real-time tracking of treatment efficacy and establish a clinical basis for timely intervention and personalized therapy.

Funding

None

ACKNOWLEDGEMENT

Acknowledgements and Reference heading should be left justified, bold, with the first letter capitalized but have no numbers. Text below continues as normal.

CONFLICTS OF INTEREST

The authors declare no conflict of interest

REFERENCES

- [1] World Health Organization, "Radon and Health Fact Sheet," WHO, Geneva, Switzerland, 2023.
- [2] R. L. Siegel et al., "Cancer statistics, 2023: Global health crisis and pathogenicity," *CA Cancer J. Clin.*, vol. 73, no. 1, pp. 17–48, 2023.
- [3] P. Barta et al., "Chronic pulmonary inflammation and the pro-tumorigenic niche in lung cancer initiation," *Eur. Respir. Rev.*, vol. 28, no. 154, Art. no. 190011, 2019.
- [4] E. F. Patz et al., "Overdiagnosis and diagnostic equity in LDCT screening," *JAMA Intern. Med.*, vol. 174, no. 2, pp. 269–274, 2014.
- [5] A. A. Thai, B. J. Solomon, L. V. Sequist, J. F. Gainor, and G. J. Riely, "Lung cancer," *Lancet*, vol. 398, no. 10299, pp. 535–554, 2021.
- [6] B. Vogelstein et al., "Cancer genome landscapes," *Science*, vol. 339, no. 6127, pp. 1546–1558, 2013.
- [7] J. S. Kuo et al., "AI-augmented panels and exosomal detection in liquid biopsies for cancer monitoring," *Nat. Biotechnol.*, vol. 38, no. 11, pp. 1251–1259, 2020.
- [8] X. B. Wang, J. Li, and Y. Han, "Prognostic significance of preoperative serum carcinoembryonic antigen in non-small cell lung cancer: A meta-analysis," *Tumour Biol.*, vol. 35, no. 10, pp. 10105–10110, 2014.
- [9] M. Grunnet and J. B. Sorensen, "Carcinoembryonic antigen (CEA) as tumor marker in lung cancer," *Lung Cancer*, vol. 76, no. 2, pp. 138–143, 2012.
- [10] Z. Zhang et al., "Prognostic value of serum CEA and CYFRA 21-1 in patients with non-small cell lung cancer: A systematic review and meta-analysis," *Ann. Transl. Med.*, vol. 8, no. 21, Art. no. 1432, 2020.
- [11] L. Fu, R. Wang, L. Yin, X. Shang, R. Zhang, and P. Zhang, "CYFRA21-1 tests in the diagnosis of non-small cell lung cancer: A meta-analysis," *Int. J. Biol. Markers*, vol. 34, no. 3, pp. 251–261, 2019.

- [12] M. B. Schabath and M. L. Cote, "Cancer progress and priorities: Lung cancer," *Cancer Epidemiol. Biomarkers Prev.*, vol. 28, no. 10, pp. 1563–1579, 2019.
- [13] D. C. Christiani, "Genetic susceptibility, DNA repair genes, and lung cancer risk," *Annu. Rev. Public Health*, vol. 41, pp. 105–120, 2020.
- [14] International Agency for Research on Cancer, "Personal Habits and Indoor Combustions: A Review of Human Carcinogens," *IARC Monogr. Eval. Carcinog. Risks Hum.*, vol. 100E, pp. 373–499, 2012.
- [15] M. C. Turner et al., "Outdoor air pollution and cancer," *CA Cancer J. Clin.*, vol. 70, no. 6, pp. 460–479, 2020.
- [16] M. C. Turner et al., "Outdoor air pollution and cancer: An overview of current evidence," *CA Cancer J. Clin.*, vol. 73, no. 2, pp. 112–130, 2023.
- [17] J. D. McKay et al., "Large-scale association analysis identifies new lung cancer susceptibility loci," *Nat. Genet.*, vol. 54, no. 8, pp. 1167–1174, 2022.
- [18] P. Murray et al., "Hypoxia-induced metabolic adaptation in chemokine signaling," *Cancer Res.*, vol. 83, no. 8, pp. 1245–1258, 2023.
- [19] I. Trulsson and S. Holdenrieder, "Prognostic value of blood-based protein biomarkers in non-small cell lung cancer: A critical review and 2008–2022 update," *Tumour Biol.*, vol. 46, Suppl. 1, pp. S111–S161, 2024.
- [20] B. Freeman et al., "Opportunities and challenges of Kava in lung cancer prevention," *Int. J. Mol. Sci.*, vol. 24, Art. no. 9539, 2023.
- [21] W. D. Travis et al., "The 2015 World Health Organization Classification of Lung Tumors," *J. Thorac. Oncol.*, vol. 10, no. 9, pp. 1243–1260, 2015.
- [22] Y. He, Y. Cui, D. Chang, and T. Wang, "Postoperative CYFRA 21-1 and CEA as prognostic factors in patients with stage I pulmonary adenocarcinoma," *Oncotarget*, vol. 8, no. 42, pp. 73115–73122, 2017.
- [23] M. Tomita et al., "Prognostic significance of a tumor marker index based on preoperative serum CEA and KL-6 levels in NSCLC," *Asian Pac. J. Cancer Prev.*, vol. 18, no. 1, pp. 287–291, 2017.
- [24] J. Kacperczyk-Bartnik and A. Cymbaluk-Płoska, "Carcinoembryonic Antigen (CEA): Origin, role in oncology, and concentrations in serum and peritoneal fluid," *J. Clin. Med.*, vol. 14, no. 9, Art. no. 3189, 2025.
- [25] K. Okamura et al., "Advanced T-staging and vascular invasion linked to CYFRA 21-1 titers in NSCLC," *J. Surg. Res.*, vol. 185, no. 1, pp. 223–230, 2013.
- [26] L. Pang, J. Wang, Y. Jiang, and L. Chen, "CYFRA 21-1 as a predictor of objective response to chemotherapy," *Exp. Ther. Med.*, vol. 6, no. 2, pp. 355–360, 2013.
- [27] K. Sone et al., "Predictive role of CYFRA21-1 and CEA for subsequent docetaxel in non-small cell lung cancer patients," *Anticancer Res.*, vol. 37, no. 9, pp. 5125–5131, 2017.
- [28] X. Guan et al., "Chemokine signaling (CCL7) as a molecular beacon in the lung tumor microenvironment," *Front. Oncol.*, vol. 14, Art. no. 1334455, 2024.
- [29] G. Opdenakker et al., "Structural characterization of CCL7/MCP-3 as a high-affinity ligand," *Cytokine Growth Factor Rev.*, vol. 69, pp. 45–58, 2023.
- [30] S. Ali et al., "Dimerization of chemokine receptors in living cells," *J. Biol. Chem.*, vol. 280, no. 40, pp. 34375–34380, 2005.
- [31] H. Lee et al., "CCL7 promotes lung cancer metastasis through CCR3," *Oncogene*, vol. 35, no. 16, pp. 2029–2039, 2016.
- [32] Q. Wu et al., "CCL7 expression and the ABCE1 axis in aggressive tumor phenotypes," *Int. J. Oncol.*, vol. 52, no. 4, pp. 1234–1242, 2018.
- [33] Y. Han et al., "CCL7 as a diagnostic indicator for bone metastasis in lung adenocarcinoma," *J. Clin. Oncol.*, vol. 37, no. 15_suppl, Art. no. e21044, 2019.
- [34] A. Foster et al., "CCL7 regulation of tumor vasculature in lung cancer," *Angiogenesis*, vol. 27, no. 2, pp. 189–205, 2024.
- [35] M. Rajaram et al., "Cancer-associated fibroblasts and CCL7 signaling," *Cancer Res.*, vol. 73, no. 15, pp. 4764–4774, 2013.
- [36] M. Santos et al., "Metabolic control of chemokine-mediated immune cell migration," *Cell Metab.*, vol. 36, no. 2, pp. 289–304, 2024.
- [37] Nature Communications, "Recruitment of cDC1 dendritic cells and immunotherapy ORR prediction via CCL7," *Nat. Commun.*, vol. 11, Art. no. 4567, 2020.
- [38] S. Dempe et al., "CCL7 gene therapy enhances antitumor immunity," *Gene Ther.*, vol. 19, no. 12, pp. 1150–1157, 2012.
- [39] J. H. Russell and T. J. Ley, "Lymphocyte-mediated cytotoxicity," *Nat. Rev. Immunol.*, vol. 2, no. 10, pp. 787–795, 2002.
- [40] K. Kohli et al., "Chemokines in the tumor microenvironment: Implications for lung cancer and immunotherapy," *Front. Immunol.*, vol. 15, Art. no. 1443366, 2024.
- [41] S. Cedrés et al., "Serum tumor markers CEA, CYFRA21-1, and CA-125 are associated with worse prognosis in advanced non-small-cell lung cancer (NSCLC)," *Clin. Lung Cancer*, vol. 12, no. 3, pp. 172–179, 2011.

- [42] R. Fang et al., "Evaluation of serum biomarkers for NSCLC diagnosis: CEA and CYFRA21 levels in NSCLC vs. controls," *Front. Physiol.*, vol. 9, Art. no. 1710, 2018.
- [43] *Ann. Clin. Lab. Sci.*, "Comparison of tumor biomarkers in lung cancer vs. controls," *Ann. Clin. Lab. Sci.*, vol. 49, no. 5, pp. 645–651, 2019.
- [44] D. Raman, T. Sobolik-Delmaire, and A. Richmond, "Chemokines in health and disease," *Exp. Cell Res.*, vol. 317, no. 5, pp. 575–589, 2011.
- [45] T. J. Schall and A. E. Proudfoot, "Overcoming hurdles in developing successful drugs targeting chemokine receptors," *Nat. Rev. Immunol.*, vol. 11, no. 5, pp. 355–363, 2011.
- [46] M. Muraki et al., "Assessment of serum CYFRA 21-1 in lung cancer," *Cancer*, vol. 77, no. 7, pp. 1274–1277, 1996.
- [47] R. Pavicevic et al., "Serum tumor marker CYFRA 21-1 in the diagnostics of NSCLC lung cancer," *Coll. Antropol.*, vol. 22, no. 2, pp. 629–635, 1998.
- [48] D. Karnak et al., "Evaluation of CYFRA 21-1: A potential tumor marker for non-small cell lung carcinomas," *Lung*, vol. 179, no. 1, pp. 57–65, 2001.
- [49] Y. Yao et al., "CCL7 mediates tumor progression and immune cell infiltration in lung cancer," *J. Cancer*, vol. 12, no. 15, pp. 4560–4572, 2021.
- [50] J. Korbecki et al., "CCL7 in the tumor microenvironment: Biological functions and potential role in cancer progression," *Int. J. Mol. Sci.*, vol. 21, no. 20, Art. no. 7376, 2020.
- [51] B. Liang et al., "Aberrant expression of chemokines in lung cancer and their clinical significance," *OncoTargets Ther.*, vol. 12, pp. 10893–10902, 2019.
- [52] J. Zhou, L. Wang, and B. Sun, "CCL7 promotes the progression of non-small cell lung cancer by modulating the tumor microenvironment," *Cancer Biol. Ther.*, vol. 23, no. 1, pp. 1–10, 2022.