World Nutrition Journal | eISSN 2580-7013

ORIGINAL PAPER

Correlation between serum vitamin C level and COPD assessment test score in chronic obstructive pulmonary disease patients

Cipuk Muhaswitri[1], Drupadi HS Dillon[1], Jamal Zaini[2]

1. *Department of Nutrition, Medical Faculty of Universitas Indonesia, Cipto Mangunkusumo General Hospital, Jakarta, Indonesia*
2. *Department of Pulmonology and Respiratory Medicine, Persahabatan General Hospital, Jakarta, Indonesia*

Received 25th October 2020, Accepted 22nd June 2020

Link to DOI: 10.25220/WNJ.V04.i1.0007

Journal Website: **www.worldnutrijournal.org**

Abstract

Background: COPD is a disease due to oxidative stress causing low pulmonary function, resulting in low quality of life. A standard test to measure the quality of life in COPD is COPD Assessment Test (CAT). Vitamin C as antioxidant is widely available in the pulmonary epithelial fluid. This study aimed to investigate the correlation between serum vitamin C level and CAT score in COPD. **Methods:** This cross-sectional study was conducted at Persahabatan Hospital, East Jakarta, involving 47 subjects using consecutive sampling method. Interview was used to assess subjects' characteristics and vitamin C intake using semi-quantitative FFQ. Clinical classification, lung function, comorbidity, and CAT scores were gathered from medical records or interview. BMI was used to determine nutritional status, while vitamin C serum level was assessed using spectrophotometry. **Results and conclusions:** All subjects were male, mean age was 66.6 years, mostly ex-heavy smokers, with decreased lung function, and 25% were undernourished. Vitamin C intake was sufficient, but low in serum vitamin C level and CAT score.There was no correlation between serum vitamin C level and CAT score.

Keywords COPD, COPD Assessment Test score, vitamin C, Indonesia

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic disease that causes high morbidity and mortality.[1] This disease is the fourth leading cause of death worldwide and is projected to be the third leading cause of death in 2020.[2,3] According to World Health Organization (WHO), in the top 10 causes of death in the world in 2012, COPD was in the third rank with 6% deaths worldwide. In Indonesia, the prevalence is 5.6%, 2.7% in Jakarta, and the highest in East Jakarta as much as 3.8%.[4,5] Persahabatan Hospital data indicate that COPD patient visits increased from 616 in 2000 to 1735 in the year 2007.[6]

Chronic obstructive pulmonary disease has an impact on the health status-related quality of life of sufferers. COPD ranks 12th as a cause of decreased quality of life (DALY, Disability Adjusted Life Years) in 1990 and is expected to rank 5th in 2020.[7,8] Patients with COPD have a cough, shortness of breath and tightness in the chest that would make the patients difficult to perform daily activities, giving an impact on the quality of life.[9] Chronic Obstructive Pulmonary disease Assessment test

Corresponding author:
Cipuk Muhaswitri, MD
Department of Nutrition, Medical Faculty of Universitas Indonesia, Cipto Mangunkusumo General Hospital, Jakarta, Indonesia
Email: muhaswitri@yahoo.com

(CAT) is a standard test to measure the impact of disease on quality of life of COPD patients.[10]

Pathogenesis of COPD is related to oxidative stress. Oxidative stress occurs when the formation of oxidants is not successfully offset by various antioxidants in the body. Oxidants come from outside the body such as cigarette smoke or air pollution and that comes from the inflammatory process. Oxidative stress will cause lipid peroxidation, which causes damage to the lungs due to decreased lung function.[11,12] Systemic impact of these mechanisms would affect the quality of life of COPD patients.[13,14] Various antioxidants are needed to counterbalance the oxidants. Vitamin C is a water-soluble antioxidant that is abundant in the lung epithelial lining fluid. Its ability as an electron donor, enabling vitamin C to scavenge and quench free radicals.[11,15]

No previous studies had investigated the correlation between serum level of vitamin C and CAT score in COPD. However, some studies show correlation between serum vitamin C level and lung function and CAT scores with lung function.[8,10,11] The aim of this study was to investigate the correlation between serum vitamin C level and quality of life based on the scores of CAT of patients with COPD.

Materials and methods

This study was a cross-sectional study in 47 outpatients with stable COPD at the Department of Asthma –COPD Persahabatan Hospital East Jakarta, from April to August 2016. Subjects were obtained using consecutive sampling method.

Study subjects were those who met some inclusion criteria of stable COPD patients aged >18 years, was diagnosed with COPD during the previous month, no diabetics, asthmatics, tuberculosis, lung cancer based on medical records, nor vitamin C and multivitamin and minerals supplements. Of 138 subjects who visited, 59 people were excluded, 29 people refused to participate, two people were unable to complete the study procedure, and one blood sample was damaged.

Data on subject's characteristics, smoking history and vitamin C intake using a semi quantitative Food Frequency Questionnaire (FFQ) obtained from interviews. Data on clinical classification of COPD by the GOLD 2015, lung function by spirometry, CAT scores and history of cardiovascular diseases obtained from interviews and medical records. Anthropometry assessment was done using stadiometer for height and SECA scale 870 for weight measurement. Lung function test was performed using spirometry Microspiro HI 28, Chest Corporation Japan, measuring forced expiratory volume in 1 second (FEV_1%), forced vital capacity (FVC%) and the ratio FEV_1 / FVC%. Vitamin C serum level was assessed spectrophotometrically using Multiskan Ascent. Two mL of non fasting venous serum was stored at -80^0C until analysis.

Statistical analysis was performed using the Statistical Program for Social Science (SPSS) for Windows version 20. Data intake of vitamin C and CAT score with a median value (minimum-maximum) and data serum level of vitamin C with a mean $\pm$ standard deviations. Statistical analysis to see the difference in the proportion of two groups using Chi-square / Fisher's exact test and the mean difference between two groups with the Mann-Whitney test. Spearman's rank test was used to see the correlation between serum vitamin C level and CAT score. Significancy level was $p<0.05$. This study has been approved by the Ethics Commission of Research and Health, Persahabatan Hospital, East Jakarta, Indonesia.

Results

Subjects were all males in this study. Figure. 1 shows study subject's characteristic: 66.6$\pm$ 8.0 years of age, mostly elderly. (Figure 1A), subjects'income was equally distributed in less or equal to Jakarta's wage index (Figure 1B). Majority of subjects was former smokers (Figure 1C), while half of them was heavy smokers (Figure 1D). BMI of subjects in this study was 21.3$\pm$3.8 kg/m2, mostly had normal weight, with about 25% were underweight (Figure 1E).

Study subjects' COPD clinical classification according to GOLD 2015 shown in Figure 2. Almost half of study subjects was categorized as severe COPD (Figure 2 A). There was a decrease in lung function, as FEV_1%, FVC% and FEV_1/FVC% ratio was 49.6$\pm$20.7%, 66.8$\pm$18.6, and 50.7$\pm$10.4, respectively. Based on spirometry test, about half of study subjects suffered from severe and very severe degree of lung function (Figure 2B). More study subjects were in the mild category of CAT score, with a median (minimum-maximum) value of 9 (1-29). About half of study subjects suffered from cardiovascular comorbidity of ischemic heart disease, hypertension or congestive heart failure (Figure 2D).

Vitamin C intake of study subjects was 124.2 (18-480.1) mg/L, while serum vitamin C level was 21.1±4.1 μmol/L. There was no significant correlation (p=0.96) between vitamin C intake and serum level in this study. Almost double proportion of study subjects with sufficient vitamin C intake according to AKG Indonesia 2013 (Figure 3A). However, majority of subjects was in low vitamin C status based on serum vitamin C level (Figure 3B).

A significant difference of vitamin C intake based on CAT score category: study subjects with mild CAT score category had higher vitamin C intake (p=0.008) as compared to those with severe CAT score. However, no significant difference of serum vitamin C level between the two CAT score categories, as shown in Table 1.

Proportion of study subjects based on vitamin C intake and serum level based by CAT score category shown in Figure 4. There were more study subjects with low vitamin C intake (p=0.021) among severe CAT score category as compared to those with mild CAT category (Figure 4A). However, no difference of serum vitamin C level between mild and severe CAT score category (Figure 4B).

Differences of vitamin C intake and serum level in groups with and without comorbidity shown in Table 2. Serum vitamin C level was lower (p=0.033) among those with comorbidity as compared to those without comorbidity.

Proportion of study subjects' vitamin C intake and serum level based on comorbidity shown in figure 5. No difference of study subjects' proportion with low vitamin C intake with or without comorbidity (Figure 5A), however, more study subjects (p= 0.028) with low vitamin C level among those with comorbidity as compared to those without comorbidity (Figure 5B).

There was no statistically significant correlation between serum vitamin C level and CAT score (p = 0.949 and r = 0.01).

Discussion

The mean age of subjects in this study was 66.6 years, mostly elderly.[17] This result was consistent with a study by Draman et al[8] in Malaysia with similar mean age of 66.4 years, but in contrast with a study by Cristovaoet al[1] in Portuguese with a higher mean age of 71.3 years. Age is one risk factor on the development of COPD. The older a person, there will be a decrease in lung function, while more exposure to harmful substances.[2,18] Fletcher and Peto's study on 792 male workers aged 35-59 years observed for 8 years found that VEP_1 declined throughout life, increasing with age.[19] Kojima et al[20] showed data that COPD incidence among non-smokers was lower at 25-49 years of age with a gradual increase at the age of 50-74 years, indicating a decline of lung function by age.

All subjects in this study were male. The result of this study was similar to Ghobadi et al[10] that all subjects were male. Data of previous studies showed that patients with COPD were more among males than females, although lately the number is not much different, due to changes in smoking habits. This may be explained by the smoking prevalence of 16x higher in males (65.9%) as compared to women (4.2%).[21]

Subjects' income in this study was consistent with Ismail et al[6], despite different socio-economic parameters. Socio-economic is one risk factor of COPD.

In this study, majority (87.2%) of study subjects was former smokers, consistent with Cristovao et al[1] who observed more former smoker patients with COPD than non-smokers, unlike Lin et al[22], who found more non-smokers than former smokers. Major risk factor of COPD is smoking. Cigarette contains more free radicals and harmful substances which can increase oxidant load in the body.[2,13] Smoke as a risk factor for COPD is dose-dependent in nature: the longer and more number of cigarettes, the higher the risks for COPD.[21]

The results of this study were consistent with Ismail et al[6] who found that 84.6% of study subjects was moderate to heavy smokers. Kojima et al[20] showed that increasing incidence of COPD was higher in the group with higher Brinkman index. This supports the hypothesis that smoking is a risk factor for COPD.

The mean BMI of subjects in this study was 21.3 kg/m^2 considered as normal BMI, which more proportion of study subjects in this category. The results of this study was consistent with Ismail et al[6] and Lin et al[22] studies with normal BMI of 22.13 kg/m^2 and 22.8 kg/m^2, respectively. Unlikely, Cristovao et al[1] observed a higher mean BMI of 27.92 kg/m^2, which was considered as overweight. The difference was also seen in the study by Dhakal et al[27] in which most of COPD subjects was with lower BMI of <18.5 kg/m^2.

BMI assessment was conducted to determine the nutritional status of patients with COPD in connection with the hypothesis that the IMT significantly affects the severity of disease.[24] Landbo et al[24] states that underweight BMI is a risk factor that stands alone on COPD mortality and had stronger relationship with COPD severity.

The CAT score in this study was 9, categorized as mild, in contrast with two other studies with higher CAT score of 19.6 (Ghobadi et al[10]). The result was also different from Draman et al[8] with CAT score of moderate category (11-20). This indicates that COPD probably provides minor health impact on more than half of study subjects.

This study recorded 23 subjects (48.9%) suffered with comorbidity such as hypertension (14.9%), ischemic heart disease (17%), and congestive heart failure (17%). This study was in line with Negro et al[25] who showed that cardiovasculer disease was important comorbidity among COPD patients. Cardiovascular diseases exist frequently amongst COPD, which would increase morbidity and mortality.[21] Smoking is a risk factor for both cardiovascular disease and COPD due to increase oxidative stress and systemic inflammation.[13] Therefore, the occurrence of comorbidity should be routinely monitored and treated in COPD patient.[2]

Vitamin C intake in this study was sufficient with median of 124.2 mg/day, with a wide range of 18-480.1 mg/day. This result was different from Lin et al[22] and Ahmadi et al[26] who showed lower vitamin C intake by COPD patients as compared to healthy individuals. This study found that 66% subjects was with sufficient vitamin C intake, in contrast to Pirabassi et al[27] who showed low intake of vitamin C among 94% subjects with COPD in Malaysia.

Low vitamin C intake may also occur due to low consumption of fruit and vegetables,[27] as sources of vitamin C. Fruit is a good source of vitamin C because it is comsumed directly without undergoing cooking process, which may damage vitamin C content.[28]

No correlation between vitamin C intake and serum level was observed in this study (p = 0.96). Many factors affect the amount of vitamin C in the diet such as processing, long storage as well as high temperature, which will reduce vitamin C content in the diet.[28,29] Boiling vegetables reduces 50.9% of vitamin C content.[29]

Vitamin C is absorbed as much as 80-90% in relation to is 30-180 mg of intake, but decreased absorption occurs as vitamin C consumption increases.[30] Therefore, the recommendation of vitamin C daily consumption is to consume several times each day with small portions.[31] Mean intake of vitamin C in this study was 124.2 mg/day, within the range of intake for 80-90% absorption. Therefore, hindering vitamin C absorption was unlikely to occur among our study subjects. The results of this study were different from a study by Dehghan et al[32] and Young et al[33] who showed a correlation between vitamin C intake and serum level in healthy subjects. The correlation between the intake and levels of several nutrients, including vitamin C is influenced by age, sex, smoking, alcohol consumption, and comorbid.[34,35]

Sufficient intake of vitamin C was more observed among subjects with mild CAT score than those with severe CAT score. There was a significant negative correlation between vitamin C intake and CAT score in this study (p=0.002; r=-0.43,).This result was consistent with Grievink et al[36] in healthy subjects as vitamin C was significantly associated with symptoms of cough (odds ratio 0.66, 95% CI: 0.50-0.87), and Menaas et al[37] also showed an association between vitamin C intake and cough symptoms among healthy smokers. The ability of vitamin C to protect respiratory symptoms such as cough, may explain these findings.

Sufficient intake of vitamin C was observed among subjects without comorbidity as compared to those with comorbidity. Congestive heart failure as observed in this study shows symptoms of reduced appetite, fatigue, and shortness of breath. These symptoms might cause less sufficient intake of vitamin C in the group with comorbidity. Furthermore, intake of antioxidants such as vitamins C and E has an effect of protecting against cardiovascular disease through stress oxidative reduction.[38]

The mean serum vitamin C level of 21.1±4.1mol/L in this study was considered low, observed among 72.3% of study subjects. The result was consistent with Lin et al[22], Cristovao et al[1] and Chittimoju et al[15] who found that serum vitamin C level was significantly lower in patients with COPD compared to healthy people. Low serum vitamin C level in this study might be due to vitamin C usage to cope with oxidative stress among COPD patients, through two mechanisms, namely reduction of free radicals, and it is needed for the regeneration of vitamin E, which in turn serves to function in oxidative stress.[11,12]

The proportion of study subjects with low serum vitamin C level was observed a lot more in the group with comorbidity than without comorbidity. This result was consistent with Padayatti et al[39] stated that low level of vitamin C was associated with hypertension and impaired endothelial function, because vitamin C improves endothelial dysfunction, and protects against heart and blood vessel system. The significantly lower serum vitamin C level in the group with comorbidity indicates that comorbid is one of the factors that affect levels of vitamin C serum.

Several studies illustrated a possible relation between serum vitamin C level and CAT score. However, the correlation between serum vitamin C level and CAT score of COPD patients was not significant (p=0.949 ; r=0.01) in our study. This maybe due to many factors that affect the quality of life in COPD in addition to symptoms such as shortness of breath, cough, sputum production and limited physical activity. Other factors that can affect the quality of life is age, sex and nutritional status based on BMI, smoking, economic status, degree of disease severity based on pulmonary function, the occurence of comorbidity, depression and anxiety, as well as other factors such as exacerbations, hospitalizations, number of used drugs, duration of illness and low education.[23] Different proportions of study subjects with serum vitamin C level in the CAT score category was not statistically significant, indicating that low serum vitamin C level was not associated with increased severity of CAT score.

Pawar et al[11,12] stated that there was a significant positive correlation between levels of vitamin C serum and lung function. Ghobadi et al[10] stated that there was a correlation between the scores of CAT with FEV_1% and FVC%. These results were corroborated by Draman et al[8] who showed that there were significant differences of CAT score on every degree of lung function. Salma et al[40] showed data on CAT score which was positively correlated with the severity of lung function based on FEV_1%. Therefore, lung function is one of the factors that influence the quality of life in COPD,[23,24] and lung function was positively significant correlated with higher levels of serum vitamin C.[11,12]

This study showed a significant negative correlation ($p = 0.001$, $r = -0.48$) between CAT score and FEV_1%, but no significant correlation between serum vitamin C level and FEV_1% ($p = 0.59$). FEV_1% indicates level of air obstruction in the respiratory system: the higher the FEV_1% - the lesser the air obstruction which means less burden of respiration experienced by the COPD patients. A burden during respiration influences quality of life as indicated by lower CAT score. Serum vitamin C level is not directly correlated with the level of air obstruction, as the effect of vitamin C in COPD patients as antioxidant is to reduce the destruction effect of oxidants on respiratory organ system. This may explain why unlike FEV_1%, there was no correlation between serum vitamin C level and CAT score in this study as FEV_1% has a more direct influence on CAT score as compared to vitamin C.

In conclusion, no correlation was observed between serum vitamin C level and CAT score in this study. Further study is needed to confirm this finding by assessing oxidative stress as well as anti oxidants among COPD patients of each clinical diagnosis.

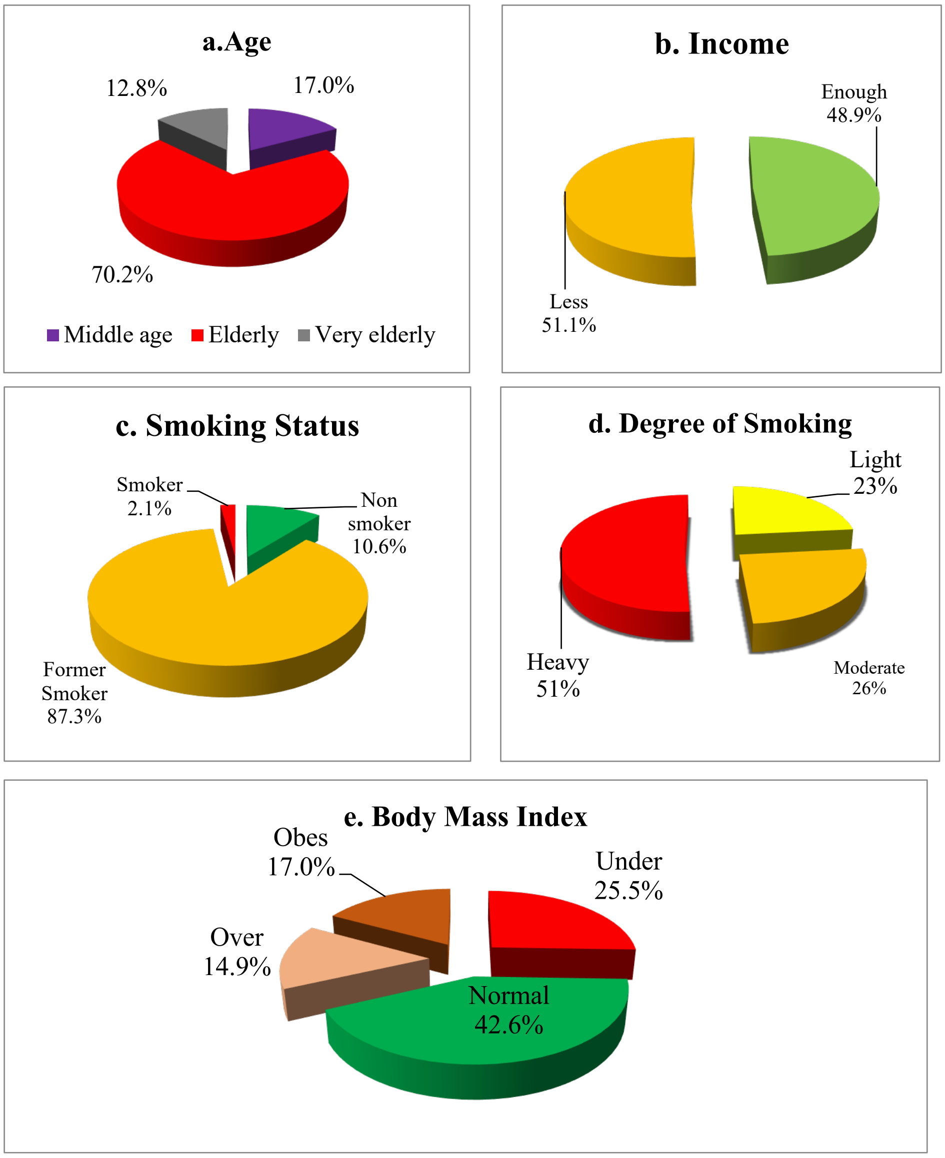

Figure 1. Distribution of Study Subjects by Age, Income, Smoking History, and Nutritional Status Based on BMI

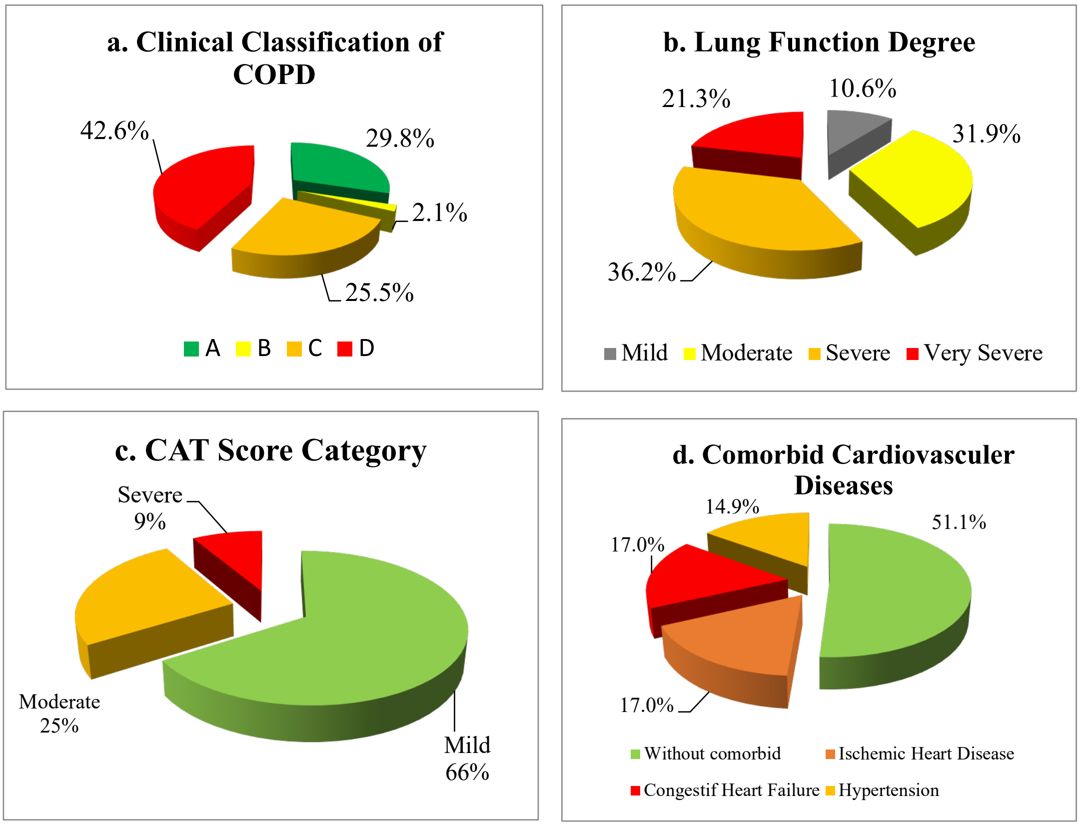

Figure 2. Distribution of Study Subject By Clinical Classification of COPD According to GOLD 2015, Lung Functon Degree Based on Spyrometri, CAT Score and Comorbid Cardiovasculer Disease

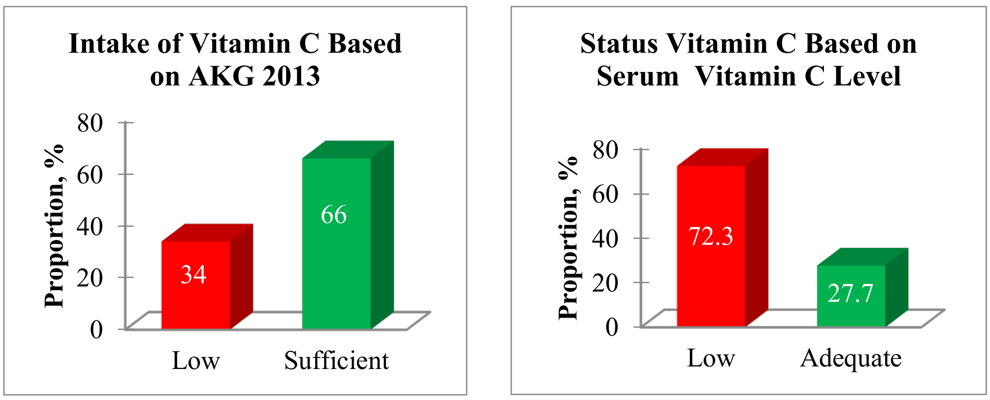

Figure 3. Proportion of Subjects Research In The Intake of Vitamin C Based on AKG Indonesia in 2013 and Status of Vitamin C Based on Serum Vitamin C Level

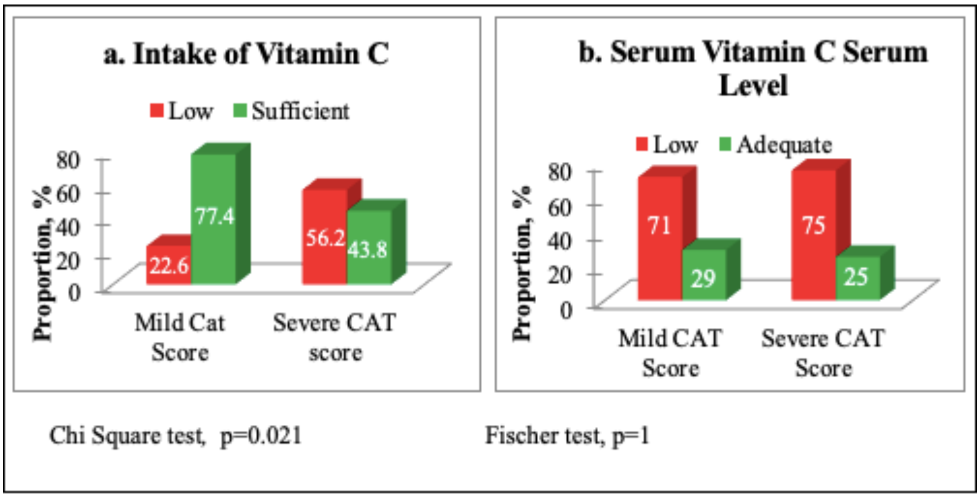

Figure 4. Proportion of Study Subjects in Case of Intake and Serum Vitamin C Level by CAT Score

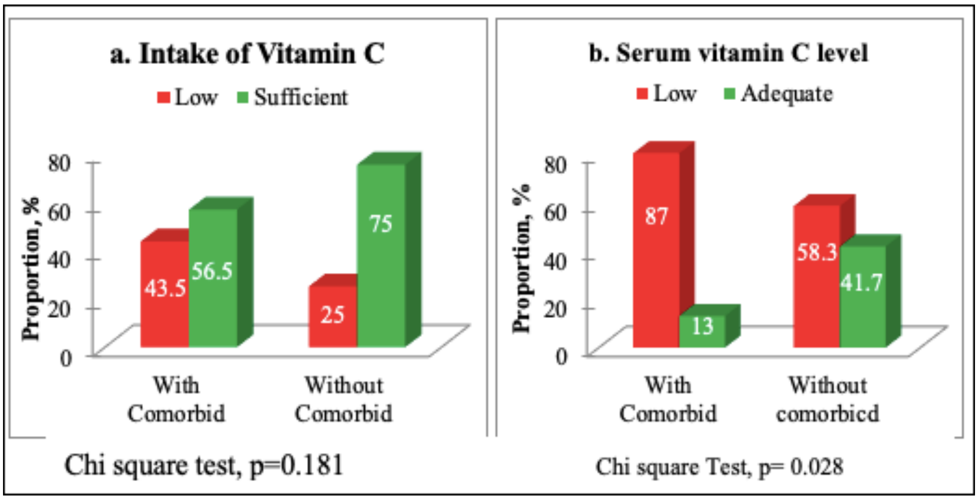

Figure 5. Proportion of Study Subjects in Case of Intake and Serum Vitamin C Level In Comorbid Cardiovascular

Table 1. Distribution of intake and serum vitamin C level by CAT score category

	CAT score category		p**
	Mild (n=31)	Severe (n=16)	
Vitamin C intake, mg/day	^158.9 (20.1-480.1)	*89.9±56.1	0.008
Serum vitamin C level, µmol/L	^20.7 (13.9-37.6)	*21.2±3.3	0.787

n:number of subject, ^median (minimum-maximum), *mean±standard deviation, **Mann-Whitney test, p value≤0.005, statistically significant

Table 2. Distribution of vitamin C intake and serum vitamin C level based on comorbidity

	Comorbidity		p*
	With (n=23)	Without (n=24)	
Vitamin C intake, mg/day	111.6(18-374.7)	143.4(20.1-480.1)	0.416
Serum vitamin C level, µmol/L	20.2(13.9-25.1)	21.7(14.9-37.6)	0.033

n:number of subject, ^median (minimum-maximum), *Mann-Whitney test, p value≤0.005, statistically significant

Acknowledgements

The study team very much appreciates all study subjects for their willingness to join the study towards the end. We also thank SEAMEO RECFON laboratories in helping us with blood samples analysis.

Conflict of Interest

Authors declared no conflict of interest regarding this article.

Open Access

Reference

1. Cristovao C, Cristovao L, Nogueira F, Bicho F. Evaluation of the oxidant and antioxidant balance in the pathogenesis of chronic obstructive pulmonary disease. *Rev Port Pneumol*. 2013;19(2):70–5.
2. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease. Update 2015. Available from www.goldcopd.org (accsesed on 20 October 2015)
3. Pirabbasi E, Cheraghi M. Antioxidant supplementation among Chronic Obstructive Pulmonary Disease (COPD): Is it necessary? *Pakistan J Nutr*. 2012;11(5):501–6.
4. Badan Penelitian dan Pengembangan Kesehatan Kementrian Kesehatan RI. *Pokok Pokok Hasil Riset Kesehatan Dasar Provinsi DKI Jakarta Tahun 2013*.
5. WHO. Burden of COPD. 2015. Internet online. http://www.who.int/respiratory/ copd/ burden/en/index. (accessed on 1 Jan 2015)
6. Ismail E, Yunus F. *Hubungan antara hasil pemeriksaan kapasitas difusi paru terhadap karbonmonoksida (DLCO) metode napas tunggal dengan derajat pasien PPOK di RSUP Persahabatan Jakarta*. (tesis). Universitas Indonesia; 2015.
7. Tsiligianni IG, van der Molen T, Moraitaki D, Lopez I, Kocks JWH, Karagiannis K, et al. Assessing health status in COPD. A head-to-head comparison between the COPD assessment test (CAT) and the clinical COPD questionnaire (CCQ). *BMC Pulm Med*. 2012;12:20.
8. Draman N, Hasnan HM, Mohd W, Wan I. The Association of the COPD Assessment Test (Cat) Score with Chronic Obstructive Lung Disease (GOLD) Grade among Chronic Obstructive Pulmonary Disease (COPD) Outpatients in the

North East of Peninsular Malaysia. *Int J Collab Res Intern Med Public Heal*. 2013;5(9):596–607.
9. COPD Assesment Test. Available from: www.catesonline.org (accessed on 29 Feb 2016)
10. Ghobadi H, Ahari SS, Kameli A, Lari SM. The relationship between COPD assessment test (CAT) scores and severity of airflow obstruction in stable COPD Patients. *Tanaffos*. 2012;11(2):22–6.
11. Pawar RS, Abhang, Subhodhini A DT, Lokhande R. Study of Oxidative/Nitrosative Stress , Non-Enzymatic Antioxidants and Markers of Airflow Obstruction (FEV1 % Predicted) in Chronic Obstructive Pulmonary Disease (COPD). *Int J Bioassay.*2014; 3(06):3092–100.
12. Pawar RS, Abhang SA, Borale P, Lokhande R. Study of Correlation of Pulmonary Function Test with the Markers of Oxidative Stress and Non-enzymatic Antioxidants in Chronic Obstructive Pulmonary Disease (COPD) Patients. *Br J Med Med Res*. 2014;4(28):4710–22.
13. Bernardo I, Bozinovski S, Vlahos R. Targeting oxidant-dependent mechanisms for the treatment of COPD and its comorbidities. *Pharmacol Ther*. 2015;155:60–79.
14. Cavalcante AG de M, Bruin PFC de. The role of oxidative stress in COPD: current concepts and perspectives. *J Bras Pneumol*. 2009;35(12):1227–37.
15. Chittimoju V, Rao K, Pasula S. Study of vitamin C and malondialdehyde in chronic obstructive pulmonary disease patients. *IJPBS*. 2014;4(2):83–8.
16. Sastroasmoro S, Ismael S. *Dasar-dasar Metodologi Penelitian Klinis*. 4th ed. Jakarta: Sagung Seto; 2011. 348-81 p.
17. Kementrian Kesehatan Republik Indonesia. *Pedoman Pelayanan Gizi Lanjut Usia*. 2012.
18. Bergman E, Hawk S. Disease of the Respiratory System. In: Nelms M, Sucher K, Lacey K, Roth S, editors. *Nutrition Therapy and Patophysiology 2/e. 2nd ed*. Wadsworth-Cengange Learning; 2010. p. 657–63.
19. Fletsher C, Peto R. The Natural History of Chronic Airflow Obstruction. *Br Med J*. 1977;1(6077):1645–8.
20. Kojima S, Sakakibara Hiroki, Shinici M, Kunihiko H, Fumio M, Masahiro O, et al. Incidence of Chronic Obstructive Pulmonary Disease and The Relationship Between Age and Smoking in Japanese Population. *J Epidemiol*. 2007;17(2):4–6.
21. Perhimpunan Dokter Paru Indonesia. *Penyakit Paru Obstruktif Kronik (PPOK) Diagnosis dan Penatalaksanaan.* 2016.
22. Lin YC, Wu TC, Chen PY, Hsieh LY, Yeh SL. Comparison of plasma and intake level of antioxidant nutrients in patients with chronic obstructive pulmonary disease and healthy people in Taiwan: A case-control study. *Asia Pac J Clin Nutr*. 2010;19(3):393–401.
23. Dhakal N, Lamsal M, Baral N, Shrestha S. Oxidative Stress and Nutritional Status in Chronic Obstructive Pulmonary Disease. *J Clin Diagnosis Res*. 2015;
24. Landbo C, Prescott EVA, Lange P, Vestbo J, Almdal TP. Prognostic Value of Nutritional Status in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med*. 1999;160:1856–61.
25. Negro RWD, Bonadiman L, Turco P. Prevalence of different comorbidities in COPD patients by gender and GOLD stage. *Multidiscip Respir Med*. 2015;1–9.
26. Afsani A, Neda H, Maryam H, Hamidreza T. Nutritional evaluation in chronic obstructive pulmonary disease patients. *Pakistan J Biol Sci*. 2016;(May 2012):501–5.
27. Pirabbasi E, Najafiyan M, Cheraghi M, Shahar S. What are the Antioxidant Status Predictors ' Factors among Male Chronic Obstructive Pulmonary Disease (COPD) Patients ? *Glob J Heal Sci*. 2013;5(1):70–8.
28. Combs GF. *The Vitamins.* Fundamental Aspects in Nutrition and Health. 3rd ed. Elsevier; 2008.
29. Pacier C, Martirosyan DM. Vitamin C : optimal dosages , supplementation and use in disease prevention. *Funct Foods Heal Dis*. 2015;5(3):89–107.
30. Bender D. The Vitamins. In: Gibney M, New S, Cassidy A, Vorster H, editors. *Introduction to Human Nutrition*. 2nd ed. Wiley Blackwell; 2009.
31. Iqbal K, Khan A, Khattak M. Biological Significance of Ascorbic Acid (Vitamin C) in Human-Health-A Review. *Pakistan J Nutr*. 2004;3(1):5–13.
32. Dehghan M, Akhtar-Danesh N, McMillan CR, Thabane L. Is plasma vitamin C an appropriate biomarker of vitamin C intake? A systematic review and meta-analysis. *Nutr J*. 2007;6:41.
33. Young IS, Fletcher A, Weinbrenner T, Asensio L, Castello A, Valencia C. Plasma concentrations of carotenoids and vitamin C are better correlated with dietary intake in normal weight than overweight and obese elderly subjects. *Br J Nutr*. 2007;97(2007):977–86.
34. Gibson R. *Principles of Nutritional Assessment*. 2nd ed. New York: Oxford University Press, Inc,;

2005.
35 Hanson C, Rutten EP. Wouters EFM, Rennard S. Diet and vitamin D as risk facotrs for lung impairment and COPD. *Transl Res*. 2016;162(4): 219–36.
36. Grievink L, Smit HA, Ocké MC, Grievink L, Smit HA, Ocké MC, et al. Dietary intake of antioxidant (pro) -vitamins , respiratory symptoms and pulmonary function : the MORGEN study. *Thorax*. 1998;53:166–71.
37. Menaas EO, Luge ÒF, Uist ASB, Ollmer WM V, Ulsvik AG. Dietary vitamin C intake is inversely related to cough and wheeze in young smokers. *Respir Med*. 2003;97.
38. Zhang P, Xu X, Li C. Cardiovascular diseases : oxidative damage and antioxidant protection. *Eur Rev Med Pharmacol*. 2014;3091–6.
39. Padayatty SJ, Katz A, Wang Y, Eck P, Kwon O, Lee JH, et al. Vitamin C as an Antioxidant : Evaluation of Its Role in Disease Prevention. *J Am Coll Nutr*. 2013;22(1):18–35.
40. S Salma, C Yoghinta. Clinical Correlation of Copd Assessment Test (Cat) Questionnaire with Severity in Acute Exacerbation of Chronic Obstructive Pulmonary Disease. *IOSR J Dent Med Sci*. 2014;14(1):12–4.