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Relationship of Serum Ascorbic Acid and CRP Levels in Non-Small Cell Lung Cancer Patients in the Medan City Population

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Abstract

Background: Lung cancer is the third-leading cause of death in cancer patients among both men and women in Indonesia. About 80% of lung cancer types are non-small cell lung cancer (NSCLC). C-reactive protein is a protein that is produced by the liver and is known as a marker of ongoing inflammation, including malignancy. Many studies have shown the susceptibility of cancer cells, especially to high doses of ascorbic acid (Vitamin C). ***Objective:*** This study was to determine the relationship between ascorbic acid and CRP serum levels in NSCLC patients in Medan City, North Sumatra, Indonesia. ***Methods:*** This study was an observational analysis of NSCLC patients from January to April 2023 with a cross-sectional method. There were 53 NSCLC patients enrolled in this study. Vitamin C and CRP serum levels were measured by a single blood sample, with vitamin C levels measured using a manual ELISA kit (BT Lab, China) and CRP quantitative levels using an immunoassay. The data was analyzed using the Spearman Correlation Test. ***Results:*** 53 subjects found more males than females (85%), with 37 patients undergoing cancer treatment. All the patients had vitamin C deficiency (< 0.2 mg/dL), with the highest value of 0.05 mg/dL and the lowest of 0.0001 mg/dL. 32 patients (60.37%) had a high CRP value (≥ 5 mg/dL), with the highest value of 7 mg/dL and the lowest value being 0.3 mg/dL. Higher CRP levels were more common in patients with on treatment and history of smoking. This study found that there was no relationship between CRP and vitamin C serum levels in NSCLC patients (r2 = 0.0034, p >0.05). ***Conclusion:*** There is no relationship between vitamin C and CRP serum levels in NSCLC patients among the Medan city population.

Keywords: ***non-small cell lung cancer, ascorbic acid, CRP.***

Introduction

The lung cancer death rate is increasing along with the increase in cancer cases throughout the world. Lung cancer is known to be the third most common cause of cancer and the leading cause of cancer deaths in Indonesia [1]. According to Logawathi's research, which examined lung cancer patients in Medan City, North Sumatra-Indonesia, there were 311 lung cancer patients treated at HAM Hospital in 2016-2018 with more men than women (78.6% VS 21, 4%) and as many as 114 lung cancer patients treated at Elisabeth Hospital in Medan in 2004-2007 found 86% of the patients were male [2,3]. Histopathologically, lung cancer is divided into two, namely Small Cell Carcinoma Lung Cancer (SCLC) and Non-Small Cell Lung Cancer (NSCLC) where the number of NSCLC patients is significantly greater, namely 80% compared to SCLC [4,5].

The process of carcinogenesis is the accumulation of genetic and epigenetic disorders that cause deregulation of cellular homeostasis. Along with the process of growth and spreading of tumor cells, this can affect the integrity and hemostasis of normal tissue, thereby triggering an inflammatory response in the body. C-reactive protein (CRP) is a protein produced by the liver and is a sign of an ongoing inflammatory process, including malignant processes [6]. Inflammatory processes and high levels of CRP are associated with poor prognosis and reduced survival rates in several types of cancer [7].

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Ascorbic acid/vitamin C is a micronutrient compound that humans obtain through food and supplements. Many studies have shown the susceptibility of cancer cells, especially to the administration of high doses of vitamin C [8]. In research conducted by Mikirova *et al*, it was found that giving vitamin C could reduce CRP levels and tumor markers in several cancer cases, and a meta-analysis study found that giving 100 mg/day could reduce the risk of lung cancer by 7% [9]. Mayland *et al*'s research found that there was a significant negative correlation between vitamin C and serum CRP values in patients with malignancy [10]. There has never been any research on vitamin C levels in lung cancer patients in Indonesia and the relationship between vitamin C levels and serum CRP values in lung cancer patients.

Materials and Methods

This research is observational analytics with an approach cross-sectional. The study's inclusion requirements included NSCLC patients' written approval to participate in the research after being informed about it (informed consent). This research has received information about passing ethical review from the Health Research Ethics Committee, Faculty of Medicine, University of North Sumatra with No: 124/KEPK/USU/2023.

Sampling took place in multiple hospitals in the province of North Sumatra, including the Adam Malik Haji Central General Hospital Medan, Prof. Dr. Chairuddin Panusunan Lubis Universitas Sumatera Utara, Murni Teguh Hospital, and Santa Elisabeth Hospital, for four months, from January 1, 2023, to April 30, 2023. A minimum sample size of 50 patients with NSCLC identified by cytology and histology was established as respondents based on the findings of sample calculations utilizing a correlation coefficient of -0.529 from prior research [10].

Samples were taken using non-probability sampling, namely using a consecutive sampling technique from patients who met the inclusion criteria. After fulfilling the criteria, blood was drawn and the respondent's serum levels of ascorbic acid/vitamin C and CRP were checked. Serum vitamin C levels were checked by ELISA manually using Human Vitamin C Elisa Kit No. E1538Hu (BT Lab, China) while serum CRP was examined quantitatively using the immunoassay method using Fuji dri-chem CRP-SIII slides with a reference value of <5mg/L. Vitamin C level status is divided into 3 categories, namely normal (>0.3mg/dL), insufficiency (0.2-0.29mg/dL), and deficiency (<0.2mg/dL) [11]. Serum CRP levels are divided into low values if the serum CRP level is <5mg/L and high if≥5mg/L.

The data obtained were analyzed descriptively to see the frequency distribution based on characteristics, while the relationship between vitamin C levels and CRP values would be analyzed using Spearman Correlation. All results are declared significant if the p-value is <0.05.

Results

There were 53 NSCLC patients found within 4 months in several designated hospitals, 37 (69.81%) of the patients underwent cancer treatment and the rest refused treatment. As for the characteristics of the research subjects (Table 1), it was found that the average age in the group with treatment was younger, namely 53 years (29-70 years) compared to the group of patients without treatment, namely 59 years (38-69 years). There were more males than females (85% vs 15%), the same was found in the group with treatment (86.4% vs 13.6%) and the group without treatment (81.2% vs 18.8%). Based on cell type, squamous cell carcinoma was found to be more common in patients with treatment, namely 51.4%, while patients without treatment had more adenocarcinoma, namely 56.2%. In this study, all respondents were advanced-stage lung cancer patients, where in the group with treatment, 51.35% were at stage III, while in the group without treatment, 81.25% were at stage IV. Most of the respondents were smoker or current smoker (86.5% and 81.2%). From the results of blood serum examination, it was found that all respondents (100%) had vitamin C deficiency status (<0.2mg/dL) in both the treatment and non-treatment groups with the lowest value being 0.0001mg/dL and the highest value being 0.05mg/dL. A total of 32 NSCLC patients (60.37%) had high CRP values. If divided based on treatment history groups, high CRP values were found more frequently in the group without treatment (51.4% vs 81.25%) with an average CRP value (4.22mg/dL vs 5.85mg/dL) where the lowest value is 0.3mg/L and the highest is 7 mg/L.

Table 1: Research characteristics

Characteristics	With Treatment (n= 37)	No Treatment (n = 16)
Mean age (range), years	53 (29-70)	59 (38-69)
<40 yr, n (%)	9 (24.33%)	9 (56.25%)
40-60 yr, n (%)	25 (67.57%)	6 (37.5%)
>60 yr, n (%)	3 (8.1%)	1 (6.25%)
Sex		
Male, n (%)	32 (86.4%)	13 (81.2%)
Female, n (%)	5 (13.6%)	3 (18.8%)
Cytology/Histopatology		
Adenocarcinoma, n (%)	18 (48.6%)	9 (56.2%)
Squamous Cell Carcinoma, n (%)	19 (51.4%)	7 (43.8%)
Staging		
III	19 (51.35%)	3 (18.75%)
IV	18 (48.65%)	13 (81.25%)
Smoking Status		
Smoker/Current Smoker	32 (86.5%)	13 (81.2%)
Never Smoker	5 (13.5%)	3 (18.8%)
Vitamin C		
Normal (>0.3 mg/dL)	0	0
Insufficiency (0.2-0.29 mg/dL)	0	0
Deficiency (<0.2 mg/dL)	37 (100%)	16 (100%)

CRP Low (<5mg/L) High (≥ 5mg/L)	 18 (48.6%) 19 (51.4%)	3 (6.25) 13 (81.25)

Table 2: Serum vitamin C and CRP values based on treatment history

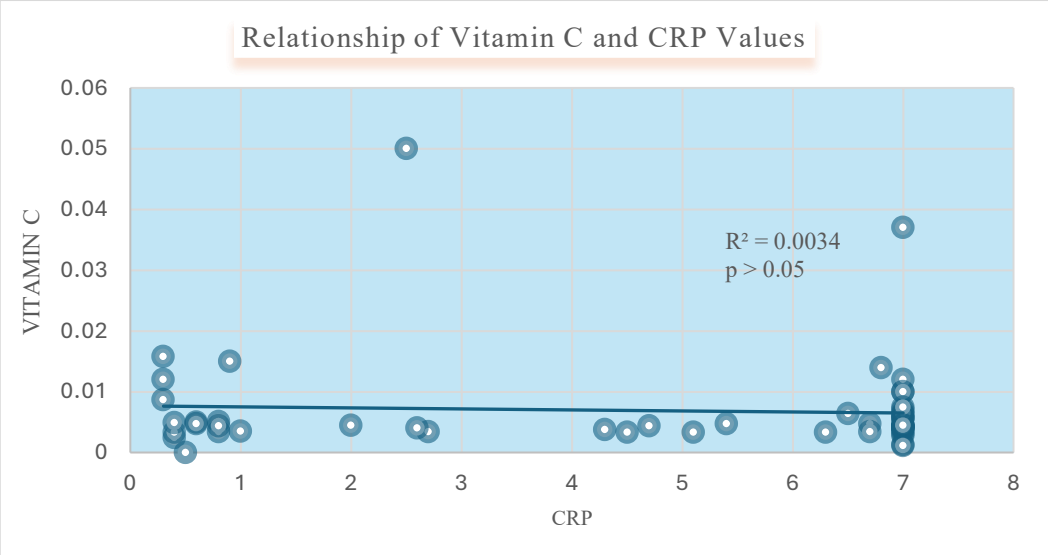
Variables	With treatment	No treatment
CRP (mean, mg/L)	4.22	5.85
Vitamin C (mean, mg/dL)	0.0068	0.007

Table 3: Serum vitamin C and CRP values based on smoking history

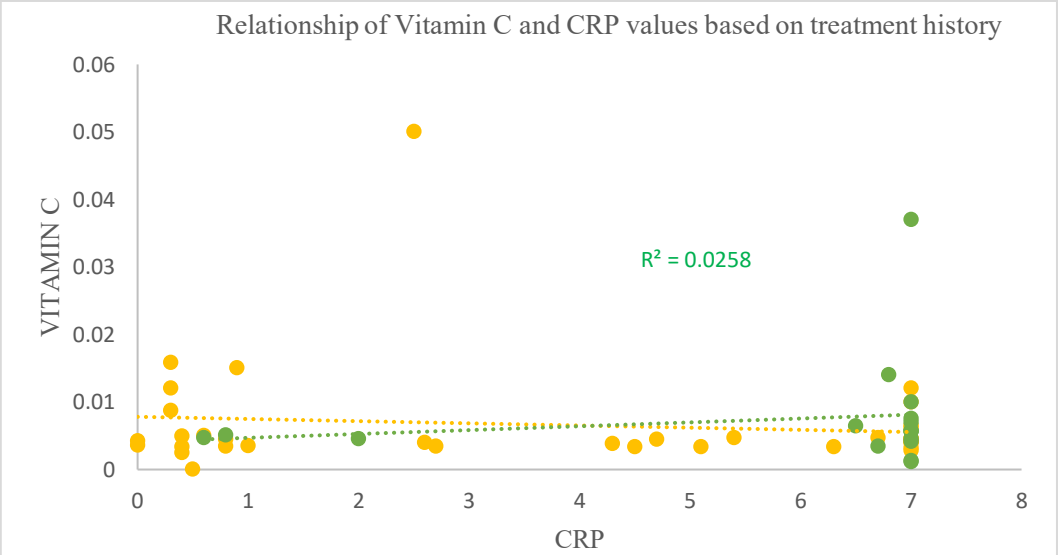
Variables	Smoker/ Current Smoker	Never Smoker
CRP (mean, mg/L)	3.6	1.81
Vitamin C (mean, mg/dL)	0.0063	0.009

From data analysis also found higher CRP value more common in no treatment respondents (5.85mg/dL vs 4.22mg/L) and respondent with history of smoking (3.6mg/dL vs 1.81mg/dL). From the data analysis also found that there was no different vitamin C value in respondents based on treatment and smoking status (**Table 2 and Table 3**).

Previously, the data was processed using Kolmogorov Smirnov and it was found that the data distribution of the patient's Vitamin C and CRP serum values was not normally distributed, so the test used was the Spearman correlation test. After processing the data using the Spearman correlation test, it was found that there was no correlation between Vitamin C and serum CRP levels in this research sample with a value of $R^2 = 0.0034$ (**Graph 1**). Based on the data obtained, the average serum CRP level of patients without treatment was higher than with treatment. After conducting additional data processing, it was shown that, in both study groups, there was no relationship between vitamin C and patient serum CRP (R2 = 0.0133 and R2 = 0.0258) (**Graph 2**).



Graph 1: Relationship of vitamin C and CRP serum values of NSCLC patients



Graph 2: Relationship of vitamin C and CRP serum values in NSCLC patients based on treatment history

Discussion

In Indonesia, lung cancer is ranked 3rd in most cancers and the top ranking in cancer deaths with the most types of cells found is NSCLC [1,4,5]. There is a need for research to determine the factors that influence the course of the disease and what can be done to increase the success of cancer treatment therapy. In this study, it can be seen that the characteristics of lung cancer patients are not much different from previous studies where male gender and age over 40 years are the demographics with the most lung cancer [2,3]. In this study, although there were more Adenocarcinoma cell types than Squamous Cell Carcinoma, they were not much different, as well as patient staging, it was found that all respondents were at an advanced stage, this is also not different from the research of Jose *et al*. [12]. Therefore, it is necessary to carry out stricter initial screening or diagnostics in the community so that in the future early-stage lung cancer patients can be found to reduce the mortality rate for lung cancer patients.

Numerous research have been done to determine how vitamin C affects the risk of lung cancer. According to Luo *et al*.'s meta-analysis research, people with lung cancer who get 100 mg/day of vitamin C have a 7% lower risk of developing the disease [9]. It is well known that vitamin C has two functions: it is a pro-oxidant and an antioxidant, and both of these prevent the development of cancer. It is commonly recognized that vitamin C has an antioxidant effect, preventing oxidative stress-induced DNA damage to cells, which in turn inhibits the carcinogenesis process [13]. Meanwhile, vitamin C can directly damage cancer cells as a pro-oxidant by forming H2O2 molecules through the Fenton reaction [8]. Vitamin C compounds have the potential to modify epigenetic pathways in cancer cells and promote immunological responses, which is another way in which they have anticancer effects [14]. Based on our research, all the respondents exhibited serum vitamin C insufficiency. This is consistent with other studies that have demonstrated the protective effects of vitamin C against lung cancer and other types of cancer. Even though none of the study's participants had a documented history of using vitamin C supplements, the study's findings showed that there was no variation in the patient's blood levels of the vitamin, suggesting that their daily consumption of the vitamin was inadequate. Therefore, it is necessary to educate people who have a high risk of developing cancer to consume vitamin C, both natural and synthetic, where the need for vitamin C to reach the daily requirement is around 75-90 mg per day. Apart from insufficient intake of vitamin C, several conditions can also affect the absorption of vitamin C in the body, such as malnutrition, malabsorption, kidney disorders, smoking, and a diet high in sugar and flavonoids that will affect vitamin C levels in the blood [15].

C-reactive protein (CRP) is an acute-phase protein produced by the liver and has a homopentamer structure with specific calcium bonds to phosphocholine. CRP has long been used as a marker of acute inflammatory responses, including in cases of cancer, CRP levels also increase in conditions of trauma, bacterial infection, and inflammation. The CRP value is checked in milligrams per liter (mg/L) and the standard CRP test results in this study are divided into 2, namely normal values if below 5 mg/L and high if ≥5 mg/L. In the process of growth, tumors can induce an inflammatory process characterized by the secretion of chemokines which ultimately promote immune cells. Tumor cells will also stimulate local cell signaling pathways that contribute to the growth and metastasis process of cancer. The presence of an inflammatory response to the extracellular matrix and tumor microenvironment through platelet recruitment, conditions of continuous oxidative stress, deposition of extracellular matrix components in the tumor microenvironment, proliferation of tumor and stromal cells, and the release of large amounts of cytokines will encourage hepatocytes to produce CRP6 compounds. In this study, 32 patients (60.37%) had CRP values ≥ 5mg/L, the average CRP value was higher in the group that did not receive treatment (5.85 vs 4.22 mg/L). A high CRP value refers to poor prognosis and reduced survival rates in some types of cancer [7]. In this study, the group of patients without treatment was more at stage IV with higher CRP values which indicated a worse prognosis.

The study by Mikirova *et al*. demonstrates that giving cancer patients large doses of vitamin C can dramatically lower their levels of CRP and tumor markers. As the body fights oxidative stress, antioxidants inhibit the inflammatory process, the body's first line of defense. Vitamin C is one antioxidant that is reduced by inflammatory conditions; consequently, oxidative stress conditions brought on by inflammation can be reversed by consuming an antioxidant-rich diet and antioxidant supplements. Enough vitamin C, the primary water-soluble antioxidant, can be consumed to lessen the inflammatory process in cancer instances. Vitamin C primarily reduces inflammation by blocking the synthesis of many cytokines, including interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and nuclear transcription factor κB (NF-κB), which in turn lowers CRP levels. In contrast to other studies that indicated a negative association, this one discovered no relationship between vitamin C levels and serum CRP after processing the data using the Spearman test to seek a correlation. Thus, it can be said that low blood levels of vitamin C do not appear to be the main factor influencing elevated CRP results. There are several other factors such as secondary infections, smoking history, and other comorbidities such as chronic obstructive pulmonary disease, rheumatoid, pericarditis, and drug reactions that affect serum CRP levels [16]. However, this research can provide input for providing vitamin C supplements, especially in populations at risk of lung cancer or patients who have been diagnosed with lung cancer, either as prevention or supporting therapy in the treatment of lung cancer.

Conclusion

Low Vitamin C levels and high CRP values are commonly found in advanced lung cancer patients. However, in this study, no relationship was found between ascorbic acid (Vitamin C) levels and serum CRP of NSCLC patients in the Medan City-North Sumatra population, because many other factors influence vitamin C levels and serum CRP values.

Declarations

Conflicts of Interest

Nil

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Authors' contributions

Elizabeth Napitupulu, Noni Novisari Soeroso, and Elisna Syahruddin contributed to the conception and design of the study, data collection, manuscript drafting, and critical revision. Putri Chairani Eyanoer was responsible for data analysis and interpretation of the results. All authors have read and approved the final version of the manuscript.

Ethical Clearance

Approved from institutional Ethics committee.

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