Original Article

Correlation of Zinc Levels on C-Reactive Protein Among Advanced-Stage Non-Small Cell Lung Cancer Patients

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Abstract

Background: Lung cancer is a leading cause of malignancy and mortality**.** Zinc and C-reactive proteins are known to affect lung cancer progression. However, inconsistent findings between zinc levels on plasma CRP levels were reported. This study aimed to determine the correlation between serum zinc and CRP levels in patients with advanced-stage non-small cell lung cancer (NSCLC)

Methods: A cross-sectional study was conducted in the Regional Hospital of Doris Sylvanus Palangkaraya between January and April 2023. Thirty-five lung cancer patients were included. The blood specimen was analyzed for serum Zinc and CRP. Spearman's correlation test was used to analyze the data.

Results: The zinc level was dominantly normal or low (71.4%), with a mean of 65.57 ug/dL. Most subjects have elevated CRP, with higher CRP in the deficiency zinc group (96.64 vs. 68.89 mg/L). However, no significant correlation was found between serum zinc and CRP levels (*P*=0.160; r=0.173).

Conclusion: Serum zinc levels were not proven statistically correlated with inflammatory markers (CRP), particularly in non-small lung cancer patients.

Keywords: CRP, NSCLC, Zinc

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INTRODUCTION

Lung cancer is the most common cancer worldwide and has the highest mortality rate due to its poor prognosis. Its incidence accounts for an estimated 2.2 million diagnosed cases and 1.8 million deaths in 2020.[1] Recent WHO data published lung cancer deaths in Indonesia placed 93rd in the world at the rate of 1.69% of total deaths.[2] The figures in Indonesia have increased over time and occur at a younger age compared to other countries.

The rise in the incidence of lung cancer has been closely linked to various risk factors. Multiple recent studies have confirmed that various factors may develop lung cancer, such as dietary, physical inactivity, tobacco smoking, occupational exposures, air pollution, genetic risk factors, chronic inflammation from infections, and other medical conditions.[2–4] Meanwhile, lung cancer progression is influenced by the immune system, genetic factors, and inflammatory response.

Inflammation involves the activation of signalling pathways that regulate inflammatory mediators in tissue and circulating immune cells.[5] Inflammation has long been recognized as a major cause of disease and 15% of human cancers are associated with chronic infection and inflammation.[6] CRP as a marker of inflammation can be relied upon as a parameter to predict cancer development. The high-sensitivity CRP test measures low levels of CRP in the blood to identify low levels of inflammation that are linked to the risk of developing cancer, including lung cancer.[7,8]

In addition, it is also reported that high zinc plasma reduces the risk of lung cancer, possibly by delaying telomere events and modulating the clearly show that zinc deficiency is a factor in lung cancer development and progression. Although zinc deficiency is not considered a public health issue in developed countries, zinc remains an important nutrient due to its antioxidant and anti-inflammatory properties.[9]

Previous findings suggested that serum zinc levels in lung cancer cases were significantly lower than among controls.[9] This supported that zinc has potential anti-inflammatory effects. However, recent findings regarding the effect of zinc on plasma C-reactive protein appeared inconsistent.

Some studies suggested a significant correlation between zinc on plasma C-reactive protein, with both positive and negative correlation.[10,11] Nonetheless, few studies revealed contrary findings.[8,12] Different characteristics and settings among studies may yield various results in the actual association between zinc and C-reactive protein levels.

This study, therefore, set out to determine the association between zinc status and C-reactive protein levels among specific populations with advanced-stage non-small cell lung cancer in Doris Sylvanus Regional Public Hospital.

METHODS

This cross-sectional study was conducted between January and April 2023. The study included patients diagnosed with advanced-stage lung cancer at Doris Sylvanus Hospital, Palangkaraya. To obtain an 80% power of study with a margin of error of 5%, we need at least 31 subjects. Subjects in the present study included a total sample of 35 adults aged 18 years or older, diagnosed with advanced-stage non-small cell lung cancer, free of surgery, radiation, or chemotherapy records.

Additionally, we excluded subjects with prior lung cancer treatment and were under 18 years old. This study was approved by the Ethics Committee of Doris Sylvanus Hospital and was conducted in accordance with the Declaration of Helsinki (Approval Letter No 785.1/UM-TU/RSUD/01-2023). All subjects provided written informed consent to participate in this study.

To determine general characteristics, including demographic information, age, gender, height (HT), body weight (BW), body mass index, smoking status, type of cancer cell, clinical symptoms, clinical stage, and metastatic a structured questionnaire was administered.

Smoking status was classified as either current smokers or non-smokers. BMI was calculated as weight in kilogram divided by the square of height in meters (kg/m^2), then categorized into underweight if BMI was less than 18.5 and normal if the BMI was 18.5-24.9. The information on clinical symptoms was obtained through anamnesis and physical examination.

Blood samples were analyzed to measure zinc levels and C-reactive protein (CRP). Zinc level was categorized into three groups: normal for higher than or equal to 80 µg/dL, low for levels between 60 and 79 µg/dL, and deficient for levels lower than 60 µg/dL. The groups were simplified and categorized as deficient and low or normal groups. Meanwhile, CRP was on a numerical value.

For numeric variables (age and CRP), a normal distribution of data was represented using means and standard deviations, while if an extreme outlier was found, the median and interquartile ranges were the best-fit presentation. Spearman's correlation coefficient was used to assess the correlation between serum zinc and CRP levels. A value of $P<0.05$ was considered significant.

RESULTS

The general characteristics of study subjects are presented in Table 1. Serum zinc levels were classified as deficient (<60 µg/dL) or normal (≥60 µg/dL). The median age was 61 years (IQR: 53–68) in the zinc-deficient group and 59 years (IQR: 52–66) in the normal zinc group.

The proportion of subjects with males in gender, current smoker status, and underweight were higher among the normal than deficient Zn group. Adenocarcinoma was mostly found among normal Zn patients. All clinical symptoms included in this study (cough, dyspnea, and chest pain) were presented higher among normal Zn subjects.

Table 1. General characteristics of the study subjects (n=35)

Characteristics	Deficient Zn	Normal Zn	Total
Age (years), (median, IQR)			
	61 (53-68)	59 (52-66)	60 (53-68)
Gender			
Male	7 (25.93%)	20 (74.07%)	27 (77.14%)
Female	3 (37.50%)	5 (62.50%)	8 (22.86%)
Smoking status			
Smokers	7 (25.93%)	20 (74.07%)	27 (77.14%)
Non-smokers	3 (37.50%)	5 (62.50%)	8 (22.86%)
BMI			
Underweight	6 (25.00%)	18 (75.00%)	24 (68.57%)
Normal	4 (36.36%)	7 (63.64%)	11 (31.43%)
Type of cancer cell			
Adenocarcinoma	4 (21.05%)	15 (78.95%)	19 (54.29%)
Squamosa cell carcinoma	6 (37.50%)	10 (62.50%)	16 (77.14%)
Clinical symptom			
Cough	3 (23.08%)	10 (76.92%)	13 (37.14%)
Dyspnea	4 (44.44%)	5 (55.56%)	9 (25.71%)
Chest pain	3 (23.08%)	10 (76.92%)	13 (37.14%)
Metastatic			
No metastatic	2 (28.57%)	5 (71.43%)	7 (20.00%)
Intrathoracic metastasis	8 (30.77%)	18 (69.23%)	26 (74.29%)
Extra*thoracic* metastasis	0 (0.00%)	2 (100.00%)	2 (5.71%)
Cancer stage			
<IV	2 (33.33%)	4 (66.67%)	6 (17.14%)
≥IV	8 (27.59%)	21 (72.41%)	29 (82.86%)
CRP (median, IQR)	94.64 (18.62-120.47)	68.89 (16.25-118.12)	87.77 (16.53-116.23)

Table 2 demonstrates the correlation of zinc levels with CRP. No significant correlation was observed between serum zinc and CRP levels (r=0.173; *P*=0.160) in patients with advanced-stage lung cancer.

Table 2. Correlation of Zinc levels and C-reactive protein (CRP)

Laboratorium parametric	r	*P*
CRP	0.173	0.160

DISCUSSION

In the present study, there was no significant correlation between Zinc levels and CRP (r=0.173; *P*=0.160) among advanced lung cancer patients. These findings suggest that zinc levels may be influenced by factors such as fasting status, diurnal variation, exercise, and sex, reflecting population trends rather than individual zinc status.[13]

Similarly, this finding was also found among children in Surabaya where no differences in CRP levels between low and normal zinc levels.[14] However, other studies showed a negative correlation in two groups of acutely ill geriatric hospital in-patients and in inflammatory status among lung cancer patients.[15–17]

In contrast, a positive correlation between those variables was proved by a large cross-sectional study that the estimated prevalence of zinc deficiency increased with increasing CRP decile.[18] These contrasting findings highlight the inconsistency in the relationship between zinc and CRP, suggesting that the true nature of this association remains unclear.

We acknowledged that this study is against the theory that zinc is an inhibitor of proinflammatory cytokines and may reduce CRP. However, this result may be influenced by the small sample size, and a multi-center study would provide more robust findings.[19] In addition, recent studies have confirmed that some factors influence the development of lung cancer, including external environment exposure, dietary factors, and trace element concentration.[20–22]

Zinc and copper proved closely involved in the risk of lung cancer through cell proliferation, growth, gene, apoptosis, and other processes.[9] Notably, these various potential factors may confound the link

between zinc deficiency and CRP to the development of lung cancer.

Some epidemiological studies have reported that CRP levels are associated with host behavior. Plasma CRP may overview the general health of females at the time of cancer diagnosis.[23,24] Smoking and elevated body mass index have been linked with higher CRP levels.[25] Thus, it is possible that the present finding of an association between zinc deficiency may not be the only specific cause of elevated CRP for developing lung cancer. Nevertheless, both zinc deficiency and elevated CRP levels have been associated with poor lung cancer prognosis.[26]

Nevertheless, a direct link between zinc levels as a diagnostic biomarker for cancer with the CRP concentrations could not be ignored. Multiple studies have suggested that Zinc increases antioxidant power and decreases CRP which suggests that Zinc has an atheroprotective effect for being at risk of developing a malignancy.[11]

Studies of cell cultures in less and enough zinc conditions found that zinc induces upregulation of the A20 protein, which is one of the inhibitors of NF-κB activation as a major transcription factor of inflammation. However, zinc deficiency conditions may also induce apoptosis and endothelial cell dysfunction due to increased concentrations of proinflammatory cytokines and oxidative stress.[20]

The present study also found that low or normal zinc levels were the most common. Consistent results were found in both European populations and Asian populations.[27] Zinc deficiency is primarily caused by poor dietary intake, insufficient absorption, increased loss, or higher utilization by the body.[28] Zinc deficiency may have adverse events, especially on immune function.[9]

In general, the zinc microenvironment may play a key role in oxidative stress, apoptosis, and/or cell signaling alterations which influence the behavior of cancer cells, and this may play a role in preventing lung cancer.[29] Overall, a direct link between zinc levels and the development of different cancer types was noted while highlighting the interdependence of micronutrient levels.[30]

The present study also indicated that the most common clinical symptoms found in this study were cough and shortness of breath in patients with normal and low zinc levels. These findings support the previous literature that cough was the most prevalent symptom, affecting 57% of lung cancer patients.[31]

Patients with lung cancer can suffer from acute causes of cough, such as an infection or smoking, and, or may have a cough due to the effects of the malignancy and its treatment. However, different subjects may have different symptoms of lung cancer. Some people whose lung cancer has spread to other parts of the body (metastasized) have symptoms specific to that part of the body.[4]

This study also found that the incidence of lung cancer of the adenocarcinoma type in 19 people, whereas in the Indonesian population, the highest incidence of lung adenocarcinoma is the most common primary lung cancer seen in the United States.[1] It falls under the umbrella of non-small cell lung cancer (NSCLC) and has a strong association with previous smoking. While incidence and mortality have declined, it remains the leading cause of cancer death in the United States.[1]

Adenocarcinoma of the lung usually evolves from the mucosal glands and represents about 40% of all lung cancers.[32] It is the most common subtype to be diagnosed in people who have never smoked. Lung adenocarcinoma usually occurs in the lung periphery and in many cases, may be found in scars or areas of chronic inflammation.

In most cases of lung carcinoma, people are often detected in metastatic stage IV due to unrecognized symptoms. Lung carcinomas metastasize by lymphatic as well as blood vessels. It needs to consider how medical examined resected lung carcinomas. Vascular invasion is often seen in low-stage tumors, which usually results in an increased incidence of recurrence as well as shortened survival of the patient. Whereas metastasis via the lymphatic route usually takes longer until distant metastases are set, spreading via blood vessels will set early on distant metastases.

Lung carcinomas have some preferential sites for metastasis, such as the brain, bones, and adrenal

glands, which are similar to the current study showing the same metastatic, and a large case of intrathoracic. Therefore, early detection of lung cancer needs to be taken into consideration.

LIMITATION

Several limitations of this study should be considered in the interpretation of our results. First, another study design may be fit to use since cross-sectional typically requires a larger sample size to have greater power and is ideal for a strong study design. This may cause the present study could not draw a causal relationship between zinc status and CRP levels through the cross-sectional study design. Second, there is a need to consider other potential factors that may confound the correlation between zinc and CRP levels among lung cancer patients. Despite these limitations, there has been no clear evidence regarding the mechanism of zinc levels known to influence CRP. Therefore, the present study is essential as one of the earliest studies addressing this issue.

CONCLUSION

There is no significant correlation between serum zinc level and c-reactive protein level in advanced stages of non-small lung cancer patients in Doris Sylvanus Hospital Palangkaraya. The lack of correlation may be influenced by the study's cross-sectional design and small sample size, limiting generalizability. These findings provide a basis for future studies to further explore the potential relationship between zinc levels and CRP in lung cancer progression.

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CONFLICT OF INTEREST

Authors have no conflict of interest to declare.

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