Original Research Article

The Relationship of CYFRA 21-1 to the Metastatic Process of Advanced Non- Small Cell Lung Carcinoma

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ABSTRACT

Lung cancer is a leading cause of death worldwide. Globally, lung cancer is estimated to cause 2.2 million new cases and 1.8 million deaths in 2020. About 85% of total lung cancer cases are estimated to be Non-Small Cell Carcinoma Lung Cancer (NSCLC). Lung cancer itself has several tumor markers because the type of cancer depends on its cell origin where Cytokeratin19 fragment (CYFRA 21-1) is used for squamous cell carcinoma type lung cancer. This study aims to assess the sensitivity of CYFRA 21-1 tumor biomarker examination in advanced non-small cell carcinoma lung cancer. This study was a cross-sectional study in lung cancer patients at Wahidin Sudirohusodo Hospital in the period January- March 2023. Each research subject collected bronchial lavage and serum samples, then tested CYFRA 21-1 levels using the ELISA method. The results showed that in subjects with JPBSK, most diagnoses were made based on the bronchial lavage method (72.7%), diagnosed at an advanced stage (88.5%) with a cytology/histology type of squamous cell carcinoma (43.2%). The research data showed that the serum level of CYFRA 21-1 in NSCLC patients was higher than non-cancer patients (p=0.015). It can be concluded that serum CYFRA 21-1 levels increased significantly in NSCLC subjects when compared to non-cancer.

BACKGROUND

Lung cancer in a broad sense is all malignant diseases found in the lung, including malignancies originating from the lung itself and malignancies from outside the lung (tumor metastases in the lung).[1] Based on the 2020 Global Burden of Cancer (GLOBOCAN) estimates, lung cancer ranks as the 2nd most common cancer case diagnosed during 2020 in men and women (2.2 million new cases, equivalent to 11.4% of the total cancer incidence in 2020) with 1.79 million deaths (18% of total cancer deaths). Lung cancer in Indonesia ranks 3rd after breast cancer and cervical cancer, with 34,783 new cases which is 8.8% of the total number of cancer cases diagnosed in 2020.[2]

The diagnosis of lung cancer requires a multidisciplinary approach to medicine as well as fast and targeted treatment and action. With the development of science and laboratory technology, it is possible to detect malignancies up to the molecular level, known as molecular markers or biomarkers of malignancy. Tumor markers are substances that can be used to detect various changes that occur due to cancer. Currently, many ideal malignancy marker

examinations are being researched and developed that can provide clues about the development of cancer, both at the extracellular, cellular and molecular levels. [3,4]

This malignant marker is an additional examination and is useful for confirmation of suspicion of a previously suspected cancer when uninformative sputum cytology or histopathology examination is not found, no endobronchial lesion is visible on fiberoptic bronchoscope, biopsy material is inadequate, tumor location is inaccessible or bronchoscopy, thoracoscopy or open lung biopsy are sometimes contraindicated due to the patient's poor general condition. Tumor markers have a considerable role in differential diagnosis and histological subtype, especially in lung tumors of unknown origin. Within the marker profile, the main markers suggest the most likely histological subtypes; Carcinoembryonic Antigen (CEA) in Adenocarcinoma; Cytokeratin fragment 19 (Cyfra 21-1) and Squamous Cell Carcinoma Antigen (SCCA) in squamous cell carcinoma. [5,6]

CYFRA21-1 has been identified as a diagnostic and prognostic factor that is useful as an effective predictor for targeted therapy or chemotherapy and as a marker of postoperative recurrence and metastasis. [7] CYFRA 21-1 research in lung cancer in previous studies was conducted on serum samples or bronchial rinses but not studied simultaneously, therefore this study was conducted to confirm the role of the CYFRA 21-1 biomarker in supporting the diagnosis of lung cancer by using both samples in patients simultaneously which is expected to provide output in the diagnosis of lung cancer.

METHODS
Research design
This study is an analytic observational study with a cross sectional design. Observations were made prospectively with sampling done on patients prodiagnostic lung cancer. The required clinical data were taken during treatment. Patients with prodiagnostic lung cancer will have blood samples and bronchial lavage taken, then examined to assess CYFRA 21-1 levels.

Subject
This study was conducted at Dr. Wahidin Sudirohusodo Hospital Makassar, South Sulawesi.

This study took patient samples from January - March 2023 involving 85 lung cancer patients aged over 18 years who sought treatment at Dr. Wahidin Sudirohusodo Hospital Makassar. The study sample was divided into 2 groups, including the first group of NSCLC patients who were upright based on Histopathology examination from the Laboratory of Dr. Wahidin Sudirohusodo Hospital and the second group consisted of prodiagnostic patients who were not upright.

Data collection techniques
All patients with a preliminary diagnosis of lung cancer admitted to Dr. Wahidin Sudirohusodo Hospital were diagnosed based on history taking, physical examination, and supporting examination. Demographic data and clinical data including age, sex, education, occupation was recorded from the patient's medical record, interview with the patient or the patient's family. Then blood samples and bronchial rinses were examined to assess CYFRA 21-1 levels. As well as histopathological examination to establish the diagnosis of advanced stages of lung cancer.

Subjects who met the inclusion criteria were sampled for bronchial lavage during diagnostic bronchoscopy and 3 ml of venous blood each. Bronchial lavage was centrifuged for 10 minutes at 2000 rpm. Serum was obtained after the blood was allowed to clot for 5 minutes at room temperature and centrifuged for 5 minutes at 3000 rpm, then separated between serum and blood components. Both samples were then stored in a freezer at -80o C. CYFRA 21-1 Level Test by ELISA Method using Human ELISA kit (No. LS-F10515) from LifeSpan BioSciences Inc.

Data analysis technique

Used for data description in the form of a description of the frequency and percentage of each characteristic of the research subject (median, minimum, and maximum values). Data normality test using Kolmogorov-Smirnov/Shapiro-Wilk. Categorical data analysis using unpaired T-test, numerical categorical data using Mann-Whitney/Kruskal-Wallis test, numerical data using Spearman correlation test. The research data were presented in the form of narratives, tables and images/graphics. Presentation in the form of narrative is used to explain tables or figures.

RESULTS

Basic Characteristics of Research Subjects

The data obtained from the study subjects were then classified according to the distribution of proportions based on gender, age, ethnicity, occupation, body mass index (BMI), smoking history, Brinkman index, disease history, main symptoms, thoracic MSCT scan images, bronchoscopy images, staging, diagnosis modality, and histopathology type of upright patients and controls (Table 1).

Most research subjects from all groups were male 54 subjects (63.5%), came from the Bugis tribe (45.5%), had a normal body mass index (BMI) (60%), active smokers (54.5%), had a history of tuberculosis (45.5%), the main symptoms experienced were shortness of breath experienced (45.5%), tumor size T4 (68.2%), and metastatic images as many as 29 subjects (65.9%).

Table 1. Basic Characteristics of Research Subjects

Characteristics	Total (*n* = 85)	KPKBSK (*n* = 44)	Control (*n* = 41)	P-value
Age				
<50	25 (29.4)	8 (18.2)	17 (41.5)	0.031 [a]
≥50	60 (70.6)	36 (81.8)	24 (58.5)	
Gender				
Male	54 (63.5)	31 (70.5)	23 (56.1)	0.185 [a]
Female	31 (36.5)	13 (29.5)	18 (43.9)	
Tribe				
Makassar	22 (25.9)	9 (20.5)	13 (31.7)	
Bugis	37 (43.5)	20 (45.5)	17 (41.5)	0.951 [c]
Toraja	7 (8.2)	4 (9.1)	3 (7.3)	
Buton	4 (4.7)	2 (4.5)	2 (1.9)	
Miscellaneous	15 (17.6)	9 (20.5)	6 (14.6)	
Jobs				
Farmers	14 (16.5)	7 (15.9)	7 (17.1)	
Labor	4 (4.7)	3 (6.8)	1 (2.4)	1.000 [c]
Fisherman	1 (1.2)	0 (0.0)	1 2.4)	
IRT	18 (21.2)	8 (18.2)	10 (24.4)	
Miscellaneous	48 (56.5)	26 (59.1)	22 (53.7)	
IMT				
Underweight	17 (20.0)	6 (13.6)	11 (26.8)	
Normal	51 (60.0)	29 (65.9)	22 (53.7)	0.854 [c]
Overweight	12 (14.1)	7 (15.9)	5 (12.2)	
Obese	5 (5.9)	2 (4.5)	3 (7.3)	
Smoking History				
Active smokers	42 (49.4)	24 (54.5)	18 (43.9)	0.608 [a]
Passive smokers	23 (27.1)	11 (25.0)	12 (29.3)	
No smoking	20 (23.5)	9 (20.5)	11 (26.8)	
Brinkman Index				
Lightweight	10 (23.8)	4 (16.7)	6 (33.3)	0.393 [a]
Medium	14 (33.3)	8 (33.3)	6(33.3)	
Weight	18 (42.9)	12 (50)	6(33.3)	
Comorbid				
Tuberculosis	34 (40)	20 (45.5)	14 (34.1)	0.376 [a]
Ferocity	2 (2.4)	0 (0.0)	2 (4.9)	0.230 [b]
Diabetes Mellitus	8 (9.4)	4 (9.1)	4 (9.8)	0.603 [b]
Hypertension	17 (20)	10 (22.7)	7 (17.1)	0.593 [a]
Main Symptoms				
Cough	18 (21.2)	8 (18.2)	10 (24.4)	0.598 [a]
Coughing up blood	11 (12.9)	2 (4.5)	9 (22.0)	0.023 [a]

Shortness of breath	32 (37.6)	20 (45.5)	12 (29.3)	0.179 a
Chest pain	24 (28.2)	14 (31.8)	10 (24.4)	0.479 a
Staging				
I/II/IIIA	5 (5.88)	5 (11.4)	NA	NA
IIIB/IV	39 (45.88)	39 (88.6)	NA	
DiagnosisModalities				
TTNA/core biopsy	7 (8.2)	7 (15.9)	NA	
				NA
CP cytology/pleuralbiopsy				
Bronchial lavage	5 (5.9)	5 (11.4)	NA	
Histopathology	32 (37.6)	32 (72.7)	NA	
Adenocarcinoma	18 (21.2)	18 (40.9)	0 (0.0)	
Adenosquamouscarcinoma	4 (4.7)	4 (9.1)	0 (0.0)	
Squamous cellcarcinoma	19 (22.4)	19 (43.2)	0 (0.0)	NA
Non-specificNSCLC	3 (3.5)	3 (6.8)	0 (0.0)	
Not cancer	41 (48.2)	0 (0.0)	41 (100)	
Tumor Size of NSCLC Group Based on Thorax CT Scan Images				
T0-T3	48 (56.5)	14 (31.8)	34 (27.9)	0.075ᵃ
T4	37 (43.5)	30 (68.2)	7 (5.7)	
Nodules of NSCLC Group Based on Thorax CT Scan Images				
N0	42 (49.4)	13 (29.5)	29 (23.8)	0.704ᵃ
N1	2 (2.4)	1 (2.3)	1 (0.8)	
N2	15 (16.6)	8 (18.2)	7 (4.9)	
N3	26 (30.6)	22 (50)	4 (3.3)	
Metastasis of NSCLC Group Based on Thorax CT Scan Picture				
None	36 (42.4)	7 (15.9)	29 (23.8)	
Intrathoracic Metastasis	21 (24.7)	16 (36.4)	5 (4.1)	0.537ᵃ
Extrathoracic Metastasis	28 (32.9)	21 (47.7)	7 (5.7)	
Bronchoscopic features of NSCLC group (n = 44)			**Total**	
CompressiveStenosis			3 (6.8)	
Infiltrative/Nodules			7 (15.9)	
Compressive Stenosis +Infiltrative/Nodules			2 (4.5)	
KGB metastasis			3 (6.8)	
KGB Metastasis + Compressive			6 (13.6)	
Stenosis			14 (31.8)	
KGB Metastasis + Infiltrative/Nodules			2 (4.5)	
KGB Metastasis + Compressive Stenosis + Infiltrative/Nodules			2 (4.5)	
Contralateral Intrabronchial Metastasis/VocalCords + Compressive Stenosis +Infiltrative/Nodules			2 (4.5)	
KGB Metastasis + Contralateral Meta Intrabronchus/VocalCords + Infiltrative/Nodules			3 (6.8)	
No Abnormalities			**Total**	
Bronchoscopy Overview of Control Group (n = 41)			9 (21.9)	
Compressive Stenosis			3 (7.3)	
Infiltrative/Nodules			1 (2.4)	
KGB metastasis			4 (9.8)	
Compressive Stenosis + KGB Metastasis			2 (4.9)	
Infiltrative/Nodule + KGB Metastasis			22 (53.7)	
No Abnormalities			**Total**	
Diagnosis in Lung Cancer Suspect Patients (n = 27)			20 (74.1)	
Lung Tumor of Unknown Type			7 (25.9)	
Mediastinal Tumor			**Total**	
Not Lung Tumor (n=14)			8 (66.7)	
Pulmonary TB on OAT			4 (28.6)	
Former Pulmonary TB			2 (16.7)	
Hemoptysis				

Data reported as mean (SD) or n (%)

a Chi-square test

b Fisher's exact test

c Kolmogorov-Smirnov Description:

Other Tribes: Morowali, Mandar, Bulukumba, Tolaki, Majene, Kajang, Chinese, Ambon

Other Occupationb: Not working, Self-employed, BUMN Employee, Civil Servant, Entrepreneur, Student, Doctor, Driver, Midwife, Retired

Other Thoracic CT Scan Features: Atelectasis, Cardiomegaly, Pulmonary TB, Aspergilloma, Emphysema, Pneumonia, Pneumothorax, Hydropneumothorax, Pleural Effusion, Empyema, Bronchiectasis, Hepatomegaly, Splenomegaly, Pulmonary Fibrosis.

Differences in CYFRA 21-1 Levels in the NSCLC vs Control Group

Examination of bronchial lavage CYFRA 21-1 levels in the NSCLC and control groups showed median results of 4.24 (0.11-62.61) ng/mL and 3.76 (0.01-107.89) ng/mL .

In addition, the serum CYFRA 21-1 level showed a result of 3.295 (0.17-42.49) ng/mL, which was significantly different when compared to the control group, which was 1.17 (0.05-29.61) ng/mL (p=0.015) (Table 2).

Table 2. Results of CYFRA 21-1 Level Examination in the NSCLC and Control Groups

Characteristics	NSCLC	Control	P-
	(median, *n* = 44)	(median, *n* = 41)	value
CYFRA 21-1 levelsBronchial lavage	4.24 (0.11-62.61)	3.76 (0.01-107.89)	0.553 [a]
CYFRA 21-1 levelsSerum	3.295 (0.17-42.49)	1.17 (0.05-29.61)	0.015 [a]

a Mann Whitney Test

Differences in CYFRA 21-1 Levels in the Lung Cancer Suspect Group vs. Non-Lung Cancer in the Control Group

Examination of bronchial lavage CYFRA 21-1 levels in the lung cancer suspect and non-lung cancer groups showed median results of 5.51 (0.16-107.89) ng/mL and 2.365 (0.01-30.69) ng/mL (respectively). In addition, serum CYFRA 21-1 levels showed results in the lung cancer suspected group of 1.56 (0.05-29.61) ng/mL and in the non-lung cancer group of 0.965 (0.05-9.07) which had no significant difference between the two groups (p=0.492 and p=0.169 for bronchial lavage and serum CYFRA 21-1 levels respectively). Although the levels of CYFRA 21-1 between the lung cancer and non- lung cancer suspected groups were not significantly different, the median value of CYFRA 21-1 in both bronchial lavage and serum samples was higher than that of non-lung cancer (Table 3).

Table 3 Examination results of CYFRA 21-1 levels in the Control Group

Characteristics	Lung Cancer Suspect	Not Lung Cancer	P-value
	(median, n = 27)	(median, n=14)	
CYFRA 21-1 levelsBronchial lavage	5.51 (0.16-107.89)	2.365 (0.01-30.69)	0.492 [a]
CYFRA 21-1 levelsSerum	1.56 (0.05-29.61)	0.965 (0.05-9.07)	0.169 [a]

Serum CYFRA 21-1 Levels and Bronchial Rinses Based on Clinical Characteristics in the NSCLC Group

Serum CYFRA 21-1 levels in the NSCLC group had differences based on gender, but not statistically significant, with males at 3.02(0.21-42.49) ng/mL and females at 19.36(0.56-38.16) ng/mL. Serum CYFRA 21-1 levels were found to be higher in subjects with a mild Brinkman index of 8.16 (0.5- 38.16) compared to moderate 4.87 (0.56-42.49) and severe 2.1 (0.21-15.28).

In bronchial lavage samples, subjects with a history of malignancy had the highest median bronchial lavage CYFRA 21-1 levels (4.03 (0.14-20.18)) compared to other disease histories such as tuberculosis (3.96 (0.14-20.18)), hypertension ((3.52 (0.71-17.48)), and diabetes mellitus (2.37 (0.64-4.10)). The thoracic CT scan of subjects in the upright type of NSCLC group showed a significant difference between serum CYFRA 21-1 levels and CT scan images with metastasis (3.99 (0.21-42.49)) and without metastasis (0.64 (0.56-6.8)) (p=0.02).

In bronchial lavage samples, thoracic CT scan images of subjects in the upright group of NSCLC types showed no significant difference between CYFRA 21-1 levels in bronchial lavage in CT scan images with metastases (4.47 (0.14-20.18)) and without metastases (2.42 (0.71-6.47)) (p=330). The histopathologic type of non-specific JPBSK had the highest serum CYFRA 21-1 level (7.35 (7.27- 7.72)), followed by adenosquamous carcinoma (5.52 (0.17-42.5)), then adenocarcinoma (3.29 (0.56-23.6)), and squamous cell carcinoma (2.17 (0.21-38.16)).

Median serum CYFRA 21-1 levels were found to be higher in subjects with advanced stage IIIB/IV (3.78 (0.17-42.49)) compared to early stage I/II/IIIA (1.01

(0.56-7.26)) although the results were not statistically significantly different (Figure 1). In bronchial rinses, the median CYFRA 21-1 level was found to be higher in subjects with advanced stage IIIB/IV (4.38 (0.14-62.61)) compared to early stage I/II/IIIA (3.96 (0.11-13.03)) although the results were not statistically significantly different (Figure 2).
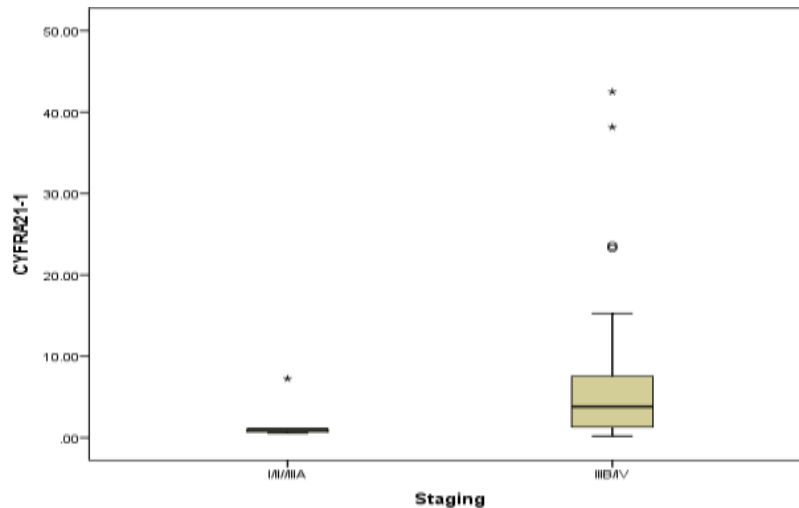

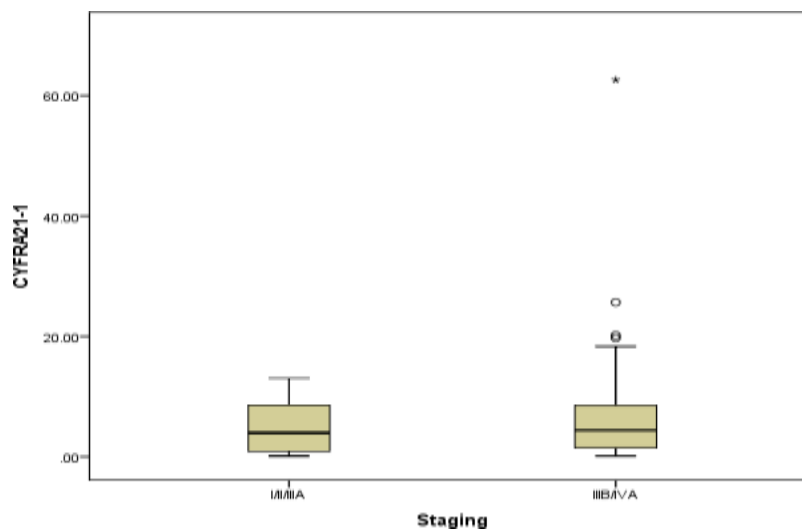**Figure 1. Distribution of serum CYFRA 21-1 levels based on the stage of the disease.**

Figure 2. Distribution of CYFRA 21-1 levels in bronchial lavage based on the stage of the disease.

CYFRA 21-1 Levels and Diagnosis Modalities

Serum CYFRA 21-1 levels did not show significant differences between the groups diagnosed with upright JPBSK by TTNA/core biopsy or CP cytology/pleural biopsy or by bronchial lavage (p=0.477), as did the results of bronchial lavage CYFRA 21-1 levels (p=0.514). (Table 4)

Table 4. Examination results of CYFRA 21-1 levels in bronchial smears and serum in the NSCLC group diagnosed by TTNA/Core Biopsy, CP Cytology/Pleural Biopsy, and Bronchial Smears.

Characteristics	*TTNA/corebiopsy* (median, *n* = 7)	Cytology *CP/pleuralbiopsy* (median, n=5)	Bronchial lavage (median, *n* = 32)	P-value
CYFRA 21-1 Serum	3.23 (0.49-7.27)	6.13 (1.71-12.9)	2.49 (0.17-42.49)	0.477 [a]
CYFRA 21-1 Bronchial lavage	3.81 (0.9-13.03)	5.74 (2.16-62.61)	4.24 (0.11-25.65)	0.514 [a]

Serum CYFRA 21-1 and Bronchial Rinse CYFRA 21-1 Levels

The linearity test conducted between serum CYFRA 21-1 and bronchial lavage CYFRA 21-1 levels gave results of p>0.05 so that it can be interpreted that there is a significant linear relationship between serum CYFRA 21-1 and bronchial lavage CYFRA 21-1 (Figure 3). Further analysis was conducted to assess whether there was a correlation between bronchial lavage CYFRA 21-1 levels and serum CYFRA 21-1 levels. The results showed a positive but statistically insignificant correlation between bronchial lavage CYFRA 21-1 levels and serum CYFRA 21-1 levels. The correlation value was found to be 0.083, indicating a positive correlation with a very weak correlation strength ($r < 0.2$) (Table 5).
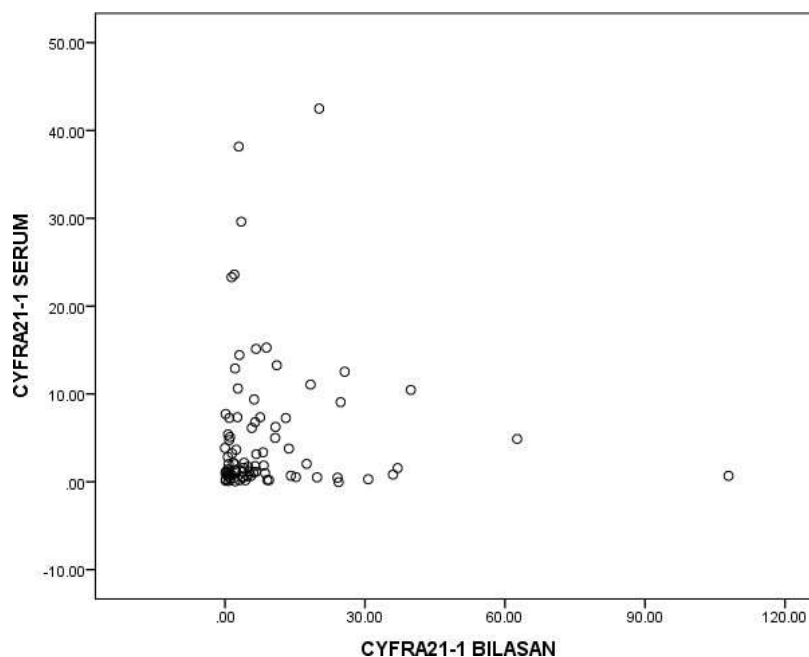

Figure 3. Linearity Test of CYFRA 21-1 Bronchial Rinse and CYFRA 21.1 Serum

Table 5. Correlation Analysis Results of CYFRA 21-1 Bronchial Rinses and Serum in the NSCLC

	CYFRA 21-1 Bronchial Rinse Levels
CYFRA 21-1 Serum	r = 0.083 p = 0.448[a]
	n = 85

a Spearman Correlation Test

Differences in AUC, Sensitivity, Specificity and Cut-off Value of CYFRA 21-1 Bronchial Rinse and Serum Levels

The ability of CYFRA 21-1 bronchial rinses and serum to detect upright versus control JPIC was analyzed using receiver operating characteristic (ROC) curves which are graphical representations of the relationship between sensitivity and 1-specificity (Figure 4.4). The area under the curve (AUC) was assessed from the ROC curve to determine the strength of the diagnostic value where it was found that CYFRA 21-1 bronchial rinse was not better in predicting upright JPIC than serum CYFRA 21-1 (0.463 (95% CI 0.339-0.587) vs 0.654 (95% CI 0.537-0.77)). Serum CYFRA 21-1 with a cut-off point of 2.02ng/mL had a higher sensitivity (61.4%) and specificity (70.7%) than bronchial lavage CYFRA 21-1 with a cut-off point of 3.78 ng/mL which had a sensitivity of 56.8% and specificity of 51.2% (Table 6).

Table 6. AUC, Sensitivity, Specificity and Cut-off Values of CYFRA 21-1 Bronchial Rinse and Serum Levels

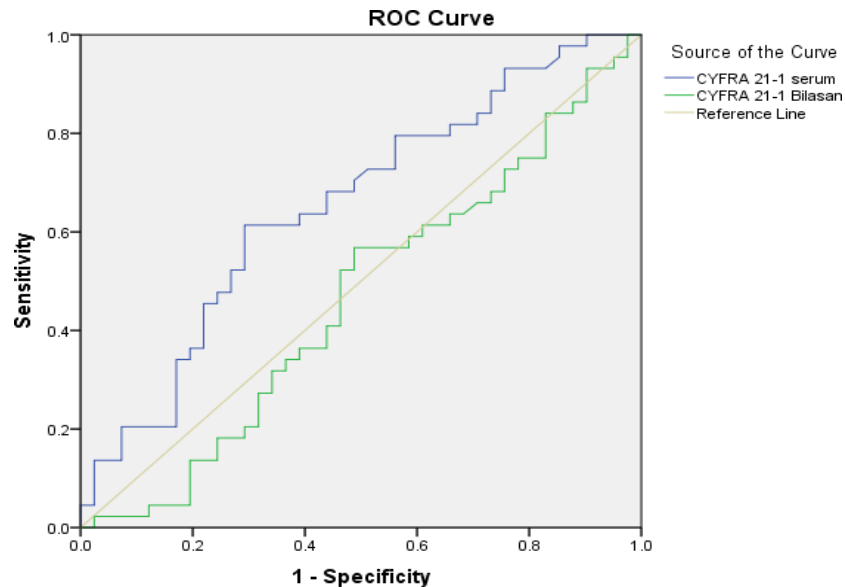| Variables	AUC	Sensitivity	Specificity	Cut offPoint
CYFRA 21-1 Bronchial lavage	0.463 (IK95% 0.339-0.587)	56.8%	51.2%	3.78[a]
CYFRA 21-1 Serum	0.654 (IK95% 0.537-0.77)	61.4%	70.7%	2.02[a]

a Youden Index

Figure 4. ROC Curve of Bronchial Rinse CYFRA 21-1 and Serum CYFRA 21-1 Levels

Histopathologic Type and Disease Stage

The correlation test was conducted to assess whether there was a relationship between histopathologic type and stage of upright type of NSCLC. The correlation value of adenocarcinoma with disease stage r=0.007, adenosquamous carcinoma with disease stage r=0.135, squamous cell carcinoma with disease stage r=0.023, non-specific NSCLC with disease stage r=0.096 which shows a positive correlation with a very weak correlation strength and is not clinically meaningful (Table 7).

Table 7. Correlation of Histopathology Type with Disease Stage

Histopathology	Stadium		Correlation Coefficient (r)	*P-value*
	I/II/IIIA	IIIB/IV		
Adenocarcinoma	2 (11.11%)	16 (88.89%)	0.007	0.956a
Adenosquamous carcinoma	1 (25%)	3 (75%)	0.135	0.367a
Cell carcinomaskuamous	2 (10.53%)	17 (89.47%)	0.023	0.879a
NSCLC non specific	0 (0%)	3 (100%)	0.096	0.521a

a Contingency Coefficient Test.

DISCUSSION

Based on the ELISA test, this study found that the levels of CYFRA 21-1 in bronchial rinses of JPBSK subjects were not significantly different from the control subjects (median values of 4.24 ng/ml and 3.76 ng/ml, respectively, p=0.553). However, serum CYFRA 21-1 levels were found to be significantly different between NSCLC subjects compared to control subjects (median values of 3.295 ng/ml and 1.17 ng/ml, respectively, p=0.015).

Cytokeratins and filamentous intermediates are present in various normal cells and pathological tissues. In the bronchus, the location of the lesion can affect the levels of CYFRA 21-1, if the lesion is intralumen or central, CYFRA 21-1 will be easily obtained while in peripheral lesions it will be difficult to obtain cytokeratin during bronchoscopy. CYFRA 21-1 can be expressed by epithelial cells such as branching bronchi and is overexpressed in lung cancer. However, in serum, cells with uncontrolled proliferation that then induce angiogenesis to form primary tumors that eventually invade and metastasize will enter the circulation so that CYFRA 21-1 is detected high in serum. [8]

The concentration of CYFRA 21-1 in human serum is elevated in most lung cancer patients and has a specificity of 87%

with a threshold of 3.6 ng/mL. Moreover, the amount of CYFRA 21-1 is related to the metastasis and status of lung cancer patients, and the correlation is higher than that of carcinoembryonic antigen and neuron-specific enolase. Therefore, a rapid, sensitive, and useful biosensor for the analysis of CYFRA 21-1 has received wide attention. [9]

This study also showed differences in CYFRA 21-1 rinse and serum levels in control subjects who were divided into lung cancer and non-cancer suspected groups. In the lung cancer suspect group, the rinse and serum samples showed significant differences (p value = 0.015). Garcia et al in the study of CYFRA 21-1 levels in cancer suspects with a median of 4.75 ng/ml and in non-cancer of 1.20 ng/ml.[10] Like the skeleton of the human body, the cytoskeleton is the skeleton of the cell. The cytoskeleton as the skeleton of the cell has important roles such as cell movement, cell division, architectural organization of organelles and the formation process of mRNA and other cellular components. Cytokeratins and filamentous intermediates are present in various normal cells and pathological tissues. There are many diseases with abnormal cell function. Abnormal cells will act as non-functional cells that eventually result in cell leakage and cytoskeleton fragments will enter the blood vessels which can cause elevated levels of CYFRA 21-1 in serum samples. [11]

The marker CYFRA 21-1 was identified as a sensitive marker for lung cancer in 1993 and has since been widely used to assess patient prognosis and monitor treatment. Elevated levels of CYFRA 21-1 indicate a poor prognosis in non-small cell lung cancer. A previous study showed that CYFRA 21- 1 levels are not affected by gender or smoking status and have been used regardless of gender, smoking status, age, and other clinical characteristics. However, later studies reported an association between CYFRA 21-1 levels and smoking status or older age. [12]

CYFRA 21-1 is a soluble fragment of CK19. CKs are intermediate filaments present in normal and malignant epithelial cells, including bronchial epithelial cells, and are part of the cytoskeleton. CKs protect epithelial cells from mechanical stress and also play important roles in cell signaling, stress response, and apoptosis. CKs are classified based on differences in molecular mass and isoelectric point. CK19 is a soluble type I CK, and it has an isoelectric pH of 5.2 and a molecular mass of 40 kDa. In lung cancer, malignant transformation of epithelial cells activates caspase 3, which is a protease that regulates the apoptotic cascade. During this transformation, CK19 is cleaved as a result of increased caspase 3 protease activity, and its soluble fragment, CYFRA 21-1 is released into the blood. [12]

In chronic inflammatory airway disease, CYFRA 21-1 is released from the injured bronchial epithelium. CYFRA 21-1 has been highlighted as a potential biomarker of epithelial damage in patients with idiopathic pulmonary fibrosis. In IPF, excessive epithelial cell apoptosis occurs and fibroblast resistance to apoptosis is thought to cause fibroproliferation. Cigarette smoke exposure induces persistent inflammation, proteolysis and oxidative stress, all of which can lead to apoptosis of epithelial cells and alveolar endothelium in the lung. [12]

Various studies have shown that lung cancer patients do not have specific symptoms, which is a contributing factor to the delay in diagnosis of lung cancer patients, especially in the early stages. Existing studies have reported chronic cough, with or without coughing up blood, to be a complaint in the majority of patients diagnosed with lung cancer.[41,42] In the main complaint of coughing up blood, serum CYFRA 21-1 levels were higher than other complaints with a median value of 19.16 ng/ml, but not significant.

CYFRA 21-1 expression is associated with tumor development and progressivity through invasive properties, migration and metastasis formation. In the radiological picture of thoracic CT scan of single

extrathoracic metastasis, there was a significant difference in serum CYFRA 21-1 levels (p value 0.013). CYFRA 21-1 on cytokeratin is distributed in various epithelial cells according to cell differentiation, so it is related to the progress and metastasis of a cancer. [13]

CONCLUSIONS

CYFRA 21-1 levels can be used as early detection for lung tumors, can be used to help diagnose lung cancer especially in serum samples and the presence of metastases from lung cancer. In this study, serum CYFRA 21-1 levels were significantly increased in NSCLC subjects when compared to non-cancer. Bronchial lavage CYFRA 21-1 levels were not significantly different when compared to non-cancer. High CYFRA 21-1 levels were associated with extrathoracic metastatic lung cancer in NSCLC.

Research Ethics

Oral and written consent was obtained from all research subjects based on the approval of the Ethics Committee of the Faculty of Medicine, Hasanuddin University with number 236/UN4.6.4.5.31/PP36/2023.
Conflict of interest: The authors declare no conflict of interest in this study.
Data availability: Research data can be accessed through the author's permission.
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