# The Association of Carcinoembryonic Antigen and Cytokeratin-19 Fragments 21-1 Levels with One-Year Survival of Advanced Non-Small Cell Lung Carcinoma at Cipto Mangunkusumo Hospital: A Retrospective Cohort Study

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## ABSTRAK

***Latar belakang:*** *non-small cell lung carcinoma (NSCLC) merupakan jenis kanker paru yang paling sering terjadi. Oleh karena itu, penelitian faktor prognostik NSCLC sangatlah penting untuk tatalaksana pasien yang lebih baik. Namun, belum ada studi mengenai hubungan CYFRA 21-1 dan CEA sebagai faktor prognostik terhadap kesintasan NSCLC di Indonesia, serta titik potongnya yang terstandarisasi. Penelitian ini bertujuan mengetahui hubungan antara CEA dan CYFRA 21-1 dengan kesintasan satu tahun NSCLC stadium lanjut di RSCM dan menentukan titik potongnya sebagai faktor prognostik.* ***Metode:*** *studi kohort retrospektif terhadap 111 subjek dengan NSCLC stadium lanjut berusia ≥ 18 tahun yang terdiagnosis dari Januari 2012 hingga Mei 2018 menghasilkan data berupa nilai CEA dan CYFRA 21-1 awal saat terdiagnosis beserta faktor-faktor perancunya, yaitu performance status (PS), jenis histologi, terapi, dan stadium. Semua data didokumentasikan dari Unit Rekam Medik RSCM.* ***Hasil:*** *area under the curve (AUC) CEA kurang dari 50% (AUC=0,446) dan tidak bermakna. Namun, sebaliknya, AUC CYFRA 21-1=0,741 (0,636–0,847) dengan p<0,001 bermakna dalam analisis ini. Nilai titik potong CYFRA 21-1 didapatkan sebesar ≥ 10,9 ng/mL dengan sensitivitas 69,5% dan spesifisitas 65,5%. Variabel-variabel yang memenuhi asumsi proportional hazard adalah CYFRA 21-1, PS, histologi, dan terapi. CYFRA 21-1 ≥ 10,9 ng/mL memiliki HR 1,744 (HR=1,744; p=0,028); PS ECOG 3-4 memiliki HR 2,434 (HR=2,434; p=0,026); histologi non-adenokarsinoma memiliki HR 1,929 (HR=1,929; p=0,029); dan kelompok yang tidak dikemoterapi memiliki HR 2,633 (HR=2,633; p=0,015).* ***Kesimpulan:*** *dari kedua penanda tumor, hanya CYFRA 21-1 yang terbukti bermakna terhadap kesintasan NSCLC. Nilai titik potong CYFRA 21-1 sebagai faktor prognostik sebesar ≥ 10,9 ng/mL.*

***Kata kunci:*** *kanker paru, NSCLC, stadium lanjut, kesintasan, CEA, CYFRA 21-1.*

## ABSTRACT

***Background:*** *non-small cell lung carcinoma (NSCLC) is the most common type of lung cancer. Therefore, research into its prognostic factor is very important for better patient management. However, there have been no studies looking for the association of CYFRA 21-1 and CEA with survival of NSCLC in Indonesia, and no cut-off value for them as standardized prognostic factors. This study aims to know the association of CEA and CYFRA 21-1 with one-year survival of advanced stage NSCLC in RSCM and determining their cut-off point as a prognostic factor.* ***Methods:*** *a retrospective cohort study of 111 subjects with advanced stage NSCLC aged ≥ 18 years who*

*were diagnosed from January 2012 to May 2018, resulted in a set of data which includes an initial score of CEA and CYFRA 21-1 at diagnosis, along with their confounding factors, namely performance status (PS), type of histology, therapy, and stadium. All data were taken from the RSCM Medical Record Unit.* ***Results:*** *the CEA area under the curve (AUC) was less than 50% (AUC=0.446) and not significant, whereas AUC CYFRA 21-1=0.741 (0.636–0.847) with p <0.001 was significant in this analysis. CYFRA 21-1 cut-off point was ≥ 10.9 ng / mL with a sensitivity of 69.5% and specificity of 65.5%. The variables that met the proportional hazard assumption were CYFRA 21-1, PS, histology, and therapy. CYFRA 21-1 ≥ 10.9 ng/mL had HR 1.744 (HR=1.744; p=0.028); ECOG 3-4 PS had HR 2.434 (HR=2.434; p=0.026); non-adenocarcinoma histology had HR 1.929 (HR=1.929; p=0.029); and the non-chemotherapy group had HR 2.633 (HR=2.633; p=2.633; p=0.015).* ***Conclusion:*** *from both tumour markers, only CYFRA 21-1 was proven to be significant to NSCLC survival. CYFRA 21-1 cut-off value as a prognostic factor was ≥ 10.9 ng/mL.*

***Keywords:*** *lung cancer, non-small cell lung carcinoma, advanced stage, one-year survival, CEA, CYFRA 21-1.*

## INTRODUCTION

In Indonesia, lung cancer is a type of cancer with the highest number of new cases and the leading cause of cancer deaths, especially in the male population. More than 60% of patients who came to the hospital had advanced stage (stage IIIB-IV) and poor prognosis. Based on data from Noorwati et al. (epidemiological data and survival of lung cancer in Indonesia), the one-year survival rate of lung cancer was 13%.[1,2]

At present, some researchers have developed several tumour markers that can be used to predict the prognosis and evaluate therapy in lung cancer. These markers can prevent inadequate therapy in aggressive diseases and prevent excessive therapy in indolent diseases. Among these tumour markers, Carcinoembryonic antigen (CEA) and cytokeratin-19 fragments 21-1 (CYFRA 21-1) are tumour markers that have high sensitivity and specificity to non-small cell lung carcinoma (NSCLC) and are postulated to be independent prognostic factors for NSCLC in both early and advanced stages.[3-6]

A study by Pang et al.[7] found CYFRA 21-1 to have sensitivity of 90.0% and specificity of 60.3% at cut-off point of 3.3 ng /mL, and CEA to have sensitivity of 81.4% and specificity of 55.6% at cut-off point of 5.0 ng/mL in detecting chemotherapy responses. It was found that both CYFRA 21-1 and CEA values significantly increased before and after therapy. A study by Ando et al. showed that the increased values of CEA and CYFRA 21-1 were associated with an advanced disease. In this study, the CYFRA 21-1 cut-off value for prognostic evaluation was 3.5 ng/mL, while the CEA cut-off value based on previous research was 10 ng/mL. However, these values vary in some studies, and none has been determined as standardized reference values.[8,9]

Research into prognostic factors in NSCLC is very important because it has the potential for leading us to better patient management. Tumour markers are thought to provide additional data related to patient's prognosis, in addition to performance status (PS), type of histology, therapy, or stages, based on TNM classification. It is expected that an increase in tumour markers from the beginning can help predict the patient's prognosis, so that lung cancer management strategies can be modified, especially at an advanced stage.[8] At Cipto Mangunkusumo Hospital (RSCM) in particular, lung cancer patients who come for treatment are mostly already in an advanced stage, so the patients are not clinically compatible to have various examinations such as lung scan. Based on this, this study was carried out to determine the function of CEA and CYFRA 21-1 as the future education strategy and management of advanced stage NSCLC patients and to analyse the cut-off value of both tumour markers as prognostic factors.

## METHODS

This research was a retrospective cohort study. The study was conducted in the RSCM Medical Record Unit. The research was performed from September 2018 to July 2019. NSCLC survival

assessments were based on medical record data for a period of one year. The patient's survival was calculated from the time when NSCLC was first diagnosed to the time of death. Data in the form of CEA and CYFRA 21-1 values were collected at the time of initial diagnosis. This data collection also included patients' confounding factors such as cancer stage, performance status (PS), therapy, and type of histology.

The study has been approved by the Ethical Committee of Faculty of Medicine Universitas Indonesia. Reference number: KET-243/UN2. F1/ETIK/PPM.00.02/2019.

The sampling in this study was carried out consecutively (consecutive sampling) with a total sample of 111, which was calculated using the survival analysis formula. The inclusion criteria in this study were that subjects were adult male and female patients aged ≥ 18 years who had been diagnosed with at least stage IIIB of NSCLC from January 2012 to July 2018. Meanwhile, the exclusion criteria in this study were that (1) no CEA and CYFR A 21-1 values were available at the time of initial diagnosis; (2) no data of confounding factors such as performance status (PS), stage, treatment history, and type of histology were available; and (3) the patients had multiple primary malignancies. The data were collected based on secondary data taken from the RSCM Medical Record Unit. The first 111 individuals who met the criteria were included as the subjects of this study.

The data obtained were analysed using IBM SPSS Statistics 20. Statistical analysis used was univariate analysis performed with data descriptions, namely numerical data presented in the form of point estimation using means for data that were normally distributed and medians for data that were not normally distributed. Interval estimation used interquartile range for ranges of data that were not normally distributed and standard deviations for data that were normally distributed. Categorical data were presented in the form of values or values with percentages. Multivariate analysis was performed with cox proportional hazards and log-rank tests, using the main variables CEA and CYFRA 21-1 and other prognostic factors thought to influence survival.

## RESULTS

From January 2012 to July 2018, there were 630 patients registered with NSCLC at Cipto Mangunkusumo General Hospital. From 630 patients, there were 487 patients who did not have initial CYFRA 21-1 and CEA data. After searching through the medical records, 111 patients were found to meet the inclusion criteria.

The study subjects were 60 years old on average and were males, but there was not much difference between the number of subjects who smoked and those who did not smoke. Adenocarcinoma was the most type of NSCLC histology obtained in this study. More than

**Table 1.** Baseline characteristics (N=111).

| Patient's characteristics | n (%) |
|---|---|
| Age, year, mean (SD) | 60.00 (10.96) |
| Gender, male, n (%) | 63 (56.8) |
| Smoking history, n (%) | |
| - Smoker | 59 (53.2) |
| - Non-smoker | 52 (46.8) |
| Performance status (ECOG), n (%) | |
| - < 2 | 54 (48.6) |
| - > 2 | 57 (51.4) |
| Stages, n (%) | |
| - IIIB | 7 (6.3) |
| - IV | 104 (93.7) |
| Histology, n (%) | |
| - Adenocarcinoma | 93 (83.8) |
| - Non-adenocarcinoma | 18 (16.2) |
| EGFR mutation, n (%) | |
| - Positive | 27 (24.3) |
| - Negative | 14 (12.6) |
| - No data | 70 (63.1) |
| Comorbidities, n (%) | |
| - Pneumonia | 58 (52.3) |
| - Other comorbidities | 41 (36.9) |
| - No comorbidities | 12 (10.8) |
| Death in one year, n (%) | |
| - Death | 82 (73.9) |
| - Alive | 29 (26.1) |
| Duration of death (months) | 1.00–13.00 |
| CEA | 6.51–125.2* |
| CYFRA 21-1 | 5.60–41.8* |

* ECOG: The Eastern Cooperative Oncology Group, EGFR: epidermal growth factor receptor, CEA: Carcinoembryonic antigen, CYFRA 21-1: cytokeratin-19 fragments 21-1

50% of study subjects presented with stage IV and died within one year of the diagnosis. The complete characteristics of patients are listed in **Table 1**.

Overall, the median of one-year survival was 4 months (95% confidence interval [95% CI] = 2.021–5.979) as illustrated in the curve below (**Figure 1**).

The area under the curve (AUC) of the CEA was found to be less than 50% (AUC=0.446),was non-significant, and could not be used for further analysis. On the other hand, the AUC of CYFRA 21-1 was significant in this analysis with a value of AUC=0.741 (0.636–0.847) and p<0.001 (**Figure 2**).

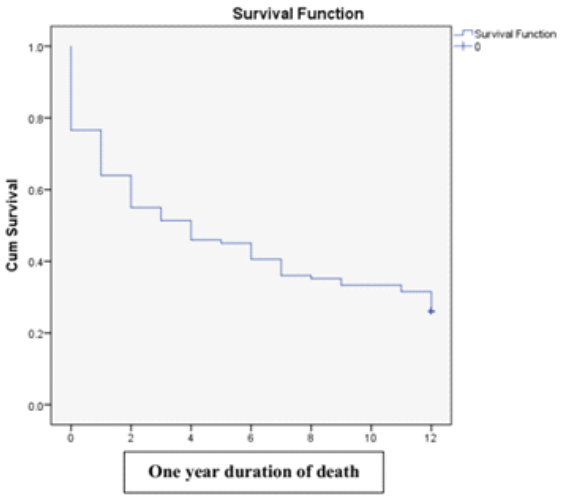


**Figure 1.** Overall 1-year survival curve (median = 4 months, 95% CI = 2.021-5.979 months).

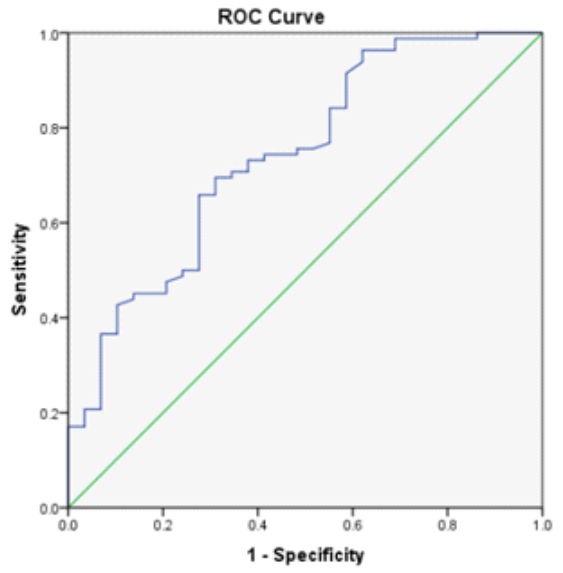


**Figure 2.** Area under the curve CYFRA 21-1. AUC = 0.741 (0.636-0.847); p = <0.001.

CEA cut-off point was >21.285 ng/mL with a sensitivity of 48.8% and specificity of 48.3%. Meanwhile, the CYFRA 21-1 cut-off point was ≥ 10.9 ng/mL with a sensitivity of 69.5% and specificity of 65.5% (**Table 2**).

**Table 2.** Cut-off analysis.

| | PPV | NPV |
|---|---|---|
| CEA ≥ 21.285 ng/ml | 72.7% | 25.0% |
| CYFRA 21-1 ≥ 10.9 ng/ml | 85.1% | 43.2% |

*CEA: Carcinoembryonic antigen, CYFRA 21-1: Cytokeratin-19 fragments 21-1, PPV: Positive predictive value, NPV: negative predictive value

The variables that met the proportional hazard assumption in this analysis were CYFRA 21-1, PS, type of histology, and therapy. A p-value >0.05 was obtained both in the CEA analysis and in the stage analysis, so the results were not significant in this study.

Variables that met proportional hazard assumptions, namely CYFRA 21-1, PS, type of histology, and therapy, were included in the analysis and presented in **Table 3**. Staging categories were analysed and did not meet the proportional hazard assumptions, so they were used as strata in the reduced model.

## DISCUSSION

In general, the study subjects had an average age of 60 years, while the median age in CEA ≥21.285 ng/mL group was 61 years and that in CYFRA 21-1 ≥ 10.9 ng/mL group was 63 years. This is consistent with previous data which state that the median age of lung cancer patients worldwide was 70 years old in both men and women.[10-11]

Overall, 73.9% of the subjects died in one year , with 48.8% having high initial CEA values and 69.5% having high CYFRA 21-1 values. Previous studies suggested that the histology type of adenocarcinoma had a better prognosis, so it was thought that patients with high initial CEA valueshave a better prognosis.[12] The median of one-year survival in this study was 4 months (95% CI=2.021–5.979 months). This result was

**Table 3.** Survival analysis and hazard ratio.

| Category | One-year survival | | | | |
|---|---|---|---|---|---|
| | Median (months) | Survivor 1 year | Hazard ratio | 95% CI | P-value |
| CYFRA 21-1 value | | | | | |
| - ≥ 10.9 ng/mL | 1.00 | 10 (14.9%) | 1.744 | 1.062-2.865 | 0.028 |
| - < 10.9 ng/mL | 9.00 | 19 (43.2%) | | | |
| Performance status (ECOG) | | | | | |
| - 3-4 | 1.00 | 0 (0%) | 2.434 | 1.115-5.315 | 0.026 |
| - 0-2 | 12.00 | 29 (53.7%) | | | |
| Histology | | | | | |
| - Non-adenocarcinoma | 1.00 | 2 (11.1%) | 1.929 | 1.068-3.485 | 0.029 |
| - Adenocarcinoma | 5.00 | 27 (29.0%) | | | |
| Therapy | | | | | |
| - Non-chemotherapy | 1.00 | 0 (0.0%) | 2.633 | 1.211-5.722 | 0.015 |
| - Chemotherapy | NA | 29 (50.9%) | | | |

*ECOG: the Eastern cooperative oncology group, CEA: Carcinoembryonic antigen, CYFRA 21-1: Cytokeratin-19 fragments 21-1, 95% CI: 95% confidence interval.

different from the results of a study by Cho et al.[13] in which the patients also had the characteristics of an advanced stage NSCLC. In that study, the median of survival was 16 months (95% CI 8.7–23.3 months). This difference was thought to be caused by the administration of tyrosine kinase inhibitor (TKI) therapy to the study subjects of Cho et al. Meanwhile, in this study, the number of subjects who were given the targeted therapy was less than 20%.

The prognostic value of CEA has been debated for a long time because there are studies with results that support and do not support CEA as a prognostic factor. Some studies such as the one by Pang et al.[7] or Barlesi et al.[8] mentioned that high CEA values do not have a significant association with poor prognosis. On the contrary, based on research by Hanagiri et al.[14], Lin et al.[15], and Fiala et al.[16] who monitored the condition of patients for up to five years, high CEA values were shown to be associated with poor prognosis in NSCLC patients. This condition, however, does not seem to apply to CYFRA 21-1 values which, based on various previous studies, always have a significant association with NSCLC prognosis. High initial CYFRA 21-1 values have been shown to represent poor survival of NSCLC.[8,9,17]

CYFRA 21-1 was found to have AUC=0.741 (0.636–0.847) with p<0.001, so the results were quite significant in this survival analysis. From the results of the study, it could be seen that CYFRA 21-1 ≥ 10.9 ng/mL at one time has a 1.744 times risk of experiencing death, with a median of 1 month (HR=1.744, p=0.028). These results were consistent with those of previous studies which also compared between high initial CYFRA 21-1 values and low ones. Fiala et al.[16] showed shorter progression-free survival (PFS) in subjects with higher initial CYFRA 21-1 values (1.9 versus 3.4 months, p<0.001) and shorter overall survival (OS) in the same group (6.1 versus 23.8 months, p<0.001), with a 2.74 times risk of experiencing death (PFS: HR=2.17; p<0.001; OS: HR=2.74; p<0.001).

Based on research data, PS with ECOG 3-4 had HR 2.434 with a median of 1 month (HR=2.434; p <0.001). This showed a significant association between PS and disease prognosis. A good PS can describe a better prognosis, and vice versa. This situation was in accordance with previous studies, as in the analysis of Cho et al. In this study, independent predictive factors for better PFS values were obtained, such as a good PS ECOG, positive EGFR mutations, high initial CEA values, and high initial CYFRA 21-1 values.[13]

In non-adenocarcinoma, HR 1.929 was found to have a median of 1 month (HR=1.929; p=0.018). These results were indeed quite

significant although the HR value of this type of histology was not as large as the HR value of the PS variable. Based on this, it was estimated that the survival of NSCLC will be more influenced by PS than the type of histology or stage of cancer. The data is in accordance with previous theories which state that adenocarcinoma has a better prognosis than other NSCLC cell types.[12]

From the results of the study, there were 51.3% of subjects who received chemotherapy in the form of single chemotherapy, combination therapy, or targeted therapy. The administration of chemotherapy, including targeted therapy in advanced NSCLC patients, has been shown to significantly affect survival. Research subjects not given chemotherapy had HR 2.633 with a median of 1 month (HR 2.633; p=0.015). A study by Pallis et al.[18] revealed that the administration of combined chemotherapy in advanced NSCLC patients could objectively increase tumour response (odds ratio [OR]: 0.42; 95% CI: 0.37–0.47; p<0.001) and one-year survival from 30% to 35% (OR: 0.80; 95% CI: 0.70–0.91; p<0.001), although the toxicity effect was also increasing. In patients with EGFR mutations, the administration of TKI therapy can bring significant improvement on the patient's condition, but this advantage is limited to NSCLC patients with certain molecular.

### Strengths of the Study

This study is the first study in Indonesia to assess the association of CEA and CYFRA 21-1 with the one-year survival of advanced stage NSCLC as a prognostic factor. The tumour marker examination can be easily done by blood collection. In addition, an analysis was also conducted to find the cut-off value of these tumour markers as a prognostic factor. Based on several previous studies, up to now, there has been no standardized cut-off value of CYFRA 21-1 and CEA as a prognostic factor.

### Limitations of the Study

The data in this study are secondary data taken from medical records retrospectively, so information is limited only to what is written on the patient's case history. Researchers did not conduct a direct examination of the research subjects, so there may be differences in the perception of patient's clinical data that may lead to bias in this study.

## CONCLUSION

High initial CEA values were not proven to be related to the survival of patients with advanced stage NSCLC in RSCM. Conversely, a high initial CYFRA 21-1 value was shown to be a significant prognostic factor for one-year survival of advanced stage NSCLC in RSCM, while the cut-off value of CYFRA 21-1 as a prognostic factor is ≥ 10.9 ng/mL.

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