

BIOCHEMICAL AND IMMUNOLOGICAL ASPECTS IN LUNG CANCER

**Daniela TIȚA¹, Tatiana CIUREA², Ionuț STOICA³, Dumitra RADUCANU^{3*}
Jean CIUREA⁴, Gina Daniela PETRESCU⁵**

¹*Emergency County Hospital, Spiru Haret Street, no.2-4, 600114, Bacau, Romania*

²*Titu Maiorescu University, Faculty of Medicine, Gheorghe Petrascu Street, no.67A, 031593, Bucharest, Romania*

³*Vasile Alecsandri University of Bacău, Faculty of Science, University, Calea Marasesti Street, no 157,600115, Bacau, Romania*

⁴*National Institute of Neurology and Neurovascular Disease, Berceni Street, no.10-12,077160, Bucharest, Romania*

⁵*Pulmonology and Phthisiology Hospital, Radu S. Campiniu Street, no.21, 810003, Braila, Romania*

KEYWORDS	ABSTRACT
Bronchopulmonary cancer CYFRA 21-1 CEA NSE Tumor biomarkers Systemic inflammation Prognosis	Bronchopulmonary cancer is a major public health problem, being one of the leading causes of cancer mortality worldwide. Late-stage detection, compounded by the biological heterogeneity of the malignancy, severely limits the available therapeutic options and worsens clinical outcomes. In this context, the identification and evaluation of accessible tumor biomarkers, such as CYFRA 21-1, carcinoembryonic antigen (CEA) and neuron-specific enolase (NSE), may have an important role in characterizing the disease and monitoring its evolution. The association of tumor markers with systemic inflammation parameters may provide additional information on the patient's biological status and prognosis. Regarding the biomarkers monitored, CYFRA 21-1 demonstrated the highest sensitivity in the patients included in the study (e.g., 42.87% of women and 33.75% of men) for monitoring tumor progression.

INTRODUCTION

Bronchopulmonary cancer is a major public health problem, characterized by a high incidence and mortality rate and a frequent diagnosis established in advanced stages (Belanger et al., 2017; Bartkiewicz et al., 2024). Globally, the main risk factor for triggering lung cancer is smoking (Botnaru V., 2018; Chmielowski et al., 2017). The 2018 Global Adult Tobacco Study reported 30.7% tobacco prevalence among Romanians aged 15+, with 30% smoking an average of 16.5 cigarettes daily. Consequently, the associated disease burden is exacerbated by frequent presentation at advanced stages and biological heterogeneity, both of which represent major barriers to effective therapeutic intervention and worsen clinical outcomes.

Another factor with a high contribution to the occurrence of lung neoplasia is environmental, occupational and home pollution (Mayo Clinic Press, 2020; Weerakkody et al 2022; Sturgeon 2018).

Biomarker profiling is essential for evaluating lung masses of unknown etiology. Specifically, CYFRA 21-1 is established as a first-line indicator for tracking treatment efficacy and disease evolution in NSCLC, while also functioning as a reliable predictor of recurrence, metastasis, and overall prognosis (Jose et al., 2013; Hiradfar et al., 2015; Pass et al., 2014; Mindray, 2022). Alongside CEA, which similarly assists in monitoring disease recurrence and prognostic trajectories, CYFRA 21-1 contributes to differentiating NSCLC (Non-Small Cell Lung Cancer) from SCLC (Small Cell Lung Cancer) histologies. Conversely, NSE (Neuron-Specific Enolase) functions as the primary oncological marker for SCLC, where its expression levels exhibit a strong correlation with tumor size and the extent of metastasis (McDonald et al., 2017; Kay et al., 2017; Genet et al., 2024).

* Corresponding author: Raducanu D.

E-mail address: dora.raducanu@ub.ro

<https://doi.org/10.29081/SCSB.2026.35.2.01>

The biochemical parameters C-reactive protein (CRP), lactate dehydrogenase (LDH) and serum calcium do not have a role as specific tumor markers (they do not make a definitive diagnosis of cancer), but they are very important in assessing the patient's general condition, prognosis, monitoring the response to treatment and detecting complications in oncological diseases (Torre et al., 2016; Visser et al., 2023).

In lung cancer management, general biochemical parameters closely reflect tumor dynamics and systemic complications. CRP represents a valuable tool for risk assessment, progression tracking, and treatment monitoring, while LDH acts as a prognostic index and metastatic marker for both NSCLC and SCLC. Additionally, serum calcium homeostasis is frequently disrupted in these patients: hypercalcemia signals a paraneoplastic manifestation of advanced disease, whereas hypocalcemia is typically induced by cytotoxic chemotherapy or active tumor lysis (Bartkiewicz et al., 2024; Blanco et al., 2015; Dingemans et al., 2021; Gebbia et al., 2021; Hiradfar et al., 2015). This study evaluated the clinical relevance of tumor markers CYFRA 21-1, CEA, and NSE in bronchopulmonary cancer patients. Additionally, it examined their correlation with inflammatory biochemical parameters to identify potential indicators of disease progression and prognosis.

MATERIALS AND METHODS

The study presented in this paper includes 94 patients with a confirmed diagnosis of bronchopulmonary cancer hospitalized between January 2025 and March 2026 at the Brăila Pneumophthisiology Hospital. Patient selection was based on medical records and laboratory results available in the health unit's IT system, with the agreement of the institution's management and patients in accordance with ethical norms regarding data protection and confidentiality of medical data.

The biological material used is venous blood, collected fasting (without eating) or postprandial. It is collected in a vacutainer without anticoagulant, with/without separator gel. The determination of tumor markers: CEA, NSE, CYFRA 21-1 was performed on the COBAS E 411 automatic analyzer, provided by Roche Diagnostics, the analyzer is designed for in vitro, quantitative and qualitative measurements of a wide range of analytes using electrochemiluminescence technology (ECLIA). To determine the biochemical parameters (LDH, CRP, CALCIUM) the automatic analyzer Alinity C, Abbott, was used. The analysis was performed using spectrophotometric methods.

RESULTS AND DISCUSSION

A total of 94 patients were enrolled, including males (85%) and females (15%), with a calculated sex ratio (F:M) of 0.175: F/B=0.175 (Figure 1):

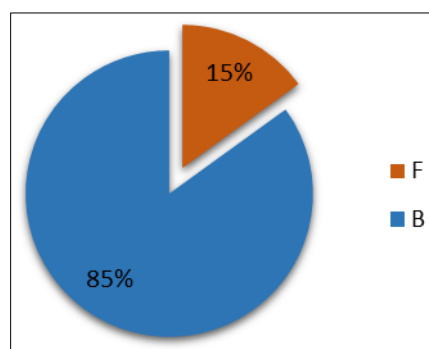


Figure 1. Gender distribution among patients with bronchopulmonary carcinoma

The analysis of the gender distribution of patients diagnosed with bronchopulmonary cancer revealed a predominance of male patients (80), compared to female patients (14). Following the distribution of patients by gender and age group, the following results were obtained (Figure 2). The age category with the most patients affected by bronchopulmonary cancer is 71-80 years with a share of 44.1%, followed by the age category 61-70 years with a proportion of 22.5% (Figure 2).

This is consistent with current epidemiological data, confirming that bronchopulmonary carcinoma primarily affects individuals in their 6th and 7th decades of life. Our results corroborate specialized literature indicating that the incidence rises sharply and is predominantly diagnosed post-50 years of age. The results show that bronchopulmonary cancer mainly affects adults of working age and the elderly (60-80 years), with a peak incidence between 71 and 80 years. This aspect supports the importance of active screening and prophylactic interventions (smoking cessation, pulmonary function assessment) among the adult population over 40 years of age. The age

category 80-90 years has a low share, possibly explained by the increased mortality associated with severe forms of bronchopulmonary cancer.

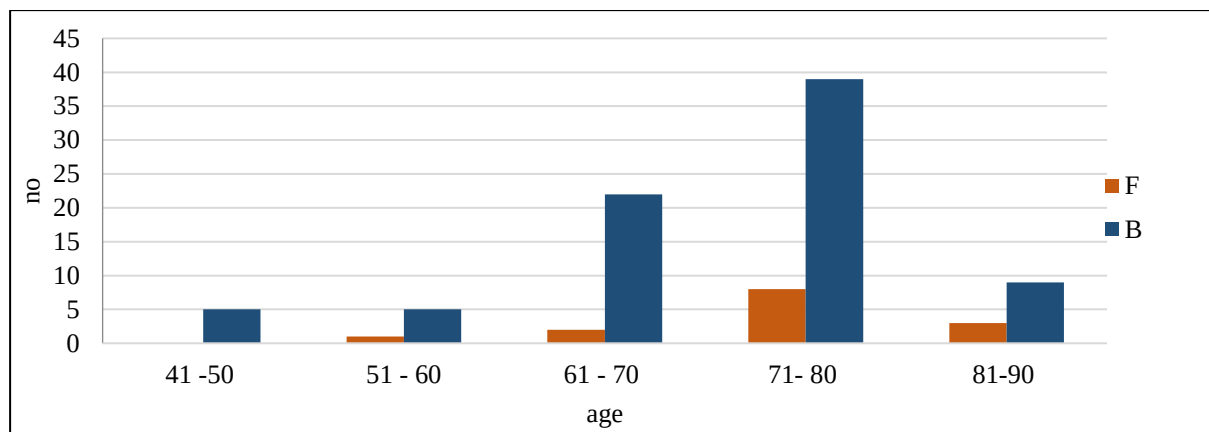


Figure 2. Distribution by gender and age group of patients diagnosed with bronchopulmonary cancer

The distribution by area of residence yielded the following results (Figure 3):

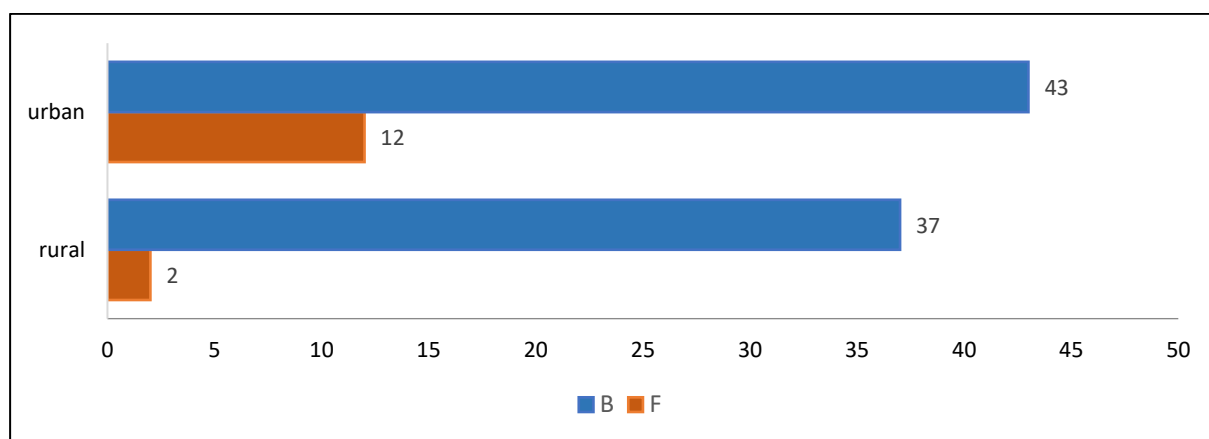


Figure 3. Distribution by gender and area of residence of patients diagnosed with bronchopulmonary cancer

Analyzing Figure 3, a higher incidence of bronchopulmonary cancer cases was found among patients from urban areas. In urban environments, the higher prevalence of smoking, including in workplace settings coupled with superior accessibility to healthcare infrastructure facilitates a more rapid diagnostic process. Conversely, the lower incidence observed in rural areas may suggest a reduced expansion potential of environmental or behavioral oncogenic triggers. However, this lower-case volume in rural regions could equally reflect a potential under diagnosis caused by reduced healthcare access.

Following the quantification of serum tumor markers in the female subgroup, the following distributions were observed (Figure 4)

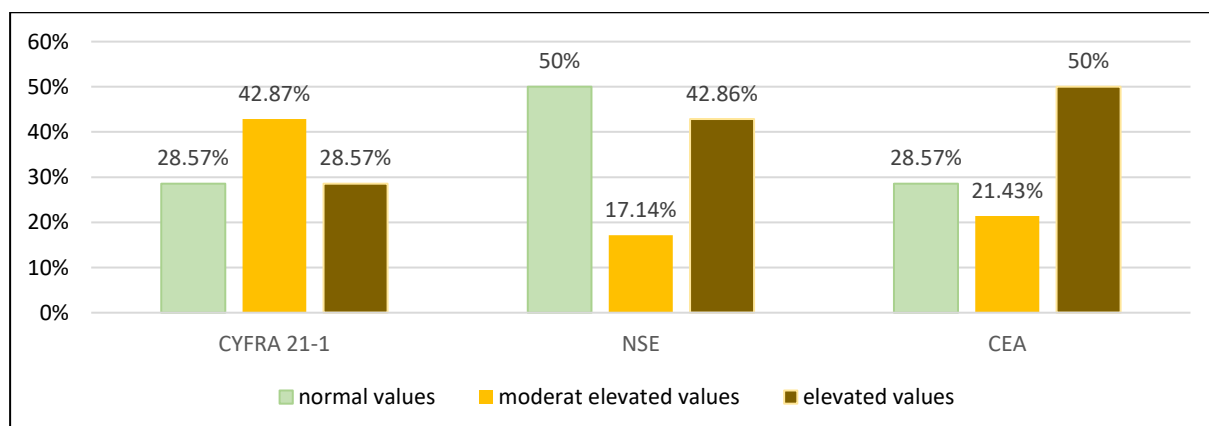


Figure 4. Distribution of female patients according to serum tumor marker levels

As illustrated in Figure 4, the analysis reveals that for the tumor marker CYFRA 21-1 (reference interval: 0–3.3 ng/mL), 4 female patients (28.57%) presented values within the physiological range. Moderately elevated values (4–10 ng/mL) were similarly identified in 28.57% of cases. Notably, markedly high to extreme concentrations (11–500 ng/mL) manifested in 42.87% of female patients. Such variations in serum levels typically reflect the pathological stage of advancement, tumor histology, and efficacy of the administered treatment. In the case of female patients, only one patient out of the 14 presented normal values for all tumor markers analyzed in this study. For the tumor marker NSE (reference range 0–16.3 ng/mL), normal values were obtained in 50% of female patients. For this specific biomarker, 17.14% of the patient population presented with moderately elevated values (16.4–25 ng/mL), while a predominant cohort fraction of 42.86% demonstrated elevated profiles spanning 26–740 ng/mL. Clinically, NSE is established as an effective oncological marker selectively tailored for SCLC, demonstrating limited diagnostic utility across other pulmonary tumor variants. Subsequent evaluation of the CEA marker indicated that 28.57% of female subjects maintained levels within the normal baseline range (0.2–5 ng/mL). Conversely, moderately increased titers (6–10 ng/mL) manifested in 21.43% of cases, and distinctly high values (11–5000 ng/mL) were detected in exactly 50% of the female subpopulation. This tumor marker is used especially for monitoring the evolution of the disease. Following the determination of tumor markers in male patients, the following results were obtained (Figure 5):

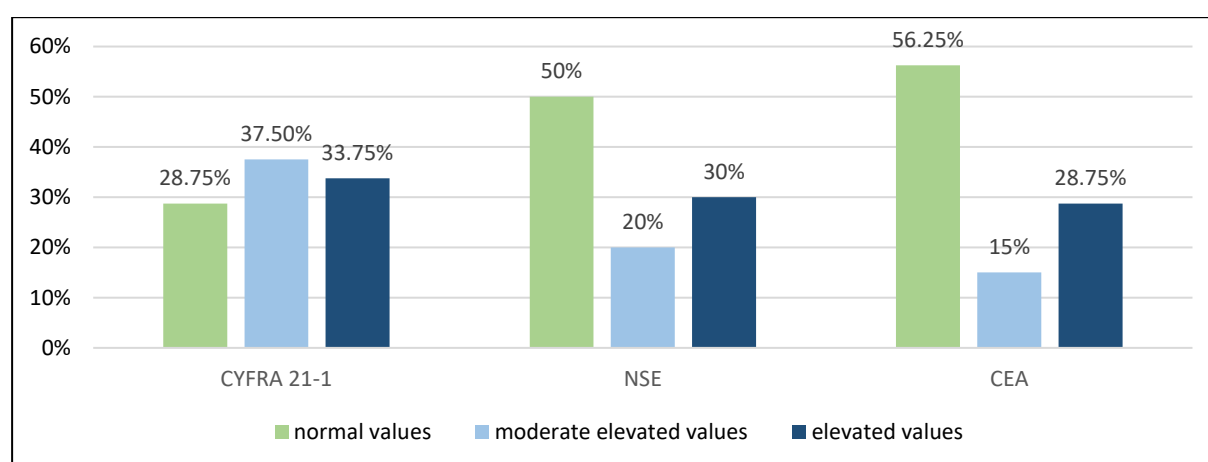


Figure 5. Distribution of male patients according to serum tumor marker levels

Regarding the male patient subgroup, evaluation of the CYFRA 21-1 biomarker profile (Figure 5) demonstrated baseline normal concentrations in 28.75% of individuals. Furthermore, moderately increased titers manifested in 37.50% of patients, whereas severely elevated profiles were detected in 33.75% of the cohort. Such variability is characteristically modulated by pathological staging, tumor histology, and efficacy of the administered treatment. Remarkably, a comprehensive baseline analysis revealed that merely 20% ($n = 16/80$) of the male subjects maintained normal parameters simultaneously for all three studied oncological markers. In the case of the tumor marker NSE (Neuron-Specific-Enolase), values that fell within the reference range were obtained in 50% of male patients. Moderately elevated concentrations were observed in 20% of the patient population, while severely elevated profiles manifested in 30% of cases. Clinically, it is critical to note that normal serum NSE concentrations do not exclude a lung cancer diagnosis. The diagnostic sensitivity of this tumor marker is highly specialized, demonstrating high efficacy for SCLC cohorts but limited performance across other pulmonary tumor variants (Figure 5). Striking gender-specific variations emerge upon evaluating serum CEA profiles, with the male cohort demonstrating a significantly altered distribution compared to female patients. A high percentage of 56.25% is presented by patients with CEA values that fall within the reference range, male patients with moderately elevated values are in the percentage of 15% and those with elevated values reach a percentage of 28.75%. This parameter is used more for monitoring the evolution of the disease.

As illustrated in Figure 6, it can be observed that: CYFRA 21-1 presented the highest average value in the age group 61–70 years, followed by the age group 71–80 years, these values may suggest the presence of more advanced forms of the disease or intense tumor activity. CYFRA 21-1 is a useful marker especially for non-small cell lung cancer, being correlated with the tumor mass and the patient's prognosis. The tumor marker NSE presented the highest average value in the age group 41–50 years followed by the age group 61–70 years, the lowest average value was recorded in the age group 71–80 years. Being a specific marker for small cell lung cancer, NSE, through its increased values, suggests a rapid evolution and a reserved prognosis. In the age categories 61–70 and 71–80 years, CEA presented high and very high mean values. This variability may reflect the diversity of histopathological types, CEA being associated especially with lung adenocarcinoma. Through increased values,

this marker may indicate disease progression or the presence of metastases, confirming its usefulness in monitoring the evolution of oncological patients.

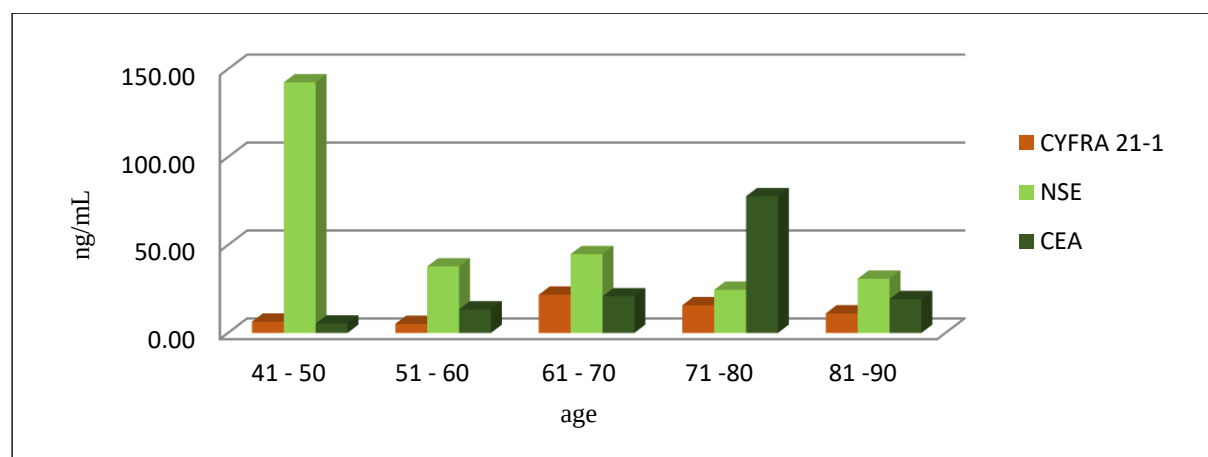


Figure 6. Graphical representation of the average values of the investigated tumor markers by age categories

For monitoring the progression of neoplastic disease in patients with bronchopulmonary cancer, the biochemical parameters: C-reactive protein (CRP), lactate dehydrogenase (LDH), and serum calcium are of paramount clinical importance (Figure 7). These biomarkers are useful in assessing the patient's general condition, estimating the prognosis, monitoring the response to treatment and early identification of complications associated with the oncological disease (Barhoum A. et al, 2023).

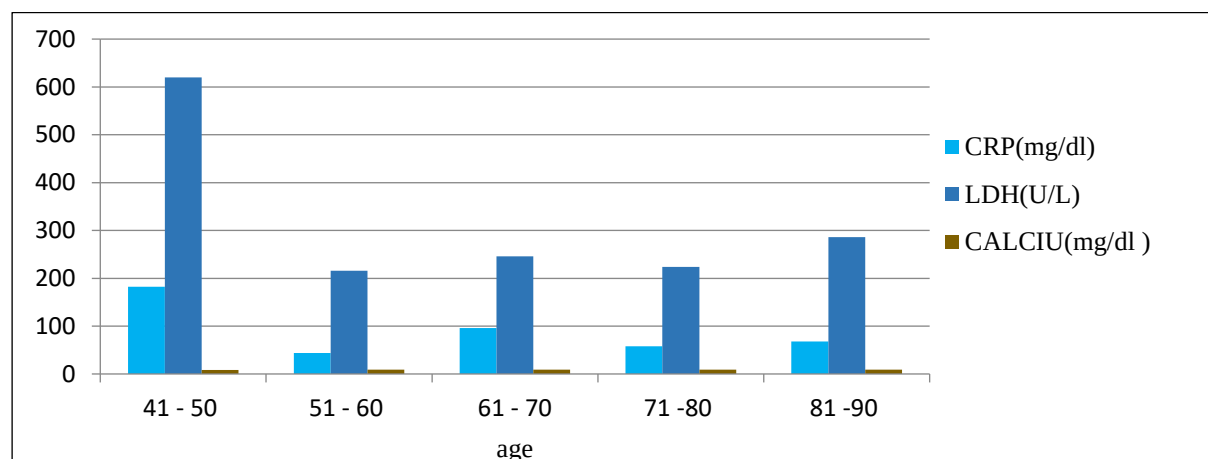


Figure 7. Mean values of investigated biochemical parameters by age group

In the group of the study participants, the values of these parameters showed important variations, correlated with the clinical condition of the patients. C-reactive protein (CRP), whose reference range is 0.2-5 mg/dl, recorded increased mean values in all age groups, the highest mean values being recorded in the 41-50 years old age group, followed by the 61-70 years old age group, suggestive of the existence of an intense systemic inflammatory process and advanced forms of the disease (Figure 7).

Regarding lactate dehydrogenase (LDH), the reference range was 135-225 U/L, and increased values indicated the presence of tissue damage and cellular destruction. The highest mean values of LDH were recorded in the 41-50 years old age group, and the lowest mean values in the 51-60 years old and 71-80 years old age groups, mean values that fell within the reference range (Figure 7).

The mean serum calcium values recorded the lowest values in the age group 41-50 years, for the other age groups, the mean serum calcium values fell within the reference range of 8.6 – 10.2 mg/dl (Figure.7). These changes can be associated both with the progression of the neoplastic disease and with the alteration of nutritional status, bone metastases or the effects of oncological treatment, being relevant for the assessment of clinical evolution and monitoring of patients. The cross-correlation of oncological markers with systemic inflammatory indices yields incremental prognostic value regarding disease progression profiling and treatment efficacy, thereby reinforcing the established paradigm of inflammation-mediated tumor progression (Zanatta et al., 2020; Yale et al., 2025). Consequently, CYFRA 21-1, CEA, and NSE represent vital assets in the comprehensive assessment of bronchopulmonary carcinoma, delivering objective evidence on tumor histology, staging evolution, and survival

prognosis. Incorporating these biomarkers into a multidisciplinary approach is essential for refining therapeutic strategies and improving overall oncological care.

CONCLUSION

Lung cancer remains one of the leading causes of mortality worldwide, being frequently diagnosed in advanced stages.

In the present study, the group consisted of 94 patients, mostly men over 60 years of age, predominantly from urban areas. This aspect reveals that there is easier access to medical units equipped with modern equipment and advanced methods such as the ECLIA method used in this study.

CYFRA 21-1 and CEA presented the highest values in patients over 60 years of age, while NSE recorded the highest values in the age category 41–50 years.

Among the biochemical parameters analyzed, CRP and LDH presented elevated values in most patients, suggesting the presence of systemic inflammation and increased tumor activity. Low serum calcium values are due to the fact that malnutrition, tumor lysis syndrome or paraneoplastic calcitonin secretion may occur quite frequently in this pathology.

Our findings demonstrate that combining tumor markers (CYFRA 21-1, CEA, and NSE) with inflammatory biochemical parameters yields complementary insights into disease progression and therapeutic response. Although these parameters have no individual diagnostic value, their integration into the clinical evaluation may contribute to the assessment of the prognosis and the monitoring of patients with bronchopulmonary cancer.

REFERENCES

1. Barhoum A., Forster R.J. *Electrochemiluminescence biosensors for detection of cancer biomarkers in biofluids: Principles, opportunities, and challenges*. Nano Today, 2023, 50, 101874.
2. Bartkiewicz P., Kunachowicz D., Filipski M., Stebel A., Ligoda J., Rembiałkowska N. *Hypercalcemia in cancer: Causes, effects, and treatment strategies*. Cells, 2024, 13 (12), 1051. <https://doi.org/10.3390/cells13121051>.
3. Belanger A.R., Akulian J.A. *An update on the role of advanced diagnostic bronchoscopy in the evaluation and staging of lung cancer*. Therapeutic Advances in Respiratory Disease, 2017, 11 (5): 211-221. <https://doi.org/10.1177/1753465817695981>.
4. Blanco R., Maestu I., de la Torre MG., Cassinello A., Nuñez I. *A review of the management of elderly patients with non-small-cell lung cancer*. Annals of Oncology, 2015 26 (3): 451-463. <https://doi.org/10.1093/annonc/mdu268>.
5. Botnaru V. *Pneumologie*, Chișinău: Balacron Publishing House, 2018.
6. Chmielowski B., Territo M. *Manual of oncology*. Wolters Kluwer, 2017. Available at: www.com/Manual-of-Clinical-Oncology/p/9781496349576cB2wAk5Yw.
7. Dingemans A.C., Früh M., Ardizzoni A., Besse B., Faivre-Finn C., Hendriks L.E., Lantuejoul S., Peters S., Reguart N., Rudin C.M., De Ruyscher D., Van Schil P.E., Vansteenkiste J., Reck M. *Small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up*. Annals of Oncology, 2021, 32 (7): 839-853. <https://doi.org/10.1016/j.annonc.2021.03.207>.
8. Gebbia V., Guarini A., Piazza D., Bertani A., Spada M., Verderame F., Sergi C., Potenza E., Fazio I., Blasi L., La Sala A., Mortillaro G., Roz E., Marchese R., Chiarenza M., Soto-Parra H., Valerio M.R., Agneta G., Amato C., Lipari H., Baldari S., Ferraù F., Di Grazia A., Mancuso G., Rizzo S., Firenze A. *Virtual multidisciplinary tumor boards: A narrative review focused on lung cancer*. Pulmonary Therapy, 2021 7 (2): 295-308. <https://doi.org/10.1007/s41030-021-00163-8>.
9. Genet S.A.A.M., van den Wildenberg S.A.H., Broeren M.A.C., van Dongen J.L.J., Brunsveld L., Scharnhorst V., van de Kerkhof D. *Quantification of the lung cancer tumor marker CYFRA 21-1 using protein precipitation, immunoaffinity bottom-up LC-MS/MS*. Clinical Chemistry and Laboratory Medicine, 2024 62 (4), 720-728. <https://doi.org/10.1515/cclm-2023-0795>.
10. Hradfar A., Pourlak T., Badebarin D. *Primary pulmonary fibrosarcoma with bone metastasis: A successful treatment with post-operation adjuvant chemotherapy*. Iranian Journal of Cancer Prevention, 2015 8 (3): e2328. <https://doi.org/10.17795/ijcp2328>.
11. Jose J., Sunil P.M., Madhavan N., Susan S. *CYFRA 21-1: An overview*. Oral & Maxillofacial Pathology Journal, 2013, 4 (2): 368-371.
12. Kay F.U., Kandathil A., Batra K., Saboo S.S., Abbata S., Rajiah P. *Revisions to the tumor, node, metastasis staging of lung cancer (8th edition): Rationale, radiologic findings and clinical implications*. World Journal of Radiology, 2017, 9 (6): 269-279. <https://doi.org/10.4329/wjr.v9.i6.269>.

13. McDonald F., De Waele M., Hendriks L.E., Faivre-Finn C., Dingemans A.C., Van Schil P.E. *Management of stage I and II nonsmall cell lung cancer*. European Respiratory Journal, 2017, 49 (1): 1600764. <https://doi.org/10.1183/13993003.00764-2016>.
14. Mayo Clinic Press. *Synovial sarcoma - Overview* 2020. Available at <https://www.mayoclinic.org>.
15. Mayo Clinic Press. *Sarcoma - Symptoms and causes* 2022. Available at <https://www.mayoclinic.org>.
16. Mindray-Understanding CLIA principles applications. Available at <https://www.mindray.com/in/media-center/blog/understanding-clia-principles-applications>.
17. Pass H.I., Ball D., Scagliotti G.V. *IASLC multidisciplinary approach to thoracic oncology*, 2014. Available at <http://hdl.handle.net/11434/349>.
18. Stanciu A.E., Caragheorgheopol A., Badiu C. *Tumor and endocrine markers. A practical guide*. Carol Davila University of Medicine and Pharmacy Publishing House, Bucharest, 2014.
19. Sturgeon C. *Tumor markers*. In: Rifai N. et al. (Eds.). *Tietz textbook of clinical chemistry and molecular diagnostics*. 6th ed. Elsevier, 2018, 436-478.
20. Torre L.A., Siegel R.L., Jemal A. *Lung cancer statistics*. Advances in Experimental Medicine and Biology, 2016, 893: 1-19. <https://doi.org/10.1007/978-3-319-24223-1>.
21. *The Global Cancer Observatory*. Romania. Available at <http://globocan.iarc.fr/Default.aspx>.
22. Visser E., Genet S.A.A.M., de Kock R.P.P.A., van den Borne B.E.E.M., Youssef-El Soud M., Belderbos H.N.A., Stege G., de Saegher M.E.A., van't Westeinde S.C., Brunsveld L., Broeren M.A.C., van de Kerkhof D., Deiman B.A.L.M., Eduati F., Scharnhorst V. *Liquid biopsy-based decision support algorithms for diagnosis and subtyping of lung cancer*. Lung Cancer 2023, 178: 28-36. <https://doi.org/10.1016/j.lungcan.2023.01.014>.
23. Weerakkody Y., *Adenocarcinoma in situ of the lung*. Available at <https://radiopaedia.org/articles/adenocarcinoma-in-situ-of-the-lung>.
24. Tang Y., Zeng S., Hou X., Tian P., Ren L., Song G. *Serum gamma glutamyl transferase. Correlation between the levels of fasting and postprandial ApoB48 with metabolic syndrome: A cross-sectional study*. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy, 2025, 18, 4631-4643.
25. Zanatta E., Martini A., Scarpieri E., Biasiolo A., Ortolan A., Benvenuti F., Cozzi F., Pontisso P., Doria A. *Squamous cell carcinoma antigen-IgM (SCCA-IgM) is associated with interstitial lung disease in systemic sclerosis*. Joint Bone Spine, 2020, 87 (4), 331-335. <https://doi.org/10.1016/j.jbspin.2020.02.003>.